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# An auditory brainstem implant for treatment of unilateral tinnitus: protocol for an interventional pilot study



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# AN AUDITORY BRAINSTEM IMPLANT FOR TREATMENT OF UNILATERAL TINNITUS: PROTOCOL FOR AN INTERVENTIONAL PILOT STUDY

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MINKE J.C. VAN DEN BERGE, J. MARC C. VAN DIJK, JAN D.M. METZEMAEKERS, ALBERTUS MAAT, ROLIEN H. FREE, PIM VAN DIJK.



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## KEYWORDS

Tinnitus; neuromodulation; auditory brainstem implant

## ABSTRACT

### INTRODUCTION

Tinnitus may have a very severe impact on the quality of life. Unfortunately, for many patients, a satisfactory treatment modality is lacking. The auditory brainstem implant (ABI) was originally indicated for hearing restoration in patients with non-functional cochlear nerves, e.g. in neurofibromatosis type II. In analogy to a cochlear implant (CI), it has been demonstrated that an ABI may reduce tinnitus as a beneficial side effect. For tinnitus treatment, an ABI may have an advantage over a CI, as cochlear implantation may harm inner ear structures due to its invasiveness, while an ABI is presumed to not damage anatomical structures. This is the first study to implant an ABI to investigate its effectiveness on the suppression of intractable tinnitus.

### METHODS & ANALYSIS

In this pilot study, ten adults having incapacitating unilateral intractable tinnitus and ipsilateral severe hearing loss will have an ABI implanted. The ABI is switched on 6 weeks after implantation, followed by several fitting sessions aimed at finding an optimal stimulation strategy. The primary outcome is the change in Tinnitus Functioning Index. Secondary goals are safety, quality of life and other questionnaires (Tinnitus Handicap Index, VAS-scales) and audiometric and vestibular function. The endpoint is set at one year after implantation. Follow-up will continue until five years after implantation.

### ETHICS & DISSEMINATION

The protocol was approved by the Institutional Review Board of the University Medical Center Groningen, the Netherlands (METc 2015/479). Results of this study will be disseminated in peer-reviewed journals and at scientific conferences.

### REGISTRATION

www.clinicaltrials.gov, identifier NCT02630589


## STRENGTHS AND LIMITATIONS OF THIS STUDY

- Tinnitus may have a severe impact on the quality of life in the absence of a satisfactory treatment.
- This is the first study to prospectively investigate the effect of the implantation of an Auditory Brainstem Implant (ABI) for the reduction of incapacitating tinnitus.
- This is a single-center, nonrandomized, interventional pilot study, including ten patients.
- The treatment effect is measured with validated tinnitus- and quality-of-life questionnaires, as well as safety endpoints.
- This is a high-risk study that imposes a significant risk on the study participants, although it is likely that the potential to ameliorate severely debilitating tinnitus outweighs the risks.

## INTRODUCTION

Tinnitus, which literally means 'ringing in the ears', is defined by the perception of sound or noise in the absence of an external physical sound source[1]. It is a very common condition (prevalence 5-18% in Western population) and, in a subgroup of patients, it causes extreme distress with far-reaching consequences for daily activities and quality of life[1-3]. Conventional treatment methods, e.g. sound generators and cognitive behavioral therapy, seem not to reduce the loudness of tinnitus, but may improve related depression and quality of life[4,5]. However, not all patients benefit from these treatments and there is a remaining group of patients with severe tinnitus for whom there is no conventional treatment modality available[4].

During the ongoing search for causal treatment methods, it has been demonstrated that a cochlear implant (CI) may be a potential treatment option. In a prospective study, CI implantation in patients with single-sided deafness and tinnitus resulted in significantly reduced tinnitus loudness in the long-term[6]. However, insertion of an electrode into the cochlea often leads to mechanical damage of intracochlear structures and subsequent, additional hearing loss. Therefore, CI is only indicated in cases where there is severe to profound hearing loss. This means that CI is not an option for the large group of tinnitus patients who still have usable hearing. To fill this gap, the auditory brainstem implant (ABI) might be an option.

In 1979, the first ABI was implanted by House and Hitselberger for the purpose of restoring hearing in a patient with neurofibromatosis type II (NF2)[7,8]. The implant hardware is comparable to that of the CI, however the ABI was specifically designed to bypass both the cochlea and the auditory nerve to directly stimulate the cochlear nucleus in the brainstem. It is thought that the dorsal cochlear nucleus (DCN) plays an important role in modulation and generation of tinnitus. For example, as a result of increased noise exposure, hyperactivity, expressed as an increased spontaneous activity, can be found in DCN; this in turn reduces residual inhibition and increases excitability[9]. In an animal model, it was demonstrated that there is behavioral evidence of tinnitus in conditions of increased hyperactivity in the DCN[10]. Thus electrical stimulation of the cochlear nucleus in rats led to suppressed behavioral evidence of tinnitus[11]. This effect might be explained by the possibility that stimulation of DCN compensates the loss of peripheral input caused by e.g. noise damage and thereby restores the disturbed balance between excitatory and inhibitory processes. Also, hyperactivity in the DCN might be modulated by direct stimulation of the neuronal circuit and interrupt pathways of hyperactivity to higher regions, such as the inferior colliculus, or it may induce a masking effect[11]. Several clinical studies have also shown a positive effect of ABI implantation on tinnitus. Soussi et al. published a study with patients who were implanted with an ABI for the indication of hearing loss. Seven out of ten patients with tinnitus before the implantation reported a decrease in their tinnitus loudness during stimulation with the ABI[12]. This finding was confirmed in several other clinical studies, showing a reduction of tinnitus in patients who suffered from tinnitus before ABI implantation after removal of vestibular schwannoma[13-15].

Together, the preclinical and clinical studies suggest that electrical stimulation of the cochlear nucleus with the ABI may be an effective method to suppress tinnitus. The potential advantage of the ABI over a CI is that it can be implanted without causing hearing damage. Therefore, we designed a pilot study. The objective of this study is to determine the efficacy of an ABI for the suppression of unilateral, incapacitating and intractable tinnitus. We hypothesize that stimulation of the cochlear

nucleus by the ABI can reduce tinnitus and, thereby, decrease the tinnitus burden and enhance the quality of life.

## METHODS & ANALYSIS

### STUDY DESIGN

This is a single-center, nonrandomized, interventional pilot study of 10 patients. There is no control group. The study site is the University Medical Center Groningen, The Netherlands.

### INCLUSION CRITERIA

Adults with unilateral, incapacitating tinnitus that is refractory to conventional treatment methods, are included in this study. The patients must have tinnitus for more than one year, with a stable situation over the last year. For the ipsilateral ear, the pure tone audiometry (PTA) thresholds averaged between 1, 2 and 4 kHz must be between 60 and 90dB. The contralateral ear should have functional hearing ability with PTA thresholds of <35dB PTA averaged between 1, 2 and 4kHz.

### EXCLUSION CRITERIA

Patients with a detectable cause for tinnitus that requires causal therapy, e.g. vestibular schwannoma or glomus tumor, are excluded from this study. Also, patients with psychiatric pathology or an unstable psychological situation as declared by a psychiatrist, are excluded. Patients with a life expectancy <5 years, a history of blood coagulation pathology, an ASA (American Society of Anesthesiologists) score >2, as well as pregnant women, are also excluded from participation. Additionally, anatomic abnormalities that prohibit appropriate placement of the implant, or a history of intolerance to materials used in the implant, are exclusion criteria. An overview of inclusion and exclusion criteria is presented in Table 1.

### STUDY DEVICE

The device used in this study is the Mi1200 SYNCHRONY Auditory Brainstem Implant, manufactured and supplied by MED-EL® (Innsbruck, Austria). The ABI is an implantable, electrically active device that consists of a stimulator, a coil with a removable magnet in its center and an active electrode array that is permanently attached to the stimulator (Figure 1). The electrode array stimulates the cochlear nucleus using 12 independent surface electrodes (Figure 2). The stimuli are controlled by an external processor that uses stimulation strategies similar to CI.

The intended use of the ABI device is for the electrical stimulation of the cochlear nucleus via an implanted stimulator and a specially designed electrode array to evoke auditory sensations in patients with non-functional cochlear nerves. In this study, the ABI will be primarily investigated for its ability to reduce tinnitus in patients having severe hearing loss despite having a functional cochlear nerve. This is regarded as an off-label use of the ABI, although the surgical method of implantation, the equipment and stimulation strategies are the same as for regular indications.

## STUDY DESCRIPTION

### PREOPERATIVE PHASE

Patients are recruited via our tertiary referral outpatient clinic and via advertisements on a patient association website. After extensive information on the nature, possible risks and benefits of this study, informed consent is obtained from eligible patients. When informed consent is obtained, a diagnostic work-up is performed. This includes otologic examination, cranial MRI, psychiatric assessment, audiometric and vestibular tests, tinnitus analysis, preoperative assessment by an anaesthesiologist, tinnitus- and quality of life-related questionnaires and a pregnancy test (if applicable). Whenever an exclusion criterion arises during this diagnostic work-up, the patient will be excluded. Otherwise, surgery is scheduled.

### IMPLANTATION

Participants are admitted to the neurosurgical ward of the University Medical Center Groningen for ABI implantation by a trained neurosurgeon. The neurosurgeons are experienced in cerebellopontine angle surgery and were specifically trained for ABI placement. The implant is subperiosteally fixed on the parietal skull. Access to the cochlear nucleus is made via retrosigmoid craniotomy. The electrode array is inserted in the lateral recess of the fourth ventricle in the direct vicinity of the cochlear nucleus. The most optimal position of the electrode is determined using a probing electrode with four contact points, applying bipolar stimulation in transverse, longitudinal and oblique directions while recording evoked auditory brainstem responses. After determining the best stimulation site, the active and definitive electrode is placed. The estimated duration of hospitalization is four to six days.

### POSTOPERATIVE PHASE

The ABI is switched on at six weeks postoperatively. This happens under monitoring of vital functions, as cranial nerves, such as the vagal nerve, may be stimulated unintentionally. The switch on is performed by a trained medical physicist, using MED-EL software (Maestro 6.0) and hardware (MAX interface). At this stage, patients receive the external audio processor. At first, the fitting and settings of the ABI are aimed at optimizing hearing performance, since this approach had given favourable results on tinnitus in earlier implant surgeries for deafness[12]. Later in the process, other stimulation strategies might be attempted. In the fitting procedure, pitch scaling and consecutive pitch ranking is performed. Electrodes are switched off if they give unwanted side effects during stimulation, e.g. facial twitching or dizziness. If electrode stimulation is without complications, further adjustments and fittings can safely take place at the outpatient clinic. Several repetitive fitting sessions are necessary to find an individual optimal stimulation strategy. In order to get the patient acquainted with the ABI and to improve their hearing ability, each fitting session is combined with training by a specialized speech therapist.

