Official Title: **Cochlear Implant and Healthy Aging: A Multinational, Multicentre Observational Study**

NCT Number: **NCT03072862**

Document Date: **10 December 2019**

OBSERVATIONAL STUDY PROTOCOL

Cochlear Implant and Healthy Aging: A Multinational, Multicentre Observational* Study

Short Study Tittle: "CI & Healthy Aging"

Study Number: **CEL5671**

ENGLISH MASTER VERSION

Date: 10 December 2019

Version number: 4.0

Authors:

[redacted]

***** Investigator does not intervene on the treatment.

Sponsor	Cochlear AG EMEA Headquarters Peter Merian-Weg 4 4052 Basel; Switzerland
Manufacturer	Cochlear Limited 1 University Avenue, Macquarie University, NSW 2109 Australia
Investigators *(by alphabetic order, full detail provided in Appendix 1)*	[redacted] - Ospedale Guglielmo da Saliceto - Piacenza - Italy [redacted] - Hôpital Purpan - Toulouse - France [redacted] - Universidad de Las Palmas de Gran Canaria - Spain [redacted] - Bnai Zion Medical Center - Haifa – Israel [redacted] – Rabin Medical Center (Beilinson) - Petah Tikva - Israel [redacted] - Clinica Universitaria de Navarra - Pamplona - Spain [redacted] - Azienda Ospedaliera di Padova - Padova -Italy [redacted] - Complejo Hospitalario Universitario Insular Materno Infantil - Las Palmas de Gran Canaria - Spain [redacted] - Hôpital La Pitié Salpêtrière - Paris - France
Clinical Research Organisation (or other institution involved)	External CRO will perform Monitoring; Company name: [redacted]

CIP Signature Page

By signing this page the Sponsor, and Principal Investigator agree to conduct this investigation in accordance with the current investigational plan. No changes to this clinical investigation plan will be permitted without the written approval of both parties. If substantial amendments to this plan become necessary, written approval by the Ethics Committee will be obtained 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

[redacted]
DATE

[redacted]
SIGNATURE

[redacted]
TITLE

Principal Investigator Signature

PRINT NAME

DATE

SIGNATURE

Principal Investigator
TITLE

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1 Clinical Investigation Synopsis

Name of device:	Commercially available Nucleus Cochlear Implant Systems, including Data Logging functionality
Short study title and study number:	CI & Healthy Aging **CEL 5671**
Principal Investigators and sites:	[redacted] - Ospedale Guglielmo da Saliceto - Piacenza - Italy [redacted] - Hôpital Purpan - Toulouse - France [redacted] - Universidad de Las Palmas de Gran Canaria - Spain [redacted] - Bnai Zion Medical Center - Haifa - Israel [redacted] – Rabin Medical Center (Beilinson) - Petah Tikva - Israel [redacted] - Clinica Universitaria de Navarra - Pamplona - Spain [redacted] - Azienda Ospedaliera di Padova - Padova -Italy [redacted] - Complejo Hospitalario Universitario Insular Materno Infantil - Las Palmas de Gran Canaria - Spain [redacted] - Hôpital La Pitié Salpétrière - Paris - France
Study start:	06 November 2017
Total expected duration of the clinical investigation:	4 years
Enrolment period:	31 months
Expected duration per subject:	20 Months (+/- 1 month)
Study design:	Observational prospective comparative cohort repeated measures
Number of subjects:	100
Inclusion criteria:	• Unilateral CI candidates with bilateral postlingual deafness with intention to treat • ≥ 60 years at *first* unilateral cochlear implant • Implant ear: meets all local criteria for CI treatment • Contralateral ear: average pure tone thresholds indicate a moderately-severe to profound hearing loss (4 freq. average: 0.5, 1, 2 and 3 or 4 kHz > 56 dBHL). • Willingness to participate in and to comply with all study procedures • Fluency in languages used to assess clinical performance • Appropriate expectations from routine CI treatment • Able to decide on study participation personally and independently sign their consent

<table>
<tr><td>Exclusion criteria:</td><td colspan="5">Significantly/severely dependent or fragile
Unable to provide consent personally
Unable to complete questionnaires for self-assessment independently
Unilateral hearing loss
Sequential and simultaneous bilateral cochlear implant recipients
Ossification or other cochlear anomalies preventing full electrode insertion
Retro cochlear or central origins of hearing impairment.
Significant comorbidities preventing study participation (e.g. blindness, immobility or in a wheel chair, severe aphasia,.)
Medical contraindications to surgery
Clinic Standard fail criteria for CI candidacy in regards to chronic depression, dementia, and cognitive disorders.
Unrealistic expectations on the part of the subject, regarding the possible benefits, risks and limitations that are inherent to the procedure and prosthetic device.</td></tr>
<tr><td>Primary objective:</td><td colspan="5">To evaluate the change in health related quality of life following CI treatment in the elderly individuals by using the generic Health Utilities Index Mark III (HUI 3) tool prospectively.</td></tr>
<tr><td>Secondary objectives:</td><td colspan="5">To evaluate the impact of CI treatment in the elderly on the domains that have an impact on healthy aging and overall well-being such as hearing ability, dependency, cognition, falls, depression.</td></tr>
<tr><td>Tertiary objective:</td><td colspan="5">To identify healthcare resource utilisation that is impacted by CI treatment versus no treatment.</td></tr>
<tr><td rowspan="21">Treatment and follow up schedule:

Q - questionnaire
A - standard audiological measure
G- standard geriatric measure
NA –not Applicable</td><td></td><td>Q/A.</td><td>Pre1
Visit 1</td><td>Post 1
Visit 2</td><td>Post 2
Visit 3</td></tr>
<tr><td>Patient Profile</td><td>Q</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>Healthcare resources</td><td>Q</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>CAP-II</td><td>Q</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>L-IADL</td><td>Q</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>Data Logging</td><td>A</td><td>NA</td><td>x</td><td>x</td></tr>
<tr><td>HUI3</td><td>Q</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>GDS-15</td><td>Q</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>HHIE-S</td><td>Q</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>SSQ</td><td>Q</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>PTA</td><td>A</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>SFT</td><td>A</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>Speech in Quiet</td><td>A</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>Speech in Noise</td><td>A</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>MMSE</td><td>G</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>DSST</td><td>G</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>TRAIL B</td><td>G</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>De Jong Loneliness scale</td><td>Q</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>TUG</td><td>G</td><td>x</td><td>x</td><td>x</td></tr>
</table>

Primary endpoints:	Change in HUI3 multi-attribute index scores preimplant to postimplant at 12 and 18 months post surgery.
Secondary endpoints:	Change in scores on evaluation tools for specified health related domains on each of the following from preimplant to post implant at 12 and 18 months surgery: MMSE, DSST & Trail B (Cognition); TUG (falls); GDS-15 (depression); L-iADL (independency); HHIE-S (hearing handicap); SSQ (hearing & communication ability); CAP-II (capabilities of audition); De Jong Loneliness Scale; Speech recognition tests in Quiet (daily hearing function); Speech recognition tests in Noise (daily hearing function); Consistent daily use of CI via automatic data logging (hrs/day and listening environments)
Tertiary endpoint	Change in healthcare resource utilisation with CI treatment postimplant versus preimplant (assessed over a 6 month time frame at each test interval).

