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Complete List of Authors:	Assouly, Kelly; University Medical Centre Utrecht Brain Centre, Otorhinolaryngology, Head and Neck Surgery Smit, Adriana; University Medisch Centrum Utrecht, Department of Otorhinolaryngology, Head and Neck Surgery Stegeman, Inge; University Medical Center Utrecht, Department of Otorhinolaryngology, Head and Neck Surgery Rhebergen, Koen S. ; University Medisch Centrum Utrecht, Department of Otorhinolaryngology, Head and Neck Surgery van Dijk, Bas; Cochlear Technology Center Stokroos, Robert; University Medical Center Utrecht, Department of Otorhinolaryngology, Head and Neck Surgery
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Tinnitus and cochlear implantation study: a randomized controlled trial

K.S. Kelly Assouly[1, 2, 3 *], L. Adriana Smit[1, 2], Inge Stegeman [1, 2], S. Koen Rhebergen[1, 2], Bas van Dijk[3] and J. Robert Stokroos[1, 2]

[1]Department of Otorhinolaryngology and Head & Neck Surgery, University Medical Center Utrecht, the Netherlands
[2]Department of Clinical and Experimental Neuroscience, University Medical Center Utrecht Brain Center, Utrecht University, Utrecht, The Netherlands
[3]Cochlear Technology Center, Mechelen, Belgium

*Corresponding author:

Postal address: University Medical Center Utrecht, Room number H.02.104, P.O. Box 85500,

3508 GA UTRECHT

Tel: +31887555555

E-mail:K.K.S.Assouly@umcutrecht.nl

Abstract

Background

Tinnitus is the perception of sound without an external stimulus, often experienced as a ringing or buzzing sound. Subjective tinnitus is assumed to origin from changes in neural activity caused by reduced or lack of auditory input, for instance due to hearing loss. Since auditory deprivation is thought to be one of the causes of tinnitus, increasing the auditory input by cochlear implantation might be a possible treatment. In studies assessing cochlear implantation for patients with hearing loss, promising results were seen to relief tinnitus as a secondary outcome. Therefore, we will assess the effect of cochlear implantation in patients with primarily tinnitus complaints.

Method and analysis

In this randomized controlled trial, patients with a primary complaint of tinnitus will be included. Fifty patients (Tinnitus Functional Index (TFI) $\geq$ 32, Beck's Depression Index (BDI) < 19, pure tone average at 0.5,1,2,4 kHz: bilateral threshold between 50 and ≤ 75 dB) will be randomized towards cochlear implantation or no intervention. Primary outcome of the study is tinnitus burden as measured by the TFI. Outcomes of interest are tinnitus severity, hearing performances (tinnitus pitch and loudness, speech perception), quality of life, depression and patient related changes. Outcomes will be evaluated prior to implantation and at 3 and 6 months after the surgery. The control group will receive questionnaires at 3 and 6 months after randomization. We expect a significant difference between the cochlear implant recipients and the control group for tinnitus burden.

Ethics and dissemination

This research protocol was approved by the Institutional Review Board of the University Medical Center (UMC) Utrecht (NL70319.041.19, V3.0, April 2020). The trial results will be made accessible to the public in a peer-review journal.

Trial registration number NL8693.

Keywords: Tinnitus, Cochlear implantation, Bilateral hearing loss, Quality of life, Electrical stimulation, Randomized Controlled Trial

Strengths and limitations of this study

- The randomized controlled study allows for high quality assessment of outcomes of cochlear implantation for patients suffering primarily from tinnitus and secondarily from moderate to moderately severe bilateral hearing loss.
- Outcomes of interest are not limited to tinnitus burden but also consider anxiety and depression, quality of life and patient related changes.
- The intervention can induce risks associated with surgery and a residual hearing deterioration in the ear implanted which will be monitored by electrocochleography measurement.
- This study is a further step towards evidence-based medicine for the clinical efficacy of cochlear implants as a tinnitus treatment.

Background

Tinnitus is the perception of sound without an external stimulus, often experienced as a ringing or buzzing sound [1,2]. It is a common symptom with an approximate prevalence of 10-30%, depending on the selected population [3], increasing to 30% of adults over the age of 50 years [4]. Tinnitus can be chronic and disabling for those individuals affected by it. It is a complex condition, in which many components are responsible for perceived burden, like loudness, comorbidity and sleep problems. The heterogeneous aspect of the disease is also accountable for differences in the tinnitus itself: localization, sound characteristics, temporal course and underlying cause. The burden that patients experience is divers and the individual needs of patients for tinnitus related health care are various. While the underlying etiology of tinnitus is still debated, one hypothesis is that the tinnitus arises from changes in neural activity caused by reduced or lack of auditory input due to hearing loss which often accompanies the tinnitus [5,6]. Till date, the only evidence-based therapy for the reduction of tinnitus burden is cognitive behavioral therapy (CBT) [5,7–9].

Since auditory deprivation is thought to be one of the causes of tinnitus, increasing the auditory input by cochlear implantation might be a possible treatment option. This hypothesis is confirmed by observations in studies assessing the effectiveness of cochlear implantation to restore hearing function in case of bilateral deafness, where tinnitus reduction is one of the secondary outcomes [10]. Analyzing the effect of intracochlear electrical stimulation with a cochlear implant (CI) on primarily tinnitus complaints has been investigated by only few studies. All studies assessing the effect of cochlear implantation for tinnitus concerned cases with single-sided deafness [11–16] or patients with asymmetrical hearing loss [6]. They all reported a significant tinnitus reduction after implantation. So far, there is no high level of evidence of the effect of intracochlear stimulation as an intervention for primary tinnitus complaint in case of bilateral moderate to severe hearing loss [10].

Above mentioned studies provide the first evidence of possible effectiveness of cochlear implantation for the reduction of tinnitus burden. To provide clear evidence of the effectiveness of cochlear implantation for the suppression of tinnitus complaints, a statistically powered study is needed aiming at patients with tinnitus as their primary complaint instead of hearing loss. To what extent electrical stimulation can reduce tinnitus , in patients with bilateral moderate to severe hearing loss (just below the current CI indication) but with primary complaint of tinnitus, is unknown [17]. Therefore, we aim to study the effect of cochlear implantation on tinnitus burden in patients suffering primarily from tinnitus accompanied by bilateral moderate to severe hearing loss in a randomized controlled trial.

Method and analysis

Study objectives

The primary objective of this study is to assess the effect of electrical stimulation by a CI on tinnitus burden, measured with the Tinnitus Functional Index (TFI) at 6 months after cochlear implantation. Secondary outcomes are to assess the effect of CI on tinnitus severity, tinnitus pitch and loudness, auditory function, speech recognition, quality of life, symptoms of depression and anxiety, patient reported change in order to attest treatment-related differences.

Patient involvement

Patients were not involved in the design, or conduct, or reporting, or dissemination plans of the study.

Study design and setting

The study is a monocenter clinical trial performed in a tertiary referral clinic (university hospital) in the Netherlands (University Medical Center Utrecht). The protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials statement [18]. In this randomized controlled trial (RCT), patients will be randomized into groups: a CI group and a control group (Fig. 1). 25 patients (CI group) shall receive a CI in the ear mostly affected by tinnitus. The other 25 patients (control group) shall follow a follow up period of 6 months with no intervention. The follow-up sessions will take place 3 and 6 months after implantation to assess the primary outcome of tinnitus burden and secondary outcomes of quality of life, treatment related outcomes and auditory function.

