Official Title: **Barriers to Early Progress in Cochlear Implant Outcomes: a Non-interventional Feasibility Study**

NCT Number: **NCT05265260**

Document Date: **20 October 2021**

Clinical Investigation Plan

Investigation Title:

Barriers to early progress in cochlear implant outcomes:

a non-interventional feasibility study

Short Title:	**PROGRESS**
CIP Number:	**EMEA5798**
Date:	**20-OCTOBER-2021**
Sponsor	**Cochlear France SAS** **(a subsidiary of Cochlear Limited)** **135 Route de Saint Simon** **Toulouse, 31100 France.** **Ph. +33 534 638 585**

This clinical investigation shall be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, International Standard ISO 14155 (2011) Clinical investigation of medical devices for human subjects - Good Clinical Practice, and any regional or national regulations, as applicable.

Manufacturer	Cochlear Limited, 1 University Ave, Macquarie Park NSW 2113, Australia
Sponsor Organisations	Cochlear France SAS 135 Route de Saint Simon CS 43574 31035 Toulouse, France.
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Clinical Research Organisation	Data Management: [redacted]
Safety Contact	Not applicable

INVESTIGATOR AGREEMENT

Principal Investigator Approval and Declaration

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

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

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

TABLE OF CONTENTS

1 DEFINITIONS AND ABBREVIATIONS

Term	Description
AC	Air conduction
ADE	Adverse Device Effect
AE	Adverse Event
AGF	Amplitude Growth Function
AMDT	Approved Medical Device on Test
BC	Bone conduction
CAP	Compound Action Potential
CER	Clinical Evaluation Report
CI	Cochlear Implant
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CL	Current level (of stimulation pulses)
CRF	Case Report Form
CRO	Contract Research Organisation
DCF	Data Clarification Form
DD	Device Deficiency
EC	Ethics Committee Synonymous abbreviations/terms include: IRB (Institutional Review Board) IEC (Institutional Ethics Committee or Independent Ethics Committee) HREC (Human Research Ethics Committee)
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practices
IB	Investigator's Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IMD	Investigational Medical Device
MoCA	Montreal Cognitive Assessment screening test for detecting cognitive impairment
NCA	National Competent Authority
PI	Principal Investigator
PIL	Principal Investigator List

Term	Description
PMS	Post-Market Surveillance
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNR	Signal to noise ratio for speech and competing babble
SNR50	Signal to noise ratio for 50% correct sentence recognition score
SOE	Spread of excitation
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

2 CLINICAL INVESTIGATION SYNOPSIS

Investigation title	Barriers to early progress in cochlear implant outcomes: a non-interventional feasibility study
Short title	PROGRESS
Investigation number	EMEA5798
Name of approved medical devices on test	Not applicable – non-interventional
Intended use of approved medical devices on test	Not applicable – non-interventional
Name and description of comparator device/product(s)	Not applicable
Recruitment period	3 months
Expected duration per subject	1 hour, time needed for the subject to discuss their participation in the study and to complete the questionnaire.
Planned number of subjects	30
Number sites	1
Inclusion criteria	1. Adult subjects, 18 years or older 2. Subjects unilaterally implanted or bilaterally implanted with at least 6 months separating the two cochlear implantations. 3. Subjects who have been implanted between January 2016 and December 2021. 4. Subjects have received a Nucleus CI: CI512, CI522 or CI532 cochlear implants with non-rotating magnet, or CI600 series equivalent CI612, CI622 and CI632 with rotating magnet and external sound processors CP900 or CP1000 behind-the-ear, or Kanso or Kanso 2 off-the-ear types. 5. Subjects who are fluent in French (language used in the questionnaire and speech tests) 6. Subjects who are not opposed to participating in the study 7. Subjects for who the medical record data is available throughout the defined data search period.
Exclusion criteria	1. Subjects with single-sided deafness (SSD). 2. Subjects who are not affiliated to the French Social Security. 3. Subjects who are under legal protection.

Objectives and Endpoints	
Primary Objective	**Primary Endpoint**
Confirm a selection of testable patient-related and device-related parameters that limit sentence recognition in quiet using CI alone at 1-month post-activation in adult CI users.	Binary classification: ≥90% correct sentence score in quiet at 1-month using CI alone considered as a good performer; <90% poor performer.
Exploratory Objectives	**Exploratory Endpoints**
• Evaluate the correlation of testable parameters with sentence score at 1-day in quiet and at 1-month in noise. • Evaluate the correlation of testable parameters, sentence scores and self-reported performance (SSQ12) at time of non-opposition. • Determine whether shifting the good/poor performer 90% cut-off score would improve the correlation with pass/fail on the parameter tests. • Explore the relationships between testable parameters measured post-implantation and demographic and hearing-related factors.	• Sentence recognition score in quiet with CI alone at 1-day. • Sentence recognition with CI alone at 1-month: scores in quiet and in fixed levels of noise 10 dB & 5 dB SNR, or SNR50. • Sentence recognition at one month near time of inclusion: scores in quiet and in fixed levels of noise 10 dB & 5 dB SNR, or SNR50. • SSQ12 score at time of inclusion.

3 SCHEDULE OF EVENTS

Visit Type	**Screening**	**Inclusion**	**Collection**	**EOS**
Timing of Investigation	**NA**	**Day 0**	**Day 0**	**Month 1**
Visit window (±)	NA		**± 30 days**	**± 30 days**
Procedures			retrospective	prospective
Written information and non-opposition form		X		
Demographics			X	
Eligibility	X			
Inclusion and exclusion criteria			X	
Hearing history (incl. preop audiogram and speech recognition)			X	
Medical, imaging and surgical history			X	
Collect CDX CustomSound device data file: Fitting parameters, NRT, Data logging			X	
Functional cognitive test scores and completion times (MoCA, Stroop, ÉCLA-16+ subtests)			X	
Sound field aided thresholds (1-day to 1-month)			X	
MBAA2 sentence recognition in quiet score at 1-day			X	
MBAA2 sentence recognition in quiet score at 1-month			X	
MBAA2 sentence recognition at 10 dB SNR score at 1-month (or verify as zero)			X	
MBAA2 sentence recognition at 5 dB SNR score at 1-month (or verify as zero)			X	
MBAA sentence recognition SNR50 at 1-month (or verify non convergent or score in quiet <80)			X	
Post-operative events related to the surgery or related to the device.			X	
Patient questionnaire (including SSQ12)				X