2 Terms and Abbreviations

Abbreviation	Definition	Category of assessment
CAP-II	Capabilities of Auditory Performance	Hearing ability
L-IADL	Lawton –Instrumental Activities of Daily Living	Independence
HUI3	Health Utilities Index Mark III	Quality of Life
GDS-15	Geriatic Depression Scale -15	Depression
HHIE-S	Hearing Handicap Inventory for the Elderly Scale	Hearing Handicap
SSQ	Speech Spatial and Qualities	Hearing ability
MMSE	Mini Mental State Examination	Cognition
DSST	Digit Symbol Substitution test	Cognition
TRAIL B	Trail Making Test version B	Cognition
PTA	Pure tone Audiometry	Hearing levels
SFT	Sound Field Thresholds	Hearing levels
TUG	Time Up and Go test	Risk of fall

3 Introduction

Burden of disease in the aging population has a high economic impact for society.

In 2014, Prince et al. published a report in Lancet on the leading contributors to the burden of disease in people aged ≥ 60 years.

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See Online for appendix

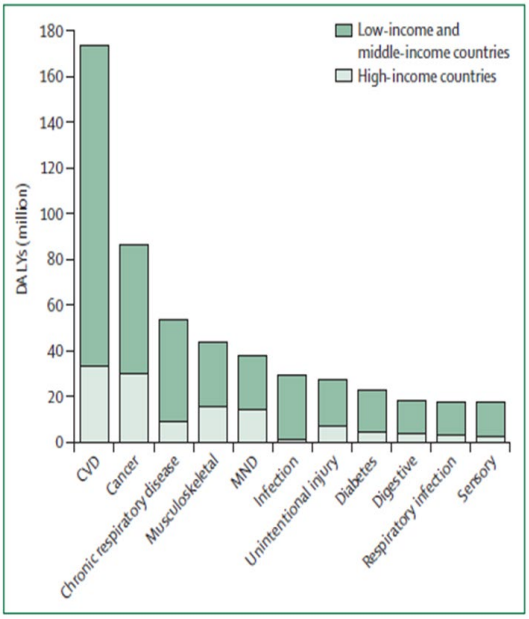


Figure 1: **Leading contributors to burden of disease in people aged 60 years and older in 2010—DALYs (million) by cause and World Bank income**
DALYs=disability-adjusted life years. CVD=cardiovascular and circulatory diseases. MND=mental and neurological disorders, combining the IHME GBD mental and behavioural disorders and neurological disorders groups.

Cochlear Implant, (CI) restores hearing function and communication abilities which in turn help to reduce social isolation (Olze et al 2012, Lachowska et al 2014). An increasing number of publications demonstrate CI treatment also has a positive impact on depression and may delay cognitive decline (Mosnier et al 2015, Lin et al 2011 Olze et al 2012). Routine clinical follow shows a trend for added benefits of CI treatment upon dependency, mobility and the risk of falls (Lin et al 2011, Lachowska et al 2014).

Therefore, we may assume that through CI treatment for permanent deafness, **there is a potential to decrease the burden of disease in aging adults by improving important social, health and cognitive functions** in addition to restoring hearing function.

With reference to Prince et al., CI treatment is expected to impact the following contributors to the global burden of disease: Sensory, MND (Mental and neurological disorders) and Unintentional injury.

Today, with aging population and its impact on the health care systems, policy makers for provision of health and social services are aiming to keep older adults in good health for longer, in other words towards "Healthy aging".

Increasing number of health technology assessment (HTA) bodies recommend the use of generic health related quality of life tools (i.e. EQ-5D, HUI, SF 36) which in the end yield generic outcome -Quality Adjusted Life Years- which enable comparison of different health technologies for the HTA bodies (Massetti et al 2015).

Our study objective is to show that CI treatment improves the overall health related quality of life and general well-being which translate into healthy aging. The study data collected will provide transparent and comparable medical evidence that can support health care policy makers to take informed decisions on the provision of health services for the treatment of hearing loss

Figure 2 Elements of Wellness (*source http://www.invivowellness.com/blog/wp-content/uploads/2013/07/seven-wellness*

The World Health Organisation, (WHO), defines active aging as *'the process of optimizing opportunities for health, participation and security in order to enhance quality of life as people age',* allowing people to 'realize their potential for physical, social and mental well-being throughout the life course'. The list of contributors to healthy aging is long and varied with the majority of items independent of hearing loss. Nevertheless, by treating deafness, positive effects upon various health related quality of life domains can occur which in turn impacts the overall health status.

Therefore, while it is anticipated to show improvement in the overall health status, the study aim is also to evaluate the impact of **consistent daily use of CI** on specific **health-related quality of life domains** (i.e. hearing, communication, dependency, physical mobility, risk of falls, depression, social isolation & cognition) and to further explore and qualify the main contributors to the better health.

The utilization of cochlear implants is low in elderly adults. It is estimated to be under 5% globally of the elderly population with a significant hearing loss. Various reasons that may contribute to the low rate of CI treatment in aging adults listed below:

- Lack of awareness by geriatricians, general practitioners on when and where to refer elderly for auditory rehabilitation.
- Lack of self-awareness within the elderly population on the benefits they can expect from cochlear implantation.
- Assumption that elderly have reduced listening demands and therefore do not need to aim for the optimal auditory function (aided condition).
- Limited funding leading to lower prioritization of treatment for elderly hearing impaired versus children, adolescents, young and working age adults.

In 2030, 20% of the population will be aged > 65 yrs; one in three will suffer from significant hearing loss. Therefore, there is a sense of urgency for:

- **Health care policy makers to build evidenced based informed decisions for the provision of interventions in the elderly, which in turn can create cost savings from a societal perspective in the long term.**
- **Increased awareness and development of guidance principles to support professionals as well as aging individuals, on the suitability for timely referral for further assessment for cochlear implant candidacy.**

The study aim is to provide medical evidence that CI treatment in aging adults has the potential to improve the overall health status including but not exclusive to hearing function, which in turn can create cost savings from a payer and societal perspective. This information may be used to support referring professionals and potential CI candidates in their decision for CI treatment as soon as significant hearing loss is diagnosed which can impact overall healthy aging.

4 Identification and description of the device

The observational study includes treatment with commercially available cochlear implant devices available for routine clinical treatment of deafness in all ages in each collaborating investigator clinic.

Devices are provided with standard product labelling and documentation and ordered through routine purchase channels regionally.

