**Official Title**: **Exploration of the specificity of an algorithm to detect anomalous electrode position**

**NCT Number**: **NCT03294681**

**Document Date**: **14 May 2018**

# Clinical Investigation Plan

## Exploration of the specificity of an algorithm to detect anomalous electrode position

### Trans-impedance matrix

CLTD5676

Date: 14 May 2018

Version number: 2.0

Windchill number: D1210600, v 2.B

Author(s): [redacted]

| | |
|---|---|
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| Manufacturer | Cochlear Limited<br>1 University Avenue<br>Macquarie University<br>NSW 2109, Australia |
| Coordinating Investigator | [redacted]<br>Complejo Hospitalario Universitario Insular Materno Infantil ; Avenida Marítima Del Sur, S/n, 35016 Las Palmas de Gran Canaria, Spain |
| Principal Investigators | Please refer to Appendix I |
| Clinical Research Organisation | Spanish monitoring activities:<br>[redacted]<br>German monitor activities:<br>[redacted]<br>Australian monitoring activities:<br>[redacted] |

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# Signature Page

By signing this page the Sponsor, Coordinating Investigator and Principal Investigator agree to conduct this investigation in accordance with the current investigational plan. Substantial amendments to the clinical investigation plan, the informed consent, or other written information provided to subjects must be approved in writing by the Ethics Committee, the Sponsor, the Coordinating Investigator and the Principal Investigators before the changes are clinically implemented, except under emergency circumstances to protect the rights, safety and well-being of the subjects.

## Sponsor Signature

[redacted]

PRINT NAME | DATE

**General Manager Cochlear Technology Centre Belgium**

SIGNATURE | TITLE

## Coordinating Investigator Signature

[redacted]

PRINT NAME | DATE

**Coordinating Investigator**

SIGNATURE | TITLE

## Principal Investigator Signature

PRINT NAME | DATE

**Principal Investigator**

SIGNATURE | TITLE

# 1 Clinical Investigation Synopsis

| | |
|---|---|
| Name of CE marked / TGA approved devices: | Custom Sound™ EP 5 (CSEP); Nucleus CP900 Series processor; Nucleus Programming Pod; Cochlear™ Nucleus® Profile with Slim Modiolar Electrode (CI532) or Contour Advance Electrode (CI512) |
| Study number and short study title: | CLTD5676 Trans-impedance matrix |
| Coordinating Investigator: | [redacted] Complejo Hospitalario Universitario Insular Materno Infantil; Avenida Marítima Del Sur, S/n, 35016 Las Palmas de Gran Canaria – Spain |
| Principal Investigator(s) and sites: | Refer Appendix I |
| Study start (Mmm yyyy): | Sep 2017 |
| Total expected duration of the clinical investigation: | 19 months |
| Enrolment period: | 16 months |
| Expected duration per subject: | 3 months |
| Study design: | Descriptive, prospective with sequential enrolment |
| Number of subjects: | 154 |
| Inclusion criteria: | 1. Candidate for cochlear implantation with the CI532 or CI512 devices<br>2. 18 years of age or older at the time of enrolment<br>3. Normal cochlea anatomy, established via pre-operative CT.<br>4. Willingness to participate in and to comply with all requirements of the protocol |
| Exclusion criteria: | 1. Prior cochlear implantation in the ear to be implanted<br>2. Ossification or any other cochlear anomaly that might prevent complete insertion of the electrode array<br>3. Abnormal cochlear anatomy on pre-operative CT or MRI imaging<br>4. Additional handicaps that would prevent participation in evaluations<br>5. Pregnant and breast feeding women, prisoners, or anyone in custody<br>6. Unrealistic expectations on the part of the subject, regarding the possible benefits, risks and limitations that are inherent to the procedure |
| Primary objective(s): | To explore the specificity (the number of true negative responses divided by the number of negative (non-anomalous) cases) of a candidate algorithm that has the ability to detect low incidence deviations from a normal electrode position using trans-impedance measurements |

<table>
<tr><td>Secondary objective(s):</td><td colspan="5">1. To explore the association between the trans-impedance and intra-cochlear voltage measurements, NRT thresholds and the intra-cochlear electrode array position.<br>2. To investigate changes in the trans-impedance and intra-cochlear voltages along with NRT thresholds over time to identify the stability of the measurements.<br>3. To establish a database of trans-impedance and intra-cochlear voltages, NRT thresholds and CT/DVT images for educational, research and development purposes.</td></tr>
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<tr><td>CT/DVT Scan</td><td>X</td><td>X (after electrode insertion, may be done after surgery)</td><td></td><td></td></tr>
<tr><td>(S)AE, ADE, DD</td><td></td><td>X</td><td>X</td><td>X</td></tr>
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<tr><td>Primary endpoint:</td><td colspan="5">Trans-impedance and intra-cochlear voltage measurements for each electrode contact after electrode insertion with post-operative CT/DVT Scan.</td></tr>
<tr><td>Secondary endpoints:</td><td colspan="5">1. NRT thresholds for each electrode contact during surgery and pre-operative CT/DVT Scan co-registered with the post-operative CT/DVT Scan collected for the primary endpoint.<br>2. Trans-impedance and intra-cochlear voltage measurements and NRT thresholds for each electrode contact at first activation and 3 months post-operative<br>3. Validated database entry of trans-impedance and intra-cochlear voltage measurement and NRT thresholds during surgery, at first activation and three months post-operative as well as the pre-operative and post-operative CT/DVT Scans respectively.</td></tr>
</table>

# 2 Terms and Abbreviations

| Term | Definition |
|---|---|
| Trans-impedance measurement | An impedance measurement is a calculated measurement obtained by dividing the voltage difference between two electrodes by the current applied to obtain this voltage. A trans-impedance measurement is similar to an impedance measurement except that the current applied to obtain the voltage is not applied to electrodes from which the voltage measurement is obtained. |
| Specificity | The **true negative rate.** The measure of the proportion of negatives that are correctly identified as such (i.e., the percentage of normal insertions, as verified by CT/DVT scan, that are correctly identified via an algorithm as not having an anomalous position). |

| Abbreviation | Definition |
|---|---|
| TIM | Trans-impedance matrix |
| CSEP | Custom Sound™ Electro Physiology |
| EC | Ethics Committee |
| NRT | Neural Response Telemetry |
| PIC | Patient Informed Consent form |
| DICOM | Digital Imaging and Communications in Medicine |
| CRF | Case Report Form |
| eCRF | Electronic Case Report Form |
| AE | Adverse Event |
| CPM | Clinical Project Manager |
| GCP | Good Clinical Practice |
| DD | Device Deficiencies |

# 3 Introduction

At the beginning of 2017 the global number of cochlear implant (CI) recipients have reached approximately 400’000. CIs are indicated for ears with moderately severe to profound hearing loss as referenced in the current labelling. It is anticipated that this number will significantly increase over the coming years because of the ageing of the population globally and an increase in awareness regarding the restorative hearing benefits a CI can bring. Given these expectations on future CI demands CI manufacturers need to focus their developments on the expectations of health care systems as well as patients’ needs and requirements of professionals.
Severe to profound deafness is typically caused by a degeneration of the inner hair cells (IHCs) in the inner ear are responsible for the initiation of neural spikes. In their absence, the information to the auditory cortex is affected. A CI bridges the IHCs by direct electrical stimulation of the peripheral auditory nerve. For optimal patient outcomes, it is important that

the CI electrode (see figure 1) is surgically placed in the inner ear (in scala tympani), close to the excitable tissue.