4 BACKGROUND INFORMATION AND RATIONALE

4.1 Introduction

Outcomes with cochlear implants (CI) are known to be variable. Quite a few studies have sought to identify factors which are associated with poor speech recognition scores: particularly word recognition scores at or greater than six months after CI activation. At that time point, word recognition scores in quiet have often reached a plateau, although speech recognition in noise may continue to improve (Cusumano et al, 2017). The most often cited variable which is associated with word recognition scores is duration of deafness. This result is also extended to those subjects with pre-lingual deafness who are implanted as adults. In the former case one supposes that long-deaf adults "forget" how to hear language, while congenitally deaf adults never learnt how to hear language fully.

These two potentially limiting factors (Holden et al., 2014; James et al., 2019) may slow progress in, or limit in the long-term speech recognition post-implantation. These two factors are generally identified from patient histories: sometimes with objective data such as audiograms, but often only from patient reports. This serves as one example of a limiting factor versus a testable effect as in Figure 1.

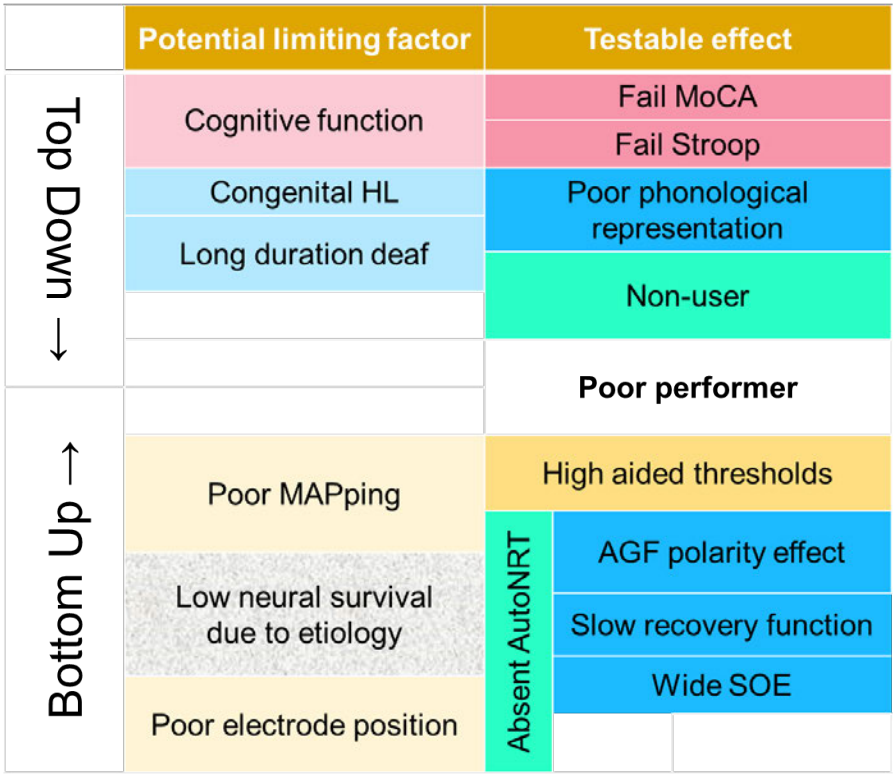

Figure 1: Simple schema of potential limiting factors for outcomes with CI and testable processing effects

For this first example the Toulouse team in reviewing the literature on speech and language development considered that the resulting deformed representation of language in long-deaf subjects

should be detectable by a standard test of phonological representation (subtests on ÉCLA-16+, Gola-Asmussen et al, 2010). Other root causes and testable effects are given in Figure 1. Self-report by patients may not be reliable in either onset or degree, however testable effects which may be linked back to root causes can be discovered at the time of treatment with CI.

The factors and corresponding effects on speech processing are divided into “top-down” and “bottom-up” processes in Figure 1, as has been previously defined by authors such as (Moberly et al, 2016). Here a manageable set of processing parameter tests was chosen by the investigational team based on the availability of norms or diagnostic certainty.

4.1.1 Top-down processing parameters

We first address top-down processing parameters, that are assumed to affect signal decoding and interpretation. General cognitive disfunction will likely affect performance on nearly any task. The MoCa is a screening test designed to detect mild cognitive impairment (Nasreddine et al, 2005). When responding to questioning such as “what was said” on speech recognition tests, executive function, such as concentration, is also a factor. The Stroop test (“Victoria”, f-SV) is a commonly used to evaluate executive functions and has age-adjusted norms. To evaluate implicit linguistic knowledge, two subtests (3 and 4) of the ECLA-16+ battery (Gola-Asmussen et al, 2010) were employed with visual support. These phonological tests were selected by the clinical team to evaluate sub lexical reading (initial phoneme deletion and ability to create Spoonerisms). Finally, the amount of time of use of the CI per day, and time listening to speech, may be measured using the inbuilt data-recording of the Nucleus 6 and 7 sound processors. Poor-use is common in congenitally or long-deaf adult CI users (Holder et al, 2020), who may find it difficult to integrate and interpret new sound sensations provided by the implant. In addition, non-use has the direct effect of impeding acclimatization to sound provided by the CI.

