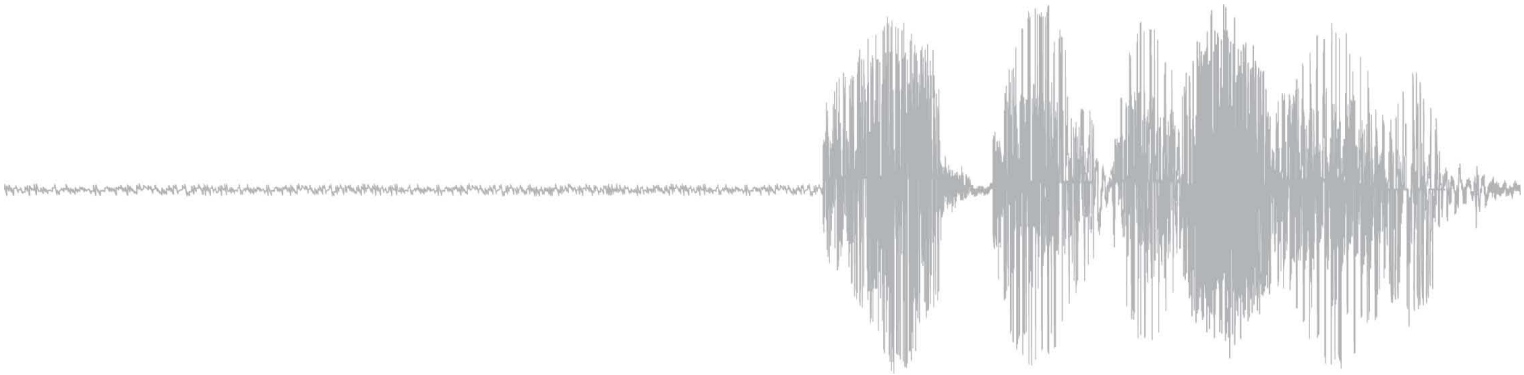

Immediate vs delayed CI on hearing handicap CLTD5693

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State: Approved (T+B)
Approver: [redacted]
Date : 23 Aug 2019

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Number of pages (include Coversheet): 34

Clinical Investigation Plan

Randomized controlled trial of immediate versus delayed cochlear implantation

Hearing Loss in Older Adults Study

Investigation Number: CLTD5693

Version Number: Version 11.0

Date: August 16, 2019

Sponsor	Cochlear Limited 1 University Avenue Macquarie University NSW 2109 Phone [redacted] Local Sponsor Representatives; Cochlear Americas 13059 East Peakview Avenue Centennial, CO 80111 USA Phone [redacted]

A complete list of participating Principal Investigators names, titles, and addresses, and the names and addresses of participating institutions (sites) will be maintained by the Sponsor and will be distributed as a separate Principal Investigator List.

1 SPONSOR AND COORDINATING INVESTIGATOR SIGNED AGREEMENT

Investigation Title	Randomized controlled trial of immediate versus delayed cochlear implantation.
Short Study Title	Hearing Loss in Older Adults Study.
Investigation Number	CLTD5693

Signature on behalf of Sponsor

I agree with the content in this clinical investigation plan, including all appendices.

Name	**Title**
Signature	**Date** (dd-mmm-yyyy)

Signature of Principal Investigator

I agree to the content of this clinical investigation plan, including all appendices.

Name	**Title**
Site	
Signature	**Date** (dd-mmm-yyyy)

2 TABLE OF CONTENTS

3 SYNOPSIS

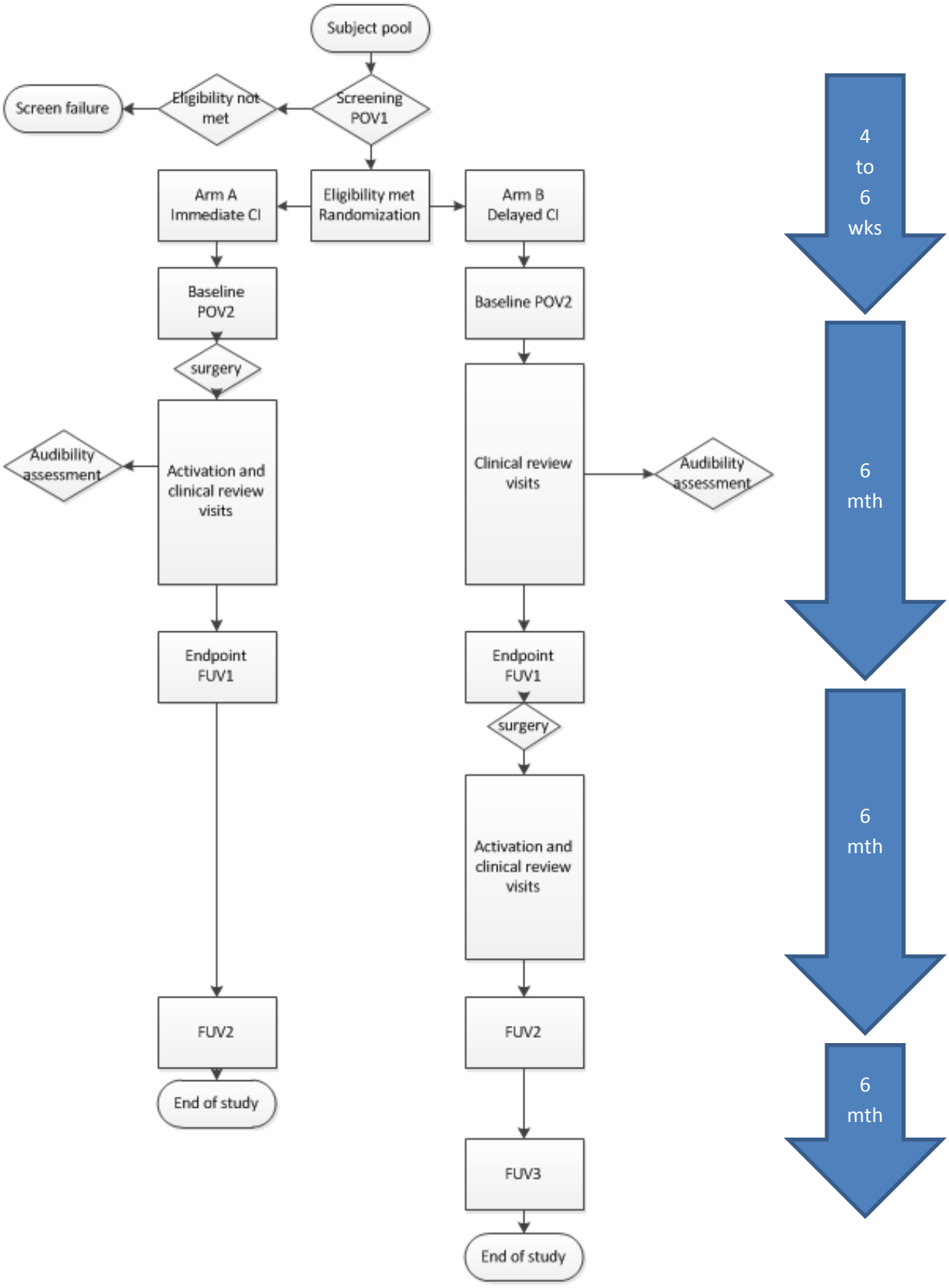
Investigation title	Randomized controlled trial of immediate versus delayed cochlear implantation.
Short Study Title	Hearing Loss in Older Adults Study[1]
Investigation number	CLTD5693
Total expected duration of the clinical investigation	30 months
Expected duration per subject	15-21 months
Investigational design	Prospective, 1:1 randomized controlled trial of immediate versus delayed cochlear implantation (CI) on hearing handicap, communicative function, loneliness, mental wellbeing, and cognitive functioning. Subjects are randomized 1:1 to an immediate cochlear implant intervention arm versus a hearing aid control intervention.
Number of subjects	Up to 60 subjects in a 1:1 allocation
Inclusion criteria	1. Aged 65 to 85 years, inclusive 2. Community-dwelling 3. Proficient in English 4. Oral communicator 5. PTA (500, 1000 & 2000 Hz) ≥ 70 dB HL hearing loss duration ≥1 and no more than 30 years. 6. Active hearing aid users: daily use of hearing aids. 7. Hearing Handicap Inventory for the Elderly - Screening (HHIE-S): Score ≥ 24 indicating a significant hearing handicap. 8. Hearing Impaired Montreal Cognitive Assessment (HI-MoCA): Score ≥ 20 indicating mild cognitive impairment to normal cognitive function. 9. Cochlear implant candidacy: Participants must have postlinguistic onset sensorineural hearing loss and meet applicable FDA and/or Medicare candidacy criteria for cochlear implantation. 10. Willingness to consent for the study, to be randomized to either the immediate or delayed cochlear implantation arm, to utilize bimodal hearing for the duration of the trial (if clinically appropriate) and follow the study protocol for the duration of the trial.
Exclusion criteria	1. Prelingual or perilingual severe-to-profound hearing loss. 2. Previous cochlear implantation in either ear. 3. Hearing loss of neural or central origin. 4. Permanent conductive hearing impairment (e.g. otosclerosis). 5. Medical, audiological or psychological conditions, as judged by the investigator that might contraindicate participation in the clinical investigation. 6. Self-reported disability in ≥ 2 activities of daily living. 7. Unwilling to wear a device or comply with the surgical and rehabilitation requirements of the study. 8. Vision impairment: worse than 20/40 (corrected) on a Near Vision Card.