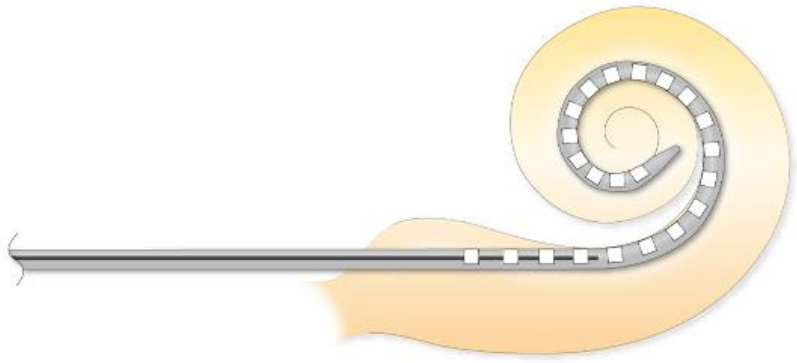

Figure 1: Optimal position of perimodiolar electrode array

For various reasons, the intra-cochlear position of the electrode may be suboptimal. The insertion angle may be too shallow or too deep; the electrode may buckle; a perimodiolar array may take a lateral trajectory away from the nerve; or the tip may fold over. Ramos et al. (in press, 2016) has addressed risk mitigation of sub-optimal intra-cochlear electrode placement after insertion. These modalities occur at a low incidence rate (a few percent, Dirr el al. 2013, Grolman et al. 2008, Zuniga et al. 2016), but may be associated with degraded hearing outcomes (Zeh & Baumann HNO 2015 63 (8):557-576.) It is therefore desirable to be able to detect these anomalies in the operating theatre so that the surgeon has the opportunity to correct them.

The gold standard to verify the electrode position currently is through radiological imaging techniques, such as CT scan or X-ray. This imaging increases the cost and duration of the procedure and often includes radiation which may put the patient at risk of 'radiation-related' disease according to the Recommendations of the International Commission on Radiological Protection. In other instances, the logistical burden of obtaining intra-operative imaging leads to the electrode array placement being verified post-operatively, meaning either the electrode position is left uncorrected or an additional surgery is required.

An alternative to medical imaging may be objective measures. State of the art implant systems can not only stimulate but also contain a measurement amplifier, e.g. to capture the auditory nerve's response to electrical stimulation, known as electrically evoked compound action potential (eCAP). The amplifier is also capable of measuring the voltage on an arbitrary electrode pair; this capability is routinely used to obtain impedance measurements during surgery by measuring the voltage on the stimulating electrode pair and dividing this voltage by the current applied(R=V/I). In addition to this routine measure, the amplifier can also be configured to measure the intra-cochlear voltage field -resulting from the stimulation of one electrode pair- along the entire electrode array; i.e. the electrical spread curve. This technique is known as electrical voltage telemetry (EVT) or electrical field imaging (EFI). The full set of electrical spread curves, normalised by the current is known as the trans-impedance [1] matrix (TIM). An example is shown in figure 2.

[1] Since the stimulation and recording electrode are not necessarily identical, this value is called a trans-impedance instead of an impedance

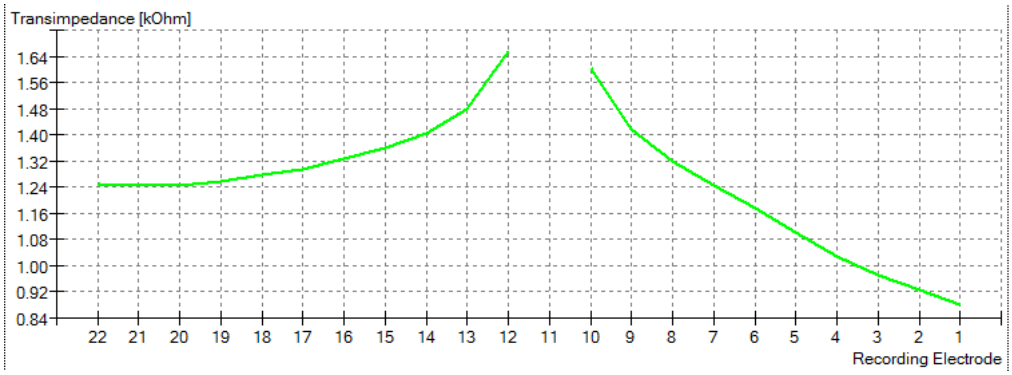


Figure 2: Trans-impedance measure for electrode 11

Literature (Vanpoucke, 2004) reports that there is significant variability in these curves, due to the variation in anatomy, electrode position and tissue reaction. However, it has been observed that the information contained in a trans-impedance matrix can be correlated to some aspects of the electrode array position (Vanpoucke et al. 2012, Zuniga et al. 2016) and algorithms are being developed that use trans-impedance and intra-cochlear voltage measurements to provide feedback on the electrode array position. One such algorithm, developed by Ramos et al. uses this information to detect whether the electrode tip has folded over or whether the electrode array is potentially outside the cochlea. However, given the variability between ears, the tuning of the threshold parameter in this algorithm (is the implantation normal or not?) needs to be explored to determine the sensitivity and the specificity.

The long-term aim is for this and other proposed algorithms, when implemented in a device that communicates with the cochlear implant, to provide feedback on the electrode array position immediately after or during insertion of the electrode. If sufficiently sensitive, the feedback provided by such algorithms can help surgeons make informed decisions on the appropriate course of action, which may include obtaining imaging to confirm the position of the electrode array and subsequent repositioning before closure of the surgical procedure, to achieve optimal outcomes. This will reduce the need for post-operative radiological diagnostics and avoid unnecessary re-operations to correct inappropriate placement of the electrode array. In addition, if it can be demonstrated that an algorithm has sufficient diagnostic specificity (the ability to correctly diagnose successful electrode insertions), its feedback might replace the need for routine intra-operative radiological imaging to confirm good electrode placement.