4.1.2 Bottom-up processing parameters

Bottom-up processing parameters generally relate to auditory sensitivity: both absolute sensitivity to sound, but also discriminating different sounds. Standard aided thresholds for tones presented in a sound field are used to test access to sounds of sufficiently low levels. Elevated thresholds are potentially caused by loss of sensitivity in any part of the CI sound processor function, but also insufficient stimulation current levels. However, current levels may be required to be substantially higher in cases of poorly positioned electrode arrays or very poor neural survival in the auditory nerve. Current levels that would produce aided thresholds in an acceptable range may not be obtained either because of device limitations or due to producing side-effects, such as facial nerve stimulation. Non-optimal electrode position may be unavoidable due to abnormal cochlear structure or morphology (either congenital or developed etiologies). Patchy or overall poor neural survival may be similarly present in these cases. We note that normal ranges for current levels (maps) used in CI processors are large (for example, larger than the typical individual dynamic ranges) and there is to date no evidence in the literature that lower or higher standard monopolar current levels are associated with poor speech recognition (excepting extreme cases). Therefore, only aided thresholds are directly pertinent to measuring sensitivity to sound.

Discriminating different sounds, once they are coded by the CI sound processor, relies on both temporal and spectral discrimination. Auditory nerve responses to the biphasic current pulses produced by the CI are highly synchronized (e.g. Tabibi et al, 2019). The compound action potential

(CAP) produced by neuronal responses elicited by a monopolar biphasic current pulse applied to a given electrode contact may be recorded using adjacent electrode contacts. The average amplitude of the resulting waveform, after removing artifacts via a forward-masking method, can be characterized by the N1-P2 amplitude. Nucleus devices use a standard measurement algorithm to determine the threshold for neural response (Auto-NRT) in terms of current level across all 22 electrode contacts. As for subjective stimulation current levels, as described above, Auto-NRT levels have a wide normal range, and absolute levels do not appear to be associated with performance outcomes with CI. However, CAP threshold levels are required to investigate supra-threshold behaviour.

From the Auto-NRT response threshold for any given electrode contact, the recruitment of neural responses with increasing current level may be inferred via the CAP amplitude growth function (AGF). Monopolar biphasic pulses used in all standard testing and sound processing are of leading-negative, following-positive polarity. However, peripheral dendrites are more sensitive to negative phases compared with positive phases. Leading phases generally have a greater stimulating effect due to the partial cancelling of the following-phase electric field by the leading phase. Therefore, more rapid growth in CAP amplitudes for leading-positive (anodic) pulses than for leading-negative (cathodic) pulses is indicative of poorer survival of peripheral axons (Hughes et al, 2018).

Refined measurement of the processing parameters of the cochlear nerve via electrically evoked CAP requires sufficient baseline amplitude in order to observe the effects of detuning the optimal stimulation parameters. Mapping out the AGF allows one to determine a baseline stimulation current level (CL) to obtain sufficient baseline wave amplitude (using standard leading negative phase). The effect of increasing the masker-probe interval on the CAP amplitude maps out the recovery function of the auditory nerve (Tabibi et al, 2019). Departures from the normal function, such as excessive absolute or relative refectory periods could indicate poor neural survival, but in any case low growth of amplitude with masker-probe interval would also indicate low effectiveness of stimulation pulses, such that the sound amplitude variations coded by the sound processor would be poorly represented at the neural level.

Similarly, the response of the auditory nerve can be mapped in a spatial sense, by varying the probe electrode relative to the masker electrode with the forward-masking measurement paradigm (e.g. (Cohen et al, 2003). This time, changing the probe electrode relative to the masker would most desirably reduce response amplitude indicating that there is low overlap between the regions stimulated by the masker and probe, and thus stimulation is tonotopically selective. A large overlap indicated by similar amplitudes across probe electrodes would indicate either poor or patchy neural survival or poor electrode placement. In both cases the frequency variations coded by the sound processor would be poorly represented at the neural level.

The benefit of using these ECAP measures is that they are objective in nature and therefore are not likely to be affected by top-down processing parameters.

4.2 Findings of Previous Nonclinical and Clinical Studies

4.2.1 Nonclinical Data

Not applicable.

4.2.2 Clinical Data

Fraysse & James (2020) provided a basis and background for the current work. Notably, a simple outcome model and population statistics for sentence recognition scores for cochlear implant patients at the Toulouse clinic were presented. Figure 2 gives scores in quiet at 1 day and 1 month, using CI alone for a sequence of 61 patients.

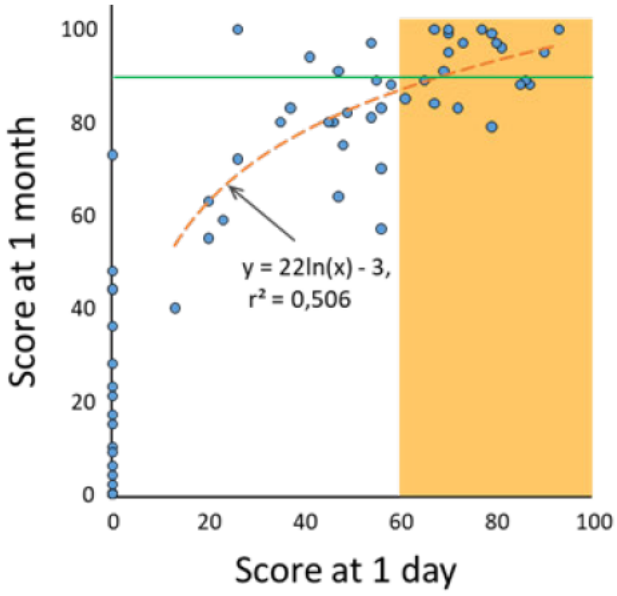

Figure 2: Sentence recognition scores in quiet at 65 dB SPL using CI alone for a sequence of 61 implanted patients.

One can observe the large variability in raw sentence recognition scores at 1-day and at 1-month after activation. Fraysse and James present a simple model for likely sentence recognition scores at 1 month assuming correct electrode placement (in terms of depth and scala position): Using data from a previous study of a series of 118 patients (James et al, 2018), median score at 1 month was approximately 72/100 if certain patient-related parameters were not accounted for. However, if both duration of deafness and etiology effects were corrected for, then median scores increased to greater than or equal to 90/100. 90/100 therefore indicates a level of performance for CI subjects which one may associate with an absence of limiting factors as introduced earlier.

