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Tinnitus and cochlear implantation study: a randomized controlled trial

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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 originate 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 relieve 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) ≥ 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 diverse 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 electronic patient file
- Additional handicaps that would prevent participation in the evaluations
- Presence of any unstable 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

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

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

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23 Patients allocated to the intervention group will receive a CI. The cochlear implantation will be
24 carried out under general anesthesia after consent of the anesthesiologist and after determination
25 of general health status. The standard surgical procedures for cochlear implantation will be
26 followed. A retro-auricular incision will be made to expose the mastoid. The electrode will be
27 inserted via a posterior tympanotomy and round window implantation by soft-surgery techniques.
28 Intraoperatively, normal functioning of the device will be checked by measurement of impedance
29 and neural response telemetry. Electrocochleography will also be recorded intraoperatively using
30 Cochlear™ Research Platform (v1.1). The cochlear implant used for the study consists of a
31 Nucleus 7 sound processor and a CI622 implant from Cochlear (or similar). Serial numbers of the
32 CIs will be registered in the operating room (OR) report by the surgeon (standard clinical care for
33 cochlear implantation) and in the master study file (MSF) (product accountability). A post-operative
34 Cone Beam CT of the mastoid will be planned to detail the electrode location within the cochlea.
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42 One week after surgery patients from the intervention group will be checked at the
43 outpatient department (OPD) of the ENT to check for wound healing. The rehabilitation phase will
44 start 4 weeks after surgery with a visit of the patient to the department of Audiology to custom fit
45 the processor software and then (bi)weekly till week eleven after surgery to fine-tune the
46 programming of the implant and improve speech perception.
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49 In the follow-up phase, the patients with CI will return to the UMC Utrecht 3 and 6 months after
50 implantation to assess study outcome by the research team. The patients of the control group will
51 come to the UMC Utrecht 3 and 6 months after randomization to assess the same study outcome.
52 A questionnaire will have to be filled in at home by the patients before every follow-up session at
53 3 and 6 months, as well as 2 weeks after surgery for the intervention group.
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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

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

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

39 Pitch match of tinnitus is performed to find the pitch corresponding to the tinnitus pitch of the
40 patient. An acoustic pitch matching and an electric pitch matching will be performed in a sound-
41 treated booth. The acoustic pitch matching will provide information about the frequency of the
42 tinnitus perceived whereas the electric pitch matching will provide information about the pitch
43 matched electrode. They are obtained using a two-Alternative Forced-Choice (2AFC) method and
44 a 1 up 2 down adaptive staircase rule [23]. The patient will be asked to concentrate on the
45 predominant pitch of their tinnitus. Two tones will be presented at the same intensity level
46 previously matched with tinnitus. The patient will indicate which option, the first or the second,
47 sounds the closest in pitch by manipulating the response switch forward and backward. The
48 difference between the first and the second will become smaller and smaller, until there is one
49 frequency that matches best. Each stimulation will be performed twice (apical-to-basal and basal-
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3 to-apical to prevent octave-confusion). The pitch matched will be identified as the pitch resulting
4 of the two runs. If the result of the two runs is not the same, the procedure will be repeated until
5 finding a consistent result at least two times [24].
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8 9 Loudness match experiment

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

23 The history of several user characteristics will be logged from the processor. This provides the
24 following outcome parameters:
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- 26 ▪ Time on air, providing the time the device was used in speech environment or the
27 device was off
- 28 ▪ Scenes, providing the time spending in different environments: quiet, speech,
29 noise, speech in noise, music and wind
- 30 ▪ Level of the environmental sound in dBA
- 31 ▪ Program usage, providing a daily average on program usage
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38 Questionnaires

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

- 49 • The Visual Analogue Scale (VAS) *Tinnitus* has 2 items. The patient answers two questions
50 about tinnitus severity and intrusiveness using a visual analogue scale that ranges from 0
51 (not at all) to 10 (extremely).
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55 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

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3 sentence is scored between 0 and 3 where 0 confirms the sentence and 3 disagrees with
4 it.
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8 **Statistical analysis**

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10 Baseline characteristics per group will be described as means or medians, depending on the
11 normality of the data, and standard deviations. Between-group mean differences will be calculated
12 with 95% confidence intervals. A p-value <0.05 is considered statistically significant.
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15 The primary outcome will be the difference in TFI score between the intervention at 6 months after
16 cochlear implantation and the control group after six months of no intervention, a continuous
17 variable. Differences between the control and intervention group will be calculated using the
18 unpaired t-test and the Mann-Whitney u test. The secondary outcome measures will be the
19 performances on the auditory tests and the questionnaires. Differences between groups will be
20 calculated using the unpaired t-test and the Mann-Whitney u test. Within-subject comparisons will
21 entail differences of mean values. These will be analyzed using paired t-tests for continuous
22 measures.
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28 Interim analyses on the safety data will be performed and reviewed by a data safety
29 monitoring board (DSMB). An interim analysis will be done every three months starting after the 5
30 first patients reached 3 months of follow-up. A statistician will perform non-parametric test on the
31 pure tone average (PTA) at 0.25, 0.5, 1, 1.5 kHz without CI and speech perception unaided and
32 aided to monitor the residual hearing preservation. The DSMB will advise on stopping the study if
33 there is a risk for the patient's safety based on tinnitus worsening and deterioration of hearing.
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38 Potential missing data will be handled using multiple imputation. Complete cases analyses will
39 be done as a sensitivity analysis. All analyses will be performed on an intention-to-treat basis.
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44 **Ethics and dissemination**

45 The study will be conducted according to the principles of the Declaration of Helsinki (version
46 2013, Fortaleza) and in accordance with the Medical Research Involving Human Subjects Act
47 (WMO). The research protocol was approved by the Institutional Review Board (IRB) of the UMC
48 Utrecht (NL70319.041.19) and the Dutch competent authorities.
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52 All amendments will be notified to the local Medical Research Ethics Committee (MREC). The
53 data from this study will be used for publication in peer-reviewed international journals, preferably
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3 open-access. To diminish possible chance on publication bias, the study will be reported using
4 the CONSORT guidelines [34].
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6 All data will be treated confidentially. The data will be encrypted by using an unique patient
7 identification number. The analysis will be performed with these coded patient data. The key code
8 will be safeguarded by the investigators. The paper data files and informed consents will be stored
9 in a locked cabin in a locked room. The data will be stored on the investigator's computer as well,
10 which is secured by a password and situated in a locked room. The handling of personal data will
11 comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of
12 the General Data Protection Regulation, the Uitvoeringswet AVG, UAVG. The final trial data set
13 will be safeguarded and available to the principal investigator and approved members of the
14 research team.
15

16 The investigator will submit a summary of the progress of the trial to the accredited MREC once
17 a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects
18 included and numbers of subjects that have completed the trial, serious adverse events/serious
19 adverse reactions, other problems, and amendments.
20

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

28 The study is currently in recruitment phase.
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38 **Abbreviations**

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

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3	CT	Computerized Tomography
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5	DTT	Digit Triplet Test
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7	ECochG	Electrocochleography
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9	ENT	Ear, Nose and Throat
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11	EQ5D	Euro-QoL 5D
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13		
14	EU	European Union
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16	GBI	Glasgow Benefit Inventory
17		
18	HADS	Hospital Anxiety and Depression Scale
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21	IC	Informed Consent
22		
23	IRB	Institutional Review Board
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25	MREC	Medical Review Ethics Committee
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27	MSF	Master Study File
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30	OPD	Outpatient department
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32	OR	Operating room
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34	PTA	Pure Tone Average
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36	QoL	Quality-of-life
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39	RCT	Randomized controlled trial
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41	SAE	Serious Adverse Event
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43	SNR	Signal-to-Noise Ratio
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45	SRT	Speech Reception Threshold
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47		
48	SSD	Single Sided Deafness
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50	SSQ	Speech, Spatial and Qualities Hearing Scale
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52	TFI	Tinnitus Functional Index
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55	UMCU	University Medical Center
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3	VAS	Visual analogue scale
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5	WMO	Medical Research Involving Human Subjects Act
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7	2AFC	Two-Alternative Forced-Choice
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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

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Ethical approval

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

Word count: 3903 words

Figure legends

Figure 1: Study flowchart.