This clinical investigation will gather trans-impedance and intra-cochlear voltage measurements intra- and post-operatively. These measurements can be used to characterise the electrical properties of the electrode array and the surrounding tissue in the cochlea after insertion. This data will be used to explore the specificity of the Prof. Ramos candidate algorithm. Given the low incidence of anomalous electrode position cases in normal clinical practice (Dirr et al. 2013) and the inability to deliberately generate anomalous electrode positions in patients; this study is only focussed on exploring the specificity.[2] (negative results divided by true negative cases) of the algorithm. An exploration of the sensitivity (positive results divided by true positive cases) of the candidate algorithm is out of scope for this study. A separate in vitro study where anomalous insertions can be purposely created will be conducted to explore the sensitivity.

[2] For statistical purposes, it is assumed that this study will show the algorithm able to achieve ≥98% specificity with a 90% confidence.

For the purpose of quantifying the accuracy of a diagnostic algorithm, the following terminology is used:

- Positive case – a case in which electrode insertion results in an anomalous position.
- Negative case – a case in which electrode insertion is successful and position is not anomalous.
- True positive response – The candidate algorithm correctly detects the presence of an anomalous electrode position.
- False positive response – The candidate algorithm incorrectly indicates an anomalous electrode position when none is present.
- True negative response– The candidate algorithm correctly indicates no anomalous electrode position when none is present.
- False negative response – The candidate algorithm fails to detect an anomalous electrode position even though one is present.
- Sensitivity - the number of true positive responses divided by the number of positive cases (anomalous positions).
- Specificity - the number of true negative responses divided by the number of negative (non-anomalous) cases.
- Positive predictive value – the probability that given a positive response the electrode position is anomalous
- Negative predictive value – the probability that given a negative response the electrode position is not anomalous

The candidate algorithm is provided with the trans-impedance measurements and indicates whether a tip fold-over or array outside the cochlea have been detected. For the feedback from this algorithm to be clinically useful it must be shown that the specificity is sufficiently high to ensure that the surgeon is not unnecessarily prompted to take action (confirmation of electrode position by imaging) when not required. Current methods for detecting anomalous electrode position without relying on imaging either use manually-perceived force feedback from the electrode array (Dirr et al. 2013, Pile et al. 2013) or measurement of neural activity, (Grolman et al. 2008, Zuniga et al. 2016). Dirr et al. shows a positive predictive value of 29% using the sense of increased physical resistance during insertion whereas Grolman did not comment on the positive predictive value of the spread of excitation technique and Zuniga stated it was not clear. In the current study the aim is to show that using an algorithm based on the trans-impedance matrix a positive predictive value of twice that observed by Dirr et al. can be achieved, thus the aim is a positive predictive value of 60%.

Following the initial analysis as outlined in this investigation plan, future candidate algorithms developed for the purpose of detecting anomalous electrode position will be evaluated using the data as collected within the current investigation.

# 4 Identification and description of the devices

The following devices will be used in this investigation:

| | | |
|---|---|---|
| Implant | CI532, CI512 | CE marked / TGA approved |
| Sound processor | CP900 series | CE marked / TGA approved |
| Software | CSEP 5 | CE marked / TGA approved |
| Interface | Nucleus Programming Pod | CE marked / TGA approved |

All hardware and software used in this clinical investigation has market approval in the European Union and in Australia. The use of all software and hardware in this clinical investigation is according to the current labelling and instructions for use.

The CSEP software, CP900 series sound processor and CI532 and CI512 implants are all used routinely by cochlear implant and hearing care professionals. The CP900series sound processor is available at the clinic in case the recipient is aided with another sound processor. CSEP is incorporated in clinical routine to perform objective measurements which may help to create hearing profiles for cochlear implant recipients. All components will be available at the investigational sites as part of the clinical routine practice.
The Investigators will be trained on the trans-impedance and intra-cochlear voltage measurement that forms part of this study.
Please refer to the package insert and user guides of the devices for further information.

# 5 Justification for the design of the clinical investigation

Several researchers have demonstrated the utility of trans-impedance matrix and other voltage measurements (Hey et al. 2015, Vanpoucke et al. 2004, Vanpoucke et al. 2012) to identify the intra-cochlear electrode positioning. The current investigation is designed to both evaluate a candidate algorithm for detecting the occurrence of gross anomalies in position (e.g. tip fold-over[3] or the electrode array not in the cochlea) and to provide a robust dataset in a clinically representative sample of cochlear implant recipients that can be used to test the specificity and sensitivity of future electrode position feedback algorithms. Such algorithms have potential clinical application in providing objective feedback to the surgeon at the time of electrode insertion to inform the surgeon on electrode placement without additional radiological imaging, and may in future lead to improved clinical outcomes for cochlear implant recipients.

No large database of combined high quality imaging of the intra-cochlear electrode position and reliable trans-impedance measurements exist. It is only relatively recently that it has become possible to determine accurate intra-cochlear electrode position, as a result of advances in scanner technology. Also, the trans-impedance measurements (contained in Custom Sound™ Electro Physiology) that will be used in the study only recently became available. Earlier versions of this tool did not provide sufficient resolution to accurately measure the electrical spread curves.

To explore the decision algorithm, a large dataset is needed. This study will systematically collect a large pool of trans-impedance measurements of CI recipients combined with state of the art imaging of the implanted electrode as part of the clinical routine. Image analysis will allow an expert radiologist/ENT surgeon to determine for each implantation whether it is a normal case or not. The trans-impedance measurements will be analysed by the decision algorithm, and the agreement with the human experts will be established. This exploration of the specificity of the candidate algorithm is the main target of this study, thus being evaluated on the bench without patient involvement.

At this point in time, little is known about the stability of the trans-impedance measurements over time. In the first months after implantation, the electrode will be encapsulated in a tissue sheath. Our assumption is that this may influence the electrical spread curves and therefore the performance of the classification algorithm. The study design therefore includes two post-operative measurements. During these sessions, the response of the auditory nerve to electrical stimulation will be monitored as well with a technique known as neural response

[3] Where the electrode array tip turns back on itself during insertion into the cochlea.

telemetry (NRT). The study visits that are performed are in line with routine clinical practice, to minimise the additional commitment required by subjects and clinicians in participating in the required test sessions.