5 Justification for the design of the observational study

5.1 Study Design

The study design is an observational prospective repeated measures study performed to evaluate the benefits for overall health following CI treatment in the elderly population treated in clinical routine practice.

The benefits of CI treatment postimplant are compared to the preimplant health status via intra-subject controls using standard assessment scales for various health domains.

CI treatment effect is examined via repeated measures for **intra-subject controls** as follows:

- Preimplant assessment before implant surgery date @ ≤ 2 months
- Postimplant assessment post surgery @ 12 months ± 1 month
- Postimplant assessment post surgery @ 18 months ±1 month

5.2 Evaluation Tools

A selection of observational clinical assessment tools have been selected for repeated assessment and to reflect changes in the overall health status of the elderly individual at pre and post CI treatment intervals. These are commonly used in audiology and/or geriatric practices.

5.2.1 Generic Health Status

Health Utility Mark III (HUI3): The HUI3 is a generic tool to assess health-related quality of life completed by the patient (Feeny et al 1995; Feeny et al 2000). The "*four-week recall*" version of the self-assessed HUI3 with 15 questions is included as the main outcome for repeated assessment at each time interval. Licensed versions per language for use in the observational study are obtained from the developers, Health Utilities Inc. The HUI3 is a sensitive measure that assesses the impact of medical treatments including CI, over time, across eight health domains: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. The 15 questions provide a descriptive response system enabling classification of the respondents into predefined HUI3 health states. The focus of the questionnaire is on health state of the individual, assessing the degree of their perceived impairment for each domain. Responses for each domain are converted to between five to six levels, and then a health state is identified among possible 972,000 health states. The scoring function was derived from Standard Gamble and Visual Analog Scale methods employed for assessment of a random sample of Canadians (n = 504), resulting in utility scores from – 0.36 to 1.00, where a negative score is a state worse than death (Feeny et al 2000) A clinically significant change is set at 0.03 or more between time points.This form can be completed in approximately 10 to 15 minutes by the candidate/recipient.

5.2.2 Hearing

5.2.2.1 Speech Spatial Qualities (SSQ).

The SSQ is a self-assessment scale of hearing ability and communication in daily environments, completed by the patient (Noble, 2006). Forty nine questions are divided into three subcategories: speech (comprehension), spatial (hearing in space) and quality (speech and sounds) and are appropriate for use in adults of all ages and children from nine years (Gatehouse and Noble 2004). Each question is scored on a 10-point rating scale, with higher numeric values reflecting greater ability for the responder. The resulting scores are generally reported as mean ratings for each category but may also be regrouped or assessed individually and the ratings over two time points compared. Clinically significant differences were set at a rating change of 1.0 for each subcategory score between test intervals, as a typically observed difference rating reported in the literature for assessment of unaided and aided hearing aid or implant users). This form can be completed in approximately 30 minutes by the candidate/recipient.

5.2.2.2 Hearing Handicap Inventory in the Elderly Screening test (HHIE-S).

The HHIE-S is a short form self-assessment scale designed to assess the effects of hearing impairment on the emotional and social adjustment in everyday life of the elderly individual before and after hearing treatment. The HHIE-S comprises ten questions (5 emotional & 5 social/situational). Possible scores range from 0 (no handicap) to 40 (maximum handicap) with a significant change at the 95% confidence interval of $\geq$ 9.3 change points (Newman, 1991). The higher the HHIE-S score, the greater the handicapping effect of a hearing impairment. This form can be completed in approximately 5 minutes by the candidate/recipient.

5.2.2.3 Categories of Auditory Perception II (CAP-II)

CAP-II is an auditory skill rating index consisting of nine hierarchical categories. The CAP-II is completed by the clinician as an observation of the individuals hearing abilities. Ranging from 1 to 9, the auditory skills increase in perplexity ranging from perception of environmental sounds to telephone conversation with an unfamiliar speaker. A score of 1 to 9 is provided for assessment at each preimplant and postimplant evaluation interval. (Archbold 1995, Gilmore 2010). This form can be completed in approximately 2 minutes by the clinician using patient hospital file.

5.2.2.4 Routine speech discrimination assessment in quiet

As is performed routinely, assessment of speech recognition in quiet, is performed and the results recorded ***at preimplant and post implant visits in the subject's daily listening condition, i.e.:***

- aided binaurally or
- aided monaurally, one ear unaided, or
- bilaterally unaided (i.e. no hearing aid available at preimplant assessment, only in cases with clinical record of a recent unsuccessful hearing aid trial).

As per local routine practices, standardly used speech materials are presented in the sound field at varied presentation levels, to determine the speech intensity function curve per individual, which includes 65 dB SPL. Recorded speech stimuli are presented from a loud speaker at 0^0 Azimuth, 1 meter away at head level. Speech test materials may include monosyllabic or disyllabic word lists in the native language.

Recorded outcomes will include the percent of items correctly identified compared to the total number of speech items presented at 65dB SPL and the speech reception threshold level,

dBSPL, at which 50% of speech items are correctly recognized, i.e. SRT50%. This routine test is completed in approximately 10 to 15 minutes by the clinician together with the candidate/recipient.

5.2.2.5 Routine speech discrimination assessment in noise

As is performed routinely, assessment of speech recognition in noise, is performed and the results recorded ***at preimplant and post implant visits in the subject's daily listening condition, i.e.:***

- aided binaurally or
- aided monaurally, one ear unaided.

Tests in noise are typically done for patients who can correctly understand a minimum of 50% of speech items in quiet. Speech tests are performed in the free field sound booth with competing background NOISE. According to local routine practices, standardly used speech materials are presented in the sound field at adaptively to obtain the SRT50% in noise, OR speech stimuli may presented fixed at 65 dBSPL and the competing background noise (i.e. pink noise) varied for each presentation list to obtain the SRT50%. Recorded speech stimuli and the competing background noise are presented from a loud speaker at 0^0 Azimuth, 1 meter away at head level. Test materials may include sentences or words as is typically used in the native language.. This routine test is completed in approximately 10 to 15 minutes by the clinician together with the candidate/recipient.

5.2.2.6 Routine assessment of unaided pure tone audiometry (PTA) for air conduction

Unaided Hearing thresholds, dBHL, for pure-tone stimuli via air conduction, presented under headphones, following routine clinical practices at the preimplant clinic visit for each individual. Frequencies for measurement include 250, 500, 1000, 2000 and 4000 Hz. Threshold data, will be combined for all subjects for descriptive analysis. This routine test is completed in approximately 5 minutes by the clinician together with the candidate/recipient.

5.2.2.7 Routine assessment of aided sound field thresholds (SFT) for warble tones

Aided thresholds, dB SPL, for warble tone stimuli presented in the sound field following routine clinical practices at preimplant and post implant visits for each individual in their daily listening condition with hearing device(s).

