Official Title: Cochlear - Implanted Recipient Observational Study Cochlear-IROS

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Cochlear - Implanted Recipient Observational Study
Cochlear- IROS
CEL 5277

REGISTRY PLAN (RP)

Version 7

04 February 2015

Devices in use	All Cochlear devices currently eligible for market release.
Sponsor	Cochlear AG Peter Merian Weg 4 4053 Basel Switzerland Telephone+41 61 2050404
Manufacturer	Cochlear Limited, 1 University Avenue, Macquarie University, NSW 2109, Australia, Telephone + 61 2 9428 6555
Clinical Research Organisation	*not applicable*
Coordinating Investigator	*not applicable*

Investigator Signature

By my signature, on the **Registry Agreement online** I confirm that I have read, understand and will adhere to the Clinical Investigation Plan.

Please note manual signature below is optional as an e-signature online is requested for data entry.

PRINT NAME	**DATE**
	Principal-Investigator
SIGNATURE	**TITLE**

Sponsor Signature

[redacted]

PRINT NAME	**DATE**
SIGNATURE	**TITLE**
	Head of Clinical, Technical, Research & Regulatory, EMEA

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1 Registry Synopsis

Device(s):	All Cochlear devices, eligible for market release.
Study title:	**Cochlear - Implanted Recipient Observational Study (Cochlear - IROS).**
Participating sites:	Sites selected for voluntary participation in the observational study (Cochlear - IROS), using any Cochlear devices that are eligible for market release.
Study Duration per subject:	**Two years follow-up from Baseline registration. Baseline registration** online occurs just after the patient is implanted and prior to the first switch-on. Follow-up at 1 and 2 years is recommended to occur in parallel to routine Clinical evaluations. Evaluation at third year post implant follow-up is optional.
Start date	Dec 2011, with ongoing roll out to clinics and countries as languages become available for use. Review of study progress at regular annual intervals.
Number of subjects:	A minimum of 50 recipients per device. Several hundred subjects across device user groups and device configurations are aimed for enrolment in the study /registry.
Study/Registry Design:	Prospective, longitudinal comparative repeated measures of benefits for implanted hearing impaired subjects, acting as their own intra-subject control, using a selection of subjective evaluation tools provided via an electronic platform for data entry and data collation within a secured environment. Longitudinal repeated evaluations commencing at Baseline (post-implant, pre-switch-on) and repeated annually for up to 3 years post implant. Patient benefits will be compared to safety records for Cochlear devices eligible for market release gathered through post market surveillance. Inter-subgroup (to be classified by device use and configuration) comparisons of performance per assessment tool per interval shall be performed pending numbers of relative data sets. *Note: The registry platform is designed to support and sustain uniform data collection on unlimited number of prospectively implanted patients long term.*
Evaluation Materials	Evaluation Tools comprising main measures for study endpoints made available electronically include: o Subjective self- assessment scales (clinically standardised: SSQ and HUI Mk III); o Patient profile forms (clinician and recipient questionnaire versions); o Hearing threshold measures (routine measures performed at the clinic) o Product specific evaluations as required
Inclusion criteria:	o Post-lingually deafened adults and adolescents who are newly implanted **AND prior to first switch-on** of their external device. o Unilateral, bilateral simultaneous recipients of any implant device(s) available with market approval from the company Cochlear®. o Children 10 years or older, and in accordance with local regulations and product labelling. o Mentally capable to respond to self-administered assessment scales o Willingness to participate and sign the Patient Informed Consent (PIC) form directly or signed by the legal representative. *NOTE: Unilateral implant-users registered at baseline, electing to opt for a second sequential implant during the course of the 3 year follow-up period shall be re-classified accordingly there-after as sequentially bilaterally implanted.*

<table>
<tr><td>Exclusion Criteria</td><td colspan="7">○ Individuals excluded from participation in a registry according to national or local regulations.</td></tr>
<tr><td>Primary Objectives:</td><td colspan="7">To evaluate longitudinal subjective benefit data using validated standardised questionnaires (HUI Mk3 and SSQ) for prospectively implanted adult and adolescent recipients compared to the preimplant condition. To assess daily use and issues reported through Cochlear's complaints and issues handling procedure.</td></tr>
<tr><td>Secondary Objectives:</td><td colspan="7">To provide statistically valid data to support patient management decisions at the clinical, administrative, reimbursement and regulatory levels locally, nationally and internationally.