CI: cochlear implant group; Control: control group

References

1. van den Berge MJC, Free RH, Arnold R, de Kleine E, Hofman R, van Dijk JMC, et al. Cluster analysis to identify possible subgroups in tinnitus patients. *Front Neurol*. 2017;8(APR):1–7.
2. Moller AR, Salvi R, De Ridder D, Kleinjung T, Vanneste S. Pathology of Tinnitus and Hyperacusis-Clinical Implications. *Biomed Res Int* [Internet]. 2015;2015:608437. Available from: <https://doi.org/10.1155/2015/608437>
3. Møller AR. Epidemiology of Tinnitus in Adults BT - Textbook of Tinnitus. In: Møller AR, Langguth B, De Ridder D, Kleinjung T, editors. New York, NY: Springer New York; 2011. p. 29–37. Available from: https://doi.org/10.1007/978-1-60761-145-5_5
4. Davis AE. The epidemiology of tinnitus. *Handb Tinnitus* (R Tyler,ed). 2000;Singluar:1–23.
5. Hoare DJ, Kowalkowski VL, Kang S, Hall DA. Systematic review and meta-analyses of randomized controlled trials examining tinnitus management. *Laryngoscope*. 2011 Jul;121(7):1555–64.
6. Mertens G, De Bodt M, Van de Heyning P. Cochlear implantation as a long-term treatment for ipsilateral incapacitating tinnitus in subjects with unilateral hearing loss up to 10 years. *Hear Res* [Internet]. 2016;331:1–6. Available from: <http://dx.doi.org/10.1016/j.heares.2015.09.016>
7. Dobie RA. A Review of Randomized Clinical Trials in Tinnitus. *Laryngoscope* [Internet]. 1999 Aug 1;109(8):1202–11. Available from: <https://doi.org/10.1097/00005537-199908000-00004>
8. Hoare DJ, Edmondson-Jones M, Sereda M, Akeroyd MA, Hall D. Amplification with hearing aids for patients with tinnitus and co-existing hearing loss. *Cochrane Database of Systematic Reviews*. 2014.
9. Martinez-Devesa P, Perera R, Theodoulou M, Waddell A. Cognitive behavioural therapy for tinnitus. *Cochrane Database Syst Rev*. 2010;
10. Ramakers GGJ, Van Zon A, Stegeman I, Grolman W. The effect of cochlear implantation on tinnitus in patients with bilateral hearing loss: A systematic review. *Laryngoscope*. 2015;125(11):2584–92.
11. Ramos Macías A, Falcón-González JC, Manrique Rodríguez M, Morera Pérez C, García-Ibáñez L, Cenjor Español C, et al. One-Year Results for Patients with Unilateral Hearing Loss and Accompanying Severe Tinnitus and Hyperacusis Treated with a Cochlear Implant. *Audiol Neurotol*. 2018;23(1):8–19.
12. Van De Heyning P, Vermeire K, Diebl M, Nopp P, Anderson I, De Ridder D. Incapacitating