- aided binaurally or
- aided monaurally, one ear unaided

Frequencies for measurement include 250, 500, 1000, 2000 and 4000 Hz. Warble tones are presented from a loud speaker at 0^0 Azimuth, 1 meter away at head level. This routine test is completed in approximately 5 minutes by the clinician together with the candidate/recipient.

Threshold data, will be combined for all subjects for descriptive analysis at each assessment interval.

5.2.3 Falls

The Time Up and Go test (TUG). The TUG test measures the time a person takes to stand up from a standard armchair, walk three meters (i.e. 10 feet), turn around, walk back to the chair, and then sit down again. The test is performed by the patient wearing regular footwear, using customary assistive devices, if any, and walks at a comfortable and safe pace. The

clinician uses a stop watch to measure the required timing accurately for the complete physical maneuver and the seconds taken to perform it recorded. The test is performed at preimplant and post implant assessment intervals. [Podsiadlo 1991]. This test can be completed in approximately 3 minutes by the clinician together with the candidate/recipient.

5.2.4 Depression

Geriatric Depression Scale-15 (GDS-15). The GDS-15 is a self-report measure of depression in older adults completed by the patient. The 15-item version was developed as a time efficient and easy to complete version with responses in a Yes/No format. The items included have demonstrated a high correlation with depressive symptoms in previous validation studies (Sheikh & Yesavage, 1986). Of the 15 items, 10 indicate the presence of depression when answered positively while the other 5 are indicative of depression when answered negatively. This form can be completed in approximately 5 to 7 minutes by the candidate/recipient.

5.2.5 Cognition

5.2.5.1 Mini Mental State Examination (MMSE).

The MMSE is a 30-point screening test used extensively in clinical and research settings to measure likely cognitive impairment. It is often used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time; thus making it an effective way to document an individual's response to treatment.

Administration of the test requires no special training or equipment and takes between 5–10 minutes. The MMSE examines functions including registration, attention and calculation, recall, language, ability to follow simple commands and orientation. Scores indicate the following cognitive functionality: $\geq$ 24/30 is normal; 19-23, mildly impaired; 10-18, moderately impaired; $\leq$ 9 severe impairment.

For analysis scores will be adjusted according to age, gender and education level as established by covariates affecting outcomes on this measure. Normative data available for the various language groups will be considered in the interpretation of the results. This form can be completed in approximately 7 minutes by the candidate/recipient together with the clinician.

5.2.5.2 Digit Symbol Substitution Test (DSST)

Digit symbol substitution test is a neurophysiological test sensitive to brain damage, dementia age and depression assessing working memory. It consists of (e.g. nine) digit-symbol pairs (e.g. 1/-, 2/ ⊥ ... 7/Λ, 8/X,9/=) followed by a list of digits. Under each digit the subject should write down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time (i.e. 120 sec) is measured. Symbol copy shows a strong decline with age.

This form can be completed in approximately 2 minutes by the candidate/recipient together with the clinician.

The DSST contained in the Wechsler Adult Intelligence Scale is called 'Digit Symbol' (WAIS-R), 'Digit-Symbol-Coding' (WAIS- IV).

5.2.5.3 Trail B Test

The **Trail B** is neuro physiological test assessing executive function requiring skills of visual search, scanning, speed processing and mental flexibility. Trail B is a Trail Making Test that

consists of 25 circles distributed over a sheet of paper. The circles include both numbers (1 – 13) and letters (A – L); the patient draws lines to connect the circles in an ascending pattern, with the task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. The time the patient takes to connect the "trail." is scored. If the patient makes an error, it is pointed out immediately and the patient is allowed to correct it. Errors affect the patient's score only in that.
The correction of errors is included in the completion time for the task. The test is stopped after 5 minutes.This form can be completed in maximum 5 minutes by the candidate/recipient together with the clinician.

5.2.6 Dependency

Lawton Instrumental Activities of Daily Living Scale, (L-IADL). The L-IADL is a valuable tool completed by the clinician to assess patients with early-stage disease, both to assess the level of disease and to determine the patient's ability to care for him or herself. Performance of IADLs requires mental as well as physical capacity. The IADL scale measures the functional impact of emotional, cognitive, and physical impairments and their need for personal care services. IADLs are scored based on what an individual can do rather than what he/she is doing. IADLs are scored based on how an individual usually performs each of eight tasks. The tasks assessed include: telephone use; food preparation; shopping; housekeeping; laundry, transportation mode; responsibility for own medication and ability to handle finances. The patient receives a score of 1 for each category item if his or her competence is rated at some minimal level or higher, or a score of zero if below minimum capacity. The total sum of scores may range from 0 – 8. A lower score indicates a higher level of dependence. This form can be completed in approximately 5 minutes by the clinician using patient hospital file & Interview

5.2.7 De Jong Loneliness

The development and testing of an explanatory loneliness model were described in De Jong Gierveld (1987 & 1998). A 6 item validated version of the **loneliness scale** was developed by De Jong Gierveld & Van Tilburg (2006), three questions assessing social isolation and 3 on emotional loneliness. The scale may be used in face-to-face interviews, telephone interviews, self-administered (mail) questionnaires, as well as in electronic data collection. It is recommended by developers that the scale be presented somewhere in the middle of the interview or questionnaire style; that is, at a moment when a considerable degree of self-disclosure from the respondents may be expected. Ideally, questions about characteristics of the respondents' networks of social relationships should precede the scale items.

The model is based on the so-called cognitive theoretical approach to loneliness. Characteristic of this approach to loneliness is the emphasis on the discrepancy between what one wants in terms of interpersonal affection and intimacy, and what one has; the greater the discrepancy, the greater the loneliness. Background characteristics (such as marital status, sex and living arrangements), descriptive characteristics of the social network, number and frequency of contacts with network members, and personality and health are identified as important loneliness-provoking factors. Other factors are found to be of crucial importance as well, such as social norms and values, expectations of support associated with certain relationships, and the positive or negative evaluation of the network of relationships-as-realized.

This form can be completed in approximately 1 minute by the clinician using patient Interview.

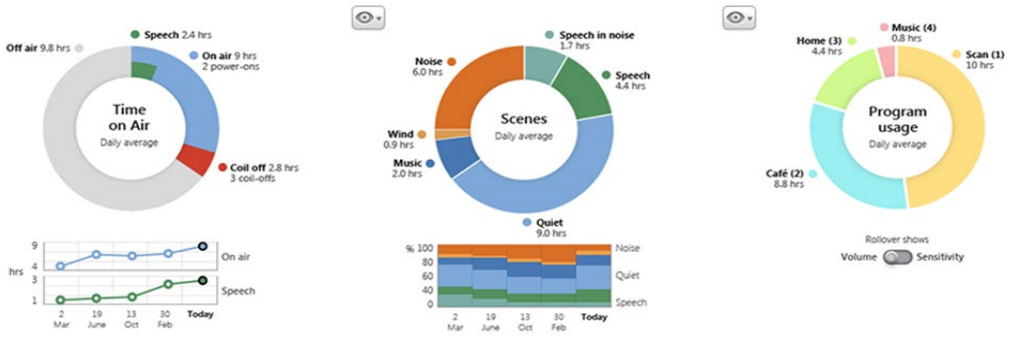
5.2.8 Data Logging

In general, healthy aging population operate in a wide range of listening environments with listening profiles that are unique to them.