[1] As registered on ClinicalTrials.gov

Primary objective	To determine the effect of treating hearing loss with cochlear implantation (CI) versus continued use of hearing aids (HA) on hearing satisfaction using the Speech, Spatial and Qualities of Hearing (SSQ12) in older adults.
Primary endpoint	Assessment of the impact of cochlear implantation versus continued hearing aid use on hearing satisfaction as measured using the Speech, Spatial and Qualities of Hearing (SSQ12) at Follow-up Visit 1 (FUV1).
Secondary objective	To assess cognition in older adults with hearing loss with a Cogstate® battery of neuropsychological tests.
Secondary endpoint	Assessment of the impact of cochlear implantation versus continued hearing aid use on cognition with a Cogstate® battery of neuropsychological tests at Follow-up Visit 1 (FUV1).

Ancillary analyses	Ancillary analyses include:
	• Investigating treatment effect on neuropsychological measures using the Hearing Impaired Montreal Cognitive Assessment (HI-MoCA) at Follow-Up Visit 1 (FUV1).
	• Investigate the treatment effect of immediate cochlear implantation vs continued use of HAs on psychosocial measures such as loneliness and depression using the UCLA Loneliness Scale and the Geriatric Depression Scale (GDS) at Follow-up Visit 1 (FUV1).
	• Investigate the treatment effect of immediate cochlear implantation vs continued use of HAs on physical functioning measures such as daily activity and lifestyle using the Lifestyle Activity Questionnaire (LAQ) at Follow-up Visit 1 (FUV1).
	• To determine the effect of treating hearing loss with CI versus continued use of HAs on quality of life in each arm (immediate CI vs continued HA use) using the Health Utilities Index Mark III (HUI-III) at Follow-up Visit 1 (FUV1).
	• To quantify pre- to post-implantation outcomes associated with cochlear implantation.
	  ○ Self-reported hearing ability using the Hearing Handicap Inventory for the Elderly – Screening (HHIE-S).
	  ○ Outcomes for both the treated ear and everyday listening condition (bimodal): speech perception in quiet using CNC Words presented 60 dBA and speech perception in speech-weighted noise using AzBio sentences presented at 65 dBA using a +10 dB Signal to Noise Ratio (SNR).
	• Investigate maintenance of treatment effect on neuropsychological, psychosocial, physical, quality of life and audiometric measures obtained at:
	  ○ FUV2 compared to FUV1 (Arm A).
	  ○ FUV3 compared to FUV2 (Arm B).

4 INVESTIGATION DESIGN



5 INVESTIGATION PROCEDURES

Procedure *Timeline*	**Screening POV1 Arm A&B**	**Baseline POV2 Arm A&B** *4-6 weeks from POV1 (+/- 2 weeks)*	**Surgery Arm A** *1 week from POV2 (+/- 1 week)*	**Clinical Review Visits Arm A&B** *1-5 months from POV2 (+/- 2 weeks)*	**FUV1 Arm A&B** *6 months from POV2 (+/- 2 weeks)*	**Surgery Arm B** *1 week from FUV1 (+/- 1 week)*	**FUV2 Arm A&B** *12 months from POV2 (+/- 4 weeks)*	**FUV3 Arm B** *18 months from POV2 (+/- 4 weeks)*
Consent	X							
Demographics	X							
Concomitant Medications		X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Medical History		X						
Hearing History	X							
Randomization	X							
HI-MoCA	X				X			
Near Vision Screening	X							
Activities of daily living	X				X		X	X
HHIE-S	X				X		X	X
Cogstate computerized test battery	X	X			X		X	X
Imaging			X-ray (Arm A)	CT scan[2] (Arm A)		X-ray (Arm B)	CT scan[3] (Arm B)	

[2] CT scan will occur post-surgery and prior to FUV1 (Arm A)
[3] CT scan will occur post-surgery and prior to FUV2 (Arm B)

Procedure *Timeline*	**Screening POV1 Arm A&B**	**Baseline POV2 Arm A&B** *4-6 weeks from POV1 (+/- 2 weeks)*	**Surgery Arm A** *1 week from POV2 (+/- 1 week)*	**Clinical Review Visits Arm A&B** *1-5 months from POV2 (+/- 2 weeks)*	**FUV1 Arm A&B** *6 months from POV2 (+/- 2 weeks)*	**Surgery Arm B** *1 week from FUV1 (+/- 1 week)*	**FUV2 Arm A&B** *12 months from POV2 (+/- 4 weeks)*	**FUV3 Arm B** *18 months from POV2 (+/- 4 weeks)*
SSQ12		X			X		X	X
UCLA Loneliness Scale		X			X		X	X
GDS-short form		X			X		X	X
LAQ		X			X		X	X
HUI-III		X			X		X	X
Rehabilitation				X (4-6 visits)				
Unaided air conduction testing	X				X		X	X
Aided soundfield testing		X		X (3 mths)				
Tympanometry	X				X		X	X
Aided AzBio Sentences in Noise Ear to be implanted/implant ear Everyday Listening		 X X			 X X		 X X	 X X
Aided CNC Words in Quiet Ear to be implanted/implant ear Everyday Listening		 X X		 X (3 mths)	 X X		 X X	 X X
Datalogs		X		X	X		X	X

6 BACKGROUND AND RATIONALE

Prospective studies have demonstrated reduced hearing handicap following cochlear implantation in adults (1, 2). However this has not been assessed in a randomized clinical trial. Epidemiologic data strongly suggest that age-related peripheral hearing loss is independently associated with accelerated rates of cognitive decline and incident dementia (2, 3). A conceptual model (Figure 1) developed by Lin and Albert (3) depicts the causal mechanisms that may mediate the effects of hearing impairment on impaired cognitive functioning and dementia. Common factors that could underlie a simple correlation between hearing and cognition include age, shared pathologic etiologies (e.g., diabetes, hypertension, neurodegenerative processes), and demographic factors (e.g., education). In contrast, mechanistic pathways through which hearing loss could contribute to poorer cognitive functioning include effects on cognitive load, brain structure/function, and decreased social engagement. The effects of poor audition and distorted peripheral encoding of sound on cognitive load could reduce capacity for other functions, such as cognition. Changes in brain structure could lead to downstream changes in brain function which may affect cognitive processing (4-10). Alternatively reduced social engagement could be a mediating factor.

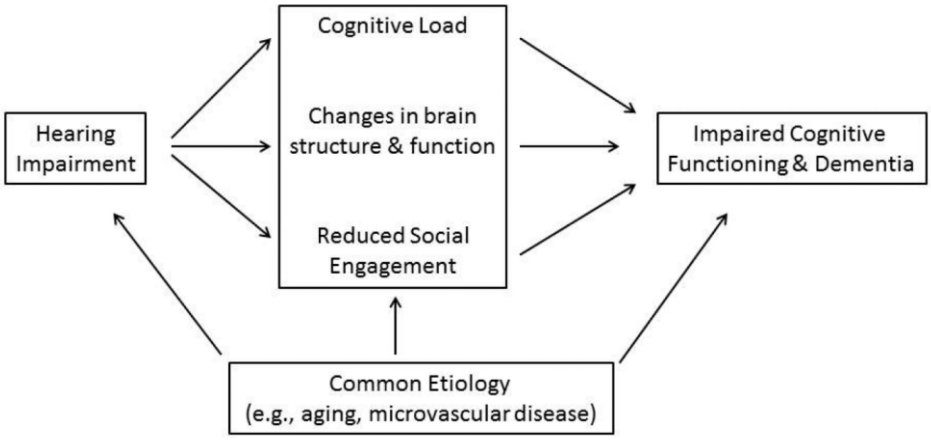


Figure 1. Conceptual model of the association of hearing impairment with cognitive functioning and dementia.