- 1
2
3 unilateral tinnitus in single-sided deafness treated by cochlear implantation. *Ann Otol*
4 *Rhinol Laryngol.* 2008;117(9):645–52.
5
6 13. Poncet-Wallet ÃC, Mamelle ÃE, Godey B, Truy E, Guevara N, Ardoint M, et al.
7 Prospective Multicentric Follow-up Study of Cochlear Implantation in Adults With Single-
8 Sided Deafness : Tinnitus and Audiological Outcomes. 2019;0.
9
10 14. Kleine Punte A, De Ridder D, Van De Heyning P. On the necessity of full length electrical
11 cochlear stimulation to suppress severe tinnitus in single-sided deafness. *Hear Res*
12 [Internet]. 2013;295:24–9. Available from: <http://dx.doi.org/10.1016/j.heares.2012.08.003>
13
14 15. Ahmed M., Khater A. Tinnitus suppression after cochlear implantation in patients with
15 single-sided deafness. *Egypt J Otolaryngol.* 2017;33(1):61.
16
17 16. Arts RAGJ, George ELJ, Janssen M, Griessner A, Zierhofer C, Stokroos RJ. Tinnitus
18 Suppression by Intracochlear Electrical Stimulation in Single Sided Deafness – A
19 Prospective Clinical Trial: Follow-Up. *PLoS One* [Internet]. 2016 Apr 25;11(4):e0153131.
20 Available from: <https://doi.org/10.1371/journal.pone.0153131>
21
22 17. Sampaio ALL, Araújo MFS, Oliveira CACP. New Criteria of Indication and Selection of
23 Patients to Cochlear Implant. *Int J Otolaryngol.* 2011;2011:1–13.
24
25 18. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013
26 explanation and elaboration: guidance for protocols of clinical trials. *BMJ.* 2013;
27
28 19. UMC Utrecht. Julius Centre Randomisation platform. Available from:
29 <http://www.juliuscentrum.nl/random/>
30
31 20. Rabau S, Wouters K, Van de Heyning P. Validation and translation of the Dutch tinnitus
32 functional index. *B-ENT* [Internet]. 2014;10(4):251–8. Available from:
33 [http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L603263](http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L603263036)
34 036
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36 21. Meikle MB, Henry JA, Griest SE, Stewart BJ, Abrams HB, McArdle R, et al. The tinnitus
37 functional index: Development of a new clinical measure for chronic, intrusive tinnitus. *Ear*
38 *Hear.* 2012;
39
40 22. Valente D. INTERNATIONAL STANDARD Acoustics — Loudness scaling by means.
41 2006;2006.
42
43 23. Neff P, Langguth B, Schecklmann M, Hannemann R, Schlee W. Comparing Three
44 Established Methods for Tinnitus Pitch Matching With Respect to Reliability, Matching
45 Duration, and Subjective Satisfaction. *Trends Hear.* 2019;23.
46
47 24. Arts RAGJ, George ELJ, Chenault MN, Stokroos RJ. Optimizing intracochlear electrical
48 stimulation to suppress tinnitus. *Ear Hear.* 2015 Jan;36(1):125–35.
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- 3 25. Theelen-Van Den Hoek FL, Boymans M, Stainsby T, Dreschler WA. Reliability of
- 4 categorical loudness scaling in the electrical domain. *Int J Audiol*. 2014;53(6):409–17.
- 5
- 6 26. BV C. Castor electronic data capture. Amsterdam, The Netherlands. 2018;
- 7
- 8 27. Guy W. CGI Clinical Global Impressions. ECDEU Assess Man. 1976;
- 9
- 10 28. Hendry J, Chin A, Swan IRC, Akeroyd MA, Browning GG. The Glasgow Benefit Inventory:
- 11 A systematic review of the use and value of an otorhinolaryngological generic patient-
- 12 recorded outcome measure. *Clin Otolaryngol*. 2016;41(3):259–75.
- 13
- 14 29. Health Policy. EuroQol - a new facility for the measurement of health-related quality of life.
- 15 1990;
- 16
- 17 30. Gatehouse S, Noble I. The Speech, Spatial and Qualities of Hearing Scale (SSQ). *Int J*
- 18 *Audiol*. 2004;
- 19
- 20 31. Beck AT, Steer RA, Ball R, Ranieri WF. Comparison of Beck depression inventories -IA
- 21 and -II in psychiatric outpatients. *J Pers Assess*. 1996;
- 22
- 23 32. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and
- 24 Depression Scale. *J Psychosom Res*. 2002;52(2):69–77.
- 25
- 26 33. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr*
- 27 *Scand*. 1983;
- 28
- 29
- 30 34. Schulz KF, Altman DC, Moher D. CONSORT 2010 Statement: Updated guidelines for
- 31 reporting parallel group randomised trials. *Ital J Public Health*. 2010;
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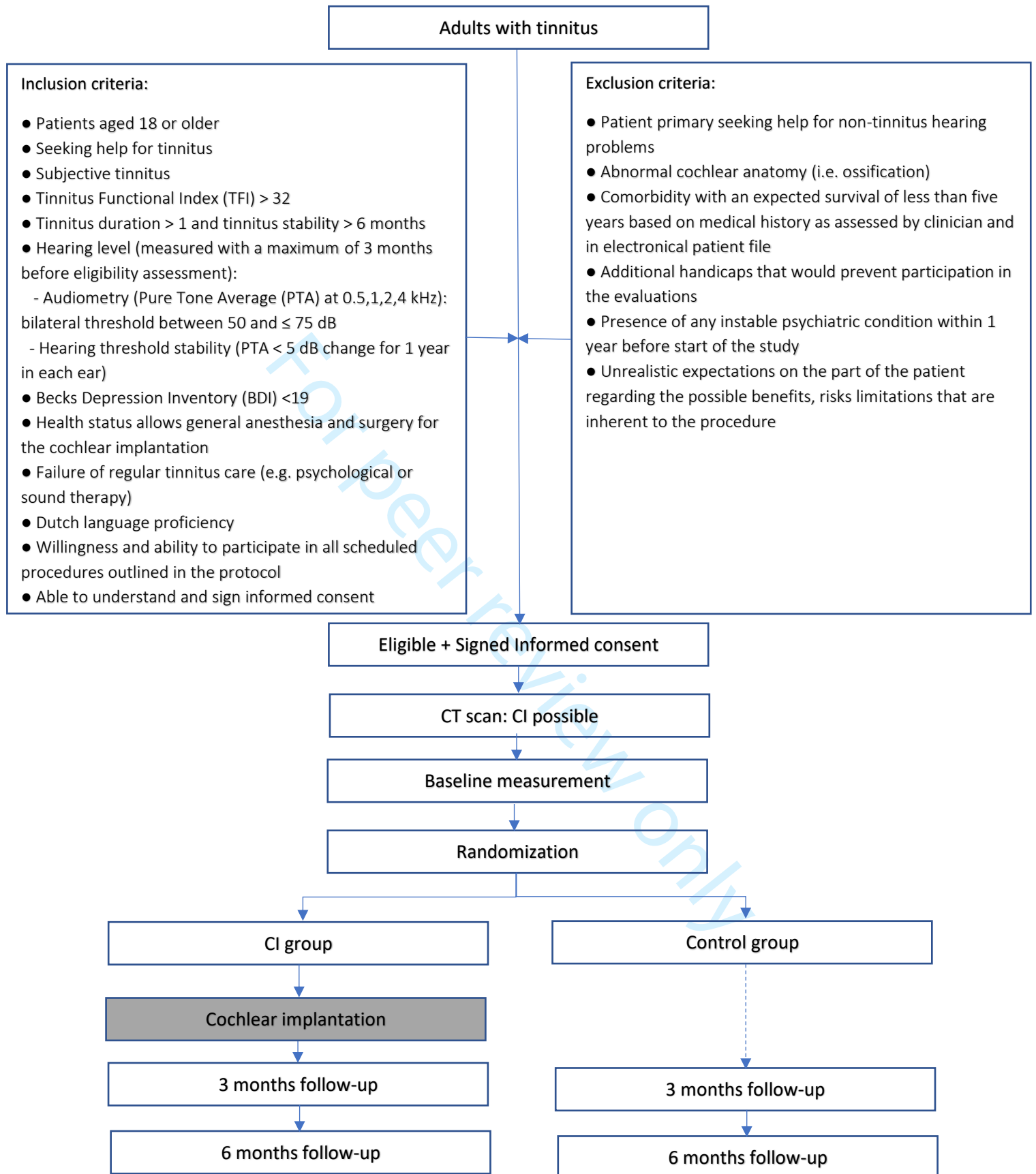


Figure 1. Study flowchart.

CI: cochlear implant group; Control: control group

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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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.

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

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	1
2			name of intended registry	
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6	Trial registration:	#2b	All items from the World Health Organization Trial	n/a
7	data set		Registration Data Set	
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11	Protocol version	#3	Date and version identifier	18
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15	Funding	#4	Sources and types of financial, material, and other	17
16			support	
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20	Roles and	#5a	Names, affiliations, and roles of protocol contributors	17
21	responsibilities:			
22				
23	contributorship			
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28	Roles and	#5b	Name and contact information for the trial sponsor	1
29	responsibilities:			
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31	sponsor contact			
32	information			
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38	Roles and	#5c	Role of study sponsor and funders, if any, in study	n/a
39	responsibilities:		design; collection, management, analysis, and	
40			interpretation of data; writing of the report; and the	
41	sponsor and funder		decision to submit the report for publication, including	
42			whether they will have ultimate authority over any of	
43			these activities	
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52	Roles and	#5d	Composition, roles, and responsibilities of the	n/a
53	responsibilities:		coordinating centre, steering committee, endpoint	
54			adjudication committee, data management team, and	
55	committees			
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1 other individuals or groups overseeing the trial, if
 2
 3 applicable (see Item 21a for data monitoring committee)
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 5

6 Introduction

7
 8
 9 Background and [#6a](#) Description of research question and justification for 2
 10
 11 rationale undertaking the trial, including summary of relevant
 12
 13 studies (published and unpublished) examining benefits
 14
 15 and harms for each intervention
 16
 17

18
 19 Background and [#6b](#) Explanation for choice of comparators 4
 20
 21 rationale: choice of
 22
 23 comparators
 24
 25

26 Objectives [#7](#) Specific objectives or hypotheses 5
 27
 28

29 Trial design [#8](#) Description of trial design including type of trial (eg, 5
 30
 31 parallel group, crossover, factorial, single group),
 32
 33 allocation ratio, and framework (eg, superiority,
 34
 35 equivalence, non-inferiority, exploratory)
 36
 37
 38