A measure of success of CI treatment is the average daily use (hrs/day). Furthermore the variety of listening environments experienced will be automatically recorded at each post implant assessments interval(s) as an indicator for social integration.

The sound processor features an in-built data-logging function. Data are extracted automatically at each programming session while the sound processor is connected to the fitting software, *Custom Sound*. Information on daily usage is saved into the local Custom Sound data base at the clinic. Subsequently the individual daily usage data can be exported through a software function (i.e. as CDX files), with the patient's details kept anonymous. Specifics of the data to be collected at each programing session includes the print screen below & additional record of:

- Connection to Custom Sound Date
- Number of days since last connection to Custom Sound
- Average Time on air per day
- Average Time in Noise, Speech in Noise, Speech, Quiet, Music, Wind



There is no form to be completed for data logging as data are contained within the CDX file exported. The investigator will send the anonymized exported CDX file after the 18-month visit has been completed to the sponsor using the Patient ID code as the file name (e.g. PatientID.CDX)

5.2.9 Patient profile data

Coded demographic data will be collected via a customized case report that is completed by the clinician. The information is used to profile and describe the patient group characteristics in terms of audiological history, telephone use, living environment and educational level at the preimplant interval.

Data gathered will be summarized for the group. Select variables may be examined for correlation with one or more outcomes.

This form can be completed in approximately 5 minutes by the clinician using the patient's hospital file & via interview.

5.2.10 Healthcare Resource Utilization (HRU) data

General Healthcare data. A customized case report is completed by the clinician.
This questionnaire has been designed by department of Health Economics from Gran-Canaria University (Author: Beatriz González López-Valcárcel & Patricia Barber). It is based on general European health survey and adapted to be relevant to the CEL5671 study . The questionnaire is color coded where data in pink should be taken from the medical records and data in black are collected through interview with the Subject.

Collected data includes

- Type of health care coverage and employments status
- Use of primary care and emergency services
- Use of specialist practices and/or outpatient surgery services
- Diagnostic tests performed such as radiology, laboratory tests,…
- All hospitalization within the time period observed
- The list and dose of prescribed medication taken
- The list and dose of non-prescription medication taken
- Visits to physiotherapy and rehabilitation
- Sessions with a speech therapist
- Sessions at psychologist
- Use of social welfare care
- Whether subject has lived in a residential care home
- Use of home help or social services
- Support and help from family, friends or others

Data collected will represent the 6-Month time-frame prior to each of the 3 test intervals.
Data will be used to quantity the use of health resource across the duration of the study. The quantification will be done in the corresponding units (i.e. number of visits, exams, doses of medication, subject's health expenses,..). In a second stage and in collaboration with national experts, these quantities will be converted in health care costs.
Data obtained would potentially be used for economic modelling of direct and indirect costs in the long term related to the intervals post CI treatment and prior to CI treatment.

This form can be completed in approximately 30 minutes by the clinician using the subject's patient hospital file & via interview.

6 Risks associated with participation in the observational study

Participation in the observational study presents no additional risk to the patient over and above routine clinical care using commercially available cochlear implant devices. There is no additional clinical visit outside the routine management.

7 Objectives and hypothesis

7.1 Study Objectives

1. To evaluate the change in health related quality of life following CI treatment in elderly individuals by using the generic Health Utilities Index Mark III (HUI 3) assessment scale prospectively.
2. To evaluate the impact of CI treatment on the domains that have impact on overall well-being and healthy aging in the elderly such as :
    a) hearing ability and communication
    b) dependency
    c) cognition
    d) falls
    e) depression/mood
3. To identify the changes in healthcare resource utilisation following CI treatment compared to preimplant.

The hypotheses:

Primary hypothesis

CI implant treatment significantly improves **the overall health related quality of life** of elderly individuals compared to their preimplant condition as measured on the HUI-3.

Secondary hypothesis

CI treatment in the elderly significantly impacts the healthy aging domains and therefore overall well-being in addition to hearing function compared to the preimplant condition as measured on clinically standard evaluation tools in the geriatric and audiological fields.

Tertiary hypothesis

CI treatment has the potential to create cost savings from the perspective of health care payer(s), health care provider(s) and society, by reducing health care resource utilisation for bilaterally severe to profound hearing impaired adults over 60 years of age, post implant compared to their preimplant status.

8 Design of the observational study

8.1 General

A repeated measure, single-subject observational design will be used for assessment of the changes in health related quality of life and overall well-being as the primary end-point of the study, in which each subject acts as his/her own control. Subjects are evaluated subjectively at pre- and post-operative intervals that coincide with their routine visits to the clinic.

This study is observational as no additional intervention is applied to the CI recipient. Outcomes from routine practice and application of CI intervention are recorded through observational measures using clinically standard scales used widely in geriatrics and audiology.

The study design is multi-centre, and multi-language; Italian, French, Spanish, Arabic and Hebrew. Translations of questionnaires have been controlled for via a validated translation process, and thus enabling collation of the data gathered cross culturally. The implant clinics have been chosen due to their long standing history in providing cochlear implant intervention for the treatment of hearing impaired individuals and for their existing capacity to recruit and treat elderly CI candidates for the study within a reasonable time frame.

Each participating clinic is anticipated to recruit a minimum of 8 and a maximum of 20 subjects in total if not agreed differently

8.2 Overview to Assessment Schedule and Visits

Figure 3 below represents an overview of the evaluation visits for each enrolled subject, designed to coincide with routine clinical visits involved in provision of CI intervention. Each subject will be assessed during three visits while participating in the study, creating three data sets and evaluation points per subject. The full battery of tests will be repeated at each of the three visits.

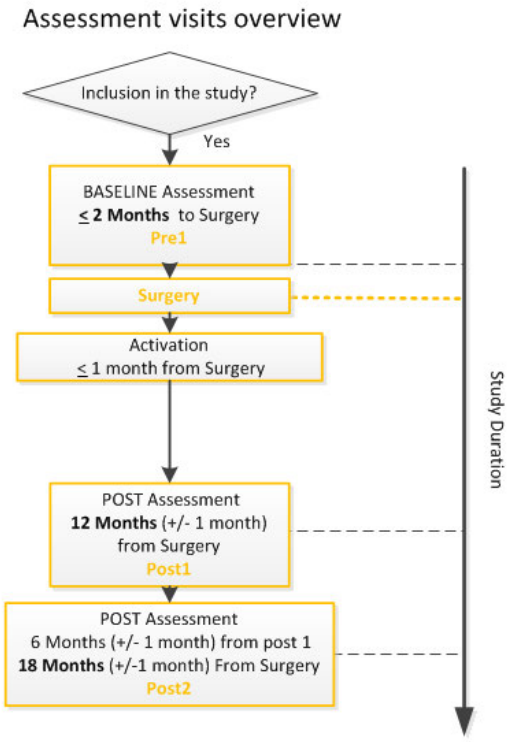


Figure 3 Overview to evaluation schedule flow and visits for each enrolled subject.