The study participants will be recruited from adults CI candidates in the participating study centres. Since the cochlear anatomy in children is identical to adults and the same electrode types are used, there is no need to include children in the study.

# 6 Risks and benefits of the device and clinical investigation

## 6.1 Anticipated clinical benefits

Patients participating in this study will follow routine cochlear implantation and treatment. Electrode position will be measured making use of CT scans routinely performed during CI treatment. There is no anticipated clinical benefit for the patients through participation in the clinical investigation.

However, understanding the specificity of the candidate algorithm, and characterisation of the measures in the clinical setting, is expected to benefit cochlear implant patients in the future through a more consistent positioning of the electrode array. Additionally, it is possible that the use of such algorithms will in future eliminate the need for post-operative imaging and so benefit implanted patients through reduced exposure to radiation.

## 6.2 Anticipated adverse device effects

The potential adverse device effects while using the components listed in section 4 to generate electrical stimulation of the cochlea during surgery and during the routine visits after surgery are no greater than that posed through the clinical routine via NRT, facial nerve monitoring, etc. All devices used in this clinical investigation are CE marked and TGA approved.

The study participants will undergo a standard cochlear implantation surgery, and are therefore identical to the risks in cochlear implant surgery as described by the package insert. No feedback on analysis of the intra-operative measurements will be provided to the surgeon during the operation.

The trans-impedance and Auto NRT measurements will be performed with the CSEP software and therefore be subject to the standard adverse events associated with the use of this software. The measurements will be performed by expert clinicians trained on the use of this software in normal clinical practice. The risks of participating in this study are therefore identical to the risks in normal clinical care.

The candidate algorithm is run on the data by an independent party at specified intervals on the data collected by the above-mentioned components. The person who performs the analysis does so in de-identified data after study closure. The algorithm evaluation will be conducted on the bench without any patient involvement. Thus, there are no anticipated adverse events resulting from the use of the algorithm.

## 6.3 Residual risks related to the device

The residual risks (e.g. overstimulation) including instructions for mitigation are listed in the labelling and investigators are instructed to follow these.

### 6.4 Risks associated with participation in the clinical investigation

Participants in the clinical investigation are exposed to the risks associated with standard cochlear implant surgery, general anaesthesia, and NRT measures as well as CT scans before and after surgery within the routine clinical procedures. The trans-impedance and voltage measurement being an interventional measurement prolongs the surgery by 1 minute. This will always happen in consultation with the surgeon and the anaesthetist and may even be conducted during the wake up phase after anaesthesia not to put the patient at an additional risk.

Interactions with concomitant medical treatments are not envisaged during the clinical investigation. Please see the labelling associated with the components used in this study.

### 6.5 Risk mitigation

This study will follow routine clinical practice and risk mitigation.

As precaution to avoid any risks associated with data protection the patient's identity and all information collected during the investigation will be kept strictly confidential and in accordance with EU and Australian data protection laws. Each participant's data will be given a unique code and the list of codes will be kept by the investigator as described in the data privacy section.

No other risks are expected that would exceed the clinical routine practice of CI implantation and clinical follow-up.

The risk of electrode position determination by an experimental telemetry processing algorithm is mitigated by executing the algorithm on the exported data completely independent of clinical procedures and by keeping the outcomes of these algorithms blind to the investigators until the study is officially closed. The patient management is not dependent on the findings from this study.

### 6.6 Risk-to-benefit rationale

The risks associated with this study will be kept to a minimum. The study population consists of conventional CI candidates, scheduled for CI treatment. Besides the trans-impedance and intra-cochlear voltage measurements, the study will capture data that are collected during routine clinical practice. The trans-impedance and intra-cochlear voltage measurements will be collected with the CE marked and TGA approved CSEP application. Collection of this data takes less than 1 minute per session in addition to the clinical routine measures and does not create any additional risks beyond a slight prolongation of the surgical procedure with the measurement time (only for the intra-operative measurement session).

The benefit-risk profile for this study is considered positive given the low risks and the potential for future improvement of CI treatment including access to a non-invasive measurement of electrode array positioning and thereby minimization radiation exposure through radiological imaging currently routinely used for detection of electrode position.

## 7 Objectives and hypothesis

| | |
|---|---|
| Primary objective(s): | To explore the specificity (the number of true negative responses divided by the number of negative (non-anomalous) cases) of a candidate algorithm that has the ability to detect low incidence deviations from a normal electrode position using trans-impedance measurements |

| | |
|---|---|
| Secondary objective(s): | 1. To explore the association between the trans-impedance and intra-cochlear voltage measurements, NRT thresholds and the intra-cochlear electrode array position.<br>2. To investigate changes in the trans-impedance and intra-cochlear voltages along with NRT thresholds over time to identify the stability of the measurements.<br>3. To establish a database of trans-impedance and intra-cochlear voltages, NRT thresholds and CT/DVT images for educational, research and development purposes. |
| Primary endpoint: | Trans-impedance and intra-cochlear voltage measurements for each electrode contact after electrode insertion with post-operative CT/DVT Scan. |
| Secondary endpoints: | 1. NRT thresholds for each electrode contact during surgery and pre-operative CT/DVT Scan co-registered with the post-operative CT/DVT Scan collected for the primary endpoint.<br>2. Trans-impedance and intra-cochlear voltage measurements and NRT thresholds for each electrode contact at first activation and 3 months post-operative<br>3. Validated database entry of trans-impedance and intra-cochlear voltage measurement and NRT thresholds during surgery, at first activation and three months post-operative as well as the pre-operative and post-operative CT/DVT Scans respectively. |
| Hypothesis | H0: The specificity of an algorithm that will detect low incidence deviations from a normal intra-cochlear electrode insertion will be < 98%.<br><br>H1: The specificity of an algorithm that will detect low incidence deviations from a normal intra-cochlear electrode insertion will be ≥ 98%. |

# 8 Design of the clinical investigation

## 8.1 General

The current clinical investigation is designed as descriptive research with sequential enrolment. The treatment schedule is according to the clinical routine visit schedule by prospectively adding a one minute trans-impedance and voltage measurement to the clinical routine measurements. The purpose of the clinical investigation is to collect and describe the characteristics of the trans-impedance and voltage measurements to explore the specificity of a candidate algorithm that has been developed to detect certain anomalous electrode array positions. Insertions will be classified based on the electrode position in relation to the cochlea structures as determined from pre- and post-operative CT scans. The classification will establish an insertion as either normal or showing one or more anomalous properties. The study will then provide the candidate algorithm with the 154 classified insertions to explore the specificity of the algorithm, this should allow a specificity of up to 98% to be established with a 90% confidence[4]. The trans-impedance and voltage measurements are obtained at repeated visits to evaluate the candidate algorithm specificity over time.