To establish benefits and device functionality for bilateral use over unilateral use for scientific, regulatory and market-oriented communications.</td></tr>
<tr><td>Evaluation Plan</td><td colspan="7">Evaluations are performed at the Baseline interval (post-implant and pre-switch-on) with annual follow-up at 1 year, 2 years (and optionally at 3 years) post-implant. Clinicians and recipients are strongly encouraged to use all evaluation tools below.
<table>
<tr><th colspan="2">Test interval</th><th>Baseline</th><th colspan="3">Follow-up</th><th>Comments</th></tr>
<tr><th>Completed by</th><th>Evaluation Tool</th><th>Post-implant/ Pre-switch-on</th><th>1yr</th><th>2yrs</th><th>3yrs optional</th><th>Baseline & 2 yrs follow-ups desirable</th></tr>
<tr><td>Clinician</td><td>1. Clinician Questionnaire. (to register the patient)</td><td>X</td><td>X</td><td>X</td><td>X</td><td>Questionnaire to capture implanted device details, demographics and hearing history.</td></tr>
<tr><td>Recipient</td><td>2. Implant Recipient Questionnaire</td><td>X</td><td>X</td><td>X</td><td>X</td><td>Questionnaire to capture patient profile on previous hearing aid use, vocational and educational status</td></tr>
<tr><td>Recipient</td><td>3. HUI Mark III</td><td>X</td><td>X</td><td>X</td><td>X</td><td>Standardised General quality of Life measure</td></tr>
<tr><td>Recipient</td><td>4. SSQ</td><td>X</td><td>X</td><td>X</td><td>X</td><td>Standardised disease specific Hearing ability measure</td></tr>
<tr><td>Clinician</td><td>5. Unaided Hearing thresholds</td><td>X</td><td>X</td><td>X</td><td></td><td>Routine clinical measures at: pre implant; immediately post implant(optional); 1^{stt} yr & 2nd yr annual reviews</td></tr>
<tr><td>Clinician</td><td>6. Product Specific</td><td></td><td></td><td></td><td></td><td>As required</td></tr>
</table>
</td></tr>
<tr><td>Withdrawal:</td><td colspan="7">Voluntary withdrawal at any time for any subject at any site.

Missing evaluation data at 1 or 2yrs post-implant following registration at Baseline will invalidate longitudinal assessment for the subject concerned.</td></tr>
<tr><td>Endpoint:</td><td colspan="7">Changes in self-ratings on each of the self-assessment measures used, at post switch on intervals compared to baseline, per subject, across subgroups/per device-user configuration.</td></tr>
</table>

2 Terms and Abbreviations

Abbreviations	Definition
CI	Cochlear Implant
HUI Mark III	Mark III Health Utility Index
SSQ	Speech Spatial Hearing Qualities questionnaire
EC	Ethics committee
PIC	Patient Informed Consent
RP	Registry Plan
RA	Registry Agreement
EDC	Electronic Data Capture
ISO	International Organisation for Standardization
Patient	Patient = Implant recipient = subject, once enrolled
Clinician	Clinician = Investigator
Cochlear - IROS	Implanted Recipient Observational Study = Registry

3 Introduction

It is important to demonstrate that intervention is clinically efficacious in a real world environment, across large and often diverse populations. Evidence is required to support the product's value proposition for a wide range of industry and non-industry stakeholders: Regulators, Payers, Providers, Patients and Policy Makers, each with a different perspective as to the acceptance and adoption of the intervention.

To address this need, this observational study has been designed to prospectively gather patient-related data for implanted patients including true baseline interval data gathered prior to implant or first activation of the device and subsequent longitudinal follow-up at consistently timed evaluation intervals.

The study will be offered in multiple languages to ensure a wide range and relatively large group of hearing impaired implanted patients across regions representing a range of health service provisions has the potential to serve as a very valuable tool.

Information derived from such this study may be used to complement data obtained through shorter term, smaller scale, controlled clinical trials.

The proposal: To establish a unified approach to assess the benefits from hearing habilitation with the aid of implantable hearing devices in adults and adolescents.

The approach shall include evaluation and collation of patient-related data longitudinally in implanted patients using hearing devices providing either electrical, electro-acoustic or mechanical stimulation in unilateral, bilateral or bimodal configuration.

The information gathered shall be used to help establish the hypothesis that implantable hearing solutions improve the auditory performance and quality of life of implant recipients with a significant hearing impairment. The hypotheses that binaural stimulation is a superior treatment for the habilitation of hearing impairment in affected individuals will also be tested.

In turn this evidence shall be provided to support decisions by clinical professionals and health authorities for provision of unilateral and bilateral implantable devices either on a case by case or as a routine clinical procedure for the treatment of bilateral hearing impairment.

4 Preliminary Investigation and justification

4.1 Preclinical testing

No preclinical testing is required for enrolment of an implanted subject into the registry outside of routine clinical practice.

5 Study Objectives

- To evaluate longitudinal subjective benefit data using validated standardised questionnaires (HUI Mark III and SSQ) for prospectively implanted adult and adolescents using unilateral; bilateral or bimodal configurations of device types.
- To provide statistically valid data to support patient management decisions at the clinical, administrative, reimbursement and regulatory levels locally, nationally and internationally.
- To establish benefits and device functionality for bilateral use over unilateral use for scientific, regulatory and market oriented communications

The hypotheses:

The information gathered shall be used to test the primary hypotheses that implantable hearing solutions improve **the auditory performance** of implant recipients compared to their preimplant condition.

