Effect of electrical stimulation with a cochlear implant on tinnitus impact: protocol of an individual patient data meta-analysis

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ABSTRACT

Introduction Tinnitus is the perception of sound without an external stimulus, often experienced as a ringing, buzzing sound. While several studies have shown a reduction in tinnitus distress following cochlear implantation, others showed an increase or no change after implantation. At this stage, clinicians have little certainty when counselling their patients prior to implantation regarding tinnitus post-implantation. To help clinicians to counsel cochlear implant (CI) candidates on the risk of developing or improving tinnitus after implantation, we aim to assess the effect of electrical stimulation with a CI on tinnitus impact for individual adult patients with tinnitus. We will also apply prediction models to individual patient data (IPD) of clinical trials to find predictive factors of the effect of electrical stimulation on tinnitus impact.

Method and analysis The IPD meta-analysis is a follow-up project of the systematic review on cochlear implantation in patients with tinnitus as a primary complaint. First, the systematic searches will be updated to date. Methodological quality of eligible studies will be assessed using the Risk of Bias In Non-randomised Studies of Intervention tool (ROBINS-I). Based on a data-sharing agreement, authors of the eligible studies will be invited to share their de-identified and complete IPD. The primary outcome is the effect of electrical stimulation with a CI on tinnitus impact 1 month or more post-implantation. IPD meta-analysis will be used to assess the primary outcome, while differentiating the tinnitus impact questionnaires. Second, linear regression analyses will be used to model the effect of electrical stimulation on tinnitus impact based on relevant predictors.

Ethics and dissemination The Medical Research Involving Human Subject Act does not apply, and ethical approval is not required. The study results will be made accessible to the public in a peer-review open access journal.

Prospero registration number CRD42022319367, review ongoing.

INTRODUCTION

Tinnitus is the perception of sound without an external stimulus, often experienced as a ringing, buzzing sound.1,2 It is a common symptom with an approximate prevalence between 10% and 30% depending on the population.3 Tinnitus can be disabling or incapacitating for people affected. Tinnitus impact can be defined by several functional effects such as tinnitus burden, distress, severity, annoyance, intrusiveness and loudness. Until now, there is no treatment for tinnitus but only therapy to reduce symptoms.4–8 While the pathophysiology of tinnitus is still not fully understood, one hypothesis is that tinnitus origins from an auditory depriviation in combination with a stressing factor resulting in neural synchrony. Hearing loss is the most common risk factor associated with tinnitus.9,10 Approximately 66%–86% of patients with severe to profound hearing loss report tinnitus.11,12

Providing electrical stimulation to the auditory pathway might be a possible treatment for tinnitus. In fact, electrical stimulation through a cochlear implant (CI) already showed positive effects on tinnitus distress in patients receiving a CI to restore hearing function.13,14 Some studies reported cases
of tinnitus worsening after cochlear implantation.\textsuperscript{11} 14 The variability of tinnitus outcomes following cochlear implantation might be associated with patient characteristics, hearing characteristics, tinnitus characteristics prior to surgery, trauma provoked by the implantation procedure or different electrical stimulation strategies.\textsuperscript{15–19} Moreover, it is still unclear what the effect of electrical stimulation with a CI will be when patients do receive an implant primarily for tinnitus and not for hearing loss. Our systematic review could not conclude on the effect of electrical stimulation for tinnitus as a primary complaint due to small sizes and considerable risk of bias within included studies.\textsuperscript{20}

At this stage, clinicians have little certainty when counselling their patients prior to implantation regarding tinnitus post-implantation. To help clinicians to counsel CI candidates on the risk of developing or improving tinnitus impact after implantation and thus to help manage patient expectations, an individual patient data (IPD) meta-analysis will be conducted. In an IPD meta-analysis, rather than extracting summary (aggregate) data from study publications, the original research data are sought directly from the researchers responsible for each study. These data can then be reanalysed centrally and combined, if appropriate, in meta-analyses. Although IPD meta-analysis requires more resources, IPD meta-analysis allows for more uniformly consistent analyses and better characterisation of subgroups and outcomes compared with meta-analysis based on aggregated data\textsuperscript{21} (Figure 1). An IPD meta-analysis can provide a more accurate estimate of treatment efficacy and help identify individual factors influencing treatment outcomes.\textsuperscript{22} We aim to assess the effect of electrical stimulation with a CI on tinnitus impact using an IPD meta-analysis. Second, we will identify predictive factors of the effect of electrical stimulation on tinnitus impact in individual adult patients with tinnitus.

**Figure 1** Level of evidence of systematic reviews, meta-analyses and IPD meta-analyses. IPD, individual patient data.
two review authors will independently perform the titles/abstracts and full-text screening of the retrieved articles according to the predefined inclusion and exclusion criteria. The screening tool used will be Rayyan. Any conflict will be resolved by a discussion between the two reviewers.