[Insert Figure 1]

Study population

The study population consists of patients seeking help for tinnitus, presenting at the outpatient clinic of Ear, Nose and Throat (ENT) of the UMC Utrecht, The Netherlands. 50 patients aged 18 or older with moderate to severe tinnitus and moderate to severe hearing loss will be included after fulfilling eligibility and informed consent. They must meet the following criteria to be eligible for the study at randomization.

Inclusion criteria

- Patients aged 18 or older

- Seeking help for tinnitus
- Subjective tinnitus
- Tinnitus Functional Index (TFI) > 32
- Tinnitus duration > 1 and tinnitus stability > 6 months
- Hearing level (measured with a maximum of 3 months before eligibility assessment):
    - Audiometry (Pure Tone Average (PTA) at 0.5,1,2,4 kHz): bilateral threshold between 50 and ≤ 75 dB
        - Hearing threshold stability (PTA < 5 dB change for 1 year in each ear)
- Becks Depression Inventory (BDI) <19
- Health status allows general anesthesia and surgery for the cochlear implantation
- Failure of regular tinnitus care (e.g. psychological or sound therapy)
- Dutch language proficiency
- Willingness and ability to participate in all scheduled procedures outlined in the protocol
- Able to understand and sign informed consent

Exclusion criteria

A potential patient who meets any of the following criteria will be excluded from participation in this study:

- Patient primary seeking help for non-tinnitus hearing problems
- Abnormal cochlear anatomy (i.e. ossification)
- Comorbidity with an expected survival of less than five years based on medical history as assessed by clinician and in electronical patient file
- Additional handicaps that would prevent participation in the evaluations
- Presence of any instable psychiatric condition within 1 year before start of the study
- Unrealistic expectations on the part of the patient regarding the possible benefits, risks and limitations that are inherent to the procedure

If a patient is eligible for the study, his/her otorhinolaryngologist will ask him/her to participate. The content of the study will be explained by the patient's otorhinolaryngologist who will provide him/her written patient information and the informed consent form. Patients will be given 2 weeks to consider participation. If a patient meets the criteria for in- and exclusion and wants to take part in the study, the patient will be asked to come to the UMC Utrecht for a computerized tomography (CT) scan to visualize the anatomy of the mastoid. If the patient's CT scan shows normal cochlear anatomy, he will, during the same visit, sign the informed consent with a member of the research

team and receive a copy of the consent. After inclusion, baseline measurement will be performed where after randomization will take place.

Randomization

After inclusion and baseline measurement, patients will be allocated into one of the two groups: CI group or control group. The randomization will be performed using a block size of 4 and 6 and stratified for TFI score. A website randomization program, developed by the Julius Centre [19] will be used for randomization. Investigators will be blinded to the randomization. Blinding is not possible during this study since both patients and caregivers will be able to see from outside whether patients have a CI or not.

Intervention

Patients allocated to the intervention group will receive a CI. The cochlear implantation will be carried out under general anesthesia after consent of the anesthesiologist and after determination of general health status. The standard surgical procedures for cochlear implantation will be followed. A retro-auricular incision will be made to expose the mastoid. The electrode will be inserted via a posterior tympanotomy and round window implantation by soft-surgery techniques. Intraoperatively, normal functioning of the device will be checked by measurement of impedance and neural response telemetry. Electrocochleography will also be recorded intraoperatively using Cochlear™ Research Platform (v1.1). The cochlear implant used for the study consists of a Nucleus 7 sound processor and a CI622 implant from Cochlear (or similar). Serial numbers of the CIs will be registered in the operating room (OR) report by the surgeon (standard clinical care for cochlear implantation) and in the master study file (MSF) (product accountability). A post-operative Cone Beam CT of the mastoid will be planned to detail the electrode location within the cochlea.

One week after surgery patients from the intervention group will be checked at the outpatient department (OPD) of the ENT to check for wound healing. The rehabilitation phase will start 4 weeks after surgery with a visit of the patient to the department of Audiology to custom fit the processor software and then (bi)weekly till week eleven after surgery to fine-tune the programming of the implant and improve speech perception.

In the follow-up phase, the patients with CI will return to the UMC Utrecht 3 and 6 months after implantation to assess study outcome by the research team. The patients of the control group will come to the UMC Utrecht 3 and 6 months after randomization to assess the same study outcome. A questionnaire will have to be filled in at home by the patients before every follow-up session at 3 and 6 months, as well as 2 weeks after surgery for the intervention group.

Participants are not allowed to start another tinnitus treatment during the study.

Sample size

To detect a clinically relevant difference of 1 grade (15 points) change measured with the TFI, in tinnitus burden at 6 months after cochlear implantation compared to the control group, with a power of 90% and alpha of 0.05, 23 patients are needed in both arms of the study. An acceptable standard deviation was set at 15, based on the results of a previous pilot study assessing CI for tinnitus patients [16]. We will include 25 patients per arm, a 10% margin, to include for possible lost to follow up. Thereby, we expect patients to have a mean TFI at baseline of 50 points on TFI (Grade 3) and a TFI decrease of 15 points at 6 months after intervention with a mean endpoint of 35 points on TFI (Grade 2).

Outcomes

The following outcomes will be assessed at the baseline visit and follow up visits at 3 and 6 months after randomization (Table 1). All measurements will be performed by the research team following the same protocol procedures.

	Baseline	**CI GROUP**				**CONTROL GROUP**	
	Rx	**CI**	**2 w post CI**	**3 m post CI**	**6 m post CI**	**Rx + 3 m**	**Rx + 6 m**
CI (surgery)		X					
CT scan	*x*	*X*					
Electro-cochleography	*x*	*X*		*X*	*X*		
Hearing level				*X*	*X*	*X*	*X*
Speech perception	*x*			*X*	*X*	*X*	*X*
Tinnitus pitch match	*x*			*X*	*X*	*X*	*X*
Tinnitus loudness match	*x*			*X*	*X*	*X*	*X*
TFI*	*x*			*X*	*X*	*X*	*X*
VAS Tinnitus *	*x*		*X*	*X*	*X*	*X*	*X*

SSQ*	x			X	X	X	X
EQ5D*	x			X	X	X	X
HADS*	x			X	X	X	X
BDI*					X		X
GBI*					X		
CGI*				X	X		

Table 1. Schedule of visits and assessments to measure study outcome per group. CI: cochlear implantation; e.o.s: end of study; Rx: randomization; * questionnaires (Q) will be filled in at home;

Primary outcome measure

Our primary outcome is tinnitus burden as measured with the validated Tinnitus Functional Index (TFI). The Tinnitus Functional Index (TFI) is a 25 items containing questionnaire with statements/questions about tinnitus burden [20,21]. The index is divided in 8 subscale items: intrusive, sense of control, cognitive, sleep, auditory, relaxation and quality of life. Possible answers are ranging between 0 and 10, resulting in a maximum score of 100, representing a maximum burden of tinnitus. This total score is then categorized into five different grades, indicating low to high burden.

Secondary outcome measures

Audiological tests

Five audiological measurements are included in the study and are performed by an audiologist according to the ISO 16832:2006 [22].

Pure tone audiometry

The first evaluation is a pure tone audiometry (PTA) at 0.25, 0.5, 1, 1.5, 2, 4 kHz. This standard measurement evaluates the audible threshold of the patient by having patients indicating audibility for frequency specific pure tone stimuli at different loudness level. The evaluation results in an audiogram which provides information about the hearing level of the patients.