6.1 Hearing interventions to reduce cognitive decline

Whether existing interventions for hearing loss can mitigate declines in cognitive function is unknown. Previous studies provide proof-of-principle that interventions that provide enhanced auditory stimuli can engage and modify the hypothesized mechanistic pathways linking hearing and cognition through reducing cognitive load (11-14), altering functional pathways and brain structure (4-10), and improving social engagement. A planned trial, the Aging, Cognition, and Hearing Evaluation Trial (ACHIEVE), will investigate the impact of best practice hearing health care, including the provision of hearing aids, on cognitive functioning in older adults with *mild-to-moderate* hearing loss.

The trial described in this protocol will be the first randomized controlled trial to investigate the impact of cochlear implantation versus continued use of hearing aids on cognitive function in individuals with severe-to-profound hearing loss. To date, only one published study has examined the effects of cochlear implantation on cognition in older adults (15). This longitudinal, multi-center study examined 94 adults aged 65-85 years who met candidacy requirements for a cochlear implant. Neuropsychological tests, speech perception tests and quality of life and depression questionnaires were administered before cochlear implantation (baseline) and at 6 and 12 months post cochlear implant activation.

To avoid potential confounding effects of audibility and diminished speech perception understanding, all instructions for the neuropsychological tests were provided in written form in the Mosnier et al. study. The number of individuals with scores classified as abnormal decreased after implantation: At baseline, 25% of subjects had normal scores on six cognitive tasks, 31% had one abnormal score, 24% had two abnormal scores, and 20% had three abnormal scores. At 12 months, 40% had normal scores on six cognitive tasks, 33% had one abnormal score, 22% had two abnormal scores and only 5% had three abnormal scores. While informative, the Mosnier et al. study did not have a control arm, so it is possible that some of the improvement could be attributed to learning effects. The CI-Cognition trial described in this protocol incorporates a watchful waiting control arm and overcomes this limitation.

An additional study, the Studying Multiple Outcomes after Aural Rehabilitative Treatment (SMART) study prospectively assessed cognitive functioning in 145 adults aged 50 years or older before receiving hearing aids or cochlear implants and at 6 and 12 months after treatment (16). Data from Li et al showed improved cognitive performance at 6 and 12 months, albeit with a smaller effect size than that found in the study previously reviewed by Mosnier et al (15). Li et al. also reported that CI subjects had significantly greater loneliness, social isolation and poorer hearing and communicative function compared to HA subjects.

7 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

We propose a randomized controlled trial design whereby up to sixty (60) participants with severe-to-profound hearing loss are randomized 1:1 to an immediate cochlear implant (CI) intervention (Arm A) versus a hearing aid (HA) control intervention (Arm B). The immediate CI treatment arm will be implanted with either the Cochlear Nucleus® Profile™ Slim Modiolar (532) cochlear implant or the Cochlear Nucleus® Profile™ Plus CI632 cochlear implant with Slim Modiolar electrode. The HA control intervention provides a comparison arm representing standard clinical care for conventional amplification (HAs). Randomization seeks balance between the two arms. The control arm will also receive the CI intervention (Nucleus CI532 or CI632 implant) after a watchful waiting delay period of 6 months post baseline. Both arms will receive the neuropsychological battery twice before the intervention (once at screening and again at baseline) to minimize the impact of learning effects on analyses of post-intervention cognitive change.

7.1 Anticipated Clinical Benefits

The information obtained from participation in the study will potentially be useful to the participating subjects, the Sponsor as well as future candidates and health care providers in better understanding the potential benefits of cochlear implantation on hearing handicap, communicative function, loneliness, mental wellbeing, and cognitive functioning.

7.2 Anticipated Adverse Device Effects

Known anticipated adverse device effects are currently detailed in the Cochlear Nucleus® Profile™ Slim Modiolar (532) cochlear implant or the Cochlear Nucleus® Profile™ Plus CI632 cochlear implant with Slim Modiolar electrode Physician's Guide (17). There are no additional anticipated adverse device effects related to participation in this clinical study. The surgeon will conduct the surgical procedure as per standard clinical practice and individuals will be exposed only to the normal risks associated with routine cochlear implantation.

7.3 Residual risks related to the use of the investigational device

The study does not involve use of an investigational device.

7.4 Risks associated with participation in the clinical investigation

Participation in this study does not include any additional risks to those known for individuals undergoing neurocognitive evaluations, cochlear implantation or hearing aid use clinically. The risks associated with each procedure will be outlined in the Informed Consent (IC) document. All risks should be thoroughly reviewed with the potential subject prior to participation in the study.

7.5 Possible interactions with concomitant medical treatments

There is potential that concomitant medical treatments may influence the outcomes of this study. All concomitant medical treatments will be collected as part of this study.

7.6 Risk mitigations

The investigators or qualified delegates will be required to review the terms of the Informed Consent with each potential subject. Information such as the subject's ongoing audiologic and medical history will be captured for the duration of the trial.

7.7 Risk to benefit rationale

Since the participants recruited for this study are already considering cochlear implantation as a hearing health option, the risk benefit rationale is such that participation in this study may provide subjects with additional useful health information pertaining to their cognitive status that they would not otherwise have.

8 OBJECTIVES AND HYPOTHESES

8.1 Primary Objective

To determine the effect of treating hearing loss with cochlear implantation (CI) versus continued use of hearing aids (HA) on hearing satisfaction using the Speech, Spatial and Qualities of Hearing (SSQ12) in older adults.

8.2 Secondary Objectives

To assess cognition in older adults with hearing loss with a Cogstate® battery of neuropsychological tests.

8.3 Primary Hypotheses

Cochlear implantation is associated with greater reduction on hearing satisfaction as measured using the Speech, Spatial and Qualities of Hearing (SSQ12) compared to continued hearing aid use at Follow-up Visit 1 (FUV1).

9 DESIGN OF THE CLINICAL INVESTIGATION

9.1 General

9.1.1 Primary Endpoint

Assessment of the impact of cochlear implantation versus continued hearing aid use on hearing satisfaction as measured using the Speech, Spatial and Qualities of Hearing (SSQ12) at Follow-up Visit 1 (FUV1).

9.1.2 Secondary Endpoints

Assessment of the impact of cochlear implantation versus continued hearing aid use on cognition with a Cogstate® battery of neuropsychological tests on at Follow-up Visit 1 (FUV1).

9.2 Assessments

9.2.1 Neuropsychological Test Battery

9.2.1.1 Hearing Impaired Montreal Cognitive Assessment (HI-MoCA)

The Montreal Cognitive Assessment (MoCA) is an interviewer administered screening tool used to detect mild cognitive impairment (18). It has been demonstrated to have high sensitivity and specificity for detecting mild cognitive impairment (18-20). The MoCA has been used in clinical evaluations to assess cognitive function and treatment effect in older patients undergoing cochlear implantation (21, 22). The MoCA has been converted into a timed PowerPoint (Microsoft Corp., Redmond, WA) presentation, and verbal instructions converted into visual instructions to assist in the assessment of severely hearing impaired adults - the Hearing Impaired Montreal Cognitive Assessment (HI-MoCA) (23). The HI-MoCA has been validated as a screening for cognitive impairment in the severely hearing impaired older populations. No conversion factor from HI-MoCA to MoCA scores were required in the cohort of cognitively intact subjects. The HI-MoCA will be used in the clinical investigation to assess cognitive function of older adults undergoing cochlear implantation.

9.2.1.2 Cogstate computerised test battery

The Cogstate® computerised test battery is a self-administered, iPad-based neuropsychological measure of processing speed, attention, visual learning, working memory and executive function. The Cogstate computerised test battery for the current clinical investigation consists of the Cogstate Brief Battery™ and the Groton Maze Learning Test.