8.2.1 Preimplant visit 1 = Pre1

Preimplant visit 1 corresponds to the first evaluation with the full assessment battery for each subject before surgery and corresponds to his/her absolute baseline.

- Preimplant assessment before implant surgery date ≤ 2 months

8.2.2 Postimplant Visit 2 = Post1

Postimplant Visit 2, (Post 1) corresponds to the first assessment after implantation @ 12 months (+/- 1 month) post surgery.

- Postimplant assessment post surgery @ 12 months ± 1 month.

8.2.3 Postimplant Visit 3 = Post2

Postimplant Visit 3, (Post 2) corresponds to the second assessment after implantation @ 18 months (+/- 1 month) post surgery.

- Postimplant assessment post surgery @ 18 months ±1 month.

8.3 Global Overview of Data Collection

Table 1 provides an overview of the standardly available assessment tools making up the test battery to be used at each evaluation Visit (1 to 3). The corresponding health domain(s) assessed by each evaluation tool, as referred to and described under the primary and secondary hypotheses are indicated. In addition to the evaluation tools listed below, customized case report forms to summarize the Patient Profile and Healthcare resource utilisation over time will be completed by the clinician for each enrolled subject. Table 2 illustrates for whom completion of each assessment is targeted and the schedule.

Table 1. Overview to Evaluation Tools and health domains assessed.

DOMAINS ↓	HUI-3	TUG	GDS-15	LS de Jong	iADL	HHIE-S	SSQ	CAP II	Speech Recognition Testing	MMSE, Trail B, DSST	Data Logging
	Health Utility Index Mark 3	The Timed Up and Go Test	Geriatric Depression Scale	Loneliness test	Lawton Instrumental Activities of Daily Living Scale	Hearing Handicap Inventory for the Elderly	Speech, Spatial, and Qualities of Hearing	Categories of Auditory Performance	As per Routine Clinical practise	Mini-Mental State Examination ,Trail B, DigitLetter Substitution	
Risk of Falls		x									
Mobility	x										
Hearing & Communication	x					x	x		Testing in Quiet and Noise for CI only and CI + contralateral ear		X (usage)
Communication	x										X (envir.)
Social Isolation				x			x				
Dependence					x						
Mood/ Depression	x		x	x							
Cognition	x									x	
Time to complete (mins)	*15*	*3*	*7*	*1*	*5*	*5*	*30*	*2*	*30*	*17*	*NA*

Quality of Life , overall Health & Health Utility – HUI-3 (Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition & Pain)
Hearing Ability – SSQ, Speech Recognition Testing, CAP II; *Impact of Hearing on daily life* – HHIE & SSQ,
Cognition – MMSE, *Physical Balance* - TUG (& VEMPS if routine), LS- Loneliness scale, DSST- Digit symbol substitution test, Trail B , Trail making task B.

Table 2 Evaluations by Visit by Clinician and by Candidate/Recipient

	Pre1	Post1	Post 2
Visits	**Visit1**	**Visit2**	**Visit3**
Questionnaires filled by clinicians using patient hospital files and/or interview			
Patient Profile	x	x	x
Societal Cost	x	x	x
CAP2	x	x	x
i-ADL	x	x	x
De Jong Loneliness	x	x	x
Self assesment Questionnaires			
HUI-3	x	x	x
GDS-15	x	x	x
HHIE-S	x	x	x
SSQ	x	x	x
Routine audiological assesments			
PTA	x	x	x
SFT	x	x	x
Speech in Quiet	x	x	x
Speech in noise	x	x	x
Routine Geriatric assesments			
DSST	x	x	x
Trail B	x	x	x
MMSE	x	x	x
TUG	x	x	x

8.4 End-points

Primary end-point

Change in overall health related quality of life via comparison of HUI3 multi-attribute utility scores at:

- **Post1** implant Visit compared to **Pre1** implant Visit
- **Post2** implant Visit compared to **Post1** implant Visit
- **Post2** implant Visit compared to **Pre1** implant Visit

Secondary end-points:

Change in scores on battery of evaluation tools for health related domains and overall well-being on each of the following:

MMSE, DSST & Trail B (Cognition); TUG (falls); GDS-15 (depression); iADL (independency); HHIE-S (hearing handicap); SSQ (hearing & communication ability); CAP-II (capabilities of audition); De Jong Loneliness Scale, Speech recognition tests in Quiet (daily hearing function); Speech recognition tests in Noise (daily hearing function); Consistent daily use of CI via automatic data logging (hrs/day and listening environments).

- **Post1** implant Visit compared to **Pre1** implant Visit
- **Post2** implant Visit compared to **Post1** implant Visit
- **Post2** implant Visit compared to **Pre1** implant Visit

Tertiary end point:

Changes in healthcare resource utilisation with CI treatment compared to preimplant, collected at each test interval, i.e., Pre 1, Post1 and Post 2 will be compared. Each assessment will reflect a 6 month period immediately before assessment. Data reviewed for this measure will be obtained from the customized HRU questionnaire completed by the clinician on behalf of the subject (data sources available for use will be in accordance with regional guidelines).

8.5 Investigational device and comparator

No investigational device is used in the study design. Only approved products for market release are used for routine CI treatment during the course of the observational study.

Each subject will act as their own control. As such the comparator for all subjects will be their daily preimplant listening situation.

8.6 Subjects

8.6.1 Inclusion Criteria

- Unilateral CI candidates with bilateral postlingual deafness with intention to treat
- ≥ 60 years at *first* unilateral cochlear implant
- Implant ear: meets all local criteria for CI treatment
- Contralateral ear: average pure tone thresholds indicate a moderately-severe to profound hearing loss (4 freq. average: 0.5, 1, 2 and 3 or 4 kHz >56dBHL).
- Willingness to participate in and to comply with all study procedures
- Fluency in languages used to asses clinical performance
- Appropriate expectations from routine CI treatment
- Able to decide on study participation personally and independently sign their consent

8.6.2 Exclusion Criteria

- Significantly/severely dependent or fragile
- Unable to provide consent personally
- Unable to complete questionnaires for self-assessment independently
- Unilateral hearing loss
- Sequential and simultaneous bilateral cochlear implant recipients
- Ossification or other cochlear anomalies preventing full electrode insertion
- Retro cochlear or central origins of hearing impairment.
- Significant comorbidities preventing study participation (e.g. blindness, immobility or in a wheel chair, severe aphasia,..)
- Medical contraindications to surgery
- Clinically standard fail criteria for CI candidacy in regards to chronic depression, dementia, and cognitive disorders.
- Unrealistic expectations on the part of the subject, regarding the possible benefits, risks and limitations that are inherent to the procedure and prosthetic device.