Figure 2 is for a continuous sequence of CI subjects: 16/61 scored >90/100 at one month. These were unfiltered for any patient-related parameter or device type. The two studies indicate that 30-50 percent of subjects should achieve the target optimal score of 90/100 at one month in a new sample.

Fraysse and James also proposed that scores in quiet at 1 day using CI alone could be useful to predict outcomes. Using the data in Figure 2 as an example, those subjects scoring ≥60/100 at 1 day were ~14 times more likely to score ≥90/100 at 1 month compared with those who did not. This

indicates that for some subjects scores increase considerably between 1 day and 1 month, but that sentence scores reliably measure performance within the population and well maintain their relative position. We can thus conclude that at least some limiting factors appear to be in place from the time of device activation. The primary measure of performance in this study will be the sentence score at 1-month post-activation, but we will also explore sentence scores at 1 day, and also sentence scores in 10 dB SNR noise at 1 month. These three measures are correlated but one or other may be more selective than the primary endpoint.

4.3 Study Rationale

In the last 2-3 years routine clinical evaluation of adult CI recipients with tests of top-down and bottom-up processing parameters has been undertaken in Toulouse. This provides us with the opportunity to determine whether they are related to speech recognition performance. The centre also has consistent collection of sentence recognition scores after cochlear implantation (as seen in their publications). These two sets of data from the same patient population allow us to test the hypothesis that sentence recognition scores are influenced by a certain set of testable limiting factors which are generally cited in the literature. Furthermore, the definition of “poor” performance has also been established for this centre using the MBAA sentence recognition test. The use of the ≥90/100 as a criterion is debateable but, as outlined in the previous section, is based upon the idea that 90/100 is the minimum expected outcome in the absence of limiting factors.

The results of the top-down and bottom-up processing parameter tests can all be mapped to a pass/fail outcome. The novelty then in the design of this study is to understand whether each limiting factor contributes to the good/poor performer status categorised using the sentence recognition test at 1 month. This contrasts with other methods which aim to develop a continuous outcome model where, for example, an expected speech recognition score can be generated and compared to an actual speech recognition score.

Some recent work within Cochlear has shown also large variability in subjective outcomes with CI measured via the SSQ12 even in the longer term (one to six years). Therefore, we include self-assessment of hearing performance outcomes by the CI recipient using the SSQ12. As outlined in the previous section, sentence recognition at 1-day could also be associated with the outcomes of the processing tests; with the assumption that listening experience during the first month after activation may influence the growth in sentence recognition score, and in the longer term. Thus, scores can also be collected for the period following 1-month, up until 1-2 years as available. This would allow us to investigate the trajectory of speech recognition learning with the CI and relate it to subjective performance at the time of data collection.

Finally, the good/poor criterion could be explored: Like the arbitrary 60/100 at 1-day criterion in Figure 2, the switching point for good/poor can be tuned using receiver-operating curve techniques to provide the highest level of categorical certainty based on the processing test outcomes.

5 MEDICAL DEVICE INFORMATION

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

No device is on test.

5.2 Identity and Description of the Comparator

There is no comparator device or control group in this investigation.

5.3 Accessory Device Requirements

Not applicable.

6 OBJECTIVES

6.1 Primary Objective

Confirm a selection of testable patient-related and device-related parameters that limit sentence recognition performance between 1-day and 1-month post-activation in adult CI users.

6.2 Exploratory Objectives

- Evaluate the correlation of testable parameters with sentence score at 1-day in quiet and at 1-month in noise.
- Evaluate the correlation of testable parameters, sentence scores and self-reported performance (SSQ12) at time of non-opposition.
- Determine whether shifting the good/poor performer 90% cut-off score would improve the correlation with pass/fail on the parameter tests.
- Explore the relationships between testable parameters measured post-implantation and demographic and hearing-related factors.

7 DESIGN OF THE CLINICAL INVESTIGATION

7.1 General

This is a study with retrospective part (medical record review) and a minor prospective element with a questionnaire completed by the subjects.

It will be undertaken in a single centre in adult CI recipients with moderately severe to profound bilateral sensorineural hearing loss.

The subjects include adults aged 18+ years who are currently using a Nucleus cochlear implant. Subjects will be screened, and 30 eligible subjects with data for the primary end point will be recruited to the clinical investigation.

After surgical implantation of the device, subjects will have attended the implant centre for device activation, 1-day follow-up and at least 1-month follow-up. During visits to the centre, subjects will have undergone hearing assessments and objective and subjective tests included in the centre's specific battery. The primary endpoint is the sentence recognition score at 1 month using their CI. The aim is to understand how audiometric, cognitive, and electrophysiological test results relate to sentence score.

Safety will be not be assessed because this is non-interventional study.

7.1.1 Design Rationale

The aim is to recruit all CI patients with a Nucleus device who have been evaluated since the centre's specific test battery was implemented in 2019. This includes some patients implanted as long ago as 2016. The centre implants approximately 25 eligible adult patients per year. As such therefore there is no bias in the selection of patients. Unilateral deaf or single-sided deaf CI recipients are excluded since natural hearing may interfere with the measure of performance of the implanted ear. Similarly, subjects who received bilateral cochlear implants will be included but their sentence recognition scores only considered for the first ear implanted up until they received the second implant.

Subjects with a cognitive impairment will also be included since the evaluation of cognitive function is one of the aims of the test battery.

The Toulouse centre has extensively studied early performance indicators of CI recipients, as well as looking at prognosis of performance in the long-term. Extension of the implications of the study findings to the long term is one of the exploratory objectives of the study, as is the subjective evaluation of performance by the recipients themselves.

7.2 Subjects

7.2.1 Inclusion Criteria

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

1) Adult subjects, 18 years or older
2) Subjects unilaterally implanted or bilaterally implanted with at least 6 months separating the two cochlear implantations.
3) Subjects who have been implanted between January 2016 and December 2021.
4) Subjects have received a Nucleus CI: CI512, CI522 or CI532 cochlear implants with non-rotating magnet, or CI600 series equivalent CI612, CI622 and CI632 with rotating magnet and external sound processors CP900 or CP1000 behind-the-ear, or Kanso or Kanso 2 off-the-ear types.
5) Subjects who are fluent in French (language used in the questionnaire and speech tests)
6) Subjects who are not opposed to participating in the study
7) Subjects for who the medical record data is available throughout the defined data search period.