Reported benefits evaluated at 1 year postimplant will remain stable at 2nd and 3rd year postimplant compared to the Baseline evaluation of the preimplant condition.

Severe to profound bilaterally impaired adults and adolescents undergoing bilateral implantation will report a higher level of benefits post implant on self-reported scales, the SSQ and HUI Mark III, compared to those reported by comparable groups of patients implanted unilaterally at the first year follow-up.

Participation in the observational study presents no additional risk to the patient as they are implanted with market released devices and there is no additional burden to the subjects beyond clinical followup.

6 Study Design and End-points

The clinical investigation is designed as a prospective repeated measures longitudinal study with intra-subject controls and inter-group comparisons for device type and configurations across multiple implant

centres cross-culturally using a selection of evaluation tools including clinically standard self-assessment scales, threshold measures, product specific and non-standardised questionnaires for the clinician and implant recipient made available through the electronic platform. Participating clinics are encouraged to collect data as per the evaluation plan outlined. Evaluation tools are provided via the electronic platform. .

The registry is aimed at collection of data for patients who have already made the decision together with their implant centre clinician for an implant device from the company Cochlear®.

Participating in the observational study for each clinic and patient is voluntary. Both the clinic and patient are free to electively remove themselves from participation in the registry at any time. Patients should be enrolled that meet the selection criteria without bias This will enable interpretation of the results and application for the implant population at large.

Clinics are asked to enrol newly implanted patients into the study in chronological order of implantation.

Enrolment should occur after implant and must be prior to the first switch-on of their implanted device.

- **All prospective implantees who are able to provide consent for their participation in the observational study or for whom consent is provided by their legal representative.**
- All prospective implantees awaiting their first switch on of their external device
- Children 10 years or older and in accordance with local regulations and product labelling.
- Implantees or carers who are physically and mentally-able to complete the questionnaires independently as self-administered and *not as an interview* are able to participate.
- Each patient is evaluated at or immediately prior to the first switch on to obtain **baseline responses related** to their hearing experiences and perception of quality of life in **their pre-implant hearing condition.** Standard clinical tools: the SSQ and HUI Mark III are available for use and non-standard questionnaires for Clinicians and Patients
- Each patient is to be followed up through routine clinical procedures and in parallel asked to complete the post-implant versions of the questionnaires at their 1st, 2nd and 3rd year(optional) follow-up appointment ± 2 months of the expected time frame.
- Inter-group comparisons of outcome data require a minimum of 100 subjects per subgroup per device type and configuration (and of comparable age group) for data analysis and formal report of their HUI Mark III data at the 1st , 2nd and 3rd year (optional) post-implant compared to their preoperative baseline responses. Statistical comparisons will be made in accordance with the recommended analytical procedures as validated by HUI Inc, the developers of the questionnaires.
- Inter-group comparisons of outcome data require ideally a minimum of 50-100 subjects per subgroup per device type and configuration (and of comparable age group) for data analysis and formal report of their SSQ data at the 1st , 2nd and 3rd year post-implant compared to their preoperative baseline responses. Analysis will performed via comparison of mean responses per subcategory scale of questions of the SSQ as proposed by the developers. Sub scale category scores will be compared across time both intra-subject and inter-subject using parametric tests of comparison.
- Data gathered from the general questionnaires will be collated to provide a descriptive report of patient characteristics of the enrolled population.

- Hearing threshold data for pure-tone stimuli under headphones for air-conduction and via a bone conductor for bone-conduction may also be recorded by the clinician following routine measurements at the clinic at the 1st, 2nd and 3rd year post-implant compared to their preoperative baseline responses. Test data collected at one additional time interval post-implant immediately post-surgery and prior to switch-on may also be entered and collated. Threshold data specifically for air-conduction measures per frequency per subject will be compared to determine the changes in threshold over time for each ear. Changes of +/-5 dB will be considered clinically insignificant. Changes in thresholds per frequency will be reported intra-subject and for inter-subject groups.
- Other evaluation measures such as speech audiometry are not specified for longitudinal data collection by the protocol. However additional clinic specific data may be recorded by each clinic on the hearing threshold summary forms provided for the same group of subjects for both formal internal and external reports.
- Participating clinics and or patients wishing to complete the questionnaires online will be required to confirm the minimum technical PC requirements and firewall conditions. (See Section 13).
- Product-specific measures (e.g. surgical experience, in situ thresholds).