The Cogstate Brief Battery (CBB) provides a measure of four core cognitive domains: processing speed, attention, visual learning and working memory. The CBB consists of the Detection Test, Identification Test, One Card Learning Test and One Back Test. The Detection test measures processing speed using a simple reaction time paradigm. The Identification test measures attention using a choice reaction time paradigm. The One Card Learning test measures visual memory using a pattern separation paradigm. The One Back test measures working memory using an n-back paradigm. For all tests in the CBB, a playing card is presented on the screen and the participant is encouraged to work as quickly as they can and be as accurate as possible.

The Cogstate Groton Maze Learning Test measures executive function using a maze learning paradigm. A 28-step pathway is hidden among these tiles. The participant must move one step at a time from the start toward the end by touching a tile next to their current location. If the correct move is made a green checkmark appears and if the move is incorrect a red cross is revealed. Once completed, they are returned to the start location to repeat the test and must try to remember the

pathway they have just completed. The outcome measure is the total number of errors made in attempting to learn the same hidden pathway on five consecutive trials during a single session.

9.2.2 Verification of Hearing Aid Fitting

Real ear insertion gain measurements (REIG) will be used to verify hearing aid fitting. The frequency response of the hearing aid should not deviate from the National Acoustic Laboratories' non-linear procedure (NAL-NL2) target by greater than +/- 5 dB for a modulated speech stimulus (International Speech Test Signal (ISTS)), except in circumstances where adjustments have been made for patient comfort/preference or feedback management.

9.2.3 Audiologic Measures

9.2.3.1 Audiometric Thresholds and Tympanometry

9.2.3.1.1 Unaided audiometric thresholds

Unaided audiometric thresholds will be obtained for each ear, with insert earphones, using the standard audiometric technique for pure-tone air-conduction testing. All preimplantation testing will be completed using an audiometer calibrated to American National Standards Institute (ANSI) standards with maximum output for frequencies of 0.5 to 4 kHz of no less than 110 dB HL. Pure tone threshold exploration will be completed using the adaptive Hughson & Westlake procedure (24).

Testing in each ear will include the following:

Air conduction thresholds: 250, 500, 1000, 2000, 4000, 6000, 8000 Hz with appropriate masking as required;

Tympanometry in each ear.

An audiogram completed up to 90 days prior to POV1 will be considered for determination of eligibility and data collection as part of POV1.

9.2.3.1.2 Aided audiometric thresholds

Aided audiometric thresholds will be obtained for the everyday listening condition (aided bilaterally or bimodally post-CI) during a clinical review visit three months post POV2 *(+/- 2 weeks)*, in a calibrated sound field, using the standard audiometric technique for sound field testing. All post-implantation testing will be completed using warble tones in a sound field calibrated to American National Standards Institute (ANSI) standards with maximum output for frequencies of 0.5 to 4 kHz of no less than 80 dB SPL.

Testing in the everyday listening condition (both ears) will include the following:

Aided sound field thresholds: 500, 1000, 2000, 4000 Hz

9.2.3.2 Speech perception in quiet

The CNC Word Test (25) is a validated test used clinically and in research to assess the performance of adults with hearing aids or cochlear implants on open-set word recognition. The test consists of 10 recorded lists of 50 monosyllabic words in CD format. For this study, two lists will be administered in quiet at a level equal to 60 dBA in the sound field and scored as total number of words and phonemes correct, which will be expressed as a percentage correct for this study. Subjects will be tested using a configuration of speech at 0º azimuth in quiet (S0).

9.2.3.3 Speech perception in noise

The AzBio Sentence Test (26) is a validated test used clinically and in research to assess the open-set sentence recognition in speech-weighted noise of adults with hearing aids or cochlear implants. It

consists of 15 lists of 20 sentences each. AzBio sentences are spoken by different talkers in a conversational style with limited contextual cues that the listener can use to predict or 'fill in' unintelligible words. The sentences will be presented at a fixed level of 65 dBA at a fixed +10 dB signal-to-noise ratio (SNR). Each list includes 5 sentences from 4 different male and female speakers. The average level of intelligibility of each list is 85% +/- 1%. Each word in the sentence counts towards the overall score. Subjects will be tested using a configuration of speech and noise at 0º azimuth (S0N0).

9.2.3.4 Hearing Handicap Inventory for the Elderly

The Hearing Handicap Inventory for the Elderly - screening (27) is an interviewer-administered questionnaire that measures the perception of the impact of hearing loss. This questionnaire assesses the social and emotional components of perceived hearing impairment such as embarrassment, and limits on personal and social life.

9.2.3.5 Speech, Spatial, and Qualities of Hearing Scale (SSQ12)

The SSQ is a validated 12-question self-assessment metric commonly used in hearing research, designed to measure auditory disability across a wide variety of everyday world domains. The SSQ-12 (28) has twelve questions and is derived from the original 49 item SSQ (29). In addition to a reduced administration time, the SSQ-12 has been shown to have similar results to the original 49 item scale (28).

9.2.4 Psychosocial Measures

9.2.4.1 UCLA Loneliness Scale

The UCLA Loneliness Scale version 3 (30) is an interviewer-administered questionnaire. The 20-item scale designed to measure one's subjective feelings of loneliness as well as feelings of social isolation. Subjects rate each item on a scale from 1 (Never) to 4 (Often). This measure is a revised version of both the original UCLA Loneliness Scale and the Revised UCLA Loneliness Scale. The first revision was done to make 10 of the 20 original items reverse scored. The second revision was done to simplify the scale so less educated populations could comprehend it.

9.2.4.2 Geriatric Depression Scale (GDS)

The GDS Short Form is an interviewer-administered 15-item questionnaire in which subjects are asked to respond by answering yes or no in reference to how they felt over the past week. Questions from the Long Form GDS which had the highest correlation with depressive symptoms in validation studies were selected for the short version (31). Of the 15 items, 10 indicated the presence of depression when answered positively, while the rest (question numbers 1, 5, 7, 11, 13) indicated depression when answered negatively. Scores of 0-4 are considered normal, depending on age, education, and complaints; 5-8 indicate mild depression; 9-11 indicate moderate depression; and 12-15 indicate severe depression. The GDS Short form has been tested and used with the older population receiving cochlear implants (15, 32-34).

9.2.5 Physical Functioning Measures

9.2.5.1 Lifestyle Activity Questionnaire

The Lifestyle Activity Questionnaire (LAQ) (35) is a self-administered questionnaire which assesses the frequency of self-reported activities over the past year. The questionnaire includes intellectual (e.g. discussing local or national issues, reading), social (e.g. caretaking, clubs), physical (e.g. shopping, gardening), creative (e.g. drawing or painting), and passive (e.g. listening to music, watching TV) activities. The LAQ has been shown to be sensitive to assessing relationships between

cognitively and socially stimulating activities and cognitive aging in both observational studies (35) and in trials (36, 37).

9.2.5.2 Near Vision Screening

The Near Vision Screening chart is an eye chart to measure visual acuity in the near field (within 16”). The first line consists of two very large letters and a number. Subsequent rows have increasing numbers of letters and numbers that decrease in size. A person (with corrected vision) taking the test with holds the card at a distance of 16” under standard room illumination, and reads aloud the letters and numbers of each row, beginning at the top. The smallest row that can be read accurately indicates the visual acuity.

9.2.6 Quality of Life Measure

9.2.6.1 Health-Utilities Index 3

The Health Utilities Index Mark 3 (HUI3) (38, 39) is a widely used self-administered generic instrument measuring health-related quality of life. This instrument covers eight domains (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain), each having five or six levels of difficulty. There are 970,000 possible combinations of levels, of which a subset has been evaluated by members of the Canadian general public (39). The HUI3 focuses on physical and emotional wellbeing and includes questions specific to hearing and the ability to be understood whilst speaking. As a result it is sensitive to improvements in quality of life due to better hearing (40-42). This questionnaire follows the principles of economic evaluation in that a utility score is derived where 1 indicates perfect health and zero corresponds to being dead, therefore it can be used in cost-effectiveness analyses.

9.2.7 Medical and Hearing History

9.2.7.1 Medical History via the Adult Comorbity Evaluation-27 (ACE-27)

Medical history will be collected at Pre-operative Visit 2. The ACE-27 is an index which includes 27 conditions or comorbid ailments across various bodily organ systems. Each of the comorbid ailments are graded on severity (none, mild, moderate, or severe) with the end result of an overall index score. Early research in patients with hearing loss indicated untreated hearing loss resulted in a higher incidence of morbidity compared to individuals with no hearing loss. This index allows for consistent collection of medical history data across subjects and clinical sites. It will be used as a minimum medical history reporting standard for this clinical investigation. Additional medical history may be added at the Investigator’s discretion for relevant study conduct.