## OUTCOME MEASURES

### PRIMARY OUTCOME MEASURES

The primary outcome measure of this study is the change in the score of the Tinnitus Functional Index (TFI) questionnaire. We compare the preoperative TFI-score to the TFI-score as measured 12 months after initial stimulation with the ABI. The validated Dutch TFI-version is used to detect changes in tinnitus outcome after the intervention[16].

### SECONDARY OUTCOME MEASURES

Secondary outcome measurements include the safety of the implant and implantation, as measured by changes in audiometric and vestibular function after implantation. All adverse events are registered. Also, changes in the Visual Analogue Scale (VAS) for tinnitus loudness and tinnitus annoyance, change in tinnitus analysis and Hospital Anxiety and Depression scale (HADS), change in Tinnitus Handicap Inventory (THI) scores and change in tinnitus analysis are secondary outcome measurements.

### FOLLOW-UP

Follow-up will take place at three and six months after switching on the ABI. The endpoint of this study is set at 12 months. Follow-up will, however, continue yearly, up to five years after initial stimulation. An overview of the assessments and their timeline is provided in Figure 3.

## DATA ANALYSIS & STATISTICAL ANALYSIS

### DATA MANAGEMENT

All collected data is entered into predesigned case report forms (CRF) in an Open Clinica database. Stored data in this database is anonymized and password-protected. The database is only accessible by the study coordinator and assigned investigators. All changes made in the database are logged. Hard-copy data will be stored in a locked cabinet. The handling of personal data will comply with the Dutch Personal Data Protection Act.

### STATISTICAL ANALYSIS

The analysis of data is mainly descriptive. Mean and standard deviations are calculated in case of normally distributed data and median and interquartile range in case of skewed-distributed data. Differences in the primary outcome measure (i.e. TFI) as well as the secondary outcome measures (i.e. VAS, THI, HADS) are checked for significance using a paired t-test (if data is normally distributed), although the outcome will be interpreted with caution, since no power calculation was instituted. SPSS (IBM, newest available version) will be used. A p-value $<0.05$ is regarded as statistically significant.

### SAMPLE SIZE

This is a pilot study. Due to the experimental nature of the study, no power analysis was performed. It was empirically decided to select a cohort of 10 patients for this study.

## ETHICS & DISSEMINATION

### ETHICS

Tinnitus can be very invalidating, with a large impact on quality of life. Previous reports have shown that the ABI is a promising method to reduce tinnitus in these patients. This prospective study imposes a significant risk on the study participants; it is, however, likely that the potential to ameliorate severely debilitating tinnitus outweighs these risks. The study is approved by the Institutional Review Board of the University Medical Center Groningen and by the Dutch Health Care Inspectorate. It is performed according to the quality standards of Good Clinical Practice. Participation in the study is completely voluntary. Patients can withdraw at any time, without giving any reason. It is stressed that withdrawal does not affect standard clinical care. Written informed consent is obtained from all participants and they are informed when new information was obtained that may have affected their willingness to participate.

### SAFETY CONSIDERATIONS

We do not expect a deterioration of hearing due to the implantation. However, because this aspect has not yet been studied, it was decided as a first step to include patients with severe ipsilateral hearing loss (i.e. 60- till 90dB mean over 1-2-4kHz in PTA). In this patient group, a small loss of hearing sensitivity would not affect daily functioning. Yet, by excluding patients with profound hearing loss (>90 dB), our study would still be able to quantify unforeseen negative effects on hearing loss. Also, these patients might be eligible for a cochlear implant.

Possible complications are mostly related to the ABI surgery. In a study describing such complications, 78 nontumor patients were analyzed[17]. These patients were not diagnosed with NF2, and therefore are comparable to our patient group. Major complications (meningitis, hydrocephalus, cerebellar contusion) occurred in 6.4% of cases. No mortality was observed. Minor complications (e.g. cerebrospinal fluid leakage, transient hydrocephalus, wound seroma) occurred in 18%. In 30% of the patients, non-auditory side effects occurred as a result of electrical stimulation. These side effects diminished over time and could be modulated by changing the stimulation settings[17]. It was concluded that ABI implantation is a safe procedure with a low major complication rate when by performed by experienced surgeons[17]. Inclusion in the study and ABI-implantation are performed consecutively, allowing adequate monitoring of any unforeseen critical event related to the surgery or to the stimulation with the ABI. Stopping rules are predefined and are described in further on in this protocol.

Patients are intensely monitored during the first year following implantation. Patients receive a remote control to switch between preset stimulation programs. All of these actions are logged. Nonauditory side-effects and disappointing results on hearing and/or tinnitus will be managed by altering stimulation strategy or, if necessary, by turning off the device. All Adverse Events (AE) will be assessed and recorded at each clinical visit. AEs are followed-up until they have abated, or until a stable situation has been reached. In case of a Serious Adverse Event (SAE) or Unanticipated Serious Adverse Device Effect (USADE), it will be reported to the IRB respectively 15 or 7 days after the first knowledge of the SAE.

## STOPPING RULES

A Data Safety Monitoring Board is not required, due to the small-scale nature of this pilot study and consecutive patient inclusion. Instead, the following 'stopping rules' were predefined:

- If >1 major complication occurs in the implanted study population (i.e. meningitis, transient hydrocephalus, symptomatic cerebellar contusion).
- If in >2 cases unacceptable worsening of tinnitus is experienced and it is decided to permanently switch off the ABI.

In case one of the stopping rules occurs, the study will be suspended and the risk/benefit balance would be reassessed, before considering pursuing the study.

## DISSEMINATION

The results of this study will be published in peer-reviewed journals. Also, findings will be presented at national and international conferences for widespread dissemination of the results.

## AUTHOR CONTRIBUTION

PD, JD, RF, AM and MB conceived and designed the study and participated in logistical planning of the study. MB and AM are responsible for data acquisition. JD, JM and RF perform surgical implantation of the auditory brainstem implants and AM takes care of the perioperative and postoperative fitting sessions. All authors made significant contributions to the development and conceptualization of the protocol. They also reviewed the draft versions of this paper and have read and approved the final manuscript.

## FUNDING STATEMENT

This study is investigator-initiated. Funding is provided by Med-EL elektromedizinische Geräte GmbH. All study materials used in this study, i.e. implants, software, hardware, monitoring devices, are supplied by Med-EL.

## COMPETING INTEREST STATEMENT

Competing interest is not declared.

## DISCLAIMER

The funding party has no role in the study design and conduct; the collection, management, analysis and interpretation of the data; or the preparation and approval of the manuscript.

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ASA PHYSICAL STATUS CLASSIFICATION SYSTEM
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Tables

Table 1

Inclusion and exclusion criteria.

| Inclusion Criteria |
|---|
| Unilateral tinnitus |
| Severely incapacitating tinnitus |
| Age ≥18 years |
| Tinnitus that is present >1 year and was stable during the last year |
| Tinnitus that is not responsive to indicated conventional existing treatments (hearing aids and cognitive behavioural therapy). If a psychologist has indicated cognitive behavioural therapy, the patient should have tried this therapy for long enough to reasonably argue that these treatments were not successful. The same applies to the use of hearing aids |
| Ipsilateral ear: pure tone audiometry thresholds >60dB and <90dB (mean over 1-2-4 kHz) |
| Functional hearing in the contralateral ear with pure tone audiometry thresholds <35dB (mean over 1-2-4 kHz) |
| Informed consent after extensive oral and written information about the surgery, complications and uncertain effect of the Auditory Brainstem Implant on tinnitus |

| Exclusion Criteria |
|---|
| Detectable cause for tinnitus that requires causal therapy (e.g. vestibular schwannoma, glomus tumor, otosclerosis, arteriovenous malformation) as investigated by radiological and otological examination |

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| Psychiatric pathology and/or an unstable psychological situation as declared by a psychiatrist |
| Unrealistic expectations as declared by the investigator and/or psychiatrist |
| Life expectancy <5 years |
| History of blood coagulation pathology |
| ASA >II |
| Pregnancy |
| Anatomic abnormalities that would prevent appropriate placement of the stimulator housing in the bone of the skull |
| Anatomical abnormalities or surgical complications that might prevent placement of the Auditory Brainstem Implant Active Electrode Array |
| If the individual is known to be intolerant of the materials used in the implant (medical grade silicone, platinum, iridium and parylene C) |

ASA: American Society of Anesthesiologists18

## FIGURES

### FIGURE 1

The auditory brainstem implant consists over several components (from left to right): a remote control; the speech processor (consisting of transducer, microphone and connecting cable) which is the external and visible part of the implant; the receiver-stimulator with electrode (implantable component); and close-up of the electrode paddle. Reproduced with permission of Med-EL.

### FIGURE 2

Overview of the position of the implant and placement of the electrode on the cochlear nucleus on the brainstem.

*Reproduced with permission of Med-EL.*

### FIGURE 3

Study timeline.

ABI: auditory brainstem implant; OR: operating room; mo: months; MRI: magnetic resonance imaging; T: time point, wk: weeks; yr: years.


Figure 1. The auditory brainstem implant consists over several components (from left to right): a remote control; the speech processor (consisting of transducer, microphone and connecting cable) which is the external and visible part of the implant; the receiver-stimulator with electrode (implantable component); and close-up of the electrode paddle. Reproduced with permission of Med-EL.

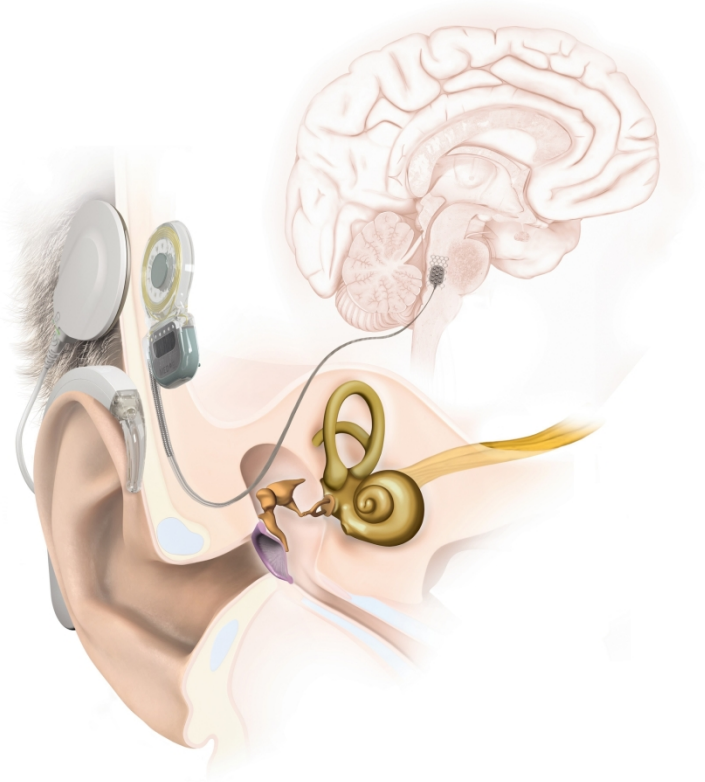

Figure 2. Overview of the position of the implant and placement of the electrode on the cochlear nucleus on the brainstem.
Reproduced with permission of Med-EL.