6.1 Evaluation Schedule

6.1.1 Subjective Evaluation schedule at routine clinic visits:

- Baseline Evaluation (This may be performed minimally on the implant date and maximally 120 days post implant and MUST be **prior to switch-on** of the external device)
- One year post-switch-on (implant day +12 months +/- 2 months)
- Two years post-switch-on (implant day +24 months +/- 2 months)
- Three years post-switch-on (optional currently (implant day +36months +/- 2 months))

6.1.2 Subjective Self Assessment Tools for completion by the Patient:

Together with the Clinician, self-evaluation tools to be completed by the patient are determined. The responsible clinician instructs the patient how to complete the forms. Each patient is asked to complete the selected self-assessment tools at each of the evaluation intervals noted above.

Completion of questionaires/data entry may be performed by the patient pending their agreement on the signed Patient Informed Consent:

- on paper (as printed out from the host environment by the clinician) and then re-entered electronically by the responsible clinician in the clinic, or
- via direct on-line electronic data entry using their own access password provided by the e-platform **on a selected computer in the clinic** at the routine annual clinic visit
- via direct on-line entry using their own access password provided by the e-platform **pending the technical compatibility of their at home computer system and internet access (see section 13)**.

(NOTE: For registered implanted recipients with visual impairment, having provided consent for their inclusion, all questionnaires may be administered verbally by the clinician or other and their responses recorded on paper or directly on line on their behalf).

Self-assessment Tools available for use

Two standardized internationally recognized clinical self-assessment subjective scales in conjunction with a general non-standard Patient questionnaire may be selected and completed by the implanted recipients at baseline and subsequently at annual evaluations.

The Speech, Spatial and Qualities of Hearing Scale (SSQ), a hearing-disease questionnaire. Established as a sensitive measure to demonstrate benefits of bilateral versus unilateral hearing ability in the a variety of daily situations and a range of hearing abilities as the title suggests. (e.g. Noble, Tyler et al. 2008) . Cross cultural version translations are validated. This questionnaire version has been assessed for self-assessment via self-administration from the age of 9 years. This questionnaire is designed and validated to be administered for prospective assessment of hearing ability.

The Health Utilities Index - Mark III (HUI3), a generic health status and health-related quality of life questionnaire. Established as a sensitive measure to demonstrate impact of medical treatments over time in 8 areas, (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain). Normative data is available. Evidence of its effectiveness as a useful tool to compare and demonstrate superiority of bilateral CI vs unilateral CI vs baseline pre-implanted status has been published to date (e.g. Bichey et al. 2008). It should be noted that strictly speaking this questionnaire is designed and validated for prospective assessment. Cross cultural validated versions have been licensed and made available for use in this study. This questionnaire version has been assessed for self assessment via self administration by individuals 6 years of age and older.

Implant recipient questionnaire, a non-standardised questionnaire (**2 versions: Baseline and Post implant evaluation**) designed to gather basic patient hearing history, degree of residual hearing pre and post-operatively, implant models and serial numbers, additional demographics and vocational aspects for each individual.

6.1.3 Evaluation forms for completion by the Clinician:

The clinician is trained on data entry procedures for Cochlear-IROS by Cochlear following agreement to participate voluntarily in the registry. Data entry is to be performed by the clinician directly or other staff member via direct on-line electronic data entry with access provided through use of their password on any suitable computer within the clinic during or coinciding with the timing for routine annual clinic visits occurring after one, two and three years (optional) post implant for the patient in question.

- **Clinician Baseline – Compulsory,** this form must be completed by the clinician with reference to each newly enrolled patient as it serves as registration of the patient at baseline evaluation. This is to ensure capture of the specific information related to technical details of the implanted device or devices and the external devices to be used, as well as any specific clinical technical details the patient does not have access to.
- **Annual Follow-up- Clinician (post implant: 1yr and 2yrs compulsory (and 3yrs optional).** This is a general questionnaire that must be completed at an annual follow-up evaluation which coincides with routine annual clinic visit for the patient. This is to ensure capture of the specific information related to technical details of the implanted device or devices and the external

devices, and to reflect any changes that may have occurred over the preceeding12 months. Again it refers only to specific clinical technical details the patient does not have access to.

- **Product Specific procedures**.
- **End of study form** is also a compulsory form required to be completed by the clinician for each registered patient upon their departure from the registry either at the end of the prescribed set of evaluations , that is at 2 years or optionally 3 years post-implant or prematurely. A patient or clinician may choose to terminate participation in the registry prematurely at the individual wish of the patient or clinician or alternative following an event requiring removal of the patient from further review and data collection by the registry by default. The clinician is asked to record the reason for removal and date of exit from the study for each patient.
- **Unaided Hearing Threshold summaries.** The hearing threshold summary data recorded at baseline must reflect measurements performed prior to the implant surgery. Additionally, hearing thresholds measured immediately after surgery, in the period between surgery and before 1st switch-on or later) can be recorded at baseline evaluation. The evaluation form aims to capture a detailed summary of the pure tone hearing threshold levels that are routinely measured for the patient.