39 Methods:

40
 41 Participants,
 42
 43 interventions, and
 44
 45 outcomes
 46
 47
 48

49 Study setting [#9](#) Description of study settings (eg, community clinic, 5
 50
 51 academic hospital) and list of countries where data will be
 52
 53 collected. Reference to where list of study sites can be
 54
 55 obtained
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1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	7
2				
3			applicable, eligibility criteria for study centres and	
4			individuals who will perform the interventions (eg,	
5			surgeons, psychotherapists)	
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11	Interventions:	#11a	Interventions for each group with sufficient detail to allow	8-9
12				
13	description		replication, including how and when they will be	
14			administered	
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18				
19	Interventions:	#11b	Criteria for discontinuing or modifying allocated	8-9
20				
21	modifications		interventions for a given trial participant (eg, drug dose	
22			change in response to harms, participant request, or	
23			improving / worsening disease)	
24				
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29	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	n/a
30				
31	adherence		and any procedures for monitoring adherence (eg, drug	
32			tablet return; laboratory tests)	
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36	Interventions:	#11d	Relevant concomitant care and interventions that are	9
37				
38	concomitant care		permitted or prohibited during the trial	
39				
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41				
42	Outcomes	#12	Primary, secondary, and other outcomes, including the	9-14
43			specific measurement variable (eg, systolic blood	
44			pressure), analysis metric (eg, change from baseline, final	
45			value, time to event), method of aggregation (eg, median,	
46			proportion), and time point for each outcome. Explanation	
47			of the clinical relevance of chosen efficacy and harm	
48			outcomes is strongly recommended	
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1	Participant timeline	#13	Time schedule of enrolment, interventions (including any	10
2			run-ins and washouts), assessments, and visits for	
3			participants. A schematic diagram is highly recommended	
4			(see Figure)	
5				
6				
7				
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10				
11	Sample size	#14	Estimated number of participants needed to achieve	9
12			study objectives and how it was determined, including	
13			clinical and statistical assumptions supporting any sample	
14			size calculations	
15				
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21	Recruitment	#15	Strategies for achieving adequate participant enrolment to	8
22			reach target sample size	
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26	Methods:			
27				
28	Assignment of			
29	interventions (for			
30	controlled trials)			
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36	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	8
37	generation		computer-generated random numbers), and list of any	
38			factors for stratification. To reduce predictability of a	
39			random sequence, details of any planned restriction (eg,	
40			blocking) should be provided in a separate document that	
41			is unavailable to those who enrol participants or assign	
42			interventions	
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53	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	8
54	concealment		central telephone; sequentially numbered, opaque,	
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56				
57				
58	mechanism			
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sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Allocation: [#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): [#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

1	Data collection plan:	#18b	Plans to promote participant retention and complete	15
2				
3	retention		follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate from	
5			intervention protocols	
6				
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11	Data management	#19	Plans for data entry, coding, security, and storage,	15
12			including any related processes to promote data quality	
13			(eg, double data entry; range checks for data values).	
14			Reference to where details of data management	
15			procedures can be found, if not in the protocol	
16				
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18	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	14
19			outcomes. Reference to where other details of the	
20			statistical analysis plan can be found, if not in the protocol	
21				
22				
23	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	14
24	analyses		adjusted analyses)	
25				
26				
27				
28	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	15
29	population and		adherence (eg, as randomised analysis), and any	
30	missing data		statistical methods to handle missing data (eg, multiple	
31			imputation)	
32				
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36	Methods: Monitoring			
37				
38				
39	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	15
40	formal committee		summary of its role and reporting structure; statement of	
41			whether it is independent from the sponsor and	
42			competing interests; and reference to where further	
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1 details about its charter can be found, if not in the
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 3 protocol. Alternatively, an explanation of why a DMC is
 4
 5 not needed
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8	Data monitoring:	#21b	Description of any interim analyses and stopping	14
9	interim analysis		guidelines, including who will have access to these	
10			interim results and make the final decision to terminate	
11			the trial	
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18	Harms	#22	Plans for collecting, assessing, reporting, and managing	15
19			solicited and spontaneously reported adverse events and	
20			other unintended effects of trial interventions or trial	
21			conduct	
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28	Auditing	#23	Frequency and procedures for auditing trial conduct, if	n/a
29			any, and whether the process will be independent from	
30			investigators and the sponsor	
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35	Ethics and			
36	dissemination			
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41	Research ethics	#24	Plans for seeking research ethics committee / institutional	15, 17
42	approval		review board (REC / IRB) approval	
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46	Protocol	#25	Plans for communicating important protocol modifications	15
47	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
48			relevant parties (eg, investigators, REC / IRBs, trial	
49			participants, trial registries, journals, regulators)	
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1	Consent or assent	#26a	Who will obtain informed consent or assent from potential	8
2			trial participants or authorised surrogates, and how (see	
3			Item 32)	
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9	Consent or assent:	#26b	Additional consent provisions for collection and use of	15
10	ancillary studies		participant data and biological specimens in ancillary	
11			studies, if applicable	
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16	Confidentiality	#27	How personal information about potential and enrolled	15
17			participants will be collected, shared, and maintained in	
18			order to protect confidentiality before, during, and after	
19			the trial	
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26	Declaration of	#28	Financial and other competing interests for principal	17
27	interests		investigators for the overall trial and each study site	
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31	Data access	#29	Statement of who will have access to the final trial	15
32			dataset, and disclosure of contractual agreements that	
33			limit such access for investigators	
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39	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	n/a
40	trial care		compensation to those who suffer harm from trial	
41			participation	
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47	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	15
48	trial results		results to participants, healthcare professionals, the	
49			public, and other relevant groups (eg, via publication,	
50			reporting in results databases, or other data sharing	
51			arrangements), including any publication restrictions	
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1 Dissemination policy: [#31b](#) Authorship eligibility guidelines and any intended use of n/a
 2
 3 authorship professional writers
 4
 5

6 Dissemination policy: [#31c](#) Plans, if any, for granting public access to the full n/a
 7
 8 reproducible protocol, participant-level dataset, and statistical code
 9
 10 research
 11
 12

13 Appendices

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 17 Informed consent [#32](#) Model consent form and other related documentation n/a
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 19 materials given to participants and authorised surrogates
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 23 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage of n/a
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 25 biological specimens for genetic or molecular analysis in
 26
 27 the current trial and for future use in ancillary studies, if
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 29 applicable
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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-043288.R1
Article Type:	Protocol
Date Submitted by the Author:	25-Mar-2021
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
Primary Subject Heading:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Evidence based practice
Keywords:	OTOLARYNGOLOGY, Audiology < OTOLARYNGOLOGY, Adult otolaryngology < OTOLARYNGOLOGY

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

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Abstract

Introduction

Tinnitus is the perception of sound without an external stimulus, often experienced as a ringing, buzzing sound. Subjective tinnitus is assumed to originate 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) ≥ 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

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

12 **Study objectives**

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

26 Patients were not involved in the design, or conduct, or reporting, or dissemination plans of the study.
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31 **Study design and setting**