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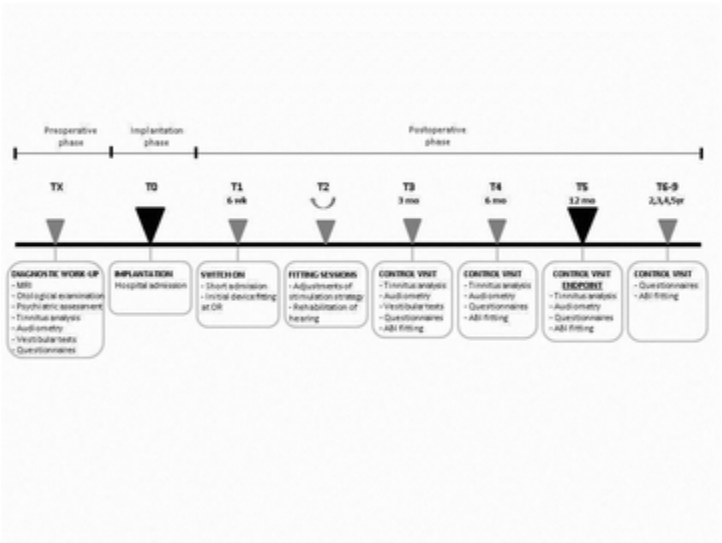


Figure 3. Study timeline.
ABI: auditory brainstem implant; OR: operating room; mo: months; MRI: magnetic resonance imaging; T: time point, wk: weeks; yr: years.

30x22mm (300 x 300 DPI)

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# AN AUDITORY BRAINSTEM IMPLANT FOR TREATMENT OF UNILATERAL TINNITUS: PROTOCOL FOR AN INTERVENTIONAL PILOT STUDY

Version January 15, 2019

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## KEYWORDS

Tinnitus; neuromodulation; auditory brainstem implant

## TRIAL STATUS

Inclusion of first patient in November 2017. Data collection is in progress. Trial is open for further inclusion. The trial ends at 5 years after inclusion of the last patient.

## ABSTRACT

### INTRODUCTION

Tinnitus may have a very severe impact on the quality of life. Unfortunately, for many patients, a satisfactory treatment modality is lacking. The auditory brainstem implant (ABI) was originally indicated for hearing restoration in patients with non-functional cochlear nerves, e.g. in neurofibromatosis type II. In analogy to a cochlear implant (CI), it has been demonstrated that an ABI may reduce tinnitus as a beneficial side effect. For tinnitus treatment, an ABI may have an advantage over a CI, as cochlear implantation may harm inner ear structures due to its invasiveness, while an ABI is presumed to not damage anatomical structures. This is the first study to implant an ABI to investigate its effect on the suppression of intractable tinnitus.

### METHODS & ANALYSIS

In this pilot study, ten adults having incapacitating unilateral intractable tinnitus and ipsilateral severe hearing loss will have an ABI implanted. The ABI is switched on 6 weeks after implantation, followed by several fitting sessions aimed at finding an optimal stimulation strategy. The primary outcome is the change in Tinnitus Functioning Index. Secondary goals are safety, quality of life and other questionnaires (Tinnitus Handicap Index, VAS-scales) and audiometric and vestibular function. The endpoint is set at one year after implantation. Follow-up will continue until five years after implantation.

### ETHICS & DISSEMINATION

The protocol was reviewed and approved by the Institutional Review Board of the University Medical Center Groningen, the Netherlands (METc 2015/479). The trial is registered at www.clinicialtrials.gov (NCT02630589) and will be updated when amendments have been made. Results of this study will be disseminated in peer-reviewed journals and at scientific conferences.

### REGISTRATION

www.clinicaltrials.gov, identifier NCT02630589


## STRENGTHS AND LIMITATIONS OF THIS STUDY

- Tinnitus may have a severe impact on the quality of life in the absence of a satisfactory treatment.
- This is the first study to prospectively investigate the effect of the implantation of an Auditory Brainstem Implant (ABI) for the reduction of incapacitating tinnitus.
- This is a single-center, nonrandomized, interventional pilot study, including ten patients.
- The treatment effect is measured with validated tinnitus- and quality-of-life questionnaires, as well as safety endpoints.
- This is a high-risk study because of the invasive surgery, however it is likely that the potential to ameliorate severely debilitating tinnitus outweighs these risks.

## INTRODUCTION

Tinnitus, which literally means 'ringing in the ears', is defined by the perception of sound or noise in the absence of an external physical sound source[1]. It is a very common condition (prevalence 5-18% in Western population) and, in a subgroup of patients, it causes extreme distress with far-reaching consequences for daily activities and quality of life[1-3]. Conventional treatment methods, e.g. sound generators and cognitive behavioral therapy, seem not to reduce the loudness of tinnitus, but may improve related depression and quality of life[4,5]. However, not all patients benefit from these treatments and there is a remaining group of patients with severe tinnitus for whom there is no conventional treatment modality available[4].

During the ongoing search for causal treatment methods, it has been demonstrated that a cochlear implant (CI) may be a potential treatment option. In a prospective study, CI implantation in patients with single-sided deafness and tinnitus resulted in significantly reduced tinnitus loudness in the long-term[6]. However, insertion of an electrode into the cochlea often leads to mechanical damage of intracochlear structures and subsequent, additional hearing loss. Therefore, CI is only indicated in cases where there is severe to profound hearing loss. This means that CI is not an option for the large group of tinnitus patients who still have usable hearing. To fill this gap, the auditory brainstem implant (ABI) might be an option.

In 1979, the first ABI was implanted by House and Hitselberger for the purpose of restoring hearing in a patient with neurofibromatosis type II (NF2)[7,8]. The implant hardware is comparable to that of the CI, however the ABI was specifically designed to bypass both the cochlea and the auditory nerve to directly stimulate the cochlear nucleus in the brainstem. It is thought that the dorsal cochlear nucleus (DCN) plays an important role in modulation and generation of tinnitus. For example, as a result of increased noise exposure, hyperactivity, expressed as an increased spontaneous activity, can be found in DCN; this in turn reduces residual inhibition and increases excitability[9]. In an animal model, it was demonstrated that there is behavioral evidence of tinnitus in conditions of increased hyperactivity in the DCN[10]. Thus electrical stimulation of the cochlear nucleus in rats led to suppressed behavioral evidence of tinnitus[11]. This effect might be explained by the possibility that stimulation of DCN compensates the loss of peripheral input caused by e.g. noise damage and thereby restores the disturbed balance between excitatory and inhibitory processes. Also, hyperactivity in the DCN might be modulated by direct stimulation of the neuronal circuit and interrupt pathways of hyperactivity to higher regions, such as the inferior colliculus, or it may induce a masking effect[11]. Several clinical studies have also shown a positive effect of ABI implantation on tinnitus. Soussi et al. published a study with patients who were implanted with an ABI for the indication of hearing loss. Seven out of ten patients with tinnitus before the implantation reported a decrease in their tinnitus loudness during stimulation with the ABI[12]. This finding was confirmed in several other clinical studies, showing a reduction of tinnitus in patients who suffered from tinnitus before ABI implantation after removal of vestibular schwannoma[13-15].

Together, the preclinical and clinical studies suggest that electrical stimulation of the cochlear nucleus with the ABI may be an effective method to suppress tinnitus. The potential advantage of the ABI over a CI is that it can be implanted without causing hearing damage. Therefore, we designed a pilot study. The objective of this study is to study the feasibility and effect of the ABI on the suppression of unilateral, incapacitating and intractable tinnitus. We hypothesize that stimulation of

the cochlear nucleus by the ABI can reduce tinnitus and, thereby, decrease the tinnitus burden and enhance the quality of life.

## METHODS & ANALYSIS

### STUDY DESIGN

This is a single-center, nonrandomized, interventional pilot study. The goal is to include10 patients. There is no control group. The study site is a tertiary academic hospital (University Medical Center Groningen, The Netherlands).

### INCLUSION CRITERIA

Adults with unilateral, incapacitating tinnitus that is refractory to conventional treatment methods, are included in this study. Lateralization (either left or right ear) and the assessment of tinnitus as unilateral was based on patients perception. The patients must have tinnitus for more than one year, with a stable situation over the last year. For the ipsilateral ear, the pure tone audiometry (PTA) thresholds averaged between 1, 2 and 4 kHz must be between 40 and 90dB. The contralateral ear should have functional hearing ability with PTA thresholds of <35dB (average between 1, 2 and 4kHz), with a minimum of 25dB (average between 1, 2 and 4kHz) difference compared to the tinnitus (ipsilateral) ear.

### EXCLUSION CRITERIA

Patients with a detectable cause for tinnitus that requires causal therapy, e.g. vestibular schwannoma or glomus tumor, are excluded from this study. Also, patients with psychiatric pathology or an unstable psychological situation as declared by a psychiatrist, are excluded. Patients with a life expectancy <5 years, a history of blood coagulation pathology, an ASA (American Society of Anesthesiologists) score >2, as well as pregnant women, are also excluded from participation. Additionally, anatomic abnormalities that prohibit appropriate placement of the implant, or a history of intolerance to materials used in the implant, are exclusion criteria. An overview of inclusion and exclusion criteria is presented in Table 1.

### STUDY DEVICE

The device used in this study is the Mi1200 SYNCHRONY Auditory Brainstem Implant, manufactured and supplied by MED-EL® (Innsbruck, Austria). The ABI is an implantable, electrically active device that consists of a stimulator, a coil with a removable magnet in its center and an active electrode array that is permanently attached to the stimulator (Figure 1). The electrode array stimulates the cochlear nucleus using 12 independent surface electrodes (Figure 2). The stimuli are controlled by an external processor that uses stimulation strategies similar to CI.

The intended use of the ABI device is for the electrical stimulation of the cochlear nucleus via an implanted stimulator and a specially designed electrode array to evoke auditory sensations in patients with non-functional cochlear nerves. In this study, the ABI will be primarily investigated for its ability to reduce tinnitus in patients having severe hearing loss despite having a functional

cochlear nerve. This is regarded as an off-label use of the ABI, although the surgical method of implantation, the equipment and stimulation strategies are the same as for regular indications.