[4] Assuming up to 9 anomalous insertions in the sample of 154 implantations.

Blinding procedures are not appropriate for the voltage and trans-impedance measures to be collected with the clinical routine software CSEP, as it is not possible to conceal the presence, or absence, of the devices from the investigators.

Since the candidate algorithm to detect certain anomalous electrode array positions has not been implemented in any CE marked and TGA approved software, no real time feedback on any insertion related events will be provided to the clinician nor surgeon throughout the surgery nor aftercare. The surgeon and the clinician shall not deviate from their established clinical routine measures as CT imaging, x-ray or objective measures to detect anomalous electrode array positions and are advised not to interpret the voltage and trans-impedance measures.

In addition, the data will be analysed to establish the normative range of trans-impedance and voltage measurements in CI532 and CI512 electrode arrays, the correlation to NRT measurement, to correlation to electrode-to-modiolus distance (from CT/DVT Scans) and the normal variations of those measures over time.

The CT/DVT imaging before and after surgery and the CSEP measurements during and after surgery is part of the clinical routine in CI treatment and patients will be selected who follow this clinical routine.

In addition, the measurements, CT/DVT scans and classifications will be de-identified and stored in a database to support the further development and validation of algorithms. Those insertions showing the presence of anomalous properties will be excluded from the dataset that is presented to the candidate algorithm but will be included in this database. To allow for the exclusion of these insertions an additional 9 subjects are added to the study.

Depending on the recommended practice in the clinics the measures of surgeries performed by experienced and unexperienced surgeons will be collected. For retracement the name of the inserting surgeon is labelled on the surgical questionnaire.

## 8.2 Treatment schedule

The treatment schedule includes a pre-operative assessment, the CI surgery, the first activation visit and well as the 3 months' post-operative visit. The CT scans before and after surgery are part of the clinical routine test battery.

| **Procedure** | **Pre-op** | **Surgery** | **First Activation** | **3 months post-op** |
|---|---|---|---|---|
| Informed Consent | X | | | |
| Demographics, Medical & Hearing History | X | | | |
| Surgical questionnaire | | X | | |
| Voltage tomography and impedance matrix | | X (after electrode insertion) | X | X |
| Auto NRT thresholds | | X (after electrode insertion) | X | X |
| CT/DVT Scan | X | X (after electrode insertion, may be done after surgery) | | |
| (S)AE, ADE, DD | | X | X | X |
| Protocol deviations | | X | X | X |

The Demographic, Medical and Hearing History is part of the pre-op assessment. The surgical questionnaire applies after the surgery to collect information on insertion related events and

the name of the surgeon who has inserted the electrode array. The Auto NRT thresholds, the voltage tomography and impedance matrix applies during surgery as well as during the first activation session and three months after surgery. An active follow-up on the occurrence of (S)AE, ADE, DD applies. Protocol Deviations will be documented as soon as possible after occurrence. The acceptable visit window tolerance is +/-1 month.

## 8.3 Subjects

### 8.3.1 Inclusion Criteria

1. Candidate for cochlear implantation with the CI532 or CI512 device
2. 18 years of age or older at the time of enrolment
3. Normal cochlea anatomy, established via pre-operative CT
4. Willingness to participate in and to comply with all requirements of the protocol

### 8.3.2 Exclusion Criteria

1. Prior cochlear implantation in the ear to be implanted
2. Ossification or any other cochlear anomaly that might prevent complete insertion of the electrode array
3. Abnormal cochlear anatomy on pre-operative CT or MRI imaging
4. Additional handicaps that would prevent participation in evaluations
5. Pregnant and breast feeding women, prisoners, or anyone in custody
6. Unrealistic expectations on the part of the subject, regarding the possible benefits, risks and limitations that are inherent to the procedure

### 8.3.3 Criteria and procedures for subject's withdrawal or discontinuation

Subjects can decide to withdraw from the investigation without indicating any reasons. The investigator may decide to discontinue a patient due to major non-compliance with the CIP requirements (e.g. visit schedule not met). The investigator may also decide to discontinue a patient's involvement in the study for several reasons, including the subject not reasonably following the visit schedule described in Chapter 8.2, the subject no longer satisfying the Inclusion/Exclusion criteria (e.g., subject becomes pregnant during the study or develops a handicap that prevents the ability to sufficiently perform the tests) or if there are any reportable (S)AE, ADE, DD. If a subject withdraws or is withdrawn from the study, that subject will still be provided with routine CI aftercare and maintenance at the investigational sites as part of the clinical routine.

### 8.3.4 Point of enrolment

Subjects who satisfy the inclusion criteria will be provided with a clear explanation of the Patient Informed Consent (PIC) with sufficient time for discussion and clarification to ensure the patient understands the requirements and expectations. Subjects are enrolled into the clinical investigation when they have signed the Informed Consent Form.

### 8.3.5 Total expected duration of the clinical investigation

19 months

### 8.3.6 Expected duration of each subject's participation

3 months

### 8.3.7 Number of subjects required to be included in the clinical investigation

154, assuming that 9 recipients will not be suitable for the evaluation of the algorithm due to the occurrence of an insertion anomaly.

### 8.3.8 Estimated time needed to select this number (i.e. enrolment period)

16 months

## 8.4 Procedures

The procedure of this clinical investigation follows the clinical routine battery of CI treatment by implementing a pre-operative visit, the surgery, the first activation as well as a 3 months' post-operative visit.

Protocol deviations, (S)AE, ADE, DD will be actively collected and reported according to national and regional requirements at each study visit after the patient has signed the PIC.

### 8.4.1 Pre-Operative

The patient will be provided the Patient Informed Consent (PIC) to review, to discuss with the principal investigator of the study and to sign. One version of the signed PIC will be collected.

Within the clinical routine, the CT/DVT Scan will be performed along with the collection of standard medical and hearing history.

Demographics, Medical and Hearing History will be completed as part of the pre-operative assessment.

### 8.4.2 Surgery

After electrode array insertion, the extra-cochlear electrode lead is placed and the plate electrode is covered by skin flap. The NRT, trans-impedance and voltage measurements are performed using CSEP. The CSEP measurements take approximately 11 minutes for Auto-NRT with conditioning on 22 electrodes and 1 minute for trans-impedance and voltage measurements. Since Auto-NRT is part of the clinical routine, the additional time effort for this study is 1 minute.