7.2.2 Exclusion Criteria

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

1) Subjects with single-sided deafness (SSD).
2) Subjects who are not affiliated to the French Social Security.
3) Subjects who are under legal protection.

7.2.3 Number of Subjects Required

For a test battery that has an underlying moderate specificity and sensitivity of ~80%, a total of 30 subjects should be sufficient to conclude that there is a relationship between pass/fail outcome of the battery (cumulatively – fail on any test -> fail) and good/poor performance based on sentence test score criterion. Therefore, we aim to recruit 30 or more subjects.

The sample size calculation is to be found in section 9.3.1.

All patients implanted since the centre started using their specific test battery will be screened for eligibility. The centre's staff currently estimate that 30 or more patients are eligible.

7.2.4 Vulnerable Populations

Not applicable.

7.2.5 Recruitment and Study Duration

The following subject status definitions apply:

- Enrolled: A subject who is has not opposed to participation in the study.
- *Screen Fail:* An Enrolled subject that has been determined to not meet one or more eligibility criteria.
- *Participated:* Has provided answers to the patient questionnaire.
- *Withdrawn:* Not applicable.
- *Completed:* Enrolled subjects who completed the patient questionnaire.

The recruitment period for the clinical investigation is estimated to be approximately 3 months from the time of first subject enrolled to the last subject.

Recruitment of subjects shall be performed in a back-chronological order from the cochlear implantation surgery. Recruitment shall start with the last subject that has undergone this procedure in the year 2021 and chronologically working backwards until recruitment targets are met.

This process will avoid any recruitment bias.

The expected duration of each subject's participation in the clinical investigation is the time it takes for the subject to read and discuss the non-opposition form with the study team, complete and return the questionnaire. Time for completing the questionnaire is estimated to be 30-40 minutes.

Clinical Investigation completion is defined as the recording and completion of the last medical record search for the last enrolled subject in the electronic Case Report Forms (eCRF).

7.2.6 Criteria for Subject Withdrawal

Subjects can decide to withdraw from the investigation at any time. The Investigator shall ask the reason(s). The reason for withdrawal should be documented in the subject's source files and the case report form (CRF).

Participating subjects who are withdrawn/discontinued will be replaced.

7.2.7 Randomisation Procedures

Not applicable.

7.2.7.1 Blinding Procedures

Not applicable.

7.2.8 Post-investigation Medical Care

The study is non-interventional. Subjects will continue to receive standard care from the centre and no specific care will be provided for the subjects after this study has been completed.

7.3 Performance Evaluations and Procedures

7.3.1 Eligibility and Informed non-opposition form

Screening of subjects include searches by site personnel in medical records for inclusion and exclusion criteria. Eligible subjects will be included based on date of cochlear implant surgery, from most recent to least recent. In a first draw, the number of subjects intended to be enrolled plus 20% (to account for non-responders) will be contacted.

Eligible subjects will be contacted by the investigator regarding the investigation. If they agree to receive a non-opposition form, this will either be sent to them by mail or shared directly at the clinic if they are scheduled for an appointment. Subjects will be given sufficient time to read the non-opposition form, ask questions and have those questions answered by the site personnel responsible for non-opposition process. If the subject is not opposed to participate, the date of the discussion will be documented in the subject´s medical records and in the non-opposition form and will be used as the date of enrolment. A copy of the non-opposition form, signed by the investigator, will be shared with the subject together with the questionnaire.

When a subject is enrolled in the investigation, data collection can start. In case subjects are due for a follow-up appointment at the clinic, as per standard of care, the questionnaire can be completed at site. For those subjects where a visit at the clinic during the investigation period is not scheduled, the questionnaire (together with a copy of the non-opposition form signed by the investigator) will be sent via mail to be completed at home. All questions regarding the questionnaire can be raised with the site personnel. If completed at home, the questionnaire shall be sent back to the clinic by registered mail using a pre-filled and stamped envelope with the address of the clinic.

The completeness of the questionnaire will be verified by site personnel. Incomplete data will be followed-up with the subject, if answered at home by sending a copy of the questionnaire back to the subject where incomplete parts requiring an answer are highlighted.

If the questionnaire is not returned; 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.

The subjects will be asked to complete the following questionnaire: Speech, Spatial and Qualities of Hearing Scale (SSQ-12 version).

7.3.2 Self-reported performance (at time of recruitment)

The SSQ12 questionnaire will be used. The Speech, Spatial, and Qualities of Hearing Scale questionnaire (SSQ-12) (Noble et al, 2013) was developed in the MRC Institute of Hearing Research, UK, and is a scaled-down version of the 49 items SSQ questionnaire (Gatehouse & Noble, 2004). It is designed to compile a sub-set of items from the longer original 49 version to represent the scale as a whole, measuring self-reported auditory disability, reflecting the reality of hearing in the everyday world. It has been shown to provide similar results to SSQ-49 (Noble et al, 2013). It covers:

• Hearing speech in a variety of competing contexts

• The directional, distance and movement components of spatial hearing

• Segregation of sounds and attending to simultaneous speech streams

• Ease of listening

• The naturalness, clarity and identifiability of different speakers, different musical pieces and instruments, and different everyday sounds.

7.3.3 Restropective study data collected from medical records

7.3.3.1 Demographic information

Demographic, hearing history, device information and general medical history will be collected from the centre's files once written informed non-opposition has been received. Comorbidities and concomitant prescription medications or therapies from activation to 1-month as reported to the clinician.

7.3.3.2 Pre-operative and intra-operative data

Surgical and imaging parameters from reports. Pre-op AC & BC audiograms, if available.Pre-op Fournier monosyllable test score in quiet (presented at 60 dB SPL).