Speech recognition test in quiet and noise

The second evaluation is a speech recognition test in quiet and noise. For the patients receiving a cochlear implant, post-intervention assessments will be applied with the CI. The participant is listening at digits, phonic words and Dutch words in a sound-treated booth. The loudness of the speech will change during the test in steps of 2 dBs, but the noise signal will be presented at a constant level of 65dB SPL. The patient is asked to repeat back the words. The patient will perform the same test in two different conditions: with or without noise. The speech in noise test will be stopped if the patient is unable to understand speech at a signal-to-noise ratio (SNR) > 20 dB. This test results in a Speech Reception Threshold (SRT) obtained by averaging the signal-to-noise ratio over the list of words presented in order to obtain a 50% correct score. The outcome will permit to set up a rehabilitation program with a speech therapist for the intervention group.

Electrocochleography

Electrocochleography (ECochG) is a technique to record electrical potentials generated in the inner ear and auditory nerve in response to acoustic stimulation. ECochG measurement will be performed intra-operatively and at 3 and 6 months after cochlear implantation. The measure will be followed by conventional audiological examination. During the measurement postoperatively, the patient will be asked to sit comfortably on a chair and not move. The operator will install the earplug in the patient's ear and connect it to an audio cable attached to a sound processor. The sound processor will generate acoustic stimulation through the audio cable and the electrical responses will be recorded in real time via the Cochlear™ Research Platform (v1.1, Cochlear Ltd). The ECochG provides a measure of the cochlear function.

Pitch match experiment

Pitch match of tinnitus is performed to find the pitch corresponding to the tinnitus pitch of the patient. An acoustic pitch matching and an electric pitch matching will be performed in a sound-treated booth. The acoustic pitch matching will provide information about the frequency of the tinnitus perceived whereas the electric pitch matching will provide information about the pitch matched electrode. They are obtained using a two-Alternative Forced-Choice (2AFC) method and a 1 up 2 down adaptive staircase rule [23]. The patient will be asked to concentrate on the predominant pitch of their tinnitus. Two tones will be presented at the same intensity level previously matched with tinnitus. The patient will indicate which option, the first or the second, sounds the closest in pitch by manipulating the response switch forward and backward. The difference between the first and the second will become smaller and smaller, until there is one frequency that matches best. Each stimulation will be performed twice (apical-to-basal and basal-

to-apical to prevent octave-confusion). The pitch matched will be identified as the pitch resulting of the two runs. If the result of the two runs is not the same, the procedure will be repeated until finding a consistent result at least two times [24].

Loudness match experiment

Loudness match of tinnitus is performed to find the loudness corresponding to the tinnitus acoustically and electrically [25]. The experiment uses different pure tones at 0.5, 1, 2, 3 and 4 kHz and a 2AFC method. The pure tones are initially presented at 6 dB above threshold. The patient is instructed to adjust the loudness of the comparison tones to match that of their tinnitus. The adjustment of the intensity is made in a range of 5dB for rough determination and then 1 dB steps until a satisfactory loudness match in obtained.

CI usage

The history of several user characteristics will be logged from the processor. This provides the following outcome parameters:

- Time on air, providing the time the device was used in speech environment or the device was off
- Scenes, providing the time spending in different environments: quiet, speech, noise, speech in noise, music and wind
- Level of the environmental sound in dBA
- Program usage, providing a daily average on program usage

Questionnaires

Questionnaires will be sent by e-mail to the study participants through the data management program Castor EDC [26]. If participants do not want to perform online questionnaires, they will receive paper versions of the questionnaires by postal services. All questionnaires will be in the Dutch language.

Tinnitus questionnaire

- The Visual Analogue Scale (*VAS) Tinnitus* has 2 items. The patient answers two questions about tinnitus severity and intrusiveness using a visual analogue scale that ranges from 0 (not at all) to 10 (extremely).

Patient reported benefits

- The *Clinical Global Impression (CGI)* consists of a 1-item observer-rated scale that measures global improvement or change (CGIC) [27]. The question is scored on a scale from 1 to 7, 1 meaning “Very much improved” to 7 meaning “Very much worse”.
- The *Glasgow Benefit Inventory (GBI)* is a validated questionnaire reporting change in health-related quality of life post-intervention [28]. It consists of 18 questions scored on a 5-points Likert scale where 1 indicates “much worse” and 5 is for “much better”. The questionnaire presents three different items: general subscale, social support and physical health.

Quality-of-life (QoL) questionnaires

- The *EQ5D* is a standardized measure of generic health status. It contains only 5 questions. Each question deals with a specific domain: mobility, self-care, usual activities, pain/discomfort and anxiety/depression [29]. The patient must choose between different sentences which corresponds to his/her health condition. The last question is a self-report of the overall health status using a visual analogue scaling from 0 (the worst health you can imagine) to 100 (the best health you can imagine).
- The *Speech, Spatial and Qualities Hearing Scale (SSQ)* measures hearing related quality of life and consists of three scales that assess different domains of hearing: 1) the speech hearing subscale consists of 15 questions that assess the ability to separate speech from competing noise in a wide range of listening contexts, 2) the spatial hearing subscale consists of 17 questions that assess the ability to locate sound sources and their direction of movement, 3) the quality of hearing subscale consists of 19 questions that assess naturalness and clarity of sound sources [30]. Possible answers are scored using a visual analogue scale ranging from 0 (not at all) to 10 (excellent).

Comorbid symptom scores

- The *Beck Depression Inventory (BDI)* is a twenty-one items questionnaire used as an indicator of the severity of depression [31]. Each question is scored on four points ranged between 0 (for example ‘I do not feel sad’) and 3 (‘I am so sad’) with a maximum of total score of 63.
- The *Hospital Anxiety and Depression Scale (HADS)* is a fourteen-item screening tool for anxiety and depression symptoms in non-psychiatric clinical populations [32,33]. Each

sentence is scored between 0 and 3 where 0 confirms the sentence and 3 disagrees with it.

Statistical analysis

Baseline characteristics per group will be described as means or medians, depending on the normality of the data, and standard deviations. Between-group mean differences will be calculated with 95% confidence intervals. A p-value <0.05 is considered statistically significant.

The primary outcome will be the difference in TFI score between the intervention at 6 months after cochlear implantation and the control group after six months of no intervention, a continuous variable. Differences between the control and intervention group will be calculated using the unpaired t-test and the Mann-Whitney u test. The secondary outcome measures will be the performances on the auditory tests and the questionnaires. Differences between groups will be calculated using the unpaired t-test and the Mann-Whitney u test. Within-subject comparisons will entail differences of mean values. These will be analyzed using paired t-tests for continuous measures.

Interim analyses on the safety data will be performed and reviewed by a data safety monitoring board (DSMB). An interim analysis will be done every three months starting after the 5 first patients reached 3 months of follow-up. A statistician will perform non-parametric test on the pure tone average (PTA) at 0.25, 0.5, 1, 1.5 kHz without CI and speech perception unaided and aided to monitor the residual hearing preservation. The DSMB will advise on stopping the study if there is a risk for the patient's safety based on tinnitus worsening and deterioration of hearing.

Potential missing data will be handled using multiple imputation. Complete cases analyses will be done as a sensitivity analysis. All analyses will be performed on an intention-to-treat basis.

Ethics and dissemination

The study will be conducted according to the principles of the Declaration of Helsinki (version 2013, Fortaleza) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The research protocol was approved by the Institutional Review Board (IRB) of the UMC Utrecht (NL70319.041.19) and the Dutch competent authorities.

All amendments will be notified to the local Medical Research Ethics Committee (MREC). The data from this study will be used for publication in peer-reviewed international journals, preferably

open-access. To diminish possible chance on publication bias, the study will be reported using the CONSORT guidelines [34].