The following sequence applies:

1. Auto NRT with conditioning on 22 electrodes
2. Trans-impedance and voltage measurements

The CT/DVT scan of the intra-cochlear electrode array positioning will be conducted as part of the clinical routine battery.

Within the surgical questionnaire the number of surgeries of the implanting surgeon, insertion related events as well as the corrective actions (if applicable) are documented. This information will be entered into the corresponding CRF after review by the surgeon.

In case the electrode array placement needs to be corrected as part of the clinical and surgical routine, the following workflow maintains:

1. If not already done as described before: Run the trans-impedance and voltage measurements before removing the electrode array.
2. Correct the electrode array placement as per normal clinical routine.
3. After successful reinsertion / corrective action of the position of the electrode array, run the Auto-NRT, trans-impedance and voltage measurements again.

The intra-operative measures with CSEP will be exported as cdx/csv files and transferred in an anonymized form to Cochlear.

An active follow-up on the occurrence of (S)AE, ADE, DD applies. Protocol Deviations (if applicable) will be documented as soon as possible after occurrence.

### 8.4.3 First Activation

At the end of the first activation CSEP 5 will be used to perform an NRT threshold measurement on 22 electrodes followed by the trans-impedance and intra-cochlear voltage measurement.

In some clinics, it is part of the clinical routine to measure NRT on 22 electrodes at the start of the first activation visit. These clinics should continue following routine practice and only perform the trans-impedance and voltage measurements at the conclusion of the first activation visit. The effort of those measures may take approximately 12 minutes.

Following the conclusion of the clinical session the measures with CSEP for this session will be exported as cdx/csv file and transferred in an anonymized form to Cochlear.

An active follow-up on the occurrence of events applies. Protocol Deviations (if applicable) will be documented as soon as possible after occurrence.

### 8.4.4 3 months post-op

At the end of the first activation CSEP 5 will be used to perform an NRT threshold measurement on 22 electrodes followed by the trans-impedance and intra-cochlear voltage measurement. The effort of those measures may take approximately 12 minutes.

Following the conclusion of the clinical session the measures with CSEP for this session will be exported as cdx/csv file and transferred in an anonymized form to Cochlear.

An active follow-up on the occurrence of events applies. Protocol Deviations (if applicable) will be documented as soon as possible after occurrence.

## 8.5 Monitoring Plan

The sponsor will appoint a study monitor to perform regular visits at the study site, as defined in the Monitoring Plan. Prior to the first subject enrolment, an initiation visit will be performed by the clinical project manager or delegate and the study monitor ensuring that assigned study personnel are familiar with this Clinical Investigation Plan and procedures and device handling, trained in Good Clinical Practice (GCP) compliance, eCRF completion, event reporting, and maintenance of study related documentation.

The study monitor will ensure compliance with the clinical investigation plan and EN ISO 14155, accurate data recording on the eCRFs, will raise data clarifications, will monitor recruitment rates and adherence to follow-up schedules. The study monitor will also check the upkeep of the investigator file. The investigator shall permit and assist the study monitor to carry out verification of completed eCRFs against data in the source documents.

Source documents are defined as any printed, optical or electronic document containing source data (hospital records, audiograms, speech test results, laboratory notes, device accountability records, radiographs, records kept at the investigational site) necessary for the reconstruction and evaluation of the clinical investigation. The extent of source data verification is defined in the Monitoring Plan. The investigator shall provide all requested documentation in a timely and organized manner.

The study monitor shall inform the sponsor about any problems relating to facilities, technical equipment or medical staff at the study site.

The study monitor shall provide the clinical project manager with written reports, after each visit or contact with the investigational site.

The investigator has to inform the sponsor about any additional local requirements that may impact the work of a monitor especially if access to source data may be limited by local

regulations. This is to ensure any necessary action to be taken before the study start to allow proper monitoring according to the EN ISO 14155 Standard.

# 9 Statistical Considerations

## 9.1 Sample Size Calculation

An in-depth description of the statistical characterisation and correlation will be part of the Statistical Analysis Plan. Final statistical analysis will be conducted on a clean and complete database after database closure.

The candidate algorithm provides the ability to detect gross electrode position anomalies (eg. tip fold-over or electrode not in the cochlea). It provides binary outputs; a value of zero (negative result) or a value of one (positive result). A value of zero indicates that the algorithm concluded that an anomalous position has not occurred and the value of one indicates that the algorithm concluded that an anomalous position has occurred. To be useful as a tool that can replace routine use of X-rays and CT scans, the algorithm is required to have a minimal false positive rate. To ensure that this expectation is reasonably fulfilled, the 98% specificity target is set to be the lower bound of the 90% binomial confidence interval for the specificity of the algorithm. An iterative approach was adopted to estimate the required patient sample size which takes into account the likelihood of anomalous position events. It was assumed that the occurrence of a tip fold-over (the principal form of position anomaly under consideration) follows a binomial distribution with a positive probability of around 4% based on the weighted average percentage for tip fold-overs in pre-curved arrays reported by Grolman et al. 2009 and Zuniga et al. 2016. Using the Clopper-Pearson method a sample size of 154 was selected, which gives an 89% chance of 9 or less tip fold-overs taking place, resulting in at least 145 'normal' insertions. If the algorithm correctly diagnoses all 145 insertions, the lower bound of the two-tailed 90% confidence interval for specificity will be 97.97% which is approximately 98%. In other words, if the algorithm correctly identifies all 145 cases as 'normal' then it can be concluded that its specificity is 98% or better with 90% confidence.

This entails that the false positive rate is no more than 2%, or that no more than 1 out of 50 insertions with normal position will be indicated as anomalous, and potentially receive medical imaging just to reveal that the insertion is normal. Assuming the incidence of tip fold-overs to be around 4% for pre-curved arrays, the 98% specificity will provide a positive predictive value of over 60%[5] which is meets the target positive predictive value from section 3.

In conclusion, 154 implantations are required.

## 9.2 Candidate algorithm exploration

To explore the specificity of the candidate algorithm it will be provided with the trans-impedance data collected at surgery, first activation and 3 months post-operatively for insertions that has been determined not to contain any anomalous electrode array position based on the CT Scans.

In each instance the result of the algorithm will be analysed to determine the specificity based on the amount of positive and negative results returned by the algorithm.

[5] For the sample size calculation, it is assumed that the sensitivity (true positive) of the candidate algorithm is 90%.