8.6.3 Criteria and procedures for subject's withdrawal or discontinuation

Subjects can decide to withdraw from the investigation without indicating any reasons at any time. The patient will then continue to be managed by the clinic as per the routine clinical practice with the intention to treat the hearing impairment accordingly.

The investigator may decide to discontinue a patient due to major non-compliance with the Observational Study Protocol requirements (e.g. three-visit schedule not met) or in the event

the patient demonstrates rapid decline in overall health and is unable to participate in the study procedures.

8.6.4 Point of enrolment

Subjects are enrolled into the clinical investigation when they have signed the Patient Informed Consent Form prior to Pre-implant assessment Visit 1 (Pre1).

8.6.5 Expected duration of the clinical investigation

From first enrollment of the first subject to final assessment at Visit 3 of the last enrolled subject the total expected duration is 4 years.

8.6.6 Expected duration of each subject's participation

The expected duration for each subject from enrolment is 20 months (+/- 1 month).

8.6.7 Number of subjects required to be included in the clinical investigation

The number of subjects to be enrolled will be **N=100** subjects across the seven investigator implant sites.

In view of possible attrition rate of 5 to 10 % of enrolled subjects, randomly lost to follow up during the course of the study any time after enrolment, all subjects enrolled will be included in the final analysis as the “intention to treat” cohort with the majority being assessed “as per protocol”.

The number of subjects recruited per site will reflect the local normal practices for treatment in the elderly population during the study enrolment time frame of 24 months. The study will aim to accrue subjects distributed across all study sites and languages to avoid site and cultural bias.

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

Thirty-one months from first to last (100th) patient enrolled at Visit 1 in 8 implant clinics.

8.7 Procedures

As an observational study, there will be no change in the treatment of the hearing impaired patient’s hearing loss compared to local routine practices. When the patient agrees to participate as a subject in the study, a set of data related to their outcomes from the routine hearing treatment will be gathered for the purposes of the study.

The dataset gathered is composed of outcomes from routine audiological and geriatric assessments that are completed by experienced professionals at the clinic, as well as self-assessments via questionnaires completed by the patient directly and with assistance as needed.

A detailed list of the evaluations performed, the data gathered and guidelines for administration of questionnaires are described in a separate document “*Procedure document”.*

8.8 Monitoring Plan

The monitoring schedule and documents viewed are detailed in a separate document *“Monitoring Plan”.*

9 Statistical Considerations

For primary, secondary and tertiary study objectives an Intra subject endpoint comparison is used: All pairwise comparisons are of interest i.e. preimplant to 12 months postimplant, preimplant to 18 months postimplant, and the change from 12 to 18 months.

The power analysis applied for the study design was based on an available data set (n= 67, Cochlear-IROS data) of repeated measures on the HUI3, collected for elderly CI-patients, at preimplant and 12 months post implant intervals. The HUI 3 will serve as the primary outcome measure for this study to measure the added health utility gain for the multi- attribute health status from preimplant (@ ≤ 2 months first activation) to the postimplant (@ 12 months post activation) interval in a population of implanted 60+ year olds.

The minimum clinically important change over two intervals for the HUI3 is 0.03 units on a scale of 0 representing poor health and 1.0 representing full health.

The power calculations were performed using the free package G*Power 3.1 by a consultant statistician at the Macquarie Sydney University.

The differences observed for the implanted elderly population in the existing Cochlear IROS dataset demonstrated a mean change = 0.165 at 95% confidence interval, with a range of 0.109 to 0.221 and a non-normal distribution for the cohort of 67 implanted elderly recipients over the age of 60 years examined.

Using this information to estimate the sample size required for significant changes on the HUI3 multi attribute score, *for intra subject comparisons of endpoints*, aiming for a change of ≥ 0.10 units between the two test intervals, and a power of 90% and using a two-side paired t-test to calculate the 5% significance level, a sample of N=68 is required for the multi-attribute health utility. For comparison of changes in self ratings individual health domains of the HUI3, aiming for a power of 80% a sample of N=100 is required.

Study statistical analysis plan is available as separate document.

10 Data Management

Data collection will be performed using eCRFs within a validated and verified electronic data capture system (EDC) with role based security and unique login credentials for each individual user. Site personnel will be trained on the completion of the eCRFs. The investigator will confirm data accuracy by providing an electronic signature.

Data will be collected, stored and analysed in a secure manner in compliance with 21 CFR Part 11 and privacy regulations.

The EDC has built-in edit checks and will generate automated data clarification forms (DCFs). The clinical project manager (CPM), monitor and data manager may review the data for medical, scientific and data integrity, and will create manual DCFs where appropriate. Responses to DCFs will be entered into the EDC, with updates to the study data where required.

Following completion of the study, investigators will be provided with the data for their site (e.g. on a CD-ROM) for national and site specific archiving requirements.

After the final clinical investigation report (CIR) has been approved the data will be stored on CD-ROM and archived with the trial master file at the sponsor's site. The data are stored for a period of 15 years.

11 Amendments to the Observational Study Protocol (CIP)

No changes in the study procedures shall be effected without mutual agreement of the investigator(s) and the Sponsor. All changes must be documented by a signed (CIP)

amendment. Substantial changes that impact the patient experience during the trial will require notification to the responsible Ethics Committee(s).

12 Deviations from the Observational Study Protocol

As an observational study, it is recommended that the investigator comply with the protocol as far as possible for all enrolled subjects. Protection of the subjects' rights, safety, privacy and well-being is always paramount throughout the study and at any time. Deviations to the study protocol shall be documented and reported to the Sponsor as soon as possible. The EC should be informed by the investigator as applicable.

13 Device accountability

Routine procedures for commercially implanted device registration and accompanying warranty are to be followed.

14 Statements of compliance

14.1 Declaration of Helsinki and compliance with standards

The observational study shall be conducted in accordance with the ethical principles that have their origin in in the most recent version of the Declaration of Helsinki (2013 or later), the EN ISO 14155:2011 and any regional or national regulations, as appropriate. The study will be registered on ClinicalTrials.gov.

14.2 Ethics Committee and Competent Authority Approval

Each clinic wishing to collaborate and publish their data must obtain Ethics Committee (EC) Approval/Opinion (or Competent Authority (CA) Approval if applicable) for their participation in the study and obtain formal approval prior to enrolling the first subject locally.