All data will be treated confidentially. The data will be encrypted by using an unique patient identification number. The analysis will be performed with these coded patient data. The key code will be safeguarded by the investigators. The paper data files and informed consents will be stored in a locked cabin in a locked room. The data will be stored on the investigator's computer as well, which is secured by a password and situated in a locked room. The handling of personal data will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation, the Uitvoeringswet AVG, UAVG. The final trial data set will be safeguarded and available to the principal investigator and approved members of the research team.

The investigator will submit a summary of the progress of the trial to the accredited MREC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

All cases of serious adverse events will be reported to the local IRB and the Dutch competent authorities. Trial quality will be monitored independently by the Julius Clinical Centre (UMC Utrecht, the Netherlands) according to regulations by the UMC Utrecht and the Dutch government. The local monitor will check 50% of signed ICs, inclusion and exclusion criteria, source data and serious adverse events (SAE).

Trial status

The study is currently in recruitment phase.

Abbreviations

BDI	Beck Depression Inventory
CBT	Cognitive Behavioral Therapy
CI	Cochlear Implant
CGI	Client Global Impression
CONSORT	Consolidated Standard of Reporting Trials

CT	Computerized Tomography
DTT	Digit Triplet Test
ECochG	Electrocochleography
ENT	Ear, Nose and Throat
EQ5D	Euro-QoL 5D
EU	European Union
GBI	Glasgow Benefit Inventory
HADS	Hospital Anxiety and Depression Scale
IC	Informed Consent
IRB	Institutional Review Board
MREC	Medical Review Ethics Committee
MSF	Master Study File
OPD	Outpatient department
OR	Operating room
PTA	Pure Tone Average
QoL	Quality-of-life
RCT	Randomized controlled trial
SAE	Serious Adverse Event
SNR	Signal-to-Noise Ratio
SRT	Speech Reception Threshold
SSD	Single Sided Deafness
SSQ	Speech, Spatial and Qualities Hearing Scale
TFI	Tinnitus Functional Index
UMCU	University Medical Center

VAS	Visual analogue scale
WMO	Medical Research Involving Human Subjects Act
2AFC	Two-Alternative Forced-Choice

Authors' contributors

All authors (KKSA, ALS, IS, KSR, RJS and BvD) developed the protocol. IS provided statistical expertise in clinical trial design. KKSA drafted the manuscript. All other authors revised the manuscript. All authors read and approved the final version.

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Competing interests

KKSA received funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant (agreement number 764604). KSSA and BvD are employed at Cochlear Technology Centre, Mechelen, Belgium. No further conflict of interest is reported by the authors.

Ethical approval

This research protocol was approved by the Institutional Review Board (IRB) of the UMC Utrecht (NL70319.041.19, V4, April 2020).

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Figure legends

Figure 1: Study flowchart.

CI: cochlear implant group; Control: control group

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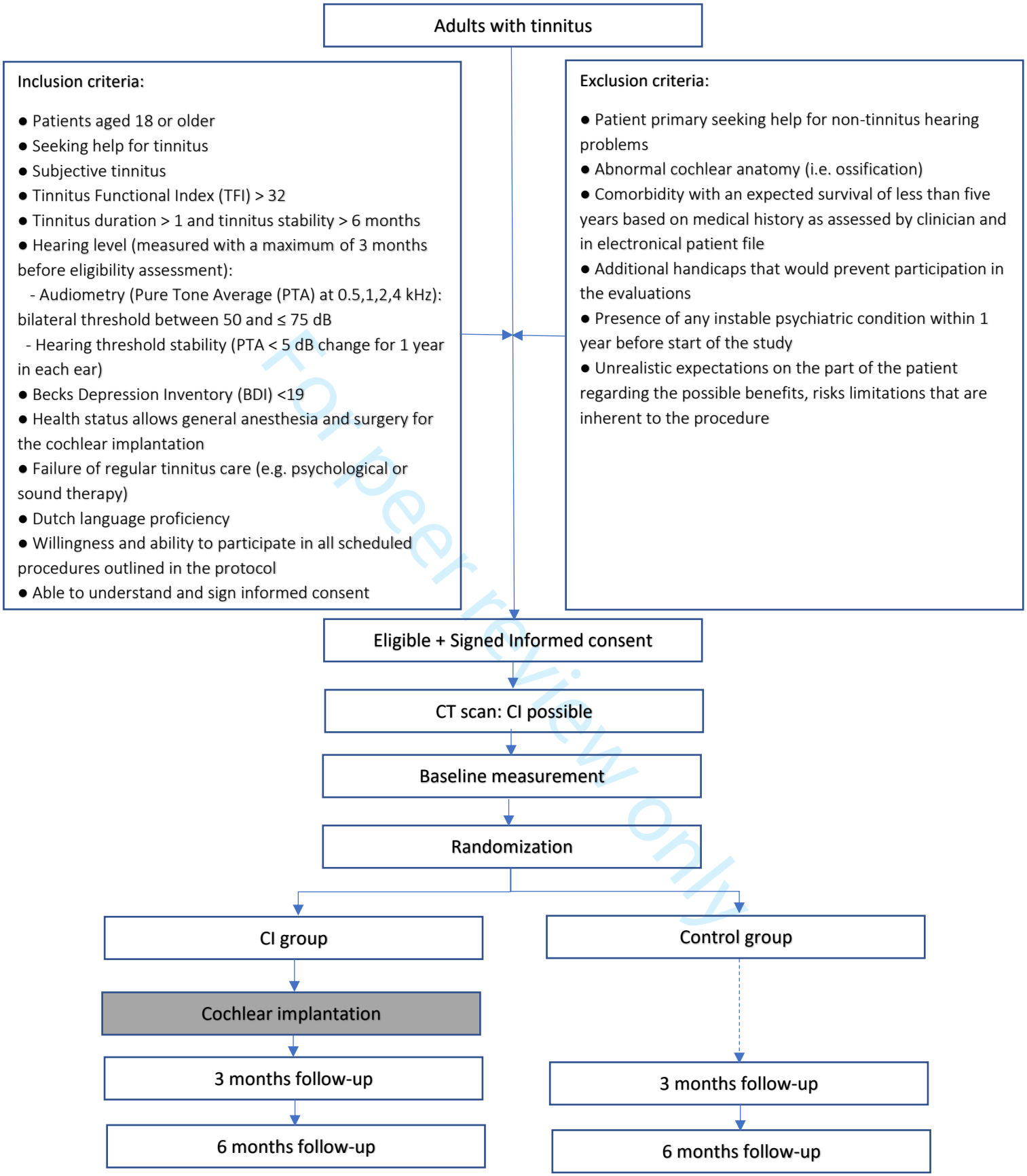

Figure 1. Study flowchart.
CI: cochlear implant group; Control: control group

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	18
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	n/a

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8-9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-14

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	8

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further	15

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15, 17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Cochlear implantation for tinnitus in adults with bilateral hearing loss: protocol of a randomized controlled trial

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Cochlear implantation for tinnitus in adults with bilateral hearing loss: protocol of a randomized controlled trial

K.S. Kelly Assouly[1, 2, 3 *], L. Adriana Smit[1, 2], Inge Stegeman [1, 2], S. Koen Rhebergen[1, 2], Bas van Dijk[3] and J. Robert Stokroos[1, 2]

[1]Department of Otorhinolaryngology and Head & Neck Surgery, University Medical Center Utrecht, the Netherlands
[2]Department of Clinical and Experimental Neuroscience, University Medical Center Utrecht Brain Center, Utrecht University, Utrecht, The Netherlands
[3]Cochlear Technology Center, Mechelen, Belgium

*Corresponding author:

Postal address: University Medical Center Utrecht, Room number H.02.104, P.O. Box 85500,

3508 GA UTRECHT

Tel: +31887555555

E-mail:K.K.S.Assouly@umcutrecht.nl

Abstract

Introduction

Tinnitus is the perception of sound without an external stimulus, often experienced as a ringing, buzzing sound. Subjective tinnitus is assumed to origin from changes in neural activity caused by reduced or lack of auditory input, for instance due to hearing loss. Since auditory deprivation is thought to be one of the causes of tinnitus, increasing the auditory input by cochlear implantation might be a possible treatment. In studies assessing cochlear implantation for patients with hearing loss, tinnitus relief was seen as a secondary outcome. Therefore, we will assess the effect of cochlear implantation in patients with primarily tinnitus complaints.