### 9.3 Insertion property analysis

From an isotropic voxel set (i.e. DICOM data) with the Ramos et al. algorithm to extract radiological parameters automatically from CT/DVT images and via surgical questionnaire the following parameters will be collected: Insertion related events (Tip-foldover, Scala displacement, Electrode extrusion/shallow-insertion, Over-insertion), Homogeneity Factor and Modiolar Proximity

For the exploration of the candidate algorithm insertions that have insertion related events or a poor medial lateral should be excluded from the dataset. These insertions should still be included in the database, with the appropriate classification.

### 9.4 Association analysis of trans-impedance and intra-cochlear voltage measurements with the NRT thresholds and intra-cochlear electrode array position over time

The intra-cochlear electrode position properties will be correlated against the trans-impedance and voltage measurements as well as the NRT thresholds using pairwise Pearson product-moment correlation coefficient.

For each implanted ear the trans-impedance and voltage measurements as well as the NRT thresholds will be compared across the three measurement times (intra-operative, first activation and 3 months) to determine the stability. Any changes in one of the measurements will be compared with the others to check for co-variance.

## 10 Data Management

Data collection is performed through [redacted] a web-based system for electronic data capturing. Site personnel will be trained to use this system. Data validity has to be confirmed by the investigator through an electronic signature. An audit trail is kept by this system and data clarifications may be generated by the system and sponsor personnel after review of data.

[redacted] is a system that has been verified and validated by the vendor. Installation of the system within Cochlear has been validated as well. Study-specific implementations are validated by data management and consist of verification that all required items are included, validity of edit checks and appropriate functionality of conditional fields. The study-specific data in [redacted] can only be accessed by those that have been allocated their individual account, which are personnel of the investigational sites, clinical project managers, study monitors and data management.

The patient's identity and all clinical information collected during the investigation will be de-identified (coded) and kept strictly confidential in accordance with Australian and EU data protection laws. Each participant will be given a unique code and the list of codes will be kept by the investigator as described in the data privacy section.

## 11 Amendments to the CIP

No changes in the study procedures shall be effected without mutual agreement of the investigator or investigators and the sponsor. All changes must be documented by signed CIP amendment. Ethics Committee (EC) needs to approve substantial changes to the CIP.

## 12 Deviations from the CIP

The investigator is not allowed to deviate from the CIP except under emergency circumstances to protect the rights, safety and well-being of the subjects. Such deviation shall be documented and reported to the sponsor and the EC as soon as possible.

# 13 Device accountability

Not applicable. The devices used within the study are CE marked / TGA approved and part of the clinical routine (CSEP (5), the Nucleus Programming Pod, CP900 series sound processor, CI532 and CI512)

# 14 Statements of compliance

## 14.1 Declaration of Helsinki and compliance with standards

The clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2013), the EN ISO 14155:2011 and any regional or national regulations, as appropriate.

## 14.2 Ethics Committee Approval

The clinical investigation shall not commence prior to the written favourable opinion or approval from the EC is obtained. Since all study hardware and software has a CE-mark and the study would not entail additional invasive or otherwise stressful examinations, no CA approval will be sought.

The investigator shall submit the final version of the Clinical investigation plan, the informed consent and all subsequently required documents to the Ethics Committee. A copy of the Ethics Committee opinion or approval shall be provided to the sponsor.

Sponsor and investigator shall continue the communication with the EC as required by national regulations, the clinical investigational plan or the responsible EC.

Any additional requirements imposed by the EC shall be followed.

The investigator shall submit the appropriate documentation if any extension or renewal of the EC approval is required. In particular substantial amendments to the clinical investigation plan, the informed consent, or other written information provided to subjects must be approved in writing by the EC.

The investigator will report to the EC any new information that may affect the safety of the subjects or the conduct of the clinical investigation. The investigator shall 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 requirement.

The clinical investigation is covered by a clinical trial insurance meeting the requirements of the participating countries. National requirements are specified in the national Informed Consent (IC).

## 14.3 Audits and Supervision

Study sites and study documentation may be subject to quality assurance audits during the course of the clinical investigation. In addition, regulatory bodies at their discretion may conduct inspections, during and after study completion.

## 14.4 Study Records

The investigational site will receive and has to maintain an Investigators File which does include without limitation at a minimum the signed Clinical Investigation Plan, the EC approval letter, completed Informed Consent Forms, (S)AE, ADE, DD reports, Investigator copies of all CRFs, correspondence with the sponsor and third parties (if applicable) related to the Study, a subject identification list, and a site delegation and signature sheet. All study records and

source documents shall be archived at the investigational centre for at least 15 years after the end of the study.

# 15 Informed consent process

## 15.1 Obtaining informed consent

The investigator must obtain written informed consent from the subject prior to any clinical investigation related examination or activity, and after explaining the rationale for and the details, aims and objectives of the study, the risks and benefits and alternative treatments, and the extent of the subject's involvement. Ample time must be provided for the subject to inquire about details of the clinical investigation and to decide whether to participate. All questions about the clinical investigation should be answered to the satisfaction of the subject or the subject's legally acceptable representative. Subjects must not be coerced or unduly influenced to participate or to continue to participate in a clinical investigation.

Each subject and the person who conducted the informed consent discussion must sign and date the informed consent form. Where required, a witness must sign and personally date the consent form.

A copy of the information leaflet and consent form must be given to the subject. All signed Informed Consent Forms must be archived in the Investigators File at the investigational site, according to the requirements of the country's health regulations, but for a minimum of 15 years after completion of the clinical investigation.

The subject or the subject's legally acceptable representative must 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.

The investigator shall forward any amendment made to the approved subject informed consent for review to the sponsor or study monitor and any other written information to be provided to the subject, prior to submission to his EC.

## 15.2 Data Privacy

Subjects will be identified on CRFs or similar documents (for example, questionnaires) by a unique subject identification code. Completed CRFs or similar documents are confidential documents and will only be available to the sponsor and their representatives, the investigator, the investigational statistician, and if requested to the Ethics Committee and national regulatory authorities.

The investigator and site staff will not include the name of any subject in any CRF or other forms, electronic files (for example, cdx/csv files), imaging items (for example, CT Scan), publication, or submission to a regulatory authority; will not otherwise disclose the identity of any subject; and, in any CRF, will refer to each subject by his or her identification code. The identification code consists of STUDY IDENTIFIER-SiteID-PATIENT NUMBER.

- SiteID consists of country code [redacted] and center code [redacted].
- PATIENT NUMBER consecutive numbering based on the point of enrolment at each site, e.g. the first patient enrolled is - 01

# 16 (Serious) Adverse Events ((S)AE), Adverse Device Effects (ADE) and device deficiencies

## 16.1 Definitions

### 16.1.1 Adverse event - AE

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the medical device. This does include events related to the medical device or the comparator as well as events related to the procedures involved.