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

50 **Study population**

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

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

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

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

44 Patients allocated to the intervention group will receive a CI. The CI will be implanted on the most
45 affected tinnitus side, and if equal tinnitus in the two ears, in the ear with the worst hearing loss.
46 Hearing aid will be allowed in the contralateral ear. The cochlear implantation will be carried out
47 under general anesthesia after consent of the anesthesiologist and after determination of general
48 health status. The standard surgical procedures for cochlear implantation will be followed. A retro-
49 auricular incision will be made to expose the mastoid. The electrode will be inserted via a posterior
50 tympanotomy and round window implantation by soft-surgery techniques. Intraoperatively, normal
51 functioning of the device will be checked by measurement of impedance and neural response
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3 telemetry. Electrocochleography will also be recorded intraoperatively using Cochlear™ Research
4 Platform (v1.1). The cochlear implant used for the study consists of a Nucleus 7 sound processor
5 and a CI622 implant with a slim straight electrode from Cochlear (or similar). Serial numbers of
6 the CIs will be registered in the operating room (OR) report by the surgeon (standard clinical care
7 for cochlear implantation) and in the master study file (MSF) (product accountability). A post-
8 operative Cone Beam CT of the mastoid will be planned to detail the electrode location within the
9 cochlea.
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14 One week after surgery patients from the intervention group will be checked at the
15 outpatient department (OPD) of the ENT to check for wound healing. The rehabilitation phase will
16 start 4 weeks after surgery with a visit of the patient to the department of Audiology to custom fit
17 the processor software and then (bi)weekly till week eleven after surgery to fine-tune the
18 programming of the implant and improve speech perception. The CI fitting will not differ from the
19 standard of care and will be optimized for every patient.
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23 In the follow-up phase, the patients with CI will return to the UMC Utrecht 3 and 6 months after
24 implantation to assess study outcome by the research team. The patients of the control group will
25 come to the UMC Utrecht 3 and 6 months after randomization to assess the same study outcome.
26 A questionnaire will have to be filled in at home by the patients before every follow-up session at
27 3 and 6 months, as well as 2 weeks after surgery for the intervention group.
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31 Participants are not allowed to start another tinnitus treatment during the study.
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35 **Sample size**

36 To detect a clinically relevant difference of 1 grade (15 points) change measured with the TFI [24],
37 in tinnitus burden at 6 months after cochlear implantation compared to the control group, with a
38 power of 90% and alpha of 0.05, 23 patients are needed in both arms of the study. An acceptable
39 standard deviation was set at 15, based on the results of a previous pilot study assessing CI for
40 tinnitus patients [20]. We will include 25 patients per arm, a 10% margin, to include for possible
41 lost to follow up. Thereby, we expect patients to have a mean TFI at baseline of 50 points on TFI
42 (Grade 3) and a TFI decrease of 15 points at 6 months after intervention with a mean endpoint of
43 35 points on TFI (Grade 2).
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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

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

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

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

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3 The history of several user characteristics will be logged from the processor. This provides the
4 following outcome parameters:
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- 6 ▪ Time on air, providing the time the device was used in speech environment or the
7 device was off
- 8 ▪ Scenes, providing the time spending in different environments: quiet, speech,
9 noise, speech in noise, music and wind
- 10 ▪ Level of the environmental sound in dBA
- 11 ▪ Program usage, providing a daily average on program usage
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18 Questionnaires

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

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

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

- 45 • The *Clinical Global Impression (CGI)* consists of a 1-item observer-rated scale that
46 measures global improvement or change (CGIC) [30]. The question is scored on a scale
47 from 1 to 7, 1 meaning “Very much improved” to 7 meaning “Very much worse”.
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- 49 • The *Glasgow Benefit Inventory (GBI)* is a validated questionnaire reporting change in
50 health-related quality of life post-intervention [31]. It consists of 18 questions scored on a
51 5-points Likert scale where 1 indicates “much worse” and 5 is for “much better”. The
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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.

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3 The primary outcome will be the difference in TFI score between the intervention at 6
4 months after cochlear implantation and the control group after six months of no intervention, a
5 continuous variable. Differences between the control and intervention group will be calculated
6 using the unpaired t-test and the Mann-Whitney u test. The secondary outcome measures will be
7 the performances on the auditory tests and the questionnaires. Differences between groups will
8 be calculated using the unpaired t-test and the Mann-Whitney u test. Within-subject comparisons
9 will entail differences of mean values. These will be analyzed using paired t-tests for continuous
10 measures.
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16 Interim analyses on the safety data will be performed and reviewed by an external data
17 safety monitoring board (DSMB). An interim analysis will be done every six months starting after
18 the 5 first patients reached 6 months of follow-up. A statistician will perform non-parametric test
19 on the aided speech perception of the implanted ear only, performed 6 months post-implantation
20 to monitor functional hearing performance. The DSMB will advise on stopping the study if there is
21 a risk for the patient's safety based on tinnitus worsening and deterioration of functional hearing.
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26 Potential missing data will be handled using multiple imputation. Complete cases analyses will
27 be done as a sensitivity analysis. All analyses will be performed on an intention-to-treat basis.
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32 **Ethics and dissemination**

33 **Protocol version**

34 The study will be conducted according to the principles of the Declaration of Helsinki (version
35 2013, Fortaleza) and in accordance with the Medical Research Involving Human Subjects Act
36 (WMO). The research protocol was approved by the Institutional Review Board (IRB) of the UMC
37 Utrecht (NL70319.041.19) and the Dutch competent authorities.
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43 **Protocol amendment**

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

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

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

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

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51 The study is currently in recruitment phase.
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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

1		
2		
3	RCT	Randomized controlled trial
4		
5	SAE	Serious Adverse Event
6		
7	SNR	Signal-to-Noise Ratio
8		
9		
10	SRT	Speech Reception Threshold
11		
12	SSD	Single Sided Deafness
13		
14	SSQ	Speech, Spatial and Qualities Hearing Scale
15		
16	TFI	Tinnitus Functional Index
17		
18		
19	UMCU	University Medical Center
20		
21	VAS	Visual analogue scale
22		
23	WMO	Medical Research Involving Human Subjects Act
24		
25		
26	2AFC	Two-Alternative Forced-Choice
27		
28		
29		

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

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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

References

1. van den Berge MJC, Free RH, Arnold R, de Kleine E, Hofman R, van Dijk JMC, et al. Cluster analysis to identify possible subgroups in tinnitus patients. *Front Neurol*. 2017;8(APR):1–7.
2. Moller AR, Salvi R, De Ridder D, Kleinjung T, Vanneste S. Pathology of Tinnitus and Hyperacusis-Clinical Implications. *Biomed Res Int* [Internet]. 2015;2015:608437. Available from: <https://doi.org/10.1155/2015/608437>
3. Møller AR. Epidemiology of Tinnitus in Adults BT - Textbook of Tinnitus. In: Møller AR, Langguth B, De Ridder D, Kleinjung T, editors. New York, NY: Springer New York; 2011. p. 29–37. Available from: https://doi.org/10.1007/978-1-60761-145-5_5
4. Davis AE. The epidemiology of tinnitus. *Handb Tinnitus* (R Tyler,ed). 2000;Singluar:1–23.
5. Hoare DJ, Kowalkowski VL, Kang S, Hall DA. Systematic review and meta-analyses of randomized controlled trials examining tinnitus management. *Laryngoscope*. 2011 Jul;121(7):1555–64.
6. Mertens G, De Bodt M, Van de Heyning P. Cochlear implantation as a long-term treatment for ipsilateral incapacitating tinnitus in subjects with unilateral hearing loss up to 10 years. *Hear Res* [Internet]. 2016;331:1–6. Available from: <http://dx.doi.org/10.1016/j.heares.2015.09.016>
7. Dobie RA. A Review of Randomized Clinical Trials in Tinnitus. *Laryngoscope* [Internet]. 1999 Aug 1;109(8):1202–11. Available from: <https://doi.org/10.1097/00005537-199908000-00004>
8. Hoare DJ, Edmondson-Jones M, Sereda M, Akeroyd MA, Hall D. Amplification with