Method and analysis

In this randomized controlled trial starting in January 2021 at the ENT department of the UMC Utrecht (the Netherlands), patients with a primary complaint of tinnitus will be included. Fifty patients (Tinnitus Functional Index (TFI) $\geq$ 32, Beck's Depression Index (BDI) < 19, pure tone average at 0.5,1,2,4 kHz: bilateral threshold between 50 and ≤ 75 dB) will be randomized towards cochlear implantation or no intervention. Primary outcome of the study is tinnitus burden as measured by the TFI. Outcomes of interest are tinnitus severity, hearing performances (tinnitus pitch and loudness, speech perception), quality of life, depression and patient related changes. Outcomes will be evaluated prior to implantation and at 3 and 6 months after the surgery. The control group will receive questionnaires at 3 and 6 months after randomization. We expect a significant difference between the cochlear implant recipients and the control group for tinnitus burden.

Ethics and dissemination

This research protocol was approved by the Institutional Review Board of the University Medical Center (UMC) Utrecht (NL70319.041.19, V5.0, January 2021). The trial results will be made accessible to the public in a peer-review journal.

Trial registration NL8693.

Keywords: Tinnitus, Cochlear implantation, Bilateral hearing loss

Strengths and limitations of this study

- The randomized controlled study allows for high quality assessment of outcomes of cochlear implantation for patients suffering primarily from tinnitus and secondarily from moderate to moderately severe bilateral hearing loss.
- Outcomes of interest are not limited to tinnitus burden but also consider anxiety and depression, quality of life and patient related changes.
- The intervention can induce risks associated with surgery and a residual hearing deterioration in the ear implanted which will be monitored by electrocochleography measurement.
- This study is a further step towards evidence-based medicine for the clinical efficacy of cochlear implants as a tinnitus treatment.

Background

Tinnitus is the perception of sound without an external stimulus, often experienced as a ringing or buzzing sound [1,2]. It is a common symptom with an approximate prevalence of 10-30%, depending on the selected population [3], increasing to 30% of adults over the age of 50 years [4]. Tinnitus can be chronic and disabling for those individuals affected by it. It is a complex condition, in which many components are responsible for perceived burden, like loudness, comorbidity and sleep problems. The heterogeneous aspect of the disease is also accountable for differences in the tinnitus itself: localization, sound characteristics, temporal course and underlying cause. The tinnitus burden and the individual needs of patients for tinnitus related health care are various. While the underlying etiology of tinnitus is still debated, one hypothesis is that the tinnitus arises from changes in neural activity caused by reduced or lack of auditory input due to hearing loss which often accompanies the tinnitus [5,6]. Till date, the only evidence-based therapy for the reduction of tinnitus burden is cognitive behavioral therapy (CBT) [5,7–9] which is offered as standard clinical care in many countries in people with bothersome tinnitus [10]. However, this therapy only improves tinnitus distress but does not reduce tinnitus loudness [11]. Sound therapy is also considered as a recommendation for patients with hearing loss according to European guidelines but there is a lack of conclusive evidence [10,12,13].

Since auditory deprivation is thought to be one of the causes of tinnitus, increasing the auditory input by cochlear implantation might be a possible treatment option. This hypothesis is confirmed by observations in studies assessing the effectiveness of cochlear implantation to restore hearing function in case of bilateral deafness, where tinnitus reduction is one of the secondary outcomes [14]. Analyzing the effect of intracochlear electrical stimulation with a cochlear implant (CI) on primarily tinnitus complaints has been investigated by only few studies. All studies assessing the effect of cochlear implantation for tinnitus concerned cases with single-sided deafness [15–20] or patients with asymmetrical hearing loss [6]. They all reported a significant tinnitus reduction after implantation. So far, there is no high level of evidence of the effect of intracochlear stimulation as an intervention for primary tinnitus complaint in case of bilateral moderate to severe hearing loss [14].

Above mentioned studies provide the first evidence of possible effectiveness of cochlear implantation for the reduction of tinnitus burden. To provide clear evidence of the effectiveness of cochlear implantation for the suppression of tinnitus complaints, a statistically powered study is needed aiming at patients with tinnitus as their primary complaint instead of hearing loss. To what extent electrical stimulation can reduce tinnitus in patients with bilateral moderate to severe hearing loss (just below the current CI indication), but with primary complaint of tinnitus, is

unknown [21]. Therefore, we aim to study the effect of cochlear implantation on tinnitus burden in patients suffering primarily from tinnitus and failed standard clinical care. For these patients which also have a bilateral moderate to severe hearing loss a randomized controlled trial will be conducted in which cochlear implantation will be compared to no intervention.

Method and analysis

Study objectives

The primary objective of this study is to assess the effect of electrical stimulation by a CI on tinnitus burden, measured with the Tinnitus Functional Index (TFI) at 6 months after cochlear implantation. Secondary outcomes are to assess the effect of CI on tinnitus severity, tinnitus pitch and loudness, auditory function, speech recognition, quality of life, symptoms of depression and anxiety, patient reported change in order to attest treatment-related differences.

Patient involvement

Patients were not involved in the design, or conduct, or reporting, or dissemination plans of the study.

Study design and setting

The study is a monocenter clinical trial performed in a tertiary referral clinic (university hospital) in the Netherlands (University Medical Center Utrecht). The protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials statement [22]. In this randomized controlled trial (RCT), patients will be randomized into groups: a CI group and a control group (Fig. 1). 25 patients (CI group) shall receive a CI in the ear mostly affected by tinnitus. The other 25 patients (control group) shall follow a follow up period of 6 months with no intervention. The follow-up sessions will take place 3 and 6 months after implantation to assess the primary outcome of tinnitus burden and secondary outcomes of quality of life, treatment related outcomes and auditory function.

[Insert Figure 1]

Study population

The study population consists of patients seeking help for tinnitus, presenting at the outpatient clinic of Ear, Nose and Throat (ENT) of the UMC Utrecht, The Netherlands. 50 patients aged 18 or older with moderate to severe tinnitus and moderate to severe hearing loss will be included

after fulfilling eligibility and informed consent. They must meet the following criteria to be eligible for the study at randomization.