7.3.3.3 Device parameters

The centre will provide anonymised data collected from the Nucleus CustomSound programming system "CDX" data files: This will include threshold and comfortable stimulation levels used in sound processors, and other sound processor parameters and data logging. All ECAP bottom-up processing test data are also stored in CDX data file (next section 7.3.3.4).

7.3.3.4 ECAP-based bottom-up tests (post-surgery)

Specific ECAP-based standard tests of bottom-up processing were established at the centre. Firstly, automatic ECAP thresholds using "AutoNRT" are measured for each intracochlear electrode using default parameters. Then one basal electrode (number 8) and one apical electrode (16) is used for subsequent tests. If there is no AutoNRT response on one of these electrodes, then an adjacent one

is used. All subsequent ECAP testing uses the forward masking artifact reduction technique with equal masker and probe levels.

Firstly, a negative-leading AGF is measured up until 220 CL or the subject indicates that the sound is too loud. Then an AGF is measured using the positive-leading polarity pulses.

The CL to obtain 100 µV is determined from the standard AGF, or the maximum tolerable CL if 100 µV was not obtained. This CL is used for subsequent recovery function and SOE tests.

Recovery functions are obtained using a standard sequence of masker-probe intervals and the CustomSound EP software computes the absolute and relative refractory periods.

SOE functions are obtained using a specific sequence of maskers so reduce overall test time. The maskers span 14 electrode locations but not all locations are used. The CustomSound EP software computes the 50% maximum amplitude width (in electrodes). The area under the curve can be computed manually (up to 14 electrode units).

7.3.3.5 Functional cognitive tests (post-surgery)

MoCA test score and number of words given in fluency subtest; raw Stroop subtest scores and number of noted errors; ÉCLA-16+ subtest 3 and 4 scores and completion times will be collected. Tests can have been performed at any time post-surgery.

7.3.3.6 Post-operative audiometric data

Aided sound-field warble-tone thresholds (dB HL: 250, 500, 1000, 2000, 4000 Hz) performed soon after activation will be collected.

The Toulouse centre presents sentence material at 65 dB SPL in quiet and in 8-talker babble presented in front from the same speaker. French MBAA2 sentence recognition scores (/100, single list per condition) will be collected for the implant ear alone where performed:

- In quiet at 1-day
- In quiet at 1-month
- 10 dB SNR at 1-month (or verify as zero)
- 5 dB SNR at 1-month (or verify as zero)

French MBAA dB SNR50 at 1-month (or verify non-convergent or score in quiet <80/100) will be collected. The SNR50 is derived from several fixed-SNR test scores using logistic interpolation.

7.3.3.7 Long-term sentence recognition scores (up until time of recruitment)

French MBAA sentence recognition scores in quiet and in noise the implant ear alone will be collected where performed between one-month post-activation and the time of recruitment. Logistic interpolation may be used to obtain scores for missing test levels or SNR50 (data analysis stage). Dates of tests will also be collected to enable longitudinal extrapolation.

7.4 Safety Evaluations and Procedures

Not applicable. Non-interventional study.

7.4.1 Concomitant Medication and Therapies

Not applicable.

7.5 Equipment Used for Evaluation of Performance and Safety

No special equipment required.

7.6 Sponsor Role in Conduct of the Clinical Investigation

The Sponsor employees (or designee) shall use standard operating procedures to ensure that clinical study procedures and documentation are consistently conducted and compliant with Declaration of Helsinki and applicable parts of GCP and any regional or national regulations.

The Sponsor shall ensure that the study is quality controlled (monitored) by a monitor who is independent from the study, scientifically and clinically competent and has good knowledge of the study plan, non-opposition process, sponsor´s SOPs, GCP and applicable laws and regulations.

The Sponsor shall monitor tasks delegated to other organizations/persons (Sponsor's oversight) e.g. contract research companies (CRO) or other consultants.

The Sponsor is responsible for developing a study plan and compile a clinical study report when the study is completed.

The Sponsor shall make sure that electronic systems used in the study are validated; that a Trial Master File is created; subjects' identities are coded so that reported data is coded but can be linked to the respective research person; that all essential study documentation is available in a safe place before, during and after the study according to applicable laws and regulations.

The Sponsor shall also make sure that the investigators have sufficient qualifications, enough resources are available at site, collect signed study plans from respectively responsible investigator and establish agreements with participating clinics.

It is the Sponsor´s responsibility to check that there is an EC approval for the study, to register the study in a public database and assure that the study results are reported within one year.

All study deviations will be documented in the CRF to enable analysis and reporting by the Sponsor in the Study Report, or to the relevant regulatory authority(s), if applicable.

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

8.1 Anticipated Clinical Benefits

Participation in this study will not directly benefit the subject nor will it alter the subject´s course of care. However, information gained from the study may identify parameters that affect the hearing outcomes, which may be used to guide more effective and personal rehabilitation in the future.

8.2 Anticipated Adverse Device Effects

Not applicable, non-interventional study.

8.3 Risks Associated with Participation in the Clinical Investigation

Participation in the study presents no risk for the subject and does not alter the subject´s course of care. Sensitive data concerning the subject's health is being handled in the study.

8.4 Risk Mitigation

All data collected will be pseudonymised and therefore the risk that any sensitive data will be disclosed to unauthorized persons is minimal. Registered post will be used when sending the non-opposition form signed by the investigator and questionnaire. For questionnaire, clinical personnel will complete header with subject identification code and request that no personal data is shared on this document, making it pseudo anonymised.

8.5 Risk-to-Benefit Rationale

The benefit of the clinical investigation of potentially identifying parameters that affect clinical hearing outcome and hence being able to guide more effective interventions in the future is regarded to outweigh the minimal anticipated risk for the subjects participating in the clinical investigation. We therefore consider it ethical to conduct the investigation.

9 STATISTICAL CONSIDERATIONS

9.1 General Considerations

Descriptive statistics will be derived for all data points. All analyses will be made on the full data set. All analyses will be presented as aggregated data without the possibility of identifying data from individual subjects.