- 1
2
3 hearing aids for patients with tinnitus and co-existing hearing loss. Cochrane Database of
4 Systematic Reviews. 2014.
5
6 9. Martinez-Devesa P, Perera R, Theodoulou M, Waddell A. Cognitive behavioural therapy
7 for tinnitus. Cochrane Database Syst Rev. 2010;
8
9 10. Cima RFF, Mazurek B, Haider H, Kikidis D, Lapira A, Noreña A, et al. A multidisciplinary
10 European guideline for tinnitus: diagnostics, assessment, and treatment. HNO.
11 2019;67(March):10–42.
12
13 11. Fuller T, Cima R, Langguth B, Mazurek B, Waddell A, Hoare DJ, et al. Cognitive
14 behavioural therapy for tinnitus. Cochrane Database Syst Rev. 2017;2017(4).
15
16 12. Sereda M, Xia J, El Refaie A, Hall DA, Hoare DJ. Sound therapy (using amplification
17 devices and/or sound generators) for tinnitus. Cochrane Database of Systematic
18 Reviews. 2018.
19
20 13. Hobson J, Chisholm E, El Refaie A. Sound therapy (masking) in the management of
21 tinnitus in adults. Cochrane Database Syst Rev. 2012;
22
23 14. Ramakers GGJ, Van Zon A, Stegeman I, Grolman W. The effect of cochlear implantation
24 on tinnitus in patients with bilateral hearing loss: A systematic review. Laryngoscope.
25 2015;125(11):2584–92.
26
27 15. Ramos Macías A, Falcón-González JC, Manrique Rodríguez M, Morera Pérez C, García-
28 Ibáñez L, Cenjor Español C, et al. One-Year Results for Patients with Unilateral Hearing
29 Loss and Accompanying Severe Tinnitus and Hyperacusis Treated with a Cochlear
30 Implant. *Audiol Neurotol*. 2018;23(1):8–19.
31
32 16. Van De Heyning P, Vermeire K, Diebl M, Nopp P, Anderson I, De Ridder D. Incapacitating
33 unilateral tinnitus in single-sided deafness treated by cochlear implantation. *Ann Otol*
34 *Rhinol Laryngol*. 2008;117(9):645–52.
35
36 17. Poncet-Wallet AC, Mamelle AE, Godey B, Truy E, Guevara N, Ardoint M, et al.
37 Prospective Multicentric Follow-up Study of Cochlear Implantation in Adults With Single-
38 Sided Deafness : Tinnitus and Audiological Outcomes. 2019;0.
39
40 18. Kleine Punte A, De Ridder D, Van De Heyning P. On the necessity of full length electrical
41 cochlear stimulation to suppress severe tinnitus in single-sided deafness. *Hear Res*
42 [Internet]. 2013;295:24–9. Available from: <http://dx.doi.org/10.1016/j.heares.2012.08.003>
43
44 19. Ahmed M., Khater A. Tinnitus suppression after cochlear implantation in patients with
45 single-sided deafness. *Egypt J Otolaryngol*. 2017;33(1):61.
46
47 20. Arts RAGJ, George ELJ, Janssen M, Griessner A, Zierhofer C, Stokroos RJ. Tinnitus
48 Suppression by Intracochlear Electrical Stimulation in Single Sided Deafness – A
49
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3 Prospective Clinical Trial: Follow-Up. PLoS One [Internet]. 2016 Apr 25;11(4):e0153131.
4 Available from: <https://doi.org/10.1371/journal.pone.0153131>
5
- 6 21. Sampaio ALL, Araújo MFS, Oliveira CACP. New Criteria of Indication and Selection of
7 Patients to Cochlear Implant. *Int J Otolaryngol*. 2011;2011:1–13.
8
- 9 22. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013
10 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. 2013;
11
- 12 23. BV C. Castor electronic data capture. Amsterdam, The Netherlands. 2018;
13
- 14 24. Meikle MB, Henry JA, Griest SE, Stewart BJ, Abrams HB, McArdle R, et al. The tinnitus
15 functional index: Development of a new clinical measure for chronic, intrusive tinnitus. *Ear*
16 *Hear*. 2012;
17
- 18 25. Rabau S, Wouters K, Van de Heyning P. Validation and translation of the Dutch tinnitus
19 functional index. *B-ENT [Internet]*. 2014;10(4):251–8. Available from:
20 [http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L603263](http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L603263036)
21 [036](http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L603263036)
22
23
24
- 25 26. Valente D. INTERNATIONAL STANDARD Acoustics — Loudness scaling by means.
26 2006;2006.
27
- 28 27. Arts RAGJ, George ELJ, Chenault MN, Stokroos RJ. Optimizing intracochlear electrical
29 stimulation to suppress tinnitus. *Ear Hear*. 2015 Jan;36(1):125–35.
30
- 31 28. Theelen-Van Den Hoek FL, Boymans M, Stainsby T, Dreschler WA. Reliability of
32 categorical loudness scaling in the electrical domain. *Int J Audiol*. 2014;53(6):409–17.
33
- 34 29. Genitsaridi E, Partyka M, Gallus S, Lopez-Escamez JA, Schecklmann M, Mielczarek M, et
35 al. Standardised profiling for tinnitus research: The European School for Interdisciplinary
36 Tinnitus Research Screening Questionnaire (ESIT-SQ). *Hear Res [Internet]*.
37 2019;377:353–9. Available from:
38 <http://www.sciencedirect.com/science/article/pii/S0378595518304684>
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40
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42
- 43 30. Guy W. CGI Clinical Global Impressions. ECDEU Assess Man. 1976;
44
- 45 31. Hendry J, Chin A, Swan IRC, Akeroyd MA, Browning GG. The Glasgow Benefit Inventory:
46 A systematic review of the use and value of an otorhinolaryngological generic patient-
47 recorded outcome measure. *Clin Otolaryngol*. 2016;41(3):259–75.
48
- 49 32. Health Policy. EuroQol - a new facility for the measurement of health-related quality of life.
50 1990;
51
- 52 33. Gatehouse S, Noble I. The Speech, Spatial and Qualities of Hearing Scale (SSQ). *Int J*
53 *Audiol*. 2004;
54
- 55 34. Beck AT, Steer RA, Ball R, Ranieri WF. Comparison of Beck depression inventories -IA
56
57
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3 and -II in psychiatric outpatients. *J Pers Assess.* 1996;
- 4 35. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and
5 Depression Scale. *J Psychosom Res.* 2002;52(2):69–77.
- 6
7 36. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr*
8 *Scand.* 1983;
- 9
10 37. Schulz KF, Altman DC, Moher D. CONSORT 2010 Statement: Updated guidelines for
11 reporting parallel group randomised trials. *Ital J Public Health.* 2010;
- 12
13 38. Ramos-Macías A, Borkoski-Barreiro SA, Falcón-González JC, Ramos-De Miguel A.
14 Hearing Preservation with the Slim Modiolar Electrode Nucleus CI532® Cochlear Implant:
15 A Preliminary Experience. *Audiol Neurotol.* 2018;
- 16
17 39. Jurawitz MC, Büchner A, Harpel T, Schüssler M, Majdani O, Lesinski-Schiedat A, et al.
18 Hearing preservation outcomes with different cochlear implant electrodes: Nucleus®
19 hybrid™-L24 and nucleus freedom™ CI422. *Audiol Neurotol.* 2014;19(5):293–309.
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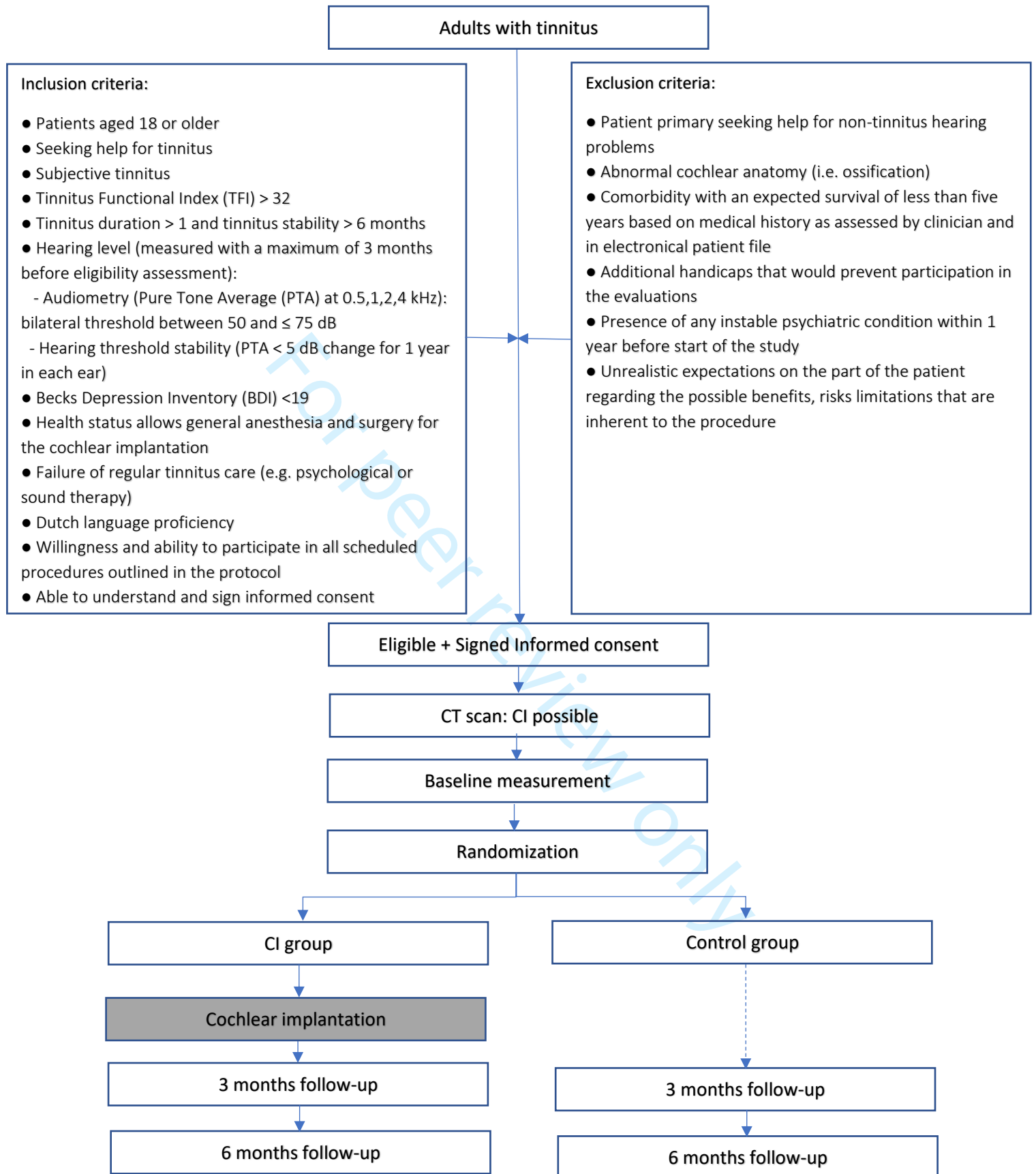