9.2.7.2 Hearing History

Hearing history will be collected at Pre-operative Visit 1 as outlined on the CRF. Information collected will include duration, type and etiology of hearing loss in addition to hearing aid details (e.g., consistent vs intermittent hearing aid use).

9.3 Methods

9.3.1 Screening and Informed Consent

Subjects who have been deemed appropriate candidates for cochlear implantation according to standard clinical practice will be considered potential research subjects for this study. Informed consent must occur prior to study related activities with the exception of an audiogram performed within 90 days of POV1. Individuals will be appropriately counseled on the risks and benefits of study participation prior to participating in any study related activity. If needed, the potential participant may take the informed consent form home with them for review prior to completion. If the participant

agrees to participate, a copy of the executed informed consent will be provided to the participant. To maintain confidentiality, subject names will not be recorded on any study document other than the informed consent form. All individuals who provide informed consent are considered enrolled into the study and will be assigned a unique identifier. A unique alphanumeric code will identify each subject throughout the course of the study. For example, US01-HOA-xxxx where:

- US = United States
- 01 = a sequential numeral corresponding to the order in which a subject is enrolled into the study for a given study site. In this case this would correspond to the first subject recruited into the study for a particular site
- HOA = an abbreviation for the study, Hearing Loss in Older Adults
- xxxx = a unique numeric study site identification

9.3.2 Randomization

The design of the clinical investigation is a prospective, 1:1 randomized clinical trial. The intervention arm to which a participant is assigned is determined by an allocation schedule developed by [redacted]

To ensure balance between the treatment arms, participants will be randomized as described in the Statistical Analysis Plan (D1309522). Block size will not be revealed to field center staff as this would allow them to determine the final treatment assignment of a block before ascertaining eligibility and obtaining consent. The randomization will be maintained by the sponsor within a data management system. Randomization will be performed at POV1.

9.3.3 Hearing Aids and Glasses

For the purposes of this study, subjects have the option to use their own hearing aids if they are appropriately fit. If a subject does not have appropriately fit hearing aids they will be provided prior to any study related assessments. Impressions will be taken and earmolds provided if needed. The decision to replace hearing aids will be based on the clinical judgement of the investigator with verification of such recorded on a study Case Report Form.

Subjects are required to have a minimum corrected near vision acuity of 20/40 as measured on a Near Vision Screening test. If a subject does not meet this criteria and does not have appropriately fit glasses, they will be withdrawn from the study.

9.3.4 Preoperative Visit 1 (POV1) - Screening

Participants are consented into the study. Eligibility for the study will be confirmed. During this preoperative screening visit, each participant will be randomized in a 1:1 ratio to either the immediate CI (Arm A) or hearing aid (delayed CI Arm B). During POV1, both Arm A and Arm B subjects will complete the neuropsychological assessments as described in Section 9.2.1 with appropriately fitted hearing aids and glasses (if required).

9.3.5 Preoperative Visit 2 (POV2) - Baseline

Preoperative visit 2 (POV2) baseline will occur 4-6 weeks post POV1 (*+/- 2 weeks*) to enable scheduling of surgery for Arm A subjects. Both Arm A and Arm B subjects will complete POV2 with appropriately fit hearing aids and glasses (if required). The full neuropsychological battery in addition to the audiologic, psychosocial, physical, and quality of life metrics will be completed as described in Section 9.2. Speech recognition will be assessed in the everyday listening condition (aided bilaterally) and the ear to be implanted listening conditions with the contralateral ear plugged. Datalogs will be retrieved for the hearing aid.

Medical history will be completed minimally via the ACE 27 index. The Investigator or appropriately delegated staff may add additional otologic history (hearing history) which they deem relevant to the study.

9.3.6 Surgery – Arm A

Arm A subjects will be implanted with the Cochlear Nucleus® Profile™ Slim Modiolar (532) cochlear implant or the Cochlear Nucleus CI632 cochlear implant 1 week (*+/- 1 week*) post POV2.

An intraoperative X-ray will be obtained (preferably a lateral or modified Stenver's view) following the placement of the electrode and prior to closing.

9.3.7 Imaging

Following surgery, subjects will undergo a Computed Tomography (CT) scan according to the specifications provided by the study sponsor. Retrospective analysis of the CT scan will be done via reconstruction to determine electrode position and distance to the modiolus by an independent centralized imaging review center and a de-identified report will be sent to the sponsor in line with HIPAA Standards.

9.3.8 Clinical Review Visits (CRV)

9.3.8.1 CI review – Arm A

CI activation will occur in the standard clinical manner at each field site at approximately two weeks post-surgery (*+/- 3 weeks*). Four to six clinical review visits will be scheduled at each field site between activation and FUV1, six (6) months from POV2. These visits can contain device adjustments as well as counselling on hearing and listening strategies, and discussion of hearing assistive technology.

We propose the following topics are discussed during the six months of cochlear implant use:

- Hearing assistive technology
- Communication strategies
- Listening in noise
- Understanding hearing loss

Needs for various hearing assistive technologies (HATs) will be assessed and, if the audiologist deems that it is appropriate, recommendations will be made.

Following each CI mapping appointment an anonymized .cdx file labelled with the Subject ID will be provided to the study sponsor in order to evaluate program settings and usage data.

9.3.8.1.1 Audibility Review – three months post POV2.

As part of a clinical review visit, at three (3) months (*+/- 4 weeks*) post POV2, audibility will be assessed:

- Implanted ear only: Aided speech recognition with CNC words at 60 dBA (2 lists)
- Everyday listening condition (bimodal): Sound field thresholds at 500, 1000, 2000, 4000 Hz

9.3.8.2 Hearing aid review – Arm B

Over the course of the hearing aid intervention, the subjects will be followed for hearing aid checks including verification of fitting, be counselled on hearing and listening strategies, and discuss hearing

assistive technology. Four to six clinical review visits will be scheduled at each field site between FUV1 and six (6) months from POV2.

We propose the following topics are discussed during the six months of the hearing aid intervention:

- Hearing assistive technology
- Communication strategies
- Listening in noise
- Understanding hearing loss

Needs for various hearing assistive technologies (HATs) will be assessed and, if the audiologist deems that it is appropriate, recommendations will be made.

Following each hearing aid fitting and follow up session an anonymized program settings file will be provided to the study sponsor in order to evaluate program settings and usage data.

9.3.8.2.1 Audibility Review – three months post POV2.

As part of the clinical review visits, at three (3) months (*+/- 4 weeks*) post POV2, audibility will be assessed.

- Implanted ear only: Aided speech recognition with CNC words at 60 dBA (2 lists)
- Everyday listening condition (bilateral hearing aids): Sound field thresholds at 500, 1000, 2000, 4000 Hz

9.3.9 Follow-up Visit 1 (FUV1)

Both Arm A and Arm B subjects will complete FUV1 in the aided condition six (6) months post POV2 (*+/- 2 weeks*). The full neuropsychological battery in addition to the audiologic, psychosocial, physical, and quality of life metrics will be completed as described in Section 9.2. Speech recognition will be assessed in the everyday listening condition (aided bilaterally) and implanted ear (Arm A) or ear to be implanted (Arm B) only listening conditions. Datalogs will be retrieved for the sound processor (Arm A) and hearing aid (Arm B).

9.3.10 Surgery – Arm B

Arm B subjects will be implanted with the Cochlear Nucleus® Profile™ Slim Modiolar (532) cochlear implant or the Cochlear Nucleus CI632 cochlear implant 1 week (*+/- 1 week*) post FUV1.

An intraoperative X-ray will be obtained (preferably a lateral or modified Stenver's view) following the placement of the electrode and prior to closing.

9.3.11 Imaging

Following surgery, subjects will undergo a Computed Tomography (CT) scan according to the specifications provided by the study sponsor. Postoperative analysis of the CT scan will be done via reconstruction to determine electrode position and distance to the modiolus. Retrospective analysis of the CT scan will be done via reconstruction to determine electrode position and distance to the modiolus by an independent centralized imaging review center and a de-identified report will be sent to the sponsor in line with HIPAA Standards.