### RECRUITMENT

Potentially eligible patients are recruited from our outpatient clinic, as well as from our tinnitus database, collected during several years of clinical practice in tertiary tinnitus care. Furthermore, advertisements were placed in magazines and on websites of patients' associations and on the research website of the University Medical Center Groningen. Awareness of this study was created by presenting this study protocol at various scientific meetings.

### PATIENT AND PUBLIC INVOLVEMENT

A plan for organization of the recruitment of eligible patients was made in consultation and collaboration with a national patients' association. Patients were not involved in the development of the research question or in the design of the study. Patient materials, such as information about the study, was screened for understandable not-medical language and approved. Results of this study will be disseminated to study participants and patients via a personal newsletter and via the patients' association website.

## STUDY DESCRIPTION

### PREOPERATIVE PHASE

Patients are recruited via our tertiary referral outpatient clinic and via advertisements on a patient association website. After extensive information on the nature, possible risks and benefits of this study, informed consent is obtained by the study coordinator from eligible patients (for informed consent form, see supplementary file). When informed consent is obtained, a diagnostic work-up is performed. This includes otologic examination, cranial MRI, psychiatric assessment, audiometric and vestibular tests, tinnitus analysis, preoperative assessment by an anaesthesiologist, tinnitus- and quality of life-related questionnaires and a pregnancy test (if applicable). Whenever an exclusion criterion arises during this diagnostic work-up, the patient will be excluded. Otherwise, surgery is scheduled.

### IMPLANTATION

Participants are admitted to the neurosurgical ward of the University Medical Center Groningen for ABI implantation by a trained neurosurgeon. The neurosurgeons are experienced in cerebellopontine angle surgery and were specifically trained for ABI placement. The implant is subperiostally fixated on the parietal skull. Access to the cochlear nucleus is made via retrosigmoid craniotomy. The electrode array is inserted in the lateral recess of the fourth ventricle in the direct vicinity of the cochlear nucleus. The most optimal position of the electrode is determined using a probing electrode with four contact points, applying bipolar stimulation in transverse, longitudinal and oblique directions while recording evoked auditory brainstem responses. After determining the best stimulation site, the active and definitive electrode is placed. The estimated duration of hospitalization is four to six days.

### POSTOPERATIVE PHASE

The ABI is switched on at six weeks postoperatively. This happens under monitoring of vital functions, as cranial nerves, such as the vagal nerve, may be stimulated unintentionally. The switch on is performed by a trained medical physicist, using MED-EL software (Maestro 7.0) and hardware (MAX interface). At this stage, patients receive the external audio processor. At first, the fitting and settings of the ABI are aimed at optimizing hearing performance, since this approach had given favourable results on tinnitus in earlier implant surgeries for deafness[12]. Later in the process, other stimulation strategies might be attempted. In the fitting procedure, pitch scaling and consecutive pitch ranking is performed. Electrodes are switched off if they give unwanted side effects during stimulation, e.g. facial twitching or dizziness. If electrode stimulation is without complications, further adjustments and fittings can safely take place at the outpatient clinic. Several repetitive fitting sessions are necessary to find an individual optimal stimulation strategy. In order to get the patient acquainted with the ABI and to improve their hearing ability, each fitting session is combined with training by a specialized speech therapist.

## OUTCOME MEASURES

### PRIMARY OUTCOME MEASURES

The primary outcome measure of this study is the change in the score of the Tinnitus Functional Index (TFI) questionnaire. We compare the preoperative (baseline) TFI-sc-score to postoperative TFI-scores at several time points (see Figure 3), with the primary end point set at one year after initial stimulation with the AB.. The validated Dutch TFI-version is used to detect changes in tinnitus outcome after the intervention and its psychometric properties are in line with the original version.[16] The minimal clinical important difference is determined at a 13 point reduction.[17]

### SECONDARY OUTCOME MEASURES

Secondary outcome measurements include:

- Change in audiogical function (as measured determining PTA thresholds and speech audiometry), with and without ABI switched on
- Change in vestibular function (as measured by vestibular testing of both labyrinths)
- Change in several questionnaires:
    - Hospital Anxiety and Depression scale (HADS)[18]
    - Tinnitus Handicap Inventory (THI)
    - Visual analogue scale (VAS) for tinnitus loudness and tinnitus annoyance
- Adverse events
- Tinnitus analysis (as measured by tone matching at the contralateral ear)
- ABI-related outcomes
    - Number of electrodes evoking auditory sensation
    - Pitch mapping
    - Hours of usage

- Preferred program

FOLLOW-UP

Follow-up will take place at three and six months after switching on the ABI. The endpoint of this study is set at 12 months. Follow-up will, however, continue yearly, up to five years after initial stimulation. An overview of the assessments and their timeline is provided in Figure 3.

## DATA ANALYSIS & STATISTICAL ANALYSIS

### DATA MANAGEMENT

All collected data are entered into predesigned electronic case report forms (eCRF) in an Open Clinica® database (www.openclinica.com) by a trained investigator. Data in this database are anonimyzed and contains range checks. Stored data in this database are anonymized and password-protected. The database is only accessible by the study coordinator and assigned investigators. All changes made in the database are logged. Hard-copy data will be stored in a locked cabinet. The handling of personal data will comply with the Dutch Personal Data Protection Act. The final dataset will be available to the authors only.

### STATISTICAL ANALYSIS

The analysis of data is mainly descriptive. Mean and standard deviations are calculated in case of normally distributed data and median and interquartile range in case of skewed-distributed data. Differences in the primary outcome measure (i.e. TFI) as well as the secondary outcome measures (i.e. VAS, THI, HADS) are checked for significance using a paired t-test (if data are normally distributed), although the outcome will be interpreted with caution, since no power calculation was instituted.
SPSS (IBM, newest available version) will be used. A p-value $<0.05$ is regarded as statistically significant.

### SAMPLE SIZE

This is a pilot study. Due to the experimental nature of the study, no power analysis was performed. It was empirically decided to select a cohort of 10 patients for this study.

## ETHICS & DISSEMINATION

### ETHICS

Tinnitus can be very incapacitating, with a large impact on quality of life. Previous reports have shown that the ABI is a promising method to reduce tinnitus in these patients. Although the major complication rate is low when performed by experienced surgeons[19], potential complications can be severe. This study imposes a significant risk on the study participants; it is, however, likely that the

potential to ameliorate severely debilitating tinnitus outweighs these risks. The study is approved by the Institutional Review Board of the University Medical Center Groningen and by the Dutch Health Care Inspectorate. It is performed according to the quality standards of Good Clinical Practice. Participation in the study is completely voluntary. Patients can withdraw at any time, without giving any reason. It is stressed that withdrawal does not affect standard clinical care. Written informed consent is obtained from all participants and they are informed when new information arises that may affecttheir willingness to participate.

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO (Wet Medisch-wetenschappelijk Onderzoek met mensen, i.e. Dutch Act for Medical Research Involving Human Subjects) . The sponsor has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

STUDY MONITORING

This study is monitored by a certified monitor from the Trial Coordination Center, which is independent from the sponsor. Study monitoring includes for example: checking in- and exclusion criteria for included patients, sample-wise data checking, correctness of data handling, storage, correctness and completeness of documentation in trial master file, etc. Monitoring will take place after every 2-3 included patients and after that, once a year for another 4 years.

## SAFETY CONSIDERATIONS

We do not expect a deterioration of hearing due to the implantation. However, because this aspect has not yet been studied, it was decided as a first step to include patients with severe ipsilateral hearing loss (i.e. 40 till 90dB mean over 1-2-4kHz in PTA). In this patient group, a small loss of hearing sensitivity would not affect daily functioning. Yet, by excluding patients with profound hearing loss (>90 dB), our study would still be able to quantify unforeseen negative effects on hearing loss. Also, these patients might be eligible for a cochlear implant.

Possible complications are mostly related to the ABI surgery. In a study describing such complications, 78 non-tumor patients were analyzed[20]. These patients were not diagnosed with NF2, and therefore are comparable to our patient group. Major complications (meningitis, hydrocephalus, cerebellar contusion) occurred in 6.4% of cases. No mortality was observed. Minor complications (e.g. cerebrospinal fluid leakage, transient hydrocephalus, wound seroma) occurred in 18%. In 30% of the patients, non-auditory side effects occurred as a result of electrical stimulation. These side effects diminished over time and could be modulated by changing the stimulation settings[20]. It was concluded that ABI implantation is a safe procedure with a low major complication rate when performed by experienced surgeons[20]. Inclusion in the study and ABI-implantation are performed consecutively, allowing adequate monitoring of any unforeseen critical event related to the surgery or to the stimulation with the ABI. Stopping rules are predefined and are described later on in this protocol.

Patients are intensely monitored during the first year following implantation. Patients receive a remote control to switch between preset stimulation programs. All of these actions are logged, as well as hours of usage of the implant. Nonauditory side-effects and disappointing results on hearing

and/or tinnitus will be managed by altering stimulation strategy or, if necessary, by turning off the device. All Adverse Events (AE) will be assessed and recorded at each clinical visit. AEs are followed-up until they have abated, or until a stable situation has been reached. In case of a Serious Adverse Event (SAE) or Unanticipated Serious Adverse Device Effect (USADE), it will be reported to the IRB respectively 15 or 7 days after the first knowledge of the SAE.

## STOPPING RULES

A Data Safety Monitoring Board is not required, due to the small-scale nature of this pilot study and consecutive patient inclusion. Instead, the following 'stopping rules' were predefined:

- If >1 major complication occurs in the implanted study population (i.e. meningitis, transient hydrocephalus, symptomatic cerebellar contusion).
- If in >2 cases unacceptable worsening of tinnitus is experienced and it is decided to permanently switch off the ABI.

In case one of the stopping rules occurs, the study will be suspended and the risk/benefit balance would be reassessed, before considering pursuing the study.

## DISSEMINATION

The final manuscript will be written by the authors as named above. The results of this study will be published in peer-reviewed journals. Also, findings will be presented at national and international conferences for widespread dissemination of the results.

## AUTHOR CONTRIBUTION

PD, RF, JD, AM and MB conceived and designed the study and participated in logistical planning of the study. MB and AM are responsible for data acquisition. JD, JM and RF perform surgical implantation of the auditory brainstem implants and AM takes care of the perioperative and postoperative fitting sessions. All authors made significant contributions to the development and conceptualization of the protocol. They also reviewed the draft versions of this paper and have read and approved the final manuscript.

## FUNDING STATEMENT

This study is investigator-initiated. Funding is provided by Med-EL elektromedizinische Geräte GmbH. All study materials used in this study, i.e. implants, software, hardware, monitoring devices, are supplied by Med-EL.