Figure 1. Study flowchart.

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.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	2
2				
3				
4			name of intended registry	
5				
6	Trial registration:	#2b	All items from the World Health Organization Trial	n/a
7				
8	data set		Registration Data Set	
9				
10				
11	Protocol version	#3	Date and version identifier	18
12				
13				
14				
15	Funding	#4	Sources and types of financial, material, and other	17
16				
17			support	
18				
19				
20	Roles and	#5a	Names, affiliations, and roles of protocol contributors	17
21				
22	responsibilities:			
23				
24	contributorship			
25				
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27				
28	Roles and	#5b	Name and contact information for the trial sponsor	1
29				
30	responsibilities:			
31				
32	sponsor contact			
33				
34	information			
35				
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37				
38	Roles and	#5c	Role of study sponsor and funders, if any, in study	n/a
39				
40	responsibilities:		design; collection, management, analysis, and	
41				
42	sponsor and funder		interpretation of data; writing of the report; and the	
43				
44			decision to submit the report for publication, including	
45				
46			whether they will have ultimate authority over any of	
47				
48			these activities	
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51				
52	Roles and	#5d	Composition, roles, and responsibilities of the	n/a
53				
54	responsibilities:		coordinating centre, steering committee, endpoint	
55				
56	committees		adjudication committee, data management team, and	
57				
58				
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60				

1 other individuals or groups overseeing the trial, if
 2 applicable (see Item 21a for data monitoring
 3 committee)
 4
 5
 6
 7

8 Introduction

10
 11 Background and [#6a](#) Description of research question and justification for 5
 12 rationale undertaking the trial, including summary of relevant
 13

14 studies (published and unpublished) examining
 15 benefits and harms for each intervention
 16
 17
 18
 19

20
 21 Background and [#6b](#) Explanation for choice of comparators 5
 22 rationale: choice of
 23 comparators
 24
 25
 26
 27

28 Objectives [#7](#) Specific objectives or hypotheses 5
 29
 30

31 Trial design [#8](#) Description of trial design including type of trial (eg, 5
 32 parallel group, crossover, factorial, single group),
 33 allocation ratio, and framework (eg, superiority,
 34 equivalence, non-inferiority, exploratory)
 35
 36
 37
 38
 39
 40

41 Methods:

42 Participants,
 43 interventions, and
 44 outcomes
 45
 46
 47
 48
 49

50
 51 Study setting [#9](#) Description of study settings (eg, community clinic, 6
 52 academic hospital) and list of countries where data will
 53
 54
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 60