9.3.12 CI review – Arm B

CI activation will occur in the standard clinical manner for each field site at approximately two weeks post-surgery (*+/- 3 weeks*). Four to six clinical review visits will be scheduled at each field site between activation and FUV2, twelve (12) months from POV2. These visits can contain device

adjustments as well as counselling on hearing and listening strategies, and discussion of hearing assistive technology.

We propose the following topics are discussed during the six months of cochlear implant use:

- Hearing assistive technology
- Communication strategies
- Listening in noise
- Understanding hearing loss

Needs for various hearing assistive technologies (HATs) will be assessed and, if the audiologist deems that it is appropriate, recommendations will be made.

Following each CI mapping appointment an anonymized .cdx file labelled with the Subject ID will be provided to the study sponsor in order to evaluate program settings and usage data.

9.3.13 Follow-up Visit 2 (FUV2)

Both Arm A and Arm B subjects will complete FUV2 in the aided condition twelve (12) months post POV2 (*+/- 4 weeks*). The full neuropsychological battery in addition to the audiologic, psychosocial, physical, and quality of life metrics will be completed as described in Section 9.2. Speech recognition will be assessed in the everyday listening condition (aided bilaterally) and implanted ear only listening condition. Datalogs will be retrieved for the sound processor.

9.3.14 Follow-up Visit 3 (FUV3)

Arm B subjects will complete FUV3 in the aided condition eighteen (18) months post POV2 (*+/- 4 weeks*). The full neuropsychological battery in addition to the audiologic, psychosocial, physical, and quality of life metrics will be completed as described in Section 9.2. Speech recognition will be assessed in the everyday listening condition (aided bilaterally) and implanted ear only listening condition. Datalogs will be retrieved for the sound processor.

9.4 Subjects

9.4.1 Inclusion Criteria

1. Aged 65 to 85 years, inclusive
2. Community-dwelling
3. Proficient in English
4. Oral communicator
5. PTA (500, 1000 & 2000 Hz) ≥ 70 dB HL hearing loss duration ≥1 year and no more than 30 years.
6. Active hearing aid users: daily use of hearing aids.
7. Hearing Handicap Inventory for the Elderly - Screening (HHIE-S): Score ≥ 24 indicating a significant hearing handicap
8. Hearing Impaired Montreal Cognitive Assessment (HI-MoCA): Score ≥ 20 indicating mild cognitive decline to normal cognitive function.
9. Cochlear implant candidacy: Participants must have postlinguistic onset sensorineural hearing loss and meet applicable FDA and/or Medicare candidacy criteria for cochlear implantation

10. Willingness to consent for the study, to be randomized to either the immediate or delayed cochlear implantation arm, to utilize bimodal hearing for the duration of the trial (if clinically appropriate) and follow the study protocol for the duration of the trial.

9.4.2 Exclusion Criteria

1. Prelingual or perilingual severe-to-profound hearing loss.
2. Previous cochlear implantation in either ear
3. Hearing loss of neural or central origin
4. Permanent conductive hearing impairment (e.g. Otosclerosis).
5. Medical, audiological or psychological conditions, as judged by the investigator that might contraindicate participation in the clinical investigation.
6. Self-reported disability in ≥ 2 activities of daily living.
7. Unwilling to wear a device or comply with the surgical and rehabilitation requirements of the study.
8. Vision impairment: Worse than 20/40 (corrected) on a Near Vision Card.

9.5 Statistical Considerations

Statistical considerations for the clinical investigation are fully described within the Randomized controlled trial of immediate versus delayed cochlear implantation Statistical Analysis Plan (D1309522).

9.6 Data Management

The Case Report Forms (CRFs) will capture subject status according to the following criteria:

- Consented: Signed consent and eligibility evaluations underway
- Screen Fail: Subject determined not to be eligible to proceed for participation
- Enrolled: Following confirmation of eligibility and randomization
- Withdrawn: Enrolled subjects who withdraw or are withdrawn by the Investigator or Sponsor before the expected End of Study visit.
- Complete: Enrolled subjects who complete the planned follow up schedule.

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

The web-based system has been verified and validated by the vendor. Investigation-specific implementations are validated and consist of verification that all required items are included, validity of edit checks and appropriate functionality of conditional fields. The investigation-specific data in in the EDC can only be accessed by those that have been allocated their individual account, which are personnel of the investigational sites, Clinical Project Managers, Investigation Monitors and Data Management.

9.7 Data Monitoring

The study will be monitored for data quality as referenced in the associated monitoring plan as well as in compliance with Cochlear Americas Standard Operating Procedures (SOPs). Monitoring considerations for the clinical investigation are described within the Randomized controlled trial of immediate versus delayed cochlear implantation Monitoring Plan (D1309523).

9.8 Amendments to the Protocol

No changes in the protocol or investigation procedures shall be effected without agreement by the sponsor. Changes related to the scientific intent of the study shall be documented in the protocol and requires signatures from the sponsor and the principal investigator. Such changes will require notification to the Institution Review Board (IRB) by the principal investigators.

9.9 Deviations from the Protocol

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

The procedure for recording and reporting protocol deviations shall be via a Protocol Deviation CRF in the EDC system. Analysis of protocol deviations shall be undertaken by the sponsor and Data Management.

In the event of a protocol deviation, the investigator shall notify the sponsor and respective IRB according to local reporting guidelines.

9.10 Device accountability

Investigational devices (iPads) will be shipped to the investigational site indicating the study number. Sites should preserve the packaging to enable them to return the iPads to Cogstate at the end of the clinical investigation.

Commercially released products shall be registered following the standard product registration process at each field site.

10 STATEMENTS OF COMPLIANCE

10.1 Declaration of Helsinki and compliance with standards

The clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2013), The U.S. Food & Drug Administration's Code of Federal Regulations, ISO 14155: 2011, and any regional or national regulations, as appropriate.

10.2 Institutional Review Board Approval

A participating site shall not commence subject enrollment prior to the written approval from the local IRB is obtained.

The final version of the protocol, the informed consent and all supporting documents to the IRB. A copy of the IRB approval shall be provided to the sponsor.

The investigator shall forward any amendment made to the approved informed consent to the sponsor for review prior to submission to the IRB.

The sponsor and principal investigator shall continue the communication with the IRB as required by national regulations and the clinical investigational plan.

Documentation if any extension, amendment or renewal of the IRB approval is required. In particular, substantial amendments to the protocol, the informed consent, or other written information provided to subjects shall be approved in writing by the IRB.

Additionally, the investigator will report to the IRB any new information that may affect the safety of the subjects or the conduct of the clinical investigation. The investigator shall send written status summaries of the investigation to the IRB as required.

Upon completion of the clinical investigation, the investigator shall provide the IRB with a brief report of the outcome of the clinical investigation as per local requirements.

The clinical investigation is covered by a clinical trial insurance as per local requirements.

11 INFORMED CONSENT PROCESS

11.1 Obtaining informed consent

The investigator shall obtain written informed consent using an approved Informed Consent Form from the subject prior to any clinical investigation related activity. NOTE: If the subject was seen as part of routine clinical care prior to study consent, information relevant to the study may be included such as but not limited to: hearing history, medical history (via completion of the ACE 27), prior hearing aid use, audiometric status, etc. as long as performed within 90 days from POV1.

The informed consent shall include the following but is not limited to: rationale for and details of the study, aims and objectives, the risks and benefits and alternative treatments, and the extent of the subject's involvement. Ample time shall be provided for the subject to inquire about details of the clinical investigation and to decide whether to participate. All questions about the clinical investigation shall be answered to the satisfaction of the subject or the subject's legally acceptable representative prior to signing the Informed Consent. Subjects shall not be coerced or unduly influenced to participate or to continue to participate in a clinical investigation.

Each subject and the person who conducted the informed consent discussion shall sign the informed consent. Where required, a witness shall sign and personally date the informed consent. The subject shall be provided a copy of the signed informed consent and the original signed version of the informed consent shall be filed in the respective subjects file at the clinical site.

11.2 Data Privacy

Subjects will be identified on CRFs or similar documents (for example, questionnaires) by a unique subject identification code. Completed CRFs or similar documents are confidential documents and will only be available to the sponsor and their representatives, the investigator, the investigational statistician, and if requested, to the local IRB. The Patient ID log CRF is explicitly excluded from this requirement. Analysis of post-operative CT scans will be undertaken by an independent centralized imaging review center and a de-identified report will be sent to the sponsor in line with HIPAA Standards.