The observational study shall not commence prior to the written favourable opinion or approval from the EC and or CA (if appropriate) is obtained.

The investigator shall submit the final version of the observational study protocol, the patient informed consent (PIC) and all subsequently required documents to the Ethics Committee. A copy of the Ethics Committee opinion/approval shall be provided to the sponsor. A copy of the EC approval shall be retained in the clinic for the locally dictated time requirements.

Sponsor and investigator shall continue the communication with the EC as required by national regulations, the observational study protocol, or the responsible EC.

Any additional requirements imposed by the EC or CA 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 observational study protocol, 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 observational study. The investigator shall send written status summaries of the observational study to the EC regularly as per local EC requirements.

Upon completion of the observational study, the investigator shall provide the EC with a brief report of the outcome of the observational study as per local EC requirement.

The observational study is covered by a clinical trial insurance meeting the requirements of the participating countries. National requirements are specified in the national patient informed consent (PIC).

14.3 Audits and Supervision

Study sites and study documentation may be subject to Quality Assurance audits during the course of the observational study. 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 Investigator's File which does include without limitation at a minimum the signed Observational Study protocol, the EC approval letter, the CA approval letter (if applicable), completed Patient Informed Consent Forms, 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 defined source documents shall be archived at the investigational centre for at least 15 years after the end of the study.

15 Patient Informed Consent (PIC) process

15.1 Obtaining informed consent

The investigator must obtain written informed consent from the subject prior to any study 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 observational study and to decide whether to participate. All questions about the observational study 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 the study.

Each subject and the person who conducted the informed consent discussion must sign and date the patient 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 Investigator's File at the investigational site, according to the requirements of the country's health regulations, after completion of the observational study.

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 observational study. 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 (e.g. questionnaires) by a unique anonymized 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 study 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, 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/her identification code.

16 Incident reporting

16.1 Incident Reporting

This investigation is performed using CE marked devices thus requiring active recording of incidents of serious and non-serious degree, and immediate reporting of serious incidents as described under the current version of the Medical Device Regulation, 2017/745. Definition of Incident:

"Any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, any inadequacy in the information supplied by the manufacturer as well as any undesirable side-effect.

A 'serious incident' means any incident that directly or indirectly led, might have led or might lead to any of the following:

- the death of a patient, user or other person,
- the temporary or permanent serious deterioration of the patient's, user's or other person's state of health,
- a serious public health threat;

16.2 Reporting process

The investigator shall report all serious incidents without undue delay to the sponsor, EC and as applicable to the National Competent Authority (NCA):

Name of contact person of the sponsor: [redacted]

Fax: [redacted]
E-mail: [redacted]

The Sponsor shall assess all reported incidents with the investigator, co-ordinate appropriate actions, if required, and provide the NCA with a final report.

Appropriate treatment of the subject shall be initiated. Study follow up shall continue when appropriate and ethical.

The investigator shall report all incidents to his/her EC using the applicable report form as per national requirement.

17 Vulnerable population

As some individuals in the elderly population may have special needs to help them understand what is involved in the process of study participation, before they can even consider to provide consent to their participation, special considerations are needed to ensure communication of the study processes, additional risks and benefits to them over routine care is understood. Communications should be tailored to help them understand through verbal and written communication with opportunities to ask questions each step of the way. The patient should understand that their participation is entirely optional and voluntary and that in no way affects the routine care they would normally receive if they do not participate.

As a well-established therapy for hearing impairment, cochlear implant treatment is approved as a safe and effective therapy in the long term for patients of all ages. Participation in the observational study presents no additional risks to the patient over routine clinical treatment as only market approved devices and indications are considered.

As elderly patients may be more susceptible to changes in health status, should the individual's general health decline during the course of the study, preventing their comfortable participation in the study processes, the clinician should react in a timely manner to remove the subject from the study formally by completion of the end of study form.

18 Suspension or premature termination

The Sponsor will withdraw from sponsorship of the observational study if,

1.) major non-adherence to the study protocol is occurring
2.) it is anticipated that the subject recruitment will not be adequate to meet the objectives of the observational study

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

An ongoing observational study can be discontinued in case of:

1) Device failure
2) Subject's death
3) Investigator's decision
4) Subject's decision

19 Publication Policy

It is planned to generate at least two joint publications by the clinical investigator(s), with support from the sponsor using collective data. Depending from the interim analysis outcomes a potential preliminary publication for completion of 1 year evaluation by a subgroup of the study cohort will be written and submitted.

The responsibility for writing the publications will be agreed with the co-investigator group. Authorship will be based on contribution of complete datasets and contribution to paper preparation according to the rules of the journal(s) chosen for publication. Publications are requested to be reviewed by the sponsor at least 30 days in advance to submission for publication. This study does not include data collection related to patency issues.

Investigators are able to publish their local data separately, ensuring statistical validity of data analysis and any conclusions made. The sponsor kindly requests a copy of manuscripts intended for submission for publication least 60 days in advance of submission.

20 Revision History

Version Number	Date	Reason for Change
CIP 2.0	15 December 2017	Additional information about HRUC. Updates about incidences definitions. Updated starting date.
CIP 3.0	15 April 2019	Change in investigators. Updated enrolment period.
CIP 4.0	10 December 2019	Change in principal investigator at site Padova.

20.1 Changes from version 2.0 to version 3.0

Cover page: [redacted] is added as author.

Introductory table: Investigators are updated to reflect the change of PI at Bnai Zion Medical Center and inclusion of the new site Rabin Medical Center (Beilinson). The sentence on sponsor activities is removed.

Section 1: Principal Investigators and sites are updated accordingly. Enrolment period is extended from 24 to 31 months.

Section 8.1: "if not agreed differently" is added as a condition to the anticipated subject recruitment number.

Section 8.6.8: Enrolment period and number of clinics are updated accordingly.

Section 11: The reference to a template is removed as no longer used to document CIP changes.

Section 22 Appendix I: List of investigators is updated accordingly.

20.2 Changes from version 1.0 to version 2.0

Cover page: A note is added for "Observational" as this terminology tends to disappear from national classification. In France and in Spain, the study is classified as "low risk intervention" in regards to the additional assessments performed.

Introductory table: The details of the Clinical Research Organisation (CRO) is updated

CIP Signature page: Sponsor signature, the name and function are updated

Section 1: Starting date is updated in the Clinical Investigation Synopsis to the real starting date: 06 November 2017

Section 5.2.10: HRCU paragraph has been updated to answer Ethical committee request to provide additional details. The time to complete the assessment has been updated.

Section 9: For clarity additional text was added in regards to Intra endpoint comparison. As well, it was added that statistical analysis plan is available as separate document.

Section 16: Definition of incidents has been updated to reflect changes in the MDR regulation

Section 19: A potential preliminary publication for completion of 1 year evaluation by a subgroup of the study cohort has been added.

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22 Appendix I: List of Investigators

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