Inclusion criteria

The eligibility criteria for patients are:

- Patients aged 18 or older
- Seeking help for tinnitus
- Subjective tinnitus
- Moderate to catastrophic tinnitus burden: Tinnitus Functional Index (TFI) > 32
- Tinnitus duration > 1 year and tinnitus stability > 6 months
- Hearing level (measured with a maximum of 3 months before eligibility assessment):
    - Audiometry (Pure Tone Average (PTA) at 0.5,1,2,4 kHz): bilateral threshold between 50 and ≤ 75 dB
        - Hearing threshold stability (PTA < 5 dB change for 1 year in each ear)
- No to mild depression: Becks Depression Inventory (BDI) <19
- Health status allows general anesthesia and surgery for the cochlear implantation
- Failure of regular tinnitus care (e.g. psychological or sound therapy)
- Dutch language proficiency
- Willingness and ability to participate in all scheduled procedures outlined in the protocol
- Able to understand and sign informed consent

Exclusion criteria

A potential patient who meets any of the following criteria will be excluded from participation in this study:

- Patient primary seeking help for non-tinnitus hearing problems
- Abnormal cochlear anatomy (i.e. ossification)
- Comorbidity with an expected survival of less than five years based on medical history as assessed by clinician and in electronical patient file
- Additional handicaps that would prevent participation in the evaluations
- Presence of any instable psychiatric condition within 1 year before start of the study
- Unrealistic expectations on the part of the patient regarding the possible benefits, risks and limitations that are inherent to the procedure

If a patient is eligible for the study, his/her otorhinolaryngologist will ask him/her to participate. The content of the study will be explained by the patient's otorhinolaryngologist who will provide him/her written patient information and the informed consent form. Patients will be given 2 weeks to consider participation. If a patient meets the criteria for in- and exclusion and wants to take part in the study, the patient will be asked to come to the UMC Utrecht for a computerized tomography (CT) scan to visualize the anatomy of the mastoid. If the patient's CT scan shows normal cochlear anatomy, he will, during the same visit, sign the informed consent with a member of the research team and receive a copy of the consent. After inclusion, baseline measurement will be performed where after randomization will take place.

Recruitment status and trial dates

Patient enrolment started in January 2021 and will be completed in June 2022. The surveys and measurement will be performed until January 2023.

Randomization

After inclusion and baseline measurement, patients will be randomly allocated into one of the two groups: CI group or control group. The randomization will be computer-generated with block sizes of 4 and 6 and stratified for TFI score. A website randomization program, developed by Castor EDC [23] will be used for randomization. A study database was set up in Castor EDC to support allocation and concealment. Investigators enter information for each eligible patient and the randomization assignment is revealed once the investigators validate the inclusion of the patient. The block design is unavailable to those who assign participants until the moment of assignment.. Blinding is not possible during this study since both patients and caregivers will be able to see from outside whether patients have a CI or not.

Intervention

Patients allocated to the intervention group will receive a CI. The CI will be implanted on the most affected tinnitus side, and if equal tinnitus in the two ears, in the ear with the worst hearing loss. Hearing aid will be allowed in the contralateral ear. The cochlear implantation will be carried out under general anesthesia after consent of the anesthesiologist and after determination of general health status. The standard surgical procedures for cochlear implantation will be followed. A retro-auricular incision will be made to expose the mastoid. The electrode will be inserted via a posterior tympanotomy and round window implantation by soft-surgery techniques. Intraoperatively, normal functioning of the device will be checked by measurement of impedance and neural response

telemetry. Electrocochleography will also be recorded intraoperatively using Cochlear™ Research Platform (v1.1). The cochlear implant used for the study consists of a Nucleus 7 sound processor and a CI622 implant with a slim straight electrode from Cochlear (or similar). Serial numbers of the CIs will be registered in the operating room (OR) report by the surgeon (standard clinical care for cochlear implantation) and in the master study file (MSF) (product accountability). A post-operative Cone Beam CT of the mastoid will be planned to detail the electrode location within the cochlea.

One week after surgery patients from the intervention group will be checked at the outpatient department (OPD) of the ENT to check for wound healing. The rehabilitation phase will start 4 weeks after surgery with a visit of the patient to the department of Audiology to custom fit the processor software and then (bi)weekly till week eleven after surgery to fine-tune the programming of the implant and improve speech perception. The CI fitting will not differ from the standard of care and will be optimized for every patient.

In the follow-up phase, the patients with CI will return to the UMC Utrecht 3 and 6 months after implantation to assess study outcome by the research team. The patients of the control group will come to the UMC Utrecht 3 and 6 months after randomization to assess the same study outcome. A questionnaire will have to be filled in at home by the patients before every follow-up session at 3 and 6 months, as well as 2 weeks after surgery for the intervention group.

Participants are not allowed to start another tinnitus treatment during the study.

Sample size

To detect a clinically relevant difference of 1 grade (15 points) change measured with the TFI [24], in tinnitus burden at 6 months after cochlear implantation compared to the control group, with a power of 90% and alpha of 0.05, 23 patients are needed in both arms of the study. An acceptable standard deviation was set at 15, based on the results of a previous pilot study assessing CI for tinnitus patients [20]. We will include 25 patients per arm, a 10% margin, to include for possible lost to follow up. Thereby, we expect patients to have a mean TFI at baseline of 50 points on TFI (Grade 3) and a TFI decrease of 15 points at 6 months after intervention with a mean endpoint of 35 points on TFI (Grade 2).

Outcomes

The following outcomes will be assessed at the baseline visit and follow up visits at 3 and 6 months after randomization (Table 1). All measurements will be performed by the research team following the same protocol procedures.

	Baseline	CI GROUP				CONTROL GROUP	
	Rx	CI	2 w post CI	3 m post CI	6 m post CI	Rx + 3 m	Rx + 6 m
CI (surgery)		X					
CT scan	X	X					
Electro-cochleography		X		X	X		
Hearing level				X	X	X	X
Speech perception	X			X	X	X	X
Tinnitus pitch match	X			X	X	X	X
Tinnitus loudness match	X			X	X	X	X
TFI*	X			X	X	X	X
VAS Tinnitus *	X		X	X	X	X	X
SSQ*	X			X	X	X	X
EQ5D*	X			X	X	X	X
HADS*	X			X	X	X	X
BDI*					X		X
GBI*					X		
CGI*				X	X		
ESIT-SQ*	X						

Table 1. Schedule of visits and assessments to measure study outcome per group.

CI: cochlear implantation; e.o.s: end of study; Rx: randomization; * questionnaires (Q) will be filled in at home;

Primary outcome measure

Our primary outcome is tinnitus burden as measured with the validated Tinnitus Functional Index (TFI). The Tinnitus Functional Index (TFI) is a 25 items containing questionnaire with statements/questions about tinnitus burden [24,25]. The index is divided in 8 subscale items: intrusive, sense of control, cognitive, sleep, auditory, relaxation and quality of life. Possible answers are ranging between 0 and 10, resulting in a maximum score of 100, representing a maximum burden of tinnitus. This total score is then categorized into five different grades, indicating low to high burden.

Secondary outcome measures

Audiological tests

Five audiological measurements are included in the study and are performed by an audiologist according to the ISO 16832:2006 [26].

Pure tone audiometry

The first evaluation is a pure tone audiometry (PTA) at 0.25, 0.5, 1, 1.5, 2, 4 kHz. This standard measurement evaluates the audible threshold of the patient by having patients indicating audibility for frequency specific pure tone stimuli at different loudness level. The evaluation results in an audiogram which provides information about the hearing level of the patients.

Speech recognition test in quiet and noise

The second evaluation is a speech recognition test in quiet and noise. For the patients receiving a cochlear implant, post-intervention assessments will be applied with the CI. The participant is listening at digits, Dutch words and sentences in a sound-treated booth. The loudness of the speech will change during the test in steps of 2 dBs, but the noise signal will be presented at a constant level of 65dB SPL. The patient is asked to repeat back the words. The patient will perform the same test in two different conditions: with or without noise. This test results in a Speech Reception Threshold (SRT) obtained by averaging the signal-to-noise ratio over the list of words presented in order to obtain a 50% correct score. The outcome will permit to set up a rehabilitation program with a speech therapist for the intervention group.