A description of this clinical investigation will be available on http://www.ClinicalTrials.gov, as required by U.S. Law.

12 SAFETY REPORTING

12.1 Definitions

All definitions are according to 21 CFR Part 812, 50, 54, 56 & 11 as well as EN ISO 14155:2011 standard and described in Section 17.

12.2 Reporting Process

The investigator shall report all serious adverse events without delay to the sponsor through the eCRF. The Sponsor will appoint a medical monitor to review any adverse events requiring adjudication.

The investigator must report all AEs, SAEs, SADEs and USADEs to their IRB using the applicable report form as per local requirement.

Subjects shall be carefully monitored during the clinical investigation for potential adverse events and shall be routinely questioned about adverse events at investigation visits. For all adverse events, information obtained by the investigator shall be recorded in the Adverse Event CRF. The investigator shall attempt to assess the relationship between the procedure and the adverse event with final review by the sponsor.

12.3 Data Monitoring Committee

Given that routine surgical procedures will be applied a DMC will not be established.

13 VULNERABLE POPULATION

The target study population is the older adult population, specifically individuals aged 65 to 85 years of age. The inclusion criteria screens for significant impaired mental capacity using the Hearing Impaired Montreal Cognitive Assessment (HI-MoCA). Specifically, adults who score ≥ 20 on the HI-MoCA. Additionally, individuals with self-reported disability and visual impairments are excluded. Potential study subjects will not be of child bearing age nor will the investigation include children. This study does not pose additional physical risks for older adults than for the general population and subjects will be under the medical supervision and care of the investigational site for the duration of the trial.

14 SUSPENSION OR PREMATURE TERMINATION

The sponsor reserves the right to discontinue the study for any safety, ethical, or administrative reason at any time. Subjects already implanted will continue to be supported by their hearing health care provider, independent of any decision made about study continuation.

The sponsor will withdraw from sponsorship of the clinical investigation if:

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

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

An ongoing clinical investigation can be discontinued in case of:

- device failure

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

15 PRESENTATION AND PUBLICATION POLICY

Cochlear is committed to the responsible publishing of data from its clinical research program. Cochlear will manage the timely publication of results in a suitable journal(s). The authors of any publication will be involved in this process. Cochlear will assess authorship eligibility according to the guidelines issued by the International Committee of Medical Journal Editors (43).

In accordance with these recommendations, authorship credit will be based on: 1) Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) Drafting the article or revising it critically for important intellectual content; and 3) Final approval of the version to be published. All three above points should be met to qualify for authorship.

The lead author for any publication must be a study investigator or a major contributor to the study, and must have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

16 REFERENCES

16.1 Internal References

ID	Document Title	Number
1	Randomized controlled trial of immediate versus delayed cochlear implantation on hearing handicap Clinical Investigation Project Plan	D1309524
2	Randomized controlled trial of immediate versus delayed cochlear implantation on hearing handicap Statistical Analysis Plan	D1309522
3	Randomized controlled trial of immediate versus delayed cochlear implantation on hearing handicap Monitoring Plan	D1309523

16.2 External References

ID	Document Title	Number
1	Clinical investigation of medical devices for human subjects – Good clinical practice	ISO 14155:2011
2	World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (2013)	N/A
3	Code of Federal Regulations for Medical Devices Title 21	Part 11, 50, 54, 56 and 812

16.3 Referenced Literature

1. Lin FR, Yaffe K, Xia J, Xue QL, Harris TB, Purchase-Helzner E, et al. Hearing loss and cognitive decline in older adults. JAMA Intern Med. 2013;173(4):293-9.
2. Lin FR, Metter EJ, O'Brien RJ, Resnick SM, Zonderman AB, Ferrucci L. Hearing loss and incident dementia. Arch Neurol. 2011;68(2):214-20.
3. Lin FR, Albert M. Hearing loss and dementia - who is listening? Aging Ment Health. 2014;18(6):671-3.
4. Li W, Li J, Xian J, Lv B, Li M, Wang C, et al. Alterations of grey matter asymmetries in adolescents with prelingual deafness: a combined VBM and cortical thickness analysis. Restorative neurology and neuroscience. 2013;31(1):1-17.
5. Sharma A, Glick H. Cross-Modal Re-Organization in Clinical Populations with Hearing Loss. Brain Sci. 2016;6(1).
6. Shiell MM, Champoux F, Zatorre RJ. Reorganization of auditory cortex in early-deaf people: functional connectivity and relationship to hearing aid use. Journal of cognitive neuroscience. 2015;27(1):150-63.
7. Philibert B, Collet L, Vesson JF, Veuillet E. Intensity-related performances are modified by long-term hearing aid use: a functional plasticity? Hear Res. 2002;165(1-2):142-51.
8. Hribar M, Suput D, Carvalho AA, Battelino S, Vovk A. Structural alterations of brain grey and white matter in early deaf adults. Hear Res. 2014;318:1-10.
9. Munro KJ. Reorganization of the adult auditory system: perceptual and physiological evidence from monaural fitting of hearing aids. Trends Amplif. 2008;12(3):254-71.
10. Hwang JH, Wu CW, Chen JH, Liu TC. Changes in activation of the auditory cortex following long-term amplification: an fMRI study. Acta Otolaryngol. 2006;126(12):1275-80.
11. Sarampalis A, Kalluri S, Edwards B, Hafter E. Objective measures of listening effort: effects of background noise and noise reduction. J Speech Lang Hear Res. 2009;52(5):1230-40.
12. Hornsby BW. The effects of hearing aid use on listening effort and mental fatigue associated with sustained speech processing demands. Ear and hearing. 2013;34(5):523-34.
13. Picou EM, Ricketts TA, Hornsby BW. How hearing aids, background noise, and visual cues influence objective listening effort. Ear and hearing. 2013;34(5):e52-64.
14. Desjardins JL. The Effects of Hearing Aid Directional Microphone and Noise Reduction Processing on Listening Effort in Older Adults with Hearing Loss. J Am Acad Audiol. 2016;27(1):29-41.
15. Mosnier I, Bebear JP, Marx M, Fraysse B, Truy E, Lina-Granade G, et al. Improvement of Cognitive Function After Cochlear Implantation in Elderly Patients. JAMA Otolaryngol Head Neck Surg. 2015.
16. Li L, Blake C, Sung Y, Shpritz B, Chen D, Genther DJ, et al. The Studying Multiple Outcomes After Aural Rehabilitative Treatment Study: Study Design and Baseline Results. Gerontol Geriatr Med. 2017;3:1-10.
17. Cochlear. Cochlear™ Nucleus CI632 cochlear implant with Slim Modiolar electrode Physician's Guide. Cochlear Limited; 2018.
18. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society. 2005;53(4):695-9.
19. Pinto TCC, Machado L, Bulgacov TM, Rodrigues-Junior AL, Costa MLG, Ximenes RCC, et al. Is the Montreal Cognitive Assessment (MoCA) screening superior to the Mini-Mental State Examination (MMSE) in the detection of mild cognitive impairment (MCI) and Alzheimer's Disease (AD) in the elderly? Int Psychogeriatr. 2018:1-14.
20. Lim MYL, Loo JHY. Screening an elderly hearing impaired population for mild cognitive impairment using Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Int J Geriatr Psychiatry. 2018;33(7):972-9.
21. Ambert-Dahan E, Routier S, Marot L, Bouccara D, Sterkers O, Ferrary E, et al. Cognitive Evaluation of Cochlear Implanted Adults Using CODEX and MoCA Screening Tests. Otol Neurotol. 2017;38(8):e282-e4.
22. Claes AJ, de Backer S, Van de Heyning P, Gilles A, Van Rompaey V, Mertens G. Postoperative cognitive dysfunction after cochlear implantation. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies. 2018;275(6):1419-27.