    1. **Pre-implanted hearing thresholds** routinely measured prior to the patients surgical procedure , for pure-tone stimuli via air and bone conduction in each ear for routinely measured frequencies between 125Hz and 8000 Hz) are required.
    2. **Immediately post-implant hearing thresholds**. At the clinic's discretion, the implanted patient's **hearing thresholds** if assessed immediately following surgery or up to some months later may be additionally recorded. This typically occurs either before the implanted patient is discharged from the implanting clinic after their surgery, or at the 1st switch-on of their device.
    3. **One year post-implant** (implant day +12 months +/- 2 months)

       Two years post-implant (implant day +24 months +/- 2 months)

6.2 Study End-points

6.2.1 Primary End-points

The intra-subject comparison of baseline and annual post-implant follow-up assessments on the HUI Mark III and SSQ will be used to examine and determine the type and degree of any changes reported on an individual basis longitudinally for all implanted patients.

Inter-subgroup comparison of baseline and post-implant annual assessments on the HUI Mark III and SSQ will be used to determine the type and degree of reported changes between comparable device type and configuration user groups.

Comparisons between device user groups and device configurations will be made for clinically logical subgroups. E.g. Patients of comparable age will be compared across the subgroups.

6.2.2 Secondary End-points

An analysis of the responses provided to the general questionnaire to be completed by both the clinician and the patient at each evaluation interval will be performed to describe various patient profiles and determine potential differences between subgroups of implanted recipients based on the implanted

device type and configuration. Furthermore the collated information from the Hearing summaries recorded at the baseline and annual intervals will be analyzed to provide further definition of the hearing loss configuration of the various patient profiles over time.

7 Subject Selection

7.1 Inclusion Criteria

- First time implantees, post-lingually deafened, awaiting first switch-on

  (i.e. registration date ≥ implant date +120 days)
- Device(s) implanted include one or more of implant devices from the company Cochlear.
- Configuration of implanted devices is either unilateral or bilateral at baseline registration
- Children 10 years or older and in accordance with local regulations and product labelling.
- Patient informed consent signed by the patient after or on the implant date (to be co-signed by their legal representative if under 18 years of age at time of registration)
- Mentally-able to complete self-assessment questionnaires
- Willingness to participate in the registry study for 2 years post-implant (and up to 3 years optionally).
- All implanted devices are routinely purchased under routine local conditions anticipated to be geographically stable.

NOTE: Unilateral device-users, electing to opt for a second sequential implant during the course of the 3 year post-implant follow-up period will be classified accordingly thereafter as sequential bilateral device users.

7.2 Exclusion Criteria

- Individuals excluded from participation in a registry according to national or local regulations.

8 Subject Identification and Confidentiality

In accordance with patient privacy laws, subjects will be identified anonymously on all evaluation forms and subsequently in the database only by a unique coded reference number that is automatically assigned by the database. This consists of the study number (assigned by Cochlear including the region managing the registry), country code, center code, and finally the patient specific code assigned in chronological order of implant at the clinic.

- Study number: Study specific **5277EU-**
- Country code: An abbreviation of the country name e.g. for Germany **GE**
- Center code: assigned by Cochlear for a specific clinic. e.g. clinic X in country Y - **02**
- Patient code: assigned automatically by the e-platform to indicate the chronological enrolment of patients at the clinic. E.g. the first patient enrolled is **-001**. No initials shall be included in the patient code which is centrally recorded. .

Example Patient Identifier code: 5277EU-GE-02-001

- The clinician will have the opportunity to include an identifier with 12 character spaces on the *"Clinician Baseline-Compulsory Form"* completed by the clinician. This will appear on the confidential patient listing for the clinic only.
- Should the patient move from the implant site where registered to another site any time after the registration for follow-up, the original clinic code defined by the system will be maintained.
- Clinicians will have the opportunity to transfer their registered implanted patient for follow-up via another participating site by completing the *Transfer patient form* online via the e-platform interface.

NOTE: Completed evaluation forms entered online or similar documents are confidential documents and will only be available to the Sponsor and their representatives, the clinic investigator, the investigational statistician, and if requested to the Ethics Committee. The name of any patient shall be kept confidential and shall not appear on any data forms, publication, or submission to regulatory authorities. Patients will be identified only by the subject code preserving anonymity.

9 Risk benefit analysis

9.1 Benefits

Patient benefits anticipated following implant treatment are listed in the accompanying product labelling issued with each market released Cochlear device.

9.2 Risks

Risks for the patient are listed in the product labelling accompanying each market released Cochlear device. There are no additional risks to the implanted patient deciding to participate in this observational study.

Investigators are informed during training on how to use the database and reminded of the compliance with data privacy for all patients on all communications externally and internally in relation to the study

10 Device Description

10.1 Investigation Product Description

All implanted recipients enrolled in the study will be implanted **with market released Cochlear products.** The accompanying product labelling for each device contains a description of the device and its intended use.