Sentence recognition scores form the basis for most study endpoints. Missing test scores will be resolved with the study team. For example, if subjects can be assumed to have scored zero at 1-day or 1-month.

For the secondary endpoints such as longitudinal sentence test scores, logarithmic interpolation can be used for data missing for any given time-point. For missing fixed SNRs, logistic interpolation from present SNRs will be used. Longitudinal data for all subjects will be fit to the standard 1-day, 1-month, 3-month, 6-month, 1-year, 2-year, 3-year follow-up schema, with scores in quiet and 10 dB, 5 dB, 2 dB and 0 dB SNR. (NB certain levels are often omitted in standard clinical testing where the subject is known to be performing at ceiling or at floor for the condition.)

There is no criterion for termination of the study on statistical grounds.

9.2 Endpoints

9.2.1 Primary Endpoint

Good or poor performer based on sentence recognition score at 1-month ≥90/100 or <90/100. Good/poor performer status will be compared to pass/fail on the processing parameter tests. (binary classification)

“Fail” status on the processing parameter tests is established as:

- MoCA: score <26/30.
- Stroop test: score below the confidence interval for age 50 years with elementary education, or one or more corrected or non-corrected errors are noted.
- ÉCLA-16+ subtests 3 or 4: one or two scores below normal range, or time taken greater than established confidence intervals.
- Aided thresholds: more than two of five thresholds greater than 30 dB SPL.

The following will be extracted from the CustomSound software database records:

- Datalogging: None-use is defined as less than 2 hours' average time-on-air per day between activation and 1-month (mean -2 standard deviations re. data of Holder et al, 2020).
- AutoNRT: Absent for more than six electrodes. Inability to run AutoNRT or all of the following three NRT tests due to lack of response at maximum comfortable level or non-auditory stimulation leading to termination of the test.
- AGF polarity: For either probe electrode, a slope of negative leading significantly smaller than positive leading, and less than 70% of positive leading.
- Recovery function: For either probe electrode, a relative or absolute recovery period significantly longer than the confidence interval for normal range (Tabibi et al, 2019).
- Spread-of-excitation: For either probe electrode, greater than 35% area under the curve (>5 across the 14-electrode range).

9.2.2 Secondary Endpoints

There are no secondary endpoints.

9.2.3 Exploratory Endpoints

- Sentence recognition score at 1-day in quiet.
- SSQ12 score at time of inclusion.
- Sentence recognition score at 1-month: In quiet and in fixed levels of babble 10 dB & 5 dB SNR, and SNR50.
- Score/s at 1-day, 1-month, and later time points post activation up until the time of recruitment for various fixed SNRs.

9.3 Hypotheses

9.3.1 Primary Hypothesis

The primary objective is to confirm a selection of testable patient-related and device-related processing parameters that limit performance between 1-day and 1-month post-activation in adult CI users. Therefore, we will test the association between being good/poor performer and the outcome of the centre's test battery. A contingency table between the performer status and processing test result can be generated (Figure 3, top left):

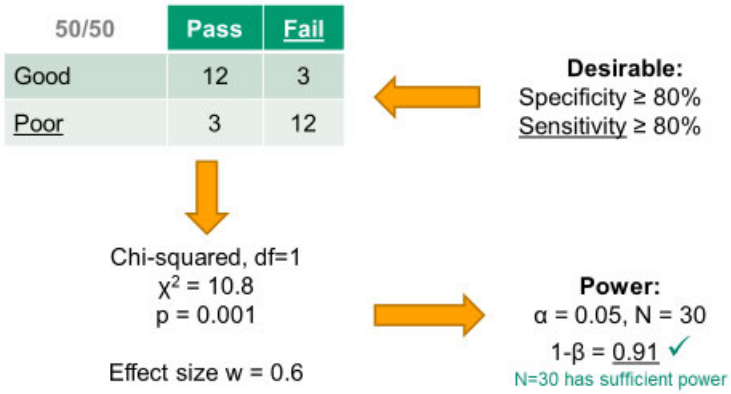

Figure 3: Sample size calculation with contingency table (upper left).

H1: The primary hypothesis is that there is a significant relationship between the good/poor classification and the test battery pass/fail.

H0: The alternative to the primary hypothesis is that there is no significant relationship.

A chi-squared test (at alpha=0.05, so $p<0.05$) can be used to test this hypothesis. If insufficient numbers are found in a single cell, a Fisher's exact test can be used instead.

9.3.2 Secondary Hypothesis

There is no secondary hypothesis.

9.3.3 Exploratory Hypotheses

9.3.3.1 Relationships between performance and test battery outcome

H1: The hypothesis is that there is a significant difference between:

H0: The hypothesis is that there is no significant difference between:

1) Sentence scores in quiet at 1-day
2) Sentence scores in 10 dB SNR at 1-month
3) SSQ12 scores

For pass versus fail groups from the test battery.

9.3.3.2 Value of classification criterion as good/poor performer

Receiver-operating characteristic analysis techniques will be applied to determine if the strength of the relationship between binary performance threshold score criterion (good vs poor) and pass/fail test-battery outcome can be increased.

9.3.3.3 Relationship between demographic and hearing-characteristics and pass/fail on processing parameter tests

H1: The hypothesis is that there is a significant relationship between duration of deafness/congenital hearing loss and:

H0: The hypothesis is that there is no significant relationship between duration of deafness/congenital hearing loss and:

1) The phonological processing test score.
2) The percent difference in slopes between negative and positive leading phase ECAP amplitude growth.
3) The width of the ECAP SOE functions.

9.3.3.4 Relationship between subjective hearing performance and sentence recognition threshold in noise

H1: The hypothesis is that there is a significant relationship between SSQ12 score and SNR50 for sentence recognition in noise.

H0: The hypothesis is that there is no significant relationship between SSQ12 score and SNR50 for sentence recognition in noise.

9.4 Sample Size Determination

Two scenarios with different underlying good/poor performer proportions were simulated (see figures 3 and 4): 50/50 and 40/60. ≥80% power is obtained under both scenarios. Higher specificity and sensitivity would increase the power. Increasing the total number of subjects would also increase power.