23. Lin VY, Chung J, Callahan BL, Smith L, Gritters N, Chen JM, et al. Development of cognitive screening test for the severely hearing impaired: Hearing-impaired MoCA. Laryngoscope. 2017;127 Suppl 1:S4-S11.
24. Hughson W, Westlake HD. Manual for program outline for rehabilitation of aural casualties both military and civilian. Trans Am Acad Ophthal Oto-lar. 1944(Suppl.):3-15.
25. Peterson GE, Lehiste I. Revised CNC lists for auditory tests. The Journal of speech and hearing disorders. 1962;27:62-70.
26. Spahr AJ, Dorman MF, Litvak LM, Van Wie S, Gifford RH, Loizou PC, et al. Development and validation of the AzBio sentence lists. Ear and hearing. 2012;33(1):112-7.
27. Ventry IM, Weinstein BE. The hearing handicap inventory for the elderly: a new tool. Ear and hearing. 1982;3(3):128-34.
28. Noble W, Jensen NS, Naylor G, Bhullar N, Akeroyd MA. A short form of the Speech, Spatial and Qualities of Hearing scale suitable for clinical use: the SSQ12. Int J Audiol. 2013;52(6):409-12.
29. Gatehouse S, Noble W. The Speech, Spatial and Qualities of Hearing Scale (SSQ). Int J Audiol. 2004;43(2):85-99.
30. Russell DW. UCLA Loneliness Scale (Version 3): reliability, validity, and factor structure. J Pers Assess. 1996;66(1):20-40.
31. Burke WJ, Roccaforte WH, Wengel SP. The Short Form of the Geriatric Depression Scale: A Comparison With the 30-Item Form. Topics in geriatrics. 1991;4(3):173-8.
32. Castiglione A, Benatti A, Velardita C, Favaro D, Padoan E, Severi D, et al. Aging, Cognitive Decline and Hearing Loss: Effects of Auditory Rehabilitation and Training with Hearing Aids and Cochlear Implants on Cognitive Function and Depression among Older Adults. Audiol Neurootol. 2016;21 Suppl 1:21-8.
33. Poissant SF, Beaudoin F, Huang J, Brodsky J, Lee DJ. Impact of cochlear implantation on speech understanding, depression, and loneliness in the elderly. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2008;37(4):488-94.
34. Sonnet MH, Montaut-Verient B, Niemier JY, Hoen M, Ribeyre L, Parietti-Winkler C. Cognitive Abilities and Quality of Life After Cochlear Implantation in the Elderly. Otol Neurotol. 2017;38(8):e296-e301.
35. Carlson MC, Parisi JM, Xia J, Xue QL, Rebok GW, Bandeen-Roche K, et al. Lifestyle activities and memory: variety may be the spice of life. The women's health and aging study II. Journal of the International Neuropsychological Society : JINS. 2012;18(2):286-94.
36. Fried LP, Carlson MC, Freedman M, Frick KD, Glass TA, Hill J, et al. A social model for health promotion for an aging population: initial evidence on the Experience Corps model. J Urban Health. 2004;81(1):64-78.
37. Parisi JM, Kuo J, Rebok GW, Xue QL, Fried LP, Gruenewald TL, et al. Increases in lifestyle activities as a result of experience Corps(R) participation. J Urban Health. 2015;92(1):55-66.
38. Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, DePauw S, et al. Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. Med Care. 2002;40(2):113-28.
39. Boyle MH, Furlong W, Feeny D, Torrance GW, Hatcher J. Reliability of the Health Utilities Index--Mark III used in the 1991 cycle 6 Canadian General Social Survey Health Questionnaire. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 1995;4(3):249-57.
40. Barton GR, Bankart J, Davis AC, Summerfield QA. Comparing utility scores before and after hearing-aid provision : results according to the EQ-5D, HUI3 and SF-6D. Applied health economics and health policy. 2004;3(2):103-5.
41. Grutters JP, Joore MA, van der Horst F, Verschuure H, Dreschler WA, Anteunis LJ. Choosing between measures: comparison of EQ-5D, HUI2 and HUI3 in persons with hearing complaints. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2007;16(8):1439-49.
42. Group UCIS. Criteria of candidacy for unilateral cochlear implantation in postlingually deafened adults II: cost-effectiveness analysis. Ear and hearing. 2004;25(4):336-60.
43. Uniform requirements for manuscripts submitted to biomedical journals: Writing and editing for biomedical publication. Journal of pharmacology & pharmacotherapeutics. 2010;1(1):42-58.

17 CHANGE HISTORY

Version	Change	Author	Date
1.0	Introduction of document	[redacted]	December 21, 2016
2.0	Addition of Windchill number and study title to footer of document. Update to Investigation Schedule to include CM/AE/MH. Update to Medical Monitor details. Rewording of primary and secondary endpoints. Addition of 12 month follow up visit (FUV2). Removal of CANTAB as electronic cognitive test battery and replacement with NIH Toolbox Removal of SF-12, Cohen Social Network Index, and York Hearing Related Quality of Life measures. Addition of Lubben Social Network Scale and EQ-D5 Change from CES-D to Geriatric Depression Scale (GDS).	[redacted]	August 31, 2017
3.0	Removal of NIH Toolbox and replacement with Cogstate test battery. Updated secondary objectives, endpoints and hypothesis. Updated reference to Statistical Analysis Plan	[redacted]	October 6, 2017
4.0	Amendment to Data Privacy Section	[redacted]	January 29, 2018
5.0	Update to short study title to 'Immediate vs Delayed Cochlear Implantation on Hearing Handicap Study' Numbering of inclusion and exclusion criteria. Typo correction for exclusion criteria #7 in synopsis. Clarification of noise type – speech-weighted noise.	[redacted]	March 9, 2018

Version	Change	Author	Date
6.0	Assessment of phonemes correct added. Changed primary objective and endpoint to assess Speech, Spatial and Qualities of Hearing (SSQ12) replacing Hearing Handicap Inventory for the Elderly - Screening (HHIE-S). Addition of FUV3 for Arm B subjects to assess outcomes at 12 months post-activation to align with Arm A post-activation follow up. Replacement of Mini Mental State Exam (MMSE) with Montreal Cognitive Assessment (MoCA). Specification of PTA (500, 1000 & 2000 Hz) ≥ 70 dB HL in inclusion criteria. Removal of EQ-5D, Lubben Social Network, SPPB, THI questionnaires. Specification of CI532 cochlear implant. Addition of clinical review visits including audibility review at 3 months after POV2. Addition of X-ray preoperatively and CT imaging post-operatively. Removal of pure tone audiometric testing during follow up visits, and requirement for bone conduction testing during screening and baseline visits.	[redacted]	December 5, 2018
7.0	Corrected visit window for surgery in Investigation Procedures table. Referred to Statistical Analysis Plan for randomization details.	[redacted]	December 6, 2018
8.0	Updated Montreal Cognitive Assessment Scale (MoCA) to utilize the Hearing Impaired version of the Montreal Cognitive Assessment Scale (HI-MoCA) with a supplemental visual presentation of instructions. Included text describing the imaging requirements for the clinical investigation.	[redacted]	February 1, 2019
9.0	Alignment of tympanometry, demographics and hearing history with EDC System.	[redacted]	March 1, 2019
10.0	Addition of Cochlear Nucleus CI632 cochlear implant with Slim Modiolar electrode and exclusion of protocol deviation for inability to perform tympanometry due to no seal with probe tip.	[redacted]	June 17, 2019
11.0	Addition of subject status language, ACE 27 index for medical history and clarification of hearing history information to be collected and protocol amendment criteria, Consistent addition of Cochlear Nucleus CI632 cochlear implant with Slim Modiolar electrode. Removal of protocol deviation for inability to perform tympanometry and removal of specific medical monitor information.	[redacted]	August 16, 2019

18 DEFINITIONS

Term	Description
Adverse event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons whether or not related to the investigational medical device. NOTE 1 This definition includes events related to the investigational medical device or the comparator NOTE 2 This definition includes events related to the procedures involved. NOTE 3 For users and other persons, this definition is restricted to events related to investigational medical devices.
Adverse device effect (ADE)	Adverse device effect is an adverse event related to the use of an investigational medical device. Note to the author: NOTE 1 This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
CRF	Case Report Form. A form to facilitate the collection of clinical data during a clinical investigation.
DMC	Data Monitoring Committee
DD	Device Deficiency. A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.
FUV	Follow-Up Visit
Incident	Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject, or USER or of other persons or to a serious deterioration in their state of health.
IC	Informed Consent
IRB	Institutional Review Board
POV	Preoperative Visit

Term	Description
Serious adverse event (SAE)	A serious adverse event is any adverse event that: a) led to a death, b) led to a serious deterioration in the health of the subject that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to foetal distress, foetal death or a congenital abnormality or birth defect NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Serious adverse device effect (SADE)	A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated serious adverse device effect (USADE)	An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis report (for the investigational device or its comparator).