Electrocochleography

Electrocochleography (ECochG) is a technique to record electrical potentials generated in the inner ear and auditory nerve in response to acoustic stimulation. ECochG measurement will be performed intra-operatively and at 3 and 6 months after cochlear implantation. The measure will be followed by conventional audiological examination. During the measurement postoperatively, the patient will be asked to sit comfortably on a chair and not move. The operator will install the earplug in the patient's ear and connect it to an audio cable attached to a sound processor. The sound processor will generate acoustic stimulation through the audio cable and the electrical responses will be recorded in real time via the Cochlear™ Research Platform (v1.1, Cochlear Ltd). The ECochG provides a measure of the cochlear function.

Pitch match experiment

Pitch match of tinnitus is performed to find the pitch corresponding to the tinnitus pitch of the patient. An acoustic pitch matching and an electric pitch matching will be performed in a sound-treated booth. The acoustic pitch matching will provide information about the frequency of the tinnitus perceived whereas the electric pitch matching will provide information about the pitch matched electrode. The patient will be asked to concentrate on the predominant pitch of their tinnitus. Two tones will be presented at the same intensity level previously matched with tinnitus. The patient will indicate which option, the first or the second, sounds the closest in pitch by manipulating the response switch forward and backward. The difference between the first and the second will become smaller and smaller, until there is one frequency that matches best. Each stimulation will be performed twice (apical-to-basal and basal-to-apical to prevent octave-confusion). The pitch matched will be identified as the pitch resulting of the two runs. If the result of the two runs is not the same, the procedure will be repeated until finding a consistent result at least two times [27].

Loudness match experiment

Loudness match of tinnitus is performed to find the loudness corresponding to the tinnitus acoustically and electrically [28]. The experiment uses the tinnitus pitch matched. The pure tones are initially presented at 6 dB above threshold. The patient is instructed to adjust the loudness of the comparison tones to match that of their tinnitus. The adjustment of the intensity is made in a range of 5dB for rough determination and then 1 dB steps until a satisfactory loudness match in obtained.

CI usage

The history of several user characteristics will be logged from the processor. This provides the following outcome parameters:

- Time on air, providing the time the device was used in speech environment or the device was off
- Scenes, providing the time spending in different environments: quiet, speech, noise, speech in noise, music and wind
- Level of the environmental sound in dBA
- Program usage, providing a daily average on program usage

Questionnaires

Questionnaires will be sent by e-mail to the study participants through the data management program Castor EDC [23]. If participants do not want to perform online questionnaires, they will receive paper versions of the questionnaires by postal services. All questionnaires will be in the Dutch language.

Tinnitus questionnaire

- The Visual Analogue Scale (*VAS) Tinnitus* has 2 items. The patient answers two questions about tinnitus severity and intrusiveness using a visual analogue scale that ranges from 0 (not at all) to 10 (extremely).

Tinnitus history

- The *ESIT Screening Questionnaire* (ESIT-SQ) [29] consists of 39 items relevant for tinnitus profiling including 17 general and 22 tinnitus-specific questions. Every question present multiple choice. The test is used a baseline questionnaire and takes approximately 10 minutes to fill in.

Patient reported benefits

- The *Clinical Global Impression (CGI)* consists of a 1-item observer-rated scale that measures global improvement or change (CGIC) [30]. The question is scored on a scale from 1 to 7, 1 meaning “Very much improved” to 7 meaning “Very much worse”.
- The *Glasgow Benefit Inventory (GBI)* is a validated questionnaire reporting change in health-related quality of life post-intervention [31]. It consists of 18 questions scored on a 5-points Likert scale where 1 indicates “much worse” and 5 is for “much better”. The

questionnaire presents three different items: general subscale, social support and physical health.

Quality-of-life (QoL) questionnaires

- The *EQ5D* is a standardized measure of generic health status. It contains only 5 questions. Each question deals with a specific domain: mobility, self-care, usual activities, pain/discomfort and anxiety/depression [32]. The patient must choose between different sentences which corresponds to his/her health condition. The last question is a self-report of the overall health status using a visual analogue scaling from 0 (the worst health you can imagine) to 100 (the best health you can imagine).
- The *Speech, Spatial and Qualities Hearing Scale (SSQ)* measures hearing related quality of life and consists of three scales that assess different domains of hearing: 1) the speech hearing subscale consists of 15 questions that assess the ability to separate speech from competing noise in a wide range of listening contexts, 2) the spatial hearing subscale consists of 17 questions that assess the ability to locate sound sources and their direction of movement, 3) the quality of hearing subscale consists of 19 questions that assess naturalness and clarity of sound sources [33]. Possible answers are scored using a visual analogue scale ranging from 0 (not at all) to 10 (excellent).

Comorbid symptom scores

- The *Beck Depression Inventory (BDI)* is a twenty-one items questionnaire used as an indicator of the severity of depression [34]. Each question is scored on four points ranged between 0 (for example 'I do not feel sad') and 3 ('I am so sad') with a maximum of total score of 63.
- The *Hospital Anxiety and Depression Scale (HADS)* is a fourteen-item screening tool for anxiety and depression symptoms in non-psychiatric clinical populations [35,36]. Each sentence is scored between 0 and 3 where 0 confirms the sentence and 3 disagrees with it.

Statistical analysis

Baseline characteristics per group will be described as means or medians, depending on the normality of the data, and standard deviations. Between-group mean differences will be calculated with 95% confidence intervals. A p-value <0.05 is considered statistically significant.

The primary outcome will be the difference in TFI score between the intervention at 6 months after cochlear implantation and the control group after six months of no intervention, a continuous variable. Differences between the control and intervention group will be calculated using the unpaired t-test and the Mann-Whitney u test. The secondary outcome measures will be the performances on the auditory tests and the questionnaires. Differences between groups will be calculated using the unpaired t-test and the Mann-Whitney u test. Within-subject comparisons will entail differences of mean values. These will be analyzed using paired t-tests for continuous measures.

Interim analyses on the safety data will be performed and reviewed by an external data safety monitoring board (DSMB). An interim analysis will be done every six months starting after the 5 first patients reached 6 months of follow-up. A statistician will perform non-parametric test on the aided speech perception of the implanted ear only, performed 6 months post-implantation to monitor functional hearing performance. The DSMB will advise on stopping the study if there is a risk for the patient's safety based on tinnitus worsening and deterioration of functional hearing.

Potential missing data will be handled using multiple imputation. Complete cases analyses will be done as a sensitivity analysis. All analyses will be performed on an intention-to-treat basis.

Ethics and dissemination

Protocol version

The study will be conducted according to the principles of the Declaration of Helsinki (version 2013, Fortaleza) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The research protocol was approved by the Institutional Review Board (IRB) of the UMC Utrecht (NL70319.041.19) and the Dutch competent authorities.

Protocol amendment

All amendments will be notified to the local Medical Research Ethics Committee (MREC). The data from this study will be used for publication in peer-reviewed international journals, preferably open-access. To diminish possible chance on publication bias, the study will be reported using the CONSORT guidelines [37].

Confidentiality

All data will be treated confidentially. The data will be encrypted by using an unique patient identification number. The analysis will be performed with these coded patient data. The key code

will be safeguarded by the investigators. The paper data files and informed consents will be stored in a locked cabin in a locked room. The data will be stored on the investigator's computer as well, which is secured by a password and situated in a locked room. The handling of personal data will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation, the Uitvoeringswet AVG, UAVG. The final trial dataset will be safeguarded and available to the principal investigator and approved members of the research team.