## COMPETING INTEREST STATEMENT

Competing interest is not declared.

## DISCLAIMER

Med-el has had an advisory role in designing the study. The funding party has no role in the study design and conduct; the collection, management, analysis and interpretation of the data; or the preparation and final approval of the manuscript(s). The final manuscript(s) will be send to Med-el prior to publication for notification.

**Word count: 3084**

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ASA PHYSICAL STATUS CLASSIFICATION SYSTEM

http://www.google.nl/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwiGkO7kiuzbAhVQJVAKHYI1CAEQFggqMAA&url=http%3A%2F%2Fwww.asahq.org%2F~%2Fmedia%2Fsites%2Fasahq%2Ffiles%2Fpublic%2Fresources%2Fstandards-guidelines%2Fasa-physical-status-classification-system.pdf&usg=AOvVaw2VpwTL1ioJ7-XXfFM7Smwq. Updated 2014. Accessed 7, 2016.

Tables

Table 1. Inclusion and exclusion criteria.

| Inclusion Criteria |
|---|
| Unilateral tinnitus |
| Severely incapacitating tinnitus |
| Men or women, Age >18 years |
| Tinnitus that is present >1 year and was stable during the last year |
| Tinnitus that is not responsive to indicated conventional existing treatments (hearing aids and cognitive behavioural therapy). If a psychologist has indicated cognitive behavioural therapy, the patient should have tried this therapy for long enough to reasonably argue that these treatments were not successful. The same applies to the use of hearing aids |
| Ipsilateral ear: pure tone audiometry thresholds >40dB and <90dB (mean over 1-2-4 kHz) |
| Functional hearing in the contralateral ear with pure tone audiometry thresholds <35dB (mean over 1-2-4 kHz) and with a minimum Δ25dB compared to the ipsilateral ear. |
| Informed consent after extensive oral and written information about the surgery, complications and uncertain effect of the Auditory Brainstem Implant on tinnitus |

| Exclusion Criteria |
|---|
| Detectable cause for tinnitus that requires causal therapy (e.g. vestibular schwannoma, glomus tumor, otosclerosis, arteriovenous malformation) as investigated by radiological and otological examination |

| |
|---|
| Psychiatric pathology and/or an unstable psychological situation as declared by a psychiatrist |
| Unrealistic expectations as declared by the investigator and/or psychiatrist |
| Life expectancy <5 years |
| History of blood coagulation pathology |
| ASA >II |
| Pregnancy |
| Anatomic abnormalities that would prevent appropriate placement of the stimulator housing in the bone of the skull |
| Anatomical abnormalities or surgical complications that might prevent placement of the Auditory Brainstem Implant Active Electrode Array |
| Known intolerance to the materials used in the implant (medical grade silicone, platinum, iridium and parylene C) |

ASA: American Society of Anesthesiologists [21]

## FIGURES

### FIGURE 1

The auditory brainstem implant consists over several components (from left to right): a remote control; the speech processor (consisting of transducer, microphone and connecting cable) which is the external and visible part of the implant; the receiver-stimulator with electrode (implantable component); and close-up of the electrode paddle. Reproduced with permission of Med-EL.

### FIGURE 2

Overview of the position of the implant and placement of the electrode on the cochlear nucleus on the brainstem.

*Reproduced with permission of Med-EL.*

### FIGURE 3

Study timeline.

ABI: auditory brainstem implant; OR: operating room; mo: months; MRI: magnetic resonance imaging; T: time point, wk: weeks; yr: years.


The auditory brainstem implant consists over several components (from left to right): a remote control; the speech processor (consisting of transducer, microphone and connecting cable) which is the external and visible part of the implant; the receiver-stimulator with electrode (implantable component); and close-up of the electrode paddle. Reproduced with permission of Med-EL.

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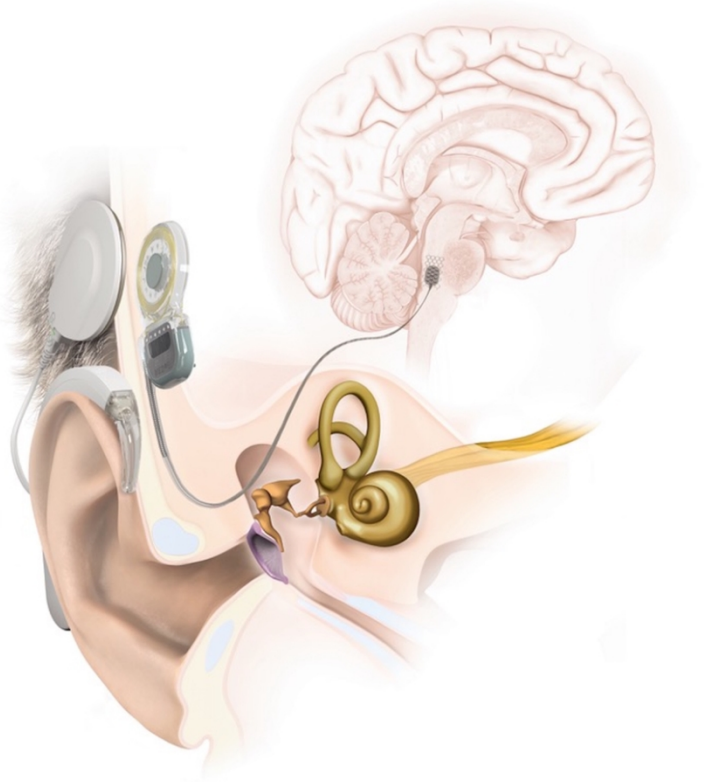
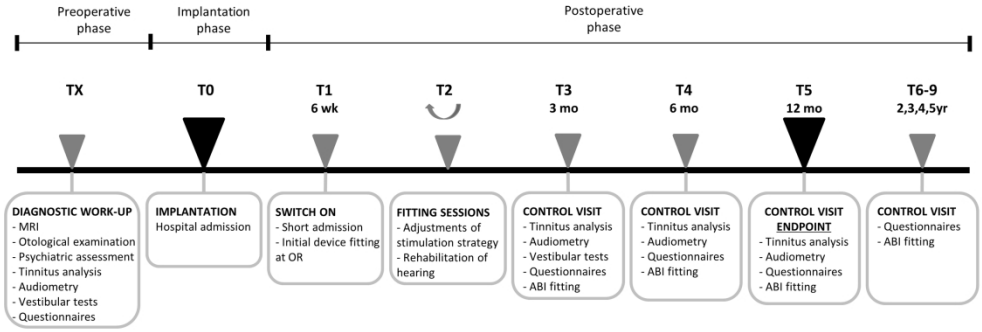


Overview of the position of the implant and placement of the electrode on the cochlear nucleus on the brainstem. Reproduced with permission of Med-EL.

99x108mm (300 x 300 DPI)




Study timeline.
"ABI: auditory brainstem implant; OR: operating room; mo: months; MRI: magnetic resonance imaging; T: time point, wk: weeks; yr: years.

253x190mm (300 x 300 DPI)

# INFORMED CONSENT FORM

for participating in scientific research

## INVESTIGATING THE EFFECT OF AN AUDITORY BRAINSTEM IMPLANT ON UNILATERAL AND SEVERE TINNITUS

Version 3.0, dd 24-4-2017

- I have been informed about this research to my satisfaction. I have read the written information (ABI v4.0) carefully. I have been given the opportunity to ask questions about this research. My questions have been answered satisfactorily. I have been able to think carefully about participation. I have the right to withdraw my consent at any time without having to give any reason for it.
- I am aware that the main risk of participation in the study is that: dizziness may occur and/or a worsening of hearing ability. In addition, there are risks of the surgery such as meningitis and wound infection.
- I am aware that this treatment cannot guarantee that the tinnitus will greatly diminish, change or disappear.
- I agree that my general practitioner will receive information about this examination and the surgery that I will undergo. I also authorize the psychiatrist to request relevant information from my general practitioner.
- I am aware that technical maintenance is guaranteed for about 10 years after implantation and that it is not yet clear who will pay for this maintenance after that.
- I agree with participation in the research.

Full name:

Date of birth:

Signature: Date:

- The undersigned declares that the abovementioned person has been informed of the abovementioned investigation both in speech and in writing. He / she also declares that a premature termination of participation by the abovementioned person will have no influence whatsoever on the medical care that is due to him or her.

Name of research investigator:

Signature: Date:


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry |
| | 2b | All items from the World Health Organization Trial Registration Data Set |
| Protocol version | 3 | Date and version identifier |
| Funding | 4 | Sources and types of financial, material, and other support |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors |
| | 5b | Name and contact information for the trial sponsor |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) |
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention |
| | 6b | Explanation for choice of comparators |
| Objectives | 7 | Specific objectives or hypotheses |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) |

| | | | |
|---|---|---|---|
| | **Methods: Participants, interventions, and outcomes** | | |
| pp 5 | Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained |
| & p. 5 | Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) |
| & p. 6/7 + fig 3 | Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered |
| p. 9 | | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) |
| & p7 | | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) |
| NA | | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial |
| pp7 | Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended |
| & fig 3 | Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) |
| & p.7 | Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations |
| & p. 6. | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size |
| | **Methods: Assignment of interventions (for controlled trials)** | | |
| | Allocation: | | |
| NA | Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions |

| | | | |
|---|---|---|---|
| NA | Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned |
| NA | Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions |
| NA | Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how |
| NA | | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial |



**Methods: Data collection, management, and analysis**

| | | | |
|---|---|---|---|
| 8 p.8 | Data collection methods | 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 |
| NA | | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols |
| 8 p.8 | Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol |
| 8 p.8 | Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol |
| | | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) |
| | | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) |

**Methods: Monitoring**

| | | | |
|---|---|---|---|
| 3 p.9 | Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed |

| | | | |
|---|---|---|---|
| | | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial |
| Harms | | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct |
| Auditing | | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor |
| **Ethics and dissemination** | | | |
| Research ethics approval | | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval |
| Protocol amendments | | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) |
| Consent or assent | | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) |
| | | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable |
| Confidentiality | | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial |
| Declaration of interests | | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site |
| Access to data | | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators |
| Ancillary and post-trial care | | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation |
| Dissemination policy | | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions |
| | | 31b | Authorship eligibility guidelines and any intended use of professional writers |
| | | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |

## Appendices

added

| | | |
|---|---|---|
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# An auditory brainstem implant for treatment of unilateral tinnitus: protocol for an interventional pilot study

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| | |

# AN AUDITORY BRAINSTEM IMPLANT FOR TREATMENT OF UNILATERAL TINNITUS: PROTOCOL FOR AN INTERVENTIONAL PILOT STUDY

Version February 27, 2019

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## KEYWORDS

Tinnitus; neuromodulation; auditory brainstem implant

## TRIAL STATUS

Inclusion of first patient in November 2017. Data collection is in progress. Trial is open for further inclusion. The trial ends at 5 years after inclusion of the last patient.