10.2 Investigational product traceability / recording

Registration cards for each implanted device are collected routinely for all implanted recipients receiving a market released **Cochlear** device and recorded through Cochlear's post-market surveillance system following receipt from the clinic.

10.3 Handling and Reporting of Incidents

Report of any incident related to any device received by an implant recipient, shall follow the normal mandatory reporting procedures (according to latest MEDDEV guidelines) in place for all **market**

released Cochlear implant devices as implemented through Cochlear's complaints and issues handling procedure for routine post market surveillance. The s**chedule for the initial reporting of an incident or near incident commences from when Cochlear is informed in accordance with Cochlear's complaints and issues handling procedure for all marketed released products.**

10.4 End of study OR Early termination or withdrawal

Following registration of the implanted recipient at baseline, the registered patient may be removed from the study at any time at the discretion of the clinician. Accordingly the clinician must complete the END OF STUDY form to reflect the date and reason for termination of the study for each patient. Any one of the following listed reasons may be applicable:

1) Patient has completed the 2nd year follow up evaluation.
2) Patient has completed the optional 3rd year follow-up evaluation
3) Failure of any of the Devices involved
4) Device related incident that led to deterioration of the patient's health and necessitating discontinuation
5) Patient death
6) Clinician's decision
7) Patient's decision
8) Sponsor decision for non-medical related reasons

11 Ethical considerations

11.1 Declaration of Helsinki

The clinical investigation will be conducted according to the guidelines established in the latest update to the Declaration of Helsinki. Subjects will be free to withdraw from the observational study at any stage without prejudice to their subsequent routine clinical treatment.

11.2 Ethics Committee Approval/Opinion

As a non-interventional clinical observational study EC approval may not be required in some regions. Local or national exceptions may exist and must be determined and addressed ahead of participation by the clinician wishing to collaborate.

Any clinic wishing to publish their data is recommended to obtain Ethics Approval/Opinion for their participation in the Registry.

As a courtesy to all governing ECs, Cochlear will provide a current version of the Cochlear Registry Plan (in English unless otherwise requested), and the Patient Information Consent form (in the native language of patients).

As applicable the collaborating clinician at the investigator site is responsible for:

- Submitting the information package to the hospital EC prior to their participation in the Registry
- Any costs associated with gaining ethics approval
- Ensuring a copy of the EC opinion/approval letter to proceed is forwarded to Cochlear prior to initiation of the registry in their centre
- Responding to any queries raised by the local EC (requesting additional information from Cochlear as needed.)

11.3 Patient Informed Consent

The clinician is responsible for and must obtain written informed consent from each patient or their legal representative, prior to collecting any study data and formally enrolling them in the registry. This must occur after the patient is implanted when the decision for type and device configuration has already been taken independently to their decision to participate. Prior to obtaining their signature, verbal explanation and exchange must be provided to include:

- aims and objectives of study participation
- extent of the subject's involvement in terms of time, test intervals and tasks
- personal data privacy in printed material and electronic records
- their ability to cease their participation at any time during the course of the registry

The clinician is responsible to ensure that:

- all patients give written informed consent prior to enrolment in the registry through signing and dating the Patient Informed Consent form.
- a copy of the patient information sheet and consent form are given to the patient and the study details explained verbally.
- all signed patient informed consents are archived in the clinician's file at the centre/clinic, as per local requirements, and **at least for 5 years** after completion of the registry.

12 Data Reporting and Statistical Analysis

12.1 Statistical Method

Review of the study design was undertaken by an independent statistical consultant, [redacted] Subsequently a proposal for the data analysis methods was made and is available as a separate report upon request (in English only).

In summary, based on the specified hypotheses assuming a 2-sided alpha error of 5%, (95% confidence interval) comparison of intra-subject performance outcomes rated via SSQ and HUI Mark III at preimplant to postimplant annual 1 and 2 years follow up intervals will require data for a minimum of **50** recipients with the same device to determine significant changes due to treatment effects.

13 Administrative Procedures of the Registry

13.1 Technical Requirements for online data entry

The minimum computer hardware and software equipment requirements must be available to enable data entry on line. Please verify and check that all of the below items are available for data entry at the clinic. Should the patient have elected to complete the forms online at their own discretion this also applies to any external computer accessed by the enrolled implanted recipient:

Hardware requirements:

- PC or Macintosh, Internet connection allowing normal and secured communications (HTTP, HTTPS)

Software requirements:

- Adobe Acrobat Reader, version min. 6.0
- Browser: Internet Explorer, Safari or Firefox.