For users or other persons this is restricted to events related to the medical device.

### 16.1.2 Adverse device effect - ADE

Adverse event related to the use of a medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device. This definition includes any event resulting from use error or from intentional misuse of the medical device.

### 16.1.3 Serious Adverse event - SAE

A serious adverse event is any adverse event that:

- led to a death,
- led to a serious deterioration in the health of the subject that either:
    - resulted in a life-threatening illness or injury, or
    - resulted in a permanent impairment of a body structure or a body function, or
    - required in-patient hospitalization or prolongation of existing hospitalization, or
    - resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
- led to foetal distress, foetal death or a congenital abnormality or birth defect.

Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

This includes device deficiencies that might have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

### 16.1.4 Serious Adverse Device Effect – SADE

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

### 16.1.5 Device deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

## 16.2 Reporting process for Serious Adverse Events

The investigator shall report all Serious Adverse Events without delay to the sponsor.

Name of contact person of the sponsor (Germany and Spain): [redacted]
Fax: [redacted]
Tel: [redacted]
[redacted]

Name of contact person of the sponsor (Australia): [redacted]
Tel: [redacted]
[redacted]

The sponsor has to report all SAEs and SADEs using the applicable report form as per national requirement.

The investigator has to report all SAEs and SADEs to his or her EC using the applicable report form as per national requirement.

Appropriate treatment of the subject shall be initiated but the study follow up shall continue when ethical.

## 16.3 Recording and assessment of AEs

Subjects shall be carefully monitored during the clinical investigation for potential AEs and shall be routinely questioned about adverse events at study visits.

For all adverse events sufficient information shall be obtained by the investigator and recorded in the CRF. The investigator shall attempt to assess the relationship between the device and the adverse event. Appropriate treatment of the subject shall be initiated but the study follow up shall continue when ethical.

## 16.4 Data Monitoring Committee

The decision to establish a Data Monitoring Committee (DMC) shall be guided by the risk analysis, taking into account both the risks associated with the use of the medical device and the risks associated with subject's participation in the clinical investigation. This study is a non-invasive study without any additional risks for the recipients that goes beyond the clinical routine for CI treatment with CE marked and TGA approved medical products. Therefore it is justified not to establish a DMC for the planned study.

## 16.5 List of anticipated Adverse Device Effects

For this clinical investigation the listed items in section 6.2 of this CIP are anticipated Adverse Device Effects.

Medical occurrences that are related to pre-existing conditions (for example, diabetes, cardial problems) are considered as unexpected adverse events in the frame of the clinical investigation.

## 16.6 Device deficiency reporting requirements

The investigator shall report any device deficiency without unjustifiable delay to the sponsor.

Name of contact person of the sponsor (Germany and Spain): [redacted]
Fax: [redacted]
Tel: [redacted]
[redacted]

Name of contact person of the sponsor (Australia): [redacted]
[redacted]

[redacted]

# 17 Suspension or premature termination

The sponsor may withdraw from sponsorship of the clinical investigation if,

- major non-adherence to the CIP is occurring
- it is anticipated that the subject recruitment will not be adequate to meet the objectives of the clinical investigation

Should the sponsor withdraw from sponsorship of the clinical investigation, the sponsor will continue sponsorship for the subjects already recruited into the study.

An ongoing clinical investigation can be discontinued in case of:

- device failure
- serious or intolerable adverse device effect, leading to the explant or discontinued use of the device
- subject's death
- investigator's decision
- subject's decision

# 18 Publication Policy

The clinical investigation will be registered at the public study register ClinicalTrials.gov.

Investigators will be able to publish and/or present their own data as well as processing their own data with their own algorithms throughout the study. The publishing investigator will provide the sponsor with a manuscript copy of the abstract and paper at least 30 days in advance of publication or presentation. If the publication contains information that the sponsor at his discretion finds worth protecting in the form of a patent or trademark etc., the sponsor has the right to delay the publication or presentation for 90 days.

After finishing the study it is planned to generate two joint publications by the clinical investigators and the sponsor. One journal is going to address rather the medical/surgical aspects and the other journal the technical aspects of this investigation. The responsibility for writing the publication is with the Coordinating Investigator. The authorship will be based on contribution of complete datasets and contribution to paper preparation according to the rules of the journal chosen for publication. The six Principal Investigators, the six Co-Investigators and the CPM will be part of the author list of both journals. In case the journal has a restriction of less than 11 authors, the surgeons may rather be part of the medical/surgical publication and the audiologists/engineers rather be part of the technical publication. The joint publication must be reviewed by the sponsor at least 30 days in advance to any release of publication. If the publication contains information that the sponsor at his discretion finds worth protecting in the form of a patent or trademark etc., the sponsor has the right to delay the publication or presentation for 90 days.

The Clinical Investigator Agreement will include details on publication.

All public presentations of data collected from this study shall be approved by the Clinical Project Manager prior to use. Where information is presented that was collected in a particular site, that clinical head shall also approve the use of the data. This is to avoid customers from one clinic attending a conference in another and discovering their data being presented to them without any warning.

## 19 Bibliography

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# 20 Change History

| Version Number | Date (DD Mon YYYY) | Summary of changes |
|---|---|---|
| 1.0 | 10.05.2017 | Approved version |
| 2.0 | 14.05.2018 | Extended study duration, HEARing CRC added |

# 21 Appendix I: List of investigators

| Site ID | Name of Investigator | Address | Telephone, email |
|---|---|---|---|
| [redacted] | [redacted] | Complejo Hospitalario Universitario Insular Materno Infantil ; Avenida Marítima Del Sur, S/n, 35016 Las Palmas de Gran Canaria, Spain | [redacted] |
| [redacted] | [redacted] | Clinica Universitaria de Navarra, Avda. Pio XII, N°36; 31008 Pamplona, Spain | [redacted] |
| [redacted] | [redacted] | Klinikum der J. W. Goethe-Universität Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt a. M., Germany | [redacted] |
| [redacted] | [redacted] | Universitätsklinikum Erlangen Hals-Nasen-Ohren-Klinik Waldstr. 1, 91054 Erlangen, Germany | [redacted] |
| [redacted] | [redacted] | Klinik für Hals-, Nasen-, Ohrenheilkunde, Kopf- und Halschirurgie Arnold-Heller-Straße 3 Haus 27 24105 Kiel, Germany | [redacted] |
| [redacted] | [redacted] | HEARing CRC 550 Swanston Street Carlton, VIC, Australia 3053 | [redacted] |