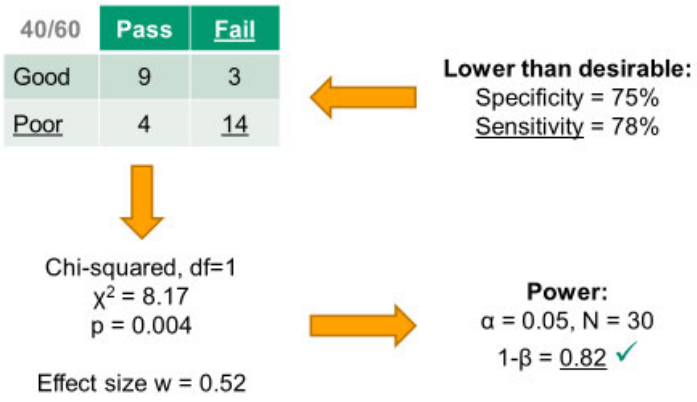

Figure 4: Power calculations for a 40%/60% good/poor performer scenario.

Based on sample size calculations, a total of 30 eligible subjects are required to provide >80 % power to reject the null hypothesis for the statistical test for the primary objective.

9.5 Analysis Population

There are no sub-populations.

9.6 Primary Endpoint Analyses

The contingency table between good/poor performer and pass/fail of processing tests will be analysed using a chi-squared or Fischer's exact tests.

9.7 Secondary Endpoint Analyses

Not applicable.

9.8 Exploratory Endpoint Analyses

Parametric (e.g., Students t) or non-parametric (e.g., Mann-Whitney U) tests will be used to test differences between groups depending on normal or non-normal value distributions.

Parametric or non-parametric correlation tests, or linear models will be used to test relationships between variables depending on normal or non-normal value distributions.

9.9 Safety Analyses

Not applicable.

9.10 Interim Analyses

Not applicable.

10 NON-OPPOSITION PROCESS

The Investigator shall contact eligible subjects regarding the investigation and if they are interested in taking part, a non-opposition form containing all relevant study information will be sent to them via mail or shared at the clinic if a follow-up appointment is planned. The rationale of the clinical investigation, as well as the risks and benefits, what participation will involve, and alternatives to participation will be explained to the subject. Ample time will be provided for the subject to enquire about details of the clinical investigation and to decide whether to participate.

All questions about the clinical investigation shall be answered to the satisfaction of the subject. Subjects shall not be coerced or unduly influenced to non-oppose participation or to continue to participate in a clinical investigation.

If the subject is not opposed to participating in the investigation, the date of the discussion must be recorded in the subject´s medical records as well as in the non-opposition form and will be used as the date of enrolment. This process needs to be done prior to any data collection for the purpose of this investigation. A copy of the non-opposition form, signed by the investigator, will be shared with the subject, either at the clinic or by registered mail, together with the questionnaire. The original signed non-opposition form shall be archived in the Investigator's Site File at the investigational site. The subject shall be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the clinical investigation. The communication of this information must be documented as an update to the non-opposition form and confirmation of non-opposition of the subject.

11 ADVERSE EVENTS AND DEVICE DEFICIENCIES

Not applicable

12 DEVICE ACCOUNTABILITY

Not applicable.

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.

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.

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.

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 certified printout must be provided. ECAP measurements made using CustomSound EP will be processed by the sponsor. The anonymised CustomSound database records (CDX files) will be provided to the sponsor via upload to the data capture portal.

Data collection will be performed using [redacted] 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.

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

The application will include programmed data consistency checks and supports manual generation of data clarifications/queries, including documentation of site responses. The application maintains a

comprehensive audit trail for all data entered, including updates and queries, and documents the time that each entry occurred and who made the entry.

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

In addition, de-identified electronically generated data will be collected from CustomSound clinical fitting software and electrophysiology software. The unamended data file shall be regarded as the source.

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]. Subjects have the right to access their data and request for its correction or deletion after withdrawal.

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

16 ETHICS COMMITTEE AND REGULATORY AUTHORITY APPROVAL

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

The final Sponsor-approved version of the CIP, the non-opposition 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 non-opposition form, 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

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 Committee (EC) by the Principal Investigator (and to the relevant regulatory authority(s) by the Sponsor, if applicable).

19 RECORD KEEPING AND RETENTION

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

The investigator must retain study-related records for a period of at least 15 years after completion of the investigation.

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 or European equivalent if active.

A joint peer-reviewed publication authored by the clinical investigator(s) and Sponsor will be prepared. In addition, the results of the clinical investigation may also be disseminated as conference presentations (for example, abstract and poster session). Manuscript authorship and responsibilities will be discussed and agreed upon prior to investigation start and in accordance with guidelines and recommendations provided by the International Committee of Medical Journal Editors (ICMJE) to

enable communication in a timely manner. All contributors who do not meet the criteria for authorship will be listed in an acknowledgments section of the publication.

21 STATEMENTS OF COMPLIANCE

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

22 QUALITY CONTROL AND ASSURANCE

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

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

22.1 Monitoring

The Sponsor will perform on-site and remote monitoring visits as frequently as necessary to oversee conduct, data collection and record keeping by sites.

The site will receive an on-site initiation visit by the Cochlear monitor and research scientist. At least one onsite monitoring visit will be performed when >80% of patient records have been entered into the database. A close-out visit will be performed by the monitor once all patient records have been entered or marked as missing.

22.2 Audits

An Investigator must, in reasonable time, upon request from a relevant health authority or regulatory agency, permit access to requested records and reports, and copy and verify any records or reports made by the Investigator. Upon notification of a visit by a regulatory authority, the Investigator will contact the Sponsor immediately.

The Investigator will grant the Sponsor representatives the same access privileges offered to relevant health authority or regulatory agents, officers, and employees.

23 TRADEMARKS AND COPYRIGHT

24 REFERENCES

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

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25 CHANGE HISTORY

Version	Change	Rationale
1	Original version	NA