13.2 Data Reporting

Evaluation case report forms to standardly gather general patient demographic data, and responses to the clinically standardised self-assessment scales, the SSQ and HUI MARK III, as well as audiometric data sheets (and product-specific measures), are provided as printable forms through the electronic user interface accessed via the allocated user password. The interface to the data sheets is designed for direct data-entry online with same time updates. Entered data is captured electronically into a central externally hosted e-platform developed, hosted and maintained by [redacted], as contracted database consultants for the company Cochlear, operating to ISO standards for data protection and data management. The project manager and select regional Cochlear staff will have access to view all raw data and data summaries. Clinics have ready access to all data entered related to their patients registered at their clinic via same time update summaries and through use of the system allocated confidential user password (delivered to each investigator by email). Subsequent automated email-reminders for patient reviews will also be provided through the e-platform as provided by the registering Clinician to alert for timely annual reviews of registered patients.

Specific instructions to complete the electronic evaluation forms shall be provided to the clinic investigator and other site personnel and registered patients online and reviewed during the initiation into the observational study onsite by Cochlear clinical staff.

Data entry at Baseline

Upon registration of the patient into the Observational study at baseline via the responsible clinician, the patient code will be automatically assigned via the platform according to the scheme outlined under the section entitled *Subject Identification and Confidentiality* of this protocol. During registration of the patient and completion of the *Clinician Baseline-Compulsory form,* the clinician and patient will agree upon which further assessments shall be included at baseline for the patient in question. The additional evaluation tools to select from include: Implant Recipient Baseline form, HUI Mark III and the SSQ and hearing threshold summaries and product specific evaluation measures.

Paper response options for the patient

Ideally if the paper option is preferred for the patient, at baseline and subsequent follow-ups, the clinician is advised to print-out the selected questionnaires prior to the evaluation interval, and to provide them to the patient for completion at the clinic, requesting return of completed questionnaires to the clinician before their departure from the clinic or upon subsequent return to the clinic. The clinician is responsible to review the forms in brief for completeness and to arrange online data entry for capture and storage of the data centrally.

Alternatively the patient may take the printed questionnaires home and return them to the clinician for data entry by post or at a later date. The clinician is responsible to review the forms in brief for completeness and to arrange online data entry.

Online response option for the patient

The patient providing consent to provide their email address through signature on the *Patient Informed Consent form,* and subsequently recorded online by the clinician on the *Clinician Baseline-Compulsory form* can provide responses on-line directly through use of a computer at home or in the clinic. The clinician can view the responses provided online by the patient and verify them at their discretion once the patient has submitted them online.

Follow-up evaluations

The clinician and patient may discuss and agree upon whether online data entry or paper entry for the patient is most desirable for follow-up evaluations.

If the patient has opted for online data entry, automated timely email reminders will notify the patient their responses for the next annual evaluation are due. Following no response by the patient a 2nd response will be sent to the patient. Following no response to the 2nd reminder by the patient, the clinician will be notified that an evaluation is due and no response to date. The clinician may review the situation with the patient at their discretion at the next appointment in the clinic. If the patient does respond to the first or 2nd reminder and enters new data, the e-platform will automatically notify the clinician that new data is available for the patient in question.

If the clinician and patient have opted for paper entry by the patient, the clinician will be reminded by email that a review of the patient in question is due at each annual review interval. If the clinician does not respond a second reminder is sent to the clinician. The clinician is ultimately responsible for re-entry of any data provided initially on paper by the registered patient at any interval.

13.3 Paper Case Report Forms (CRFs)

Paper case report forms are printable for data entry by the clinician for the patient. Paper forms are not required to be stored by the clinic following entry of the data electronically online.

13.4 Electronic Evaluation Forms (eCRFs)

All data forms are available on line for ease of data entry through click responses on PDF format forms with pull down menus to facilitate responses with helpful and prompting messages to guide you through the form and requested information. Once a form is saved the data is automatically updated same time for review by the responsible clinician.

Note: Please also refer to instructions online following access to the [redacted] *interface has been provided to you by Cochlear.*

13.5 Monitoring

There will be no routine on site monitoring of data entered. Participating clinics are not asked to store paper documents as source documents for data entered online; hence, no cross checks between data entered and source data is possible. Online spot-checks of recorded data to ensure quality assurance of data entered in terms of logic and ranges of data entered will be undertaken at random intervals and of randomly selected subsets of data during the course of the registry long-term. Data collected through observation of controlled market release of specific products may be subject to monitoring at regular intervals following prior agreement with the principal investigator for the defined period of the controlled market release. [redacted] for the Cochlear-IROS database, utilises an in-built audit trail for automated registration of all data entries and amendments by the authorised clinic personal and or patient.

13.6 Study Documents Online and Study Records

For convenience and ready access, all study documents are provided for viewing online upon access to the interface at any time after the chief investigator has signed the Registry Agreement online by all users in the clinic.