## ABSTRACT

### INTRODUCTION

Tinnitus may have a very severe impact on the quality of life. Unfortunately, for many patients, a satisfactory treatment modality is lacking. The auditory brainstem implant (ABI) was originally indicated for hearing restoration in patients with non-functional cochlear nerves, e.g. in neurofibromatosis type II. In analogy to a cochlear implant (CI), it has been demonstrated that an ABI may reduce tinnitus as a beneficial side effect. For tinnitus treatment, an ABI may have an advantage over a CI, as cochlear implantation can harm inner ear structures due to its invasiveness, while an ABI is presumed to not damage anatomical structures. This is the first study to implant an ABI to investigate its effect on intractable tinnitus.

### METHODS & ANALYSIS

In this pilot study, ten adults having incapacitating unilateral intractable tinnitus and ipsilateral severe hearing loss will have an ABI implanted. The ABI is switched on 6 weeks after implantation, followed by several fitting sessions aimed at finding an optimal stimulation strategy. The primary outcome will be the change in Tinnitus Functioning Index. Secondary outcomes will be tinnitus burden and quality of life (using THI and HADS questionnaires), tinnitus characteristics (using VAS-scales an tinnitus analysis), safety, audiometric and vestibular function. The endpoint is set at one year after implantation. Follow-up will continue until five years after implantation.

### ETHICS & DISSEMINATION

The protocol was reviewed and approved by the Institutional Review Board of the University Medical Center Groningen, the Netherlands (METc 2015/479). The trial is registered at www.clinicialtrials.gov (NCT02630589) and will be updated if amendments are made. Results of this study will be disseminated in peer-reviewed journals and at scientific conferences.

### REGISTRATION

www.clinicaltrials.gov, identifier NCT02630589


## STRENGTHS AND LIMITATIONS OF THIS STUDY

- Tinnitus may have a severe impact on the quality of life in the absence of a satisfactory treatment.
- This is the first study to prospectively investigate the effect of the implantation of an Auditory Brainstem Implant (ABI) for the reduction of incapacitating tinnitus.
- This is a single-center, nonrandomized, interventional pilot study, including ten patients.
- The treatment effect is measured with validated tinnitus- and quality of life questionnaires, as well as safety endpoints.
- This is a high-risk study because of the invasive surgery, however it is likely that the potential to ameliorate severely debilitating tinnitus outweighs these risks.

## INTRODUCTION

Tinnitus, which literally means 'ringing in the ears', is defined by the perception of sound or noise in the absence of an external physical sound source[1]. It is a very common condition (prevalence 5-18% in Western population) and, in a subgroup of patients, it causes extreme distress with far-reaching consequences for daily activities and quality of life[1-3]. Conventional treatment methods, e.g. sound generators and cognitive behavioral therapy, seem not to reduce the loudness of tinnitus, but may improve related depression and quality of life[4,5]. However, not all patients benefit from these treatments and there is a remaining group of patients with severe tinnitus for whom there is no conventional treatment modality available[6].

During the ongoing search for causal treatment methods, it has been demonstrated that a cochlear implant (CI) may be a potential treatment option. In a prospective study, CI implantation in patients with single-sided deafness and tinnitus resulted in significantly reduced tinnitus loudness in the long-term[7]. However, insertion of an electrode into the cochlea often leads to mechanical damage of intracochlear structures and subsequent, additional hearing loss. Therefore, CI is only indicated in cases where there is severe to profound hearing loss. This means that CI is not an option for the large group of tinnitus patients who still have usable hearing. To fill this gap, the auditory brainstem implant (ABI) might be an option.

In 1979, the first ABI was implanted by House and Hitselberger for the purpose of restoring hearing in a patient with neurofibromatosis type II (NF2)[8,9]. The implant hardware is comparable to that of the CI, however the ABI was specifically designed to bypass both the cochlea and the auditory nerve to directly stimulate the cochlear nucleus in the brainstem. It is thought that the dorsal cochlear nucleus (DCN) plays an important role in modulation and generation of tinnitus. For example, as a result of increased noise exposure, hyperactivity, expressed as an increased spontaneous activity, can be found in DCN; this in turn reduces residual inhibition and increases excitability[10]. In an animal model, it was demonstrated that there is behavioral evidence of tinnitus in conditions of increased hyperactivity in the DCN[11]. Thus electrical stimulation of the cochlear nucleus in rats led to suppressed behavioral evidence of tinnitus[12]. This effect might be explained by the possibility that stimulation of DCN compensates the loss of peripheral input caused by e.g. noise damage and thereby restores the disturbed balance between excitatory and inhibitory processes. Also, hyperactivity in the DCN might be modulated by direct stimulation of the neuronal circuit and interrupt pathways of hyperactivity to higher regions, such as the inferior colliculus, or it may induce a masking effect[12]. Several clinical studies have also shown a positive effect of ABI implantation on tinnitus. Soussi et al. published a study with patients who were implanted with an ABI for the indication of hearing loss. Seven out of ten patients with tinnitus before the implantation reported a decrease in their tinnitus loudness during stimulation with the ABI[13]. This finding was confirmed in several other clinical studies, showing a reduction of tinnitus in patients who suffered from tinnitus before ABI implantation after removal of vestibular schwannoma[14-16].

Together, the preclinical and clinical studies suggest that electrical stimulation of the cochlear nucleus with the ABI may be an effective method to suppress tinnitus. The potential advantage of the ABI over a CI is that it can be implanted without causing hearing damage. Therefore, we designed a pilot study. The objective of this study is to study the effect of the ABI on the suppression of unilateral, incapacitating and intractable tinnitus. We hypothesize that stimulation of the cochlear

nucleus by the ABI can reduce tinnitus and, thereby, decrease the tinnitus burden and enhance the quality of life.

## METHODS & ANALYSIS

### STUDY DESIGN

This is a single-center, nonrandomized, interventional pilot study. The goal is to include 10 patients. There is no control group. The study site is a tertiary academic hospital (University Medical Center Groningen, The Netherlands).

### INCLUSION CRITERIA

Adults with unilateral, incapacitating tinnitus that is refractory to conventional treatment methods, are included in this study. Lateralization (either left or right ear) and the assessment of tinnitus as unilateral was based on patients perception. The patients must have tinnitus for more than one year, with a stable situation over the last year. For the ipsilateral ear, the pure tone audiometry (PTA) thresholds averaged between 1, 2 and 4 kHz must be between 40 and 90dB. The contralateral ear should have functional hearing ability with PTA thresholds of <35dB (average between 1, 2 and 4kHz), with a minimum of 25dB (average between 1, 2 and 4kHz) difference compared to the tinnitus (ipsilateral) ear.

### EXCLUSION CRITERIA

Patients with a detectable cause for tinnitus that requires causal therapy, e.g. vestibular schwannoma or glomus tumor, are excluded from this study. Also, patients with psychiatric pathology or an unstable psychological situation as declared by a psychiatrist, are excluded. Patients with a life expectancy <5 years, a history of blood coagulation pathology, an ASA (American Society of Anesthesiologists) score >2, as well as pregnant women, are also excluded from participation. Additionally, anatomic abnormalities that prohibit appropriate placement of the implant, or a history of intolerance to materials used in the implant, are exclusion criteria. An overview of inclusion and exclusion criteria is presented in Table 1.

### STUDY DEVICE

The device used in this study is the Mi1200 SYNCHRONY Auditory Brainstem Implant, manufactured and supplied by MED-EL® (Innsbruck, Austria). The ABI is an implantable, electrically active device that consists of a stimulator, a coil with a removable magnet in its center and an active electrode array that is permanently attached to the stimulator (Figure 1). The electrode array stimulates the cochlear nucleus using 12 independent surface electrodes (Figure 2). The stimuli are controlled by an external processor that uses stimulation strategies similar to CI.

The intended use of the ABI device is for the electrical stimulation of the cochlear nucleus via an implanted stimulator and a specially designed electrode array to evoke auditory sensations in patients with non-functional cochlear nerves. In this study, the ABI will be primarily investigated for its ability to reduce tinnitus in patients having moderate to severe hearing loss despite having a

functional cochlear nerve. This is regarded as an off-label use of the ABI, although the surgical method of implantation, the equipment and stimulation strategies are the same as for regular indications.

### RECRUITMENT

Potentially eligible patients are recruited from our outpatient clinic, as well as from our tinnitus database, collected during several years of clinical practice in tertiary tinnitus care. Furthermore, advertisements were placed in magazines and on websites of patients' associations and on the research website of the University Medical Center Groningen. Awareness of this study was created by presenting this study protocol at various scientific meetings.

### PATIENT AND PUBLIC INVOLVEMENT

A plan for organization of the recruitment of eligible patients was made in consultation and collaboration with a national patients' association. Patients were not involved in the development of the research question or in the design of the study. Patient materials, such as information about the study, was screened by the Institutional Review Board (IRB) for understandable not-medical language and approved. Results of this study will be disseminated to study participants and patients via a personal newsletter and via the patients' association website.

## STUDY DESCRIPTION

### PREOPERATIVE PHASE

After extensive information on the nature, possible risks and benefits of this study, informed consent is obtained by the study coordinator from eligible patients (for informed consent form, see supplementary file). When informed consent is obtained, a diagnostic work-up is performed. This includes otologic examination, cranial MRI, psychiatric assessment, audiometric and vestibular tests, tinnitus analysis, preoperative assessment by an anaesthesiologist, tinnitus- and quality of life-related questionnaires and a pregnancy test (if applicable). Whenever an exclusion criterion arises during this diagnostic work-up, the patient will be excluded. Otherwise, surgery is scheduled.

### IMPLANTATION

Participants are admitted to the neurosurgical ward of the University Medical Center Groningen for ABI implantation by a trained neurosurgeon. The neurosurgeons are experienced in cerebellopontine angle surgery and were specifically trained for ABI placement. The implant is subperiostally fixated on the parietal skull. Access to the cochlear nucleus is made via retrosigmoid craniotomy. The electrode array is inserted in the lateral recess of the fourth ventricle in the direct vicinity of the cochlear nucleus. The most optimal position of the electrode is determined using a probing electrode with four contact points, applying bipolar stimulation in transverse, longitudinal and oblique directions while recording evoked auditory brainstem responses. After determining the best stimulation site, the active and definitive electrode is placed. With the definite electrode in position, all electrodes are checked for optimal responses. The estimated duration of hospitalization is 4 to 6 days.