Data monitoring and auditing

The investigator will submit a summary of the progress of the trial to the accredited MREC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments. Trial quality will be monitored independently by the Julius Clinical Centre (UMC Utrecht, the Netherlands) according to regulations by the UMC Utrecht and the Dutch government. The local monitor will check 50% of signed ICs, inclusion and exclusion criteria, source data and serious adverse events (SAE). Due to the high-risk nature of the study, an external data safety monitoring board (DSMB) will be in place to perform ongoing safety surveillance. An interim analysis will be performed by the statistician of the research group and will be analyzed by the DSMB every 6 months after the 5th first inclusions.

Adverse events

Besides the normal risks associated with surgery and general anaesthesia, adverse events related to cochlear implantation will be monitored by assessment and documentation of intra- and post-operative complications and device failures. Deterioration of the hearing < 30 dBs (PTA) is expected after implantation because of the cochlear trauma and should not be considered as an adverse event [38,39]. All adverse events will be followed until they have abated or until a stable situation has been reached. All cases of serious adverse events will be reported to the local IRB and the Dutch competent authorities.

Trial status

The study is currently in recruitment phase.

Abbreviations

BDI	Beck Depression Inventory
CBT	Cognitive Behavioral Therapy
CI	Cochlear Implant
CGI	Client Global Impression
CONSORT	Consolidated Standard of Reporting Trials
CT	Computerized Tomography
DSMB	Data Safety Monitoring Board
DTT	Digit Triplet Test
ECochG	Electrocochleography
ENT	Ear, Nose and Throat
EQ5D	Euro-QoL 5D
ESIT-SQ	European School for Interdisciplinary Tinnitus Research Screening Questionnaire
EU	European Union
GBI	Glasgow Benefit Inventory
HADS	Hospital Anxiety and Depression Scale
IC	Informed Consent
IRB	Institutional Review Board
MREC	Medical Review Ethics Committee
MSF	Master Study File
OPD	Outpatient department
OR	Operating room
PTA	Pure Tone Average
QoL	Quality-of-life

RCT	Randomized controlled trial
SAE	Serious Adverse Event
SNR	Signal-to-Noise Ratio
SRT	Speech Reception Threshold
SSD	Single Sided Deafness
SSQ	Speech, Spatial and Qualities Hearing Scale
TFI	Tinnitus Functional Index
UMCU	University Medical Center
VAS	Visual analogue scale
WMO	Medical Research Involving Human Subjects Act
2AFC	Two-Alternative Forced-Choice

Authors' contributors

All authors (KKSA, ALS, IS, KSR, RJS and BvD) developed the protocol. IS provided statistical expertise in clinical trial design. KKSA drafted the manuscript. All other authors revised the manuscript. All authors read and approved the final version.

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Competing interests

KKSA received funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant (agreement number 764604). KSSA and BvD are employed at Cochlear Technology Centre, Mechelen, Belgium. No further conflict of interest is reported by the authors.

Ethical approval

This research protocol was approved by the Institutional Review Board (IRB) of the UMC Utrecht (NL70319.041.19, V5, January 2021).

Word count: 3926 words

Figure legends

Figure 1: Study flowchart.

CI: cochlear implant group; Control: control group

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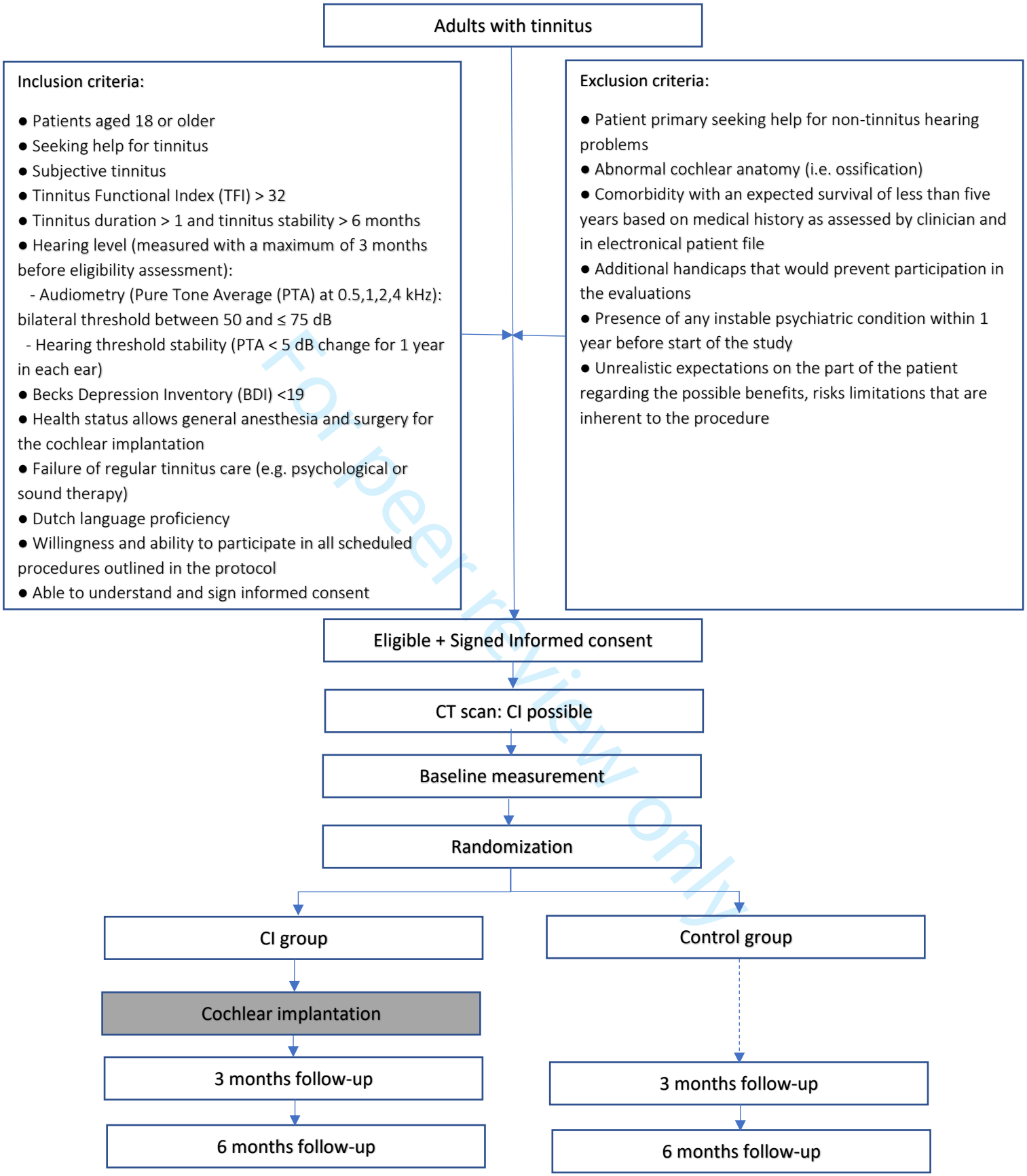

Figure 1. Study flowchart.
CI: cochlear implant group; Control: control group

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	18
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	n/a

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	6

		be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8-9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome.	9-14

		Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity,	15-16

		if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15-16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14, 16
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15-16, 17

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15-16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Extra documents
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a