The study documents include:

1. Registry Plan
2. Registry Agreement Letter(s)
3. Patient Information Consent Form template.

Paper copies of the Registry records maintained by the clinic/centre and records will include:

- EC opinion/approval (as applicable for registry participation for the clinic)
- Individually signed Patient Informed Consent forms on Clinic letter head
- Clinic specific patient identification list/log of system automated confidential patient codes

Optional for paper records pending regional regulations include:

- Signed Registry Agreement (*E-signature recorded & stored electronically via the IROS interface upon first access by a collaborating clinic Chief investigator)*
- Signed Registry Plan
- Clinic specific patient identification list/log of system automated confidential patient codes
- Individual confidential EDC interface passwords for identification for multiple users at the same clinic.

The clinician is responsible to ensure all locally required paper study documents are stored for at least 5 years after the end of the study.

Electronic records of data entered on each evaluation tool per patient at each interval is stored in the centrally hosted database as mentioned in Section 13.2 of this Registry Plan. Clinics can access the raw data for each patient and patient groups entered for their clinic, at any time for download and storage onto local systems. Global data records are not available for local download.

13.7 Data Management

All international data shall be collected and collated over several years in an externally hosted electronic database with complete access to raw data provided to Cochlear AG in Basel and the Cochlear Technology Centre in Mechelen. All data shall be treated confidentially by Cochlear. The data management process for this clinical investigation is described in the related Data Management Plan. All electronic data shall be kept for a minimum period of **5 years** both in electronic format and on paper by the company Cochlear as per Good Clinical Practices.

All clinics will have access to the individual raw data and data summaries of registrations and progress for all patients in their care that is entered into the observational study at any time.

All requests for data reports and summaries shall be coordinated via the global project manager.

14 Reporting of Results

14.1 Investigator

Please refer to the *Registry Agreement Letter(s)* also available online under Documents. Confirmation of agreement to the conditions must be electronically submitted. This may also be printed out and filed on paper if desired by the clinic. Confirmation of having read and agreeing to the Registry Agreement is requested the first time the interface is accessed by a new collaborating clinic by the lead investigator

at the clinic. Once the lead investigator at the clinic has confirmed agreement electronically the interface will permit access to create the first patient at the clinic. If there is no agreement patient data may not be entered. The Registry Agreement states in brief that each clinic owns their own clinic data which is available for publication of statistically valid data at their own discretion. The investigator must also ensure each patient continues to receive routine clinical treatment and care, irrespective of participation in the registry. Cochlear owns and has access to global data entered into the e-platform for the registry and intends to use it as appropriate for non-peer reviewed reports to support decision makers across regions.

14.2 Sponsor

Cochlear, the sponsor will use this data to provide statistically valid data to support patient management decisions at the clinical, administrative, marketing, reimbursement and regulatory levels locally, nationally and internationally. Reports are to be developed at regular intervals back to the contributing clinics and at request of the relevant health and government bodies. Established benefits will be used to support benefit claims from use of bilateral stimulation over unilateral stimulation for scientific, regulatory and market oriented communications.

The study obligations for the Sponsor and the investigator are followed as outlined in guidelines for ISO14155 and the Declaration of Helsinki. These will be reviewed with the clinician prior to the start of the registry at initiation visit.

15 Withdrawal of Sponsor

Following written communication to notify in advance all participating collaborating clinics, the sponsor may elect to withdraw sponsorship of the registry if,

- patient recruitment rate is not growing sufficiently over time to warrant the support of resources involved..
- there is no willingness to collaborate in the registry by the clinicians on the whole.

Note: In the event the registry is closed, patients enrolled to this date would be permitted to complete evaluation to 2 years post-implant

16 Overview of Case Report Forms and Questionnaires available online

Baseline evaluation

By the patient
Implant Recipient Baseline
HUI Mark III questionnaire
Speech Spatial Qualities questionnaire
By the Clinician

Clinician Baseline (compulsory)
Unaided Hearing threshold summary- pre-implant
Unaided Hearing thresholds - immediately post implant
End of study form (if needed)
Product specific forms

1st year follow up

By the patient
Implant Recipient follow-up
HUI Mark III questionnaire
Speech Spatial Qualities questionnaire
By the Clinician
Annual Follow-Up Clinician Yr 1 (compulsory)
Unaided Hearing Thresholds - Yr 1
End of study form (as needed)
Product specific forms

2nd year follow up

By the patient
Implant Recipient follow-up form
HUI Mark III questionnaire
Speech Spatial Qualities questionnaire
By the Clinician
Annual Follow-Up Clinician Yr 2 (compulsory)
Unaided Hearing Thresholds -Yr 2
End of study form (as needed)
Product specific forms

3rd year follow up (optional)

By the patient
Implant Recipient follow-up form
HUI Mark III questionnaire
Speech Spatial Qualities questionnaire
By the Clinician
Annual Follow-Up Clinician -Yr 3 (compulsory)
End of study form (compulsory)
Product specific forms