1		be collected. Reference to where list of study sites can	
2			
3		be obtained	
4			
5			
6	Eligibility criteria	#10 Inclusion and exclusion criteria for participants. If	7
7			
8		applicable, eligibility criteria for study centres and	
9			
10		individuals who will perform the interventions (eg,	
11			
12		surgeons, psychotherapists)	
13			
14			
15			
16	Interventions:	#11a Interventions for each group with sufficient detail to	8-9
17			
18	description	allow replication, including how and when they will be	
19			
20		administered	
21			
22			
23	Interventions:	#11b Criteria for discontinuing or modifying allocated	8-9
24			
25	modifications	interventions for a given trial participant (eg, drug dose	
26			
27		change in response to harms, participant request, or	
28			
29		improving / worsening disease)	
30			
31			
32			
33	Interventions:	#11c Strategies to improve adherence to intervention	n/a
34			
35	adherence	protocols, and any procedures for monitoring	
36			
37		adherence (eg, drug tablet return; laboratory tests)	
38			
39			
40			
41	Interventions:	#11d Relevant concomitant care and interventions that are	8
42			
43	concomitant care	permitted or prohibited during the trial	
44			
45			
46	Outcomes	#12 Primary, secondary, and other outcomes, including the	9-14
47			
48		specific measurement variable (eg, systolic blood	
49			
50		pressure), analysis metric (eg, change from baseline,	
51			
52		final value, time to event), method of aggregation (eg,	
53			
54		median, proportion), and time point for each outcome.	
55			
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1		Explanation of the clinical relevance of chosen efficacy	
2		and harm outcomes is strongly recommended	
3			
4			
5			
6	Participant timeline	#13 Time schedule of enrolment, interventions (including	10
7		any run-ins and washouts), assessments, and visits for	
8		participants. A schematic diagram is highly	
9		recommended (see Figure)	
10			
11			
12			
13			
14			
15	Sample size	#14 Estimated number of participants needed to achieve	9
16		study objectives and how it was determined, including	
17		clinical and statistical assumptions supporting any	
18		sample size calculations	
19			
20			
21			
22			
23			
24			
25	Recruitment	#15 Strategies for achieving adequate participant enrolment	8
26		to reach target sample size	
27			
28			
29			
30			
31	Methods:		
32			
33	Assignment of		
34			
35	interventions (for		
36			
37	controlled trials)		
38			
39			
40			
41	Allocation: sequence	#16a Method of generating the allocation sequence (eg,	8
42	generation	computer-generated random numbers), and list of any	
43		factors for stratification. To reduce predictability of a	
44		random sequence, details of any planned restriction	
45		(eg, blocking) should be provided in a separate	
46		document that is unavailable to those who enrol	
47		participants or assign interventions	
48			
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1	Allocation	#16b	Mechanism of implementing the allocation sequence	8
2				
3	concealment		(eg, central telephone; sequentially numbered, opaque,	
4				
5	mechanism		sealed envelopes), describing any steps to conceal the	
6				
7				
8			sequence until interventions are assigned	
9				
10				
11	Allocation:	#16c	Who will generate the allocation sequence, who will	8
12				
13	implementation		enrol participants, and who will assign participants to	
14				
15				
16			interventions	
17				
18				
19	Blinding (masking)	#17a	Who will be blinded after assignment to interventions	8
20				
21			(eg, trial participants, care providers, outcome	
22				
23			assessors, data analysts), and how	
24				
25				
26	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	n/a
27				
28	emergency		permissible, and procedure for revealing a participant's	
29				
30	unblinding		allocated intervention during the trial	
31				
32				
33				
34	Methods: Data			
35				
36	collection,			
37				
38	management, and			
39				
40	analysis			
41				
42				
43				
44	Data collection plan	#18a	Plans for assessment and collection of outcome,	15-16
45				
46			baseline, and other trial data, including any related	
47				
48			processes to promote data quality (eg, duplicate	
49				
50			measurements, training of assessors) and a	
51				
52				
53			description of study instruments (eg, questionnaires,	
54				
55			laboratory tests) along with their reliability and validity,	
56				
57				
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1		if known. Reference to where data collection forms can	
2			
3		be found, if not in the protocol	
4			
5			
6	Data collection plan:	#18b Plans to promote participant retention and complete	15
7			
8	retention	follow-up, including list of any outcome data to be	
9			
10		collected for participants who discontinue or deviate	
11			
12		from intervention protocols	
13			
14			
15			
16	Data management	#19 Plans for data entry, coding, security, and storage,	15-16
17			
18		including any related processes to promote data quality	
19			
20		(eg, double data entry; range checks for data values).	
21			
22		Reference to where details of data management	
23			
24		procedures can be found, if not in the protocol	
25			
26			
27			
28	Statistics: outcomes	#20a Statistical methods for analysing primary and	14
29			
30		secondary outcomes. Reference to where other details	
31			
32		of the statistical analysis plan can be found, if not in the	
33			
34		protocol	
35			
36			
37			
38	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	14
39			
40	analyses	adjusted analyses)	
41			
42			
43	Statistics: analysis	#20c Definition of analysis population relating to protocol	15
44			
45	population and	non-adherence (eg, as randomised analysis), and any	
46			
47	missing data	statistical methods to handle missing data (eg, multiple	
48			
49		imputation)	
50			
51			
52			

53 Methods: Monitoring

1	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	15
2				
3	formal committee		summary of its role and reporting structure; statement	
4			of whether it is independent from the sponsor and	
5			competing interests; and reference to where further	
6			details about its charter can be found, if not in the	
7			protocol. Alternatively, an explanation of why a DMC is	
8			not needed	
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17				
18	Data monitoring:	#21b	Description of any interim analyses and stopping	14, 16
19	interim analysis		guidelines, including who will have access to these	
20			interim results and make the final decision to terminate	
21			the trial	
22				
23				
24				
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28	Harms	#22	Plans for collecting, assessing, reporting, and	16
29			managing solicited and spontaneously reported	
30			adverse events and other unintended effects of trial	
31			interventions or trial conduct	
32				
33				
34				
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38	Auditing	#23	Frequency and procedures for auditing trial conduct, if	n/a
39			any, and whether the process will be independent from	
40			investigators and the sponsor	
41				
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43				
44				
45	Ethics and			
46	dissemination			
47				
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51	Research ethics	#24	Plans for seeking research ethics committee /	15-16, 17
52	approval		institutional review board (REC / IRB) approval	
53				
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1	Protocol	#25	Plans for communicating important protocol	15
2				
3	amendments		modifications (eg, changes to eligibility criteria,	
4			outcomes, analyses) to relevant parties (eg,	
5			investigators, REC / IRBs, trial participants, trial	
6			registries, journals, regulators)	
7				
8				
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12				
13	Consent or assent	#26a	Who will obtain informed consent or assent from	8
14			potential trial participants or authorised surrogates, and	
15			how (see Item 32)	
16				
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21	Consent or assent:	#26b	Additional consent provisions for collection and use of	15
22	ancillary studies		participant data and biological specimens in ancillary	
23			studies, if applicable	
24				
25				
26				
27				
28	Confidentiality	#27	How personal information about potential and enrolled	15
29			participants will be collected, shared, and maintained in	
30			order to protect confidentiality before, during, and after	
31			the trial	
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38	Declaration of	#28	Financial and other competing interests for principal	17
39	interests		investigators for the overall trial and each study site	
40				
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43				
44	Data access	#29	Statement of who will have access to the final trial	15-16
45			dataset, and disclosure of contractual agreements that	
46			limit such access for investigators	
47				
48				
49				
50				
51	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and	n/a
52	trial care		for compensation to those who suffer harm from trial	
53			participation	
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1	Dissemination policy: #31a	Plans for investigators and sponsor to communicate	15
2			
3	trial results	trial results to participants, healthcare professionals,	
4		the public, and other relevant groups (eg, via	
5		publication, reporting in results databases, or other	
6		data sharing arrangements), including any publication	
7		restrictions	
8			
9			
10			
11	Dissemination policy: #31b	Authorship eligibility guidelines and any intended use	n/a
12			
13	authorship	of professional writers	
14			
15			
16	Dissemination policy: #31c	Plans, if any, for granting public access to the full	n/a
17			
18	reproducible	protocol, participant-level dataset, and statistical code	
19			
20	research		
21			
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28	Appendices		
29			
30			
31	Informed consent	#32 Model consent form and other related documentation	Extra
32			
33	materials	given to participants and authorised surrogates	documents
34			
35			
36			
37	Biological specimens	#33 Plans for collection, laboratory evaluation, and storage	n/a
38			
39		of biological specimens for genetic or molecular	
40		analysis in the current trial and for future use in	
41		ancillary studies, if applicable	
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 49 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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