### POSTOPERATIVE PHASE

Shortly postoperative, a CT-scan is made to determine the position of the electrode and to screen for intracranial complications. The ABI will be switched on at 6 weeks postoperatively. This happens under monitoring of vital functions, as cranial nerves, such as the vagal nerve, may be stimulated unintentionally. The switch on is performed by a trained medical physicist, using MED-EL software (Maestro 7.0) and hardware (MAX interface). At this stage, patients receive the external audio processor. At first, the fitting and settings of the ABI will be aimed at optimizing hearing performance, since this approach had given favourable results on tinnitus in earlier implant surgeries for deafness[13]. Later in the process, other stimulation strategies might be attempted. In the fitting procedure, pitch scaling and consecutive pitch ranking is performed. Electrodes are switched off if they give unwanted side effects during stimulation, e.g. facial twitching or dizziness. If electrode stimulation is without complications, further adjustments and fittings can safely take place at the outpatient clinic. Several repetitive fitting sessions will be necessary to find an individual optimal stimulation strategy. In order to get the patient acquainted with the ABI and to improve their hearing ability, each fitting session is combined with training by a specialized speech therapist.

## OUTCOME MEASURES

### PRIMARY OUTCOME MEASURES

The primary outcome measure of this study is the change in the score of the Tinnitus Functional Index (TFI) questionnaire. We compare the preoperative (baseline) TFI-score to postoperative TFI-scores at several time points (see Figure 3), with the primary end point set at one year after initial stimulation with the ABI. The TFI consists of 25-items and scores range from 0 (no tinnitus complaints) to 100. The validated Dutch TFI-version is used to detect changes in tinnitus outcome after the intervention and its psychometric properties are in line with the original version[17]. For the Dutch version, no minimal clinical important difference (MCID) was calculated. The MCID in the US version is determined at a 13 point reduction[18], however the smallest detectable change in TFI is still debated[19].

### SECONDARY OUTCOME MEASURES

Secondary outcome measurements include:

- Audiometric function
    - *When*: preoperatively (baseline) and several time points postoperatively. Audiometric function is determined with the ABI switch on and switched off.
    - *Measure*: determining PTA thresholds and speech audiometry, performed according to guidelines from the Nederlandse Vereniging van Audiologie (Dutch Association of Audiology, www.audiologieboek.nl).
    - *Important change scores*: a change of more than 5dB is considered as clinically relevant (±5 dB is considered measurement error).

- Vestibular function
  - *When*: preoperatively (baseline) and at 3 months postoperatively.
  - *Measure*: videonystagmography, rotation tests and calorisation tests of both labyrinths performed according to local hospital protocol.
  - *Important change scores*: clinical relevant changes in vestibular function, i.e. newly arisen asymmetrical function during calorisation.
- Tinnitus burden
  - *When*: preoperatively (baseline) and several time points postoperatively.
  - *Measures*:
    - Hospital Anxiety and Depression scale (HADS)[20]: scores for anxiety/depression range from 0 to a maximum of 21, with a score >8 indicating a possible anxiety/depression.
    - Tinnitus Handicap Inventory (THI): scores range from 0 (no tinnitus complaints) to 100 (catastrophic complaints).
    - Visual analogue scale (VAS) for tinnitus loudness and tinnitus annoyance: patients are instructed to draw a vertical line on a 10cm horizontal scale as to how they would rate their tinnitus loudness and annoyance. With 0 being not loud/not annoyed by tinnitus and 100 most thinkable loud/ annoyed by tinnitus.
  - *Important change scores*:
    - HADS: not calculated for the Dutch version.
    - THI: 6-7 points[21], although not calculated for the Dutch version.
    - VAS: between 10 and 15 points[22].
- Tinnitus analysis
  - *When*: preoperatively (baseline) and several time points postoperatively.
  - *Measure*: by tone matching at the contralateral ear (in intensity and frequency), according to guidelines from the Nederlandse Vereniging van Audiologie (Dutch Association of Audiology, www.audiologieboek.nl).
- ABI-related outcomes
  - *When*: several time points after ABI is implanted and switched on.
  - *Measure*:
    - Number of electrodes evoking auditory sensation (out of a total of 12 electrodes).
    - Pitch matching: frequency matching per electrode using a tone stimulus on the contralateral ear, based on the method for pitch mapping in single sided deafness with unilateral cochlear implants[23].
    - Tonotopic organisation: tonotopical electrode ordering according to subjective tonal perception, this is performed using the Bubblesort procedure.
    - Hours of usage, based on data logging and patient interview.
    - Preferred program (in percentage, out of 4 programs).
- Safety
  - *When*: during the complete course of the study
  - *Measure*: safety in terms of (serious) adverse events, (serious) adverse device effect.

FOLLOW-UP

Follow-up will take place at three and 6 months after switching on the ABI. The endpoint of this study is set at 12 months. Follow-up will, however, continue yearly, up to 5 years after initial stimulation. An overview of the assessments and their timeline is provided in Figure 3.

## DATA ANALYSIS & STATISTICAL ANALYSIS

### DATA MANAGEMENT

All collected data are entered into predesigned electronic case report forms (eCRF) in an Open Clinica® database (www.openclinica.com) by a trained investigator. Data in this database are anonimyzed and contains range checks. Stored data in this database are anonymized and password-protected. The database is only accessible by the study coordinator and assigned investigators. All changes made in the database are logged. Hard-copy data will be stored in a locked cabinet. The handling of personal data will comply with the Dutch Personal Data Protection Act. The final dataset will be available to the authors only.

### STATISTICAL ANALYSIS

The analysis of data is mainly descriptive. Mean and standard deviations are calculated in case of normally distributed data and median and interquartile range in case of skewed-distributed data. Differences in the primary outcome measure (i.e. TFI) as well as the secondary outcome measures (i.e. VAS, THI, HADS) are checked for significance using a paired t-test (if data are normally distributed), although the outcome will be interpreted with caution, since no power calculation was instituted.
SPSS (IBM, newest available version) will be used. A p-value <0.05 is regarded as statistically significant. If needed, analysis will be adjusted for multiple comparisons.

### SAMPLE SIZE

This is a pilot study. Due to the experimental nature of the study, no power analysis was performed. It was empirically decided to select a cohort of 10 patients for this study.

## ETHICS & DISSEMINATION

### ETHICS

Tinnitus can be very incapacitating, with a large impact on quality of life. Previous reports have shown that the ABI is a promising method to reduce tinnitus in these patients. Although the major complication rate is low when performed by experienced surgeons[24], potential complications can be severe. This study imposes a significant risk on the study participants; it is, however, likely that the potential to ameliorate severely debilitating tinnitus outweighs these risks. The study is approved by the IRB of the University Medical Center Groningen and by the Dutch Health Care Inspectorate. It is performed according to the quality standards of Good Clinical Practice. Participation in the study is completely voluntary. Patients can withdraw at any time, without giving any reason. It is stressed

that withdrawal does not affect standard clinical care. Written informed consent is obtained from all participants and they are informed when new information arises that may affect their willingness to participate.

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO (Wet Medisch-wetenschappelijk Onderzoek met mensen, i.e. Dutch Act for Medical Research Involving Human Subjects) . The sponsor has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

STUDY MONITORING

This study is monitored by a certified monitor from the Trial Coordination Center, which is independent from the sponsor. Study monitoring includes for example: checking in- and exclusion criteria for included patients, sample-wise data checking, correctness of data handling, storage, correctness and completeness of documentation in trial master file, etc. Monitoring will take place after every 2-3 included patients and after that, once a year for another 4 years.

## SAFETY CONSIDERATIONS

We do not expect a deterioration of hearing due to the implantation. However, because this aspect has not yet been studied, it was decided as a first step to include patients with severe ipsilateral hearing loss (i.e. 40 till 90dB mean over 1, 2, and 4kHz in PTA). In this patient group, a small loss of hearing sensitivity would not affect daily functioning. Yet, by excluding patients with profound hearing loss (>90 dB), our study would still be able to quantify unforeseen negative effects on hearing loss. Also, these patients might be eligible for a cochlear implant.

Possible complications are mostly related to the ABI surgery. In a study describing such complications, 78 non-tumor patients were analyzed[25]. These patients were not diagnosed with NF2, and therefore are comparable to our patient group. Major complications (meningitis, hydrocephalus, cerebellar contusion) occurred in 6.4% of cases. No mortality was observed. Minor complications (e.g. cerebrospinal fluid leakage, transient hydrocephalus, wound seroma) occurred in 18%. In 30% of the patients, non-auditory side effects occurred as a result of electrical stimulation. These side effects diminished over time and could be modulated by changing the stimulation settings[25]. It was concluded that ABI implantation is a safe procedure with a low major complication rate when performed by experienced surgeons[25]. Inclusion in the study and ABI-implantation are performed consecutively, allowing adequate monitoring of any unforeseen critical event related to the surgery or to the stimulation with the ABI. Stopping rules are predefined and are described later on in this protocol.

Patients are intensely monitored during the first year following implantation. Patients receive a remote control to switch between 4 preset stimulation programs. All of these actions are logged, as well as hours of usage of the implant. Nonauditory side-effects and disappointing results on hearing and/or tinnitus will be managed by altering stimulation strategy or, if necessary, by turning off the device. All Adverse Events (AE) will be assessed and recorded at each clinical visit. AEs are followed-up until they have abated, or until a stable situation has been reached. In case of a Serious Adverse Event (SAE) or Unanticipated Serious Adverse Device Effect (USADE), this will be reported to the IRB

15 days (SAE) or 7 days (USADE) after the first knowledge of the event. Also, a report will be made to the Dutch Health and Youth care Inspectorate.

## STOPPING RULES

A Data Safety Monitoring Board is not required, due to the small-scale nature of this pilot study and consecutive patient inclusion. Instead, the following 'stopping rules' were predefined:

- If >1 major complication occurs in the implanted study population (i.e. meningitis, transient hydrocephalus, symptomatic cerebellar contusion).
- If in >2 cases unacceptable worsening of tinnitus is experienced and it is decided to permanently switch off the ABI.

In case one of the stopping rules occurs, the study will be suspended and the risk/benefit balance would be reassessed in accordance with the IRB and/or Dutch Health and Youth care Inspectorate, before considering pursuing the study.

## DISSEMINATION AND DATA SHARING STATEMENT

The final manuscript will be written by the authors as named above. The results of this study will be published in peer-reviewed journals. Also, findings will be presented at national and international conferences for widespread dissemination of the results. When the trial is finished, data will be available upon request.

## AUTHOR CONTRIBUTION

PD, RF, JD, AM and MB conceived and designed the study and participated in logistical planning of the study. MB and AM are responsible for data acquisition. JD, JM and RF perform surgical implantation of the auditory brainstem implants and AM takes care of the perioperative and postoperative fitting sessions. All authors made significant contributions to the development and conceptualization of the protocol. MB wrote the manuscript with input from all co-authors. All co-authors reviewed the draft versions of this paper and have read and approved the final manuscript.

## FUNDING STATEMENT

This study is investigator-initiated. Funding is provided by Med-EL elektromedizinische Geräte GmbH. All study materials used in this study, i.e. implants, software, hardware, monitoring devices, are supplied by Med-EL.

## COMPETING INTEREST STATEMENT

Competing interest is not declared.

## DISCLAIMER

Med-el has had an advisory role in designing the study. The funding party has no role in the study design and conduct; the collection, management, analysis and interpretation of the data; or the preparation and final approval of the manuscript(s). The final manuscript(s) will be send to Med-el prior to publication for notification.

**Word count: 3511**

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ASA PHYSICAL STATUS CLASSIFICATION SYSTEM
http://www.google.nl/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwiGkO7kiuzbAhVQJVAKHYI1CAEQFggqMAA&url=http%3A%2F%2Fwww.asahq.org%2F~%2Fmedia%2Fsites%2Fasahq%2Ffiles%2Fpublic%2Fresources%2Fstandards-guidelines%2Fasa-physical-status-classification-system.pdf&usg=AOvVaw2VpwTL1ioJ7-XXfFM7Smwq. Updated 2014. Accessed 7, 2016.

Tables

Table 1. Inclusion and exclusion criteria.

| Inclusion Criteria |
| --- |
| Unilateral tinnitus |
| Severely incapacitating tinnitus |
| Men or women, Age >18 years |
| Tinnitus that is present >1 year and was stable during the last year |
| Tinnitus that is not responsive to indicated conventional existing treatments (hearing aids and cognitive behavioural therapy). If a psychologist has indicated cognitive behavioural therapy, the patient should have tried this therapy for long enough to reasonably argue that these treatments were not successful. The same applies to the use of hearing aids |
| Ipsilateral ear: pure tone audiometry thresholds >40dB and <90dB (mean over 1-2-4 kHz) |
| Functional hearing in the contralateral ear with pure tone audiometry thresholds <35dB (mean over 1-2-4 kHz) and with a minimum Δ25dB compared to the ipsilateral ear. |
| Informed consent after extensive oral and written information about the surgery, complications and uncertain effect of the Auditory Brainstem Implant on tinnitus |

| Exclusion Criteria |
| --- |
| Detectable cause for tinnitus that requires causal therapy (e.g. vestibular schwannoma, glomus tumor, otosclerosis, arteriovenous malformation) as investigated by radiological and otological examination |

| |
|---|
| Psychiatric pathology and/or an unstable psychological situation as declared by a psychiatrist |
| Unrealistic expectations as declared by the investigator and/or psychiatrist |
| Life expectancy <5 years |
| History of blood coagulation pathology |
| ASA >II |
| Pregnancy |
| Anatomic abnormalities that would prevent appropriate placement of the stimulator housing in the bone of the skull |
| Anatomical abnormalities or surgical complications that might prevent placement of the Auditory Brainstem Implant Active Electrode Array |
| Known intolerance to the materials used in the implant (medical grade silicone, platinum, iridium and parylene C) |

ASA: American Society of Anesthesiologists[26]

## FIGURES

### FIGURE 1

The auditory brainstem implant consists over several components (from left to right): a remote control; the speech processor (consisting of transducer, microphone and connecting cable) which is the external and visible part of the implant; the receiver-stimulator with electrode (implantable component); and close-up of the electrode paddle. Reproduced with permission of Med-EL.

### FIGURE 2

Overview of the position of the implant and placement of the electrode on the cochlear nucleus on the brainstem.

*Reproduced with permission of Med-EL.*

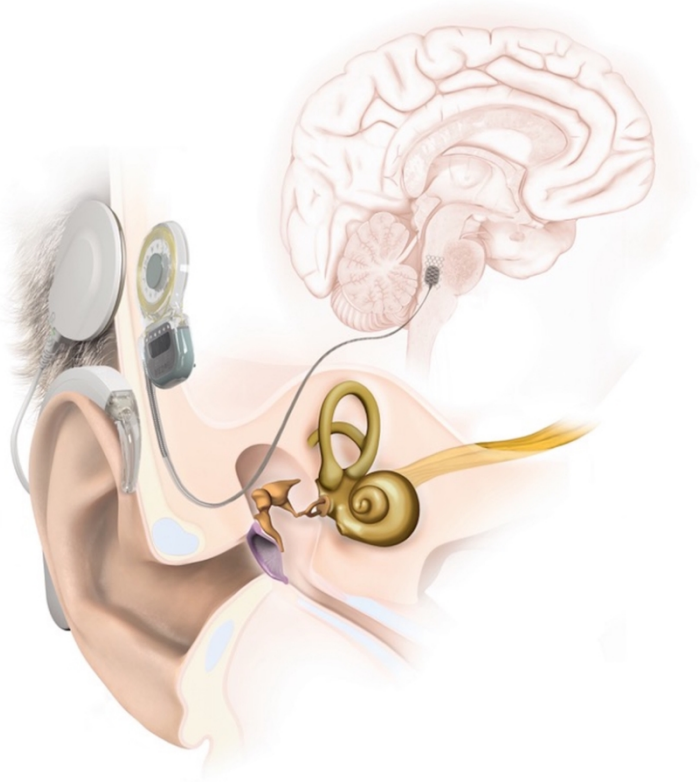
### FIGURE 3

Study timeline.

ABI: auditory brainstem implant; OR: operating room; mo: months; MRI: magnetic resonance imaging; T: time point, wk: weeks; yr: years.

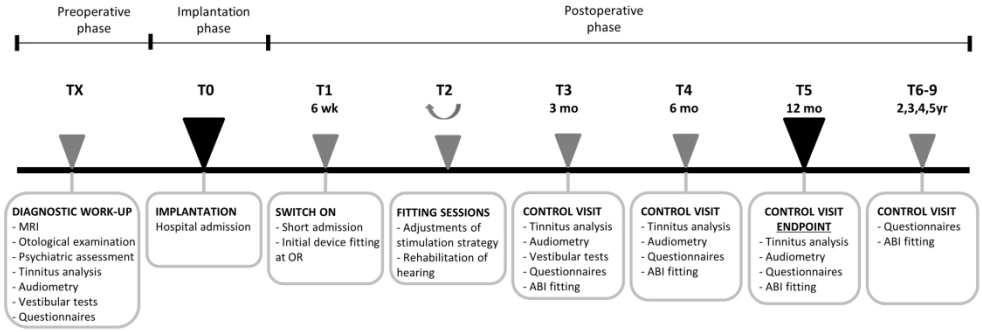
The auditory brainstem implant consists over several components (from left to right): a remote control; the speech processor (consisting of transducer, microphone and connecting cable) which is the external and visible part of the implant; the receiver-stimulator with electrode (implantable component); and close-up of the electrode paddle. Reproduced with permission of Med-EL.

199x112mm (600 x 600 DPI)



Overview of the position of the implant and placement of the electrode on the cochlear nucleus on the brainstem. Reproduced with permission of Med-EL.

99x108mm (300 x 300 DPI)




Study timeline.
"ABI: auditory brainstem implant; OR: operating room; mo: months; MRI: magnetic resonance imaging; T: time point, wk: weeks; yr: years.

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# INFORMED CONSENT FORM

for participating in scientific research

## INVESTIGATING THE EFFECT OF AN AUDITORY BRAINSTEM IMPLANT ON UNILATERAL AND SEVERE TINNITUS

Version 3.0, dd 24-4-2017

- I have been informed about this research to my satisfaction. I have read the written information (ABI v4.0) carefully. I have been given the opportunity to ask questions about this research. My questions have been answered satisfactorily. I have been able to think carefully about participation. I have the right to withdraw my consent at any time without having to give any reason for it.
- I am aware that the main risk of participation in the study is that: dizziness may occur and/or a worsening of hearing ability. In addition, there are risks of the surgery such as meningitis and wound infection.
- I am aware that this treatment cannot guarantee that the tinnitus will greatly diminish, change or disappear.
- I agree that my general practitioner will receive information about this examination and the surgery that I will undergo. I also authorize the psychiatrist to request relevant information from my general practitioner.
- I am aware that technical maintenance is guaranteed for about 10 years after implantation and that it is not yet clear who will pay for this maintenance after that.
- I agree with participation in the research.

Full name:

Date of birth:

Signature: Date:

- The undersigned declares that the abovementioned person has been informed of the abovementioned investigation both in speech and in writing. He / she also declares that a premature termination of participation by the abovementioned person will have no influence whatsoever on the medical care that is due to him or her.

Name of research investigator:

Signature: Date:


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry |
| | 2b | All items from the World Health Organization Trial Registration Data Set |
| Protocol version | 3 | Date and version identifier |
| Funding | 4 | Sources and types of financial, material, and other support |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors |
| | 5b | Name and contact information for the trial sponsor |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) |
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention |
| | 6b | Explanation for choice of comparators |
| Objectives | 7 | Specific objectives or hypotheses |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) |

| | | | |
|---|---|---|---|
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | |

| | | | |
|---|---|---|---|
| NA | Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned |
| NA | Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions |
| NA | Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how |
| NA | | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial |



**Methods: Data collection, management, and analysis**

| | | | |
|---|---|---|---|
| 8 p.8 | Data collection methods | 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 |
| NA | | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols |
| 8 p.8 | Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol |
| 8 p.8 | Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol |
| | | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) |
| | | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) |

**Methods: Monitoring**

| | | | |
|---|---|---|---|
| 3 p.9 | Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed |

| | | | |
|---|---|---|---|
| | | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial |
| | Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct |
| | Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor |
| | **Ethics and dissemination** | | |
| | Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval |
| | Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) |
| | Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) |
| | | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable |
| | Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial |
| | Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site |
| | Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators |
| | Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation |
| | Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions |
| | | 31b | Authorship eligibility guidelines and any intended use of professional writers |
| | | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |

## Appendices

| | | |
|---|---|---|
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

# Correction: *An auditory brainstem implant for treatment of unilateral tinnitus: protocol for an interventional pilot study*

van den Berge MJC, van Dijk MJMC, Metzemaekers JDM, *et al*. An auditory brainstem implant for treatment of unilateral tinnitus: protocol for an interventional pilot study. *BMJ Open* 2019;9:e026185. doi: 10.1136/bmjopen-2018-026185

This article was previously published with an error in Co-author's name. Marc J M C van Dijk was misspelled. The correct name is JMC van Dijk.



*BMJ Open* 2019;**9**:e026185corr1. doi:10.1136/bmjopen-2018-026185corr1