Data extraction and management

Corresponding authors of eligible studies published will be contacted by email by one review author. They will be invited to collaborate and share their deidentified and complete dataset. They will be asked to provide unpublished data, where available. A data-sharing agreement will be used before data transfer. Corresponding authors replying to the request email will be mentioned in the Acknowledgement section of the study manuscript. Study data will be considered unavailable when none of the authors indicate that the requested data are not available or cannot be shared.

After retrieval, the IPD of individual studies will be compared with published data. In case of discrepancies, collaborators will be contacted to ask for clarification. The amount of missing data within each study will be discussed with collaborators and will be reduced as much as possible.

An aggregated database will be created containing a trial ID variable, patient demographics and characteristics, treatment conditions (surgery used, CI type, follow-up period) and outcome measure of interest. The aggregated database will have a multilevel structure, with individual trials as levels.

Quality assessment of included studies

Two reviewers will independently assess the methodological quality of eligible studies using the ROBINS-I. With this tool, the risk of bias will be evaluated in seven domains: confounding, selection of participants, classification of interventions, deviation from intended intervention, missing data, measurement of outcomes and selection of reported results. The criteria will be defined and adapted to our research question. Items will be scored as low risk of bias, moderate risk of bias, serious risk of bias, critical risk of bias or unclear. Studies will be judged as having an overall low, moderate, serious or critical risk of bias based on the guidelines of the ROBINS-I tool. Consensus will be obtained after discussion between the two reviewers. If the quality of eligible studies remains unclear, corresponding study authors will be contacted to obtain complementary information.

Data synthesis

Descriptive analysis and evidence synthesis

Study and participant characteristics will be extracted from the data. If any, we will review the characteristics of eligible studies that did not contribute to the IPD to find any evidence of selection bias. Proportion will be used for categorical or binary variables and mean and standard deviation (SD) or median and interquartile range (IQR) will be used for continuous variables.

The efficacy of electrical stimulation for each included study will be summarised at fixed time points by the IPD meta-analysis approach.

IPD meta-analysis

Outcomes of interest

The primary outcome will be the effect of electrical stimulation on tinnitus impact (or synonyms) measured by multi-item tinnitus questionnaires or single-item VAS scores of acceptance, annoyance, awareness, intrusiveness, unpleasantness or loudness.

Sample size considerations

Missing data will be studied and appropriate methods for handling them, such as multiple imputation, will be used. Heterogeneity will be assessed with I².

Statistical analysis

A two-stage approach will be used for the IPD meta-analysis. In the first stage, each individual study will be analysed independently and a summary of the aggregated data will be provided. In the second stage, individual data will be combined to provide a pooled estimate of effect. Standard statistics and forest plots will result from the second phase. Odds ration with 95% CIs (95% CI) will be reported.

We will conduct one main and two sensitivity analyses. First, for the main analysis, individual meta-analysis will be performed for each type of multi-item and single-item tinnitus questionnaire scores included. High convergent validities between different multi-item and single-item questionnaires are summarised in table 1. Thereafter, as a first sensitivity analysis, multi-item and single-item tinnitus questionnaire scores measuring tinnitus impact will be pooled and analysed together if enough data are available. A regression analysis will be performed to correct scores from each type of tinnitus multi-item validated questionnaires. Finally, as a second sensitivity analysis, multi-item and single-item tinnitus questionnaire scores will be standardised to a scale ranging between 0 and 100. The analysis will then be performed using the standardised tinnitus questionnaires’ scores per domain (eg, loudness, distress, impact on daily life).

Secondary analysis using linear regression model

Outcome of interest

The secondary outcome is the prediction model of the effect of electrical stimulation on tinnitus impact (or synonyms) measured by multi-item tinnitus questionnaires or single-item VAS scores of acceptance, annoyance, awareness, intrusiveness, unpleasantness or loudness.

Sample size considerations

Analysis of the secondary outcome will be carried out provided enough data are available; else, only summary statistics will be reported.
Potential candidate predictors that are missing in more than 50% of the included studies will not be included in multivariable analyses. Variables with missing data will be studied and appropriate methods for handling them, such as multiple imputation, will be used.33

### Model development

As a secondary analysis, we will predict the effect of electrical stimulation on tinnitus impact using potential candidate predictors a priori selected by coauthors (table 2). The selected predictors will be included in the linear regression analysis to assess their relative importance. Initially, all possible predictors will be examined individually in an unvariable model to assess its relationships with the outcome of interest. All significant variables with a p value lower than 0.05 will then be added to the multivariable model. The multivariable model will be fitted using backwards selection by eliminating candidate predictors one by one using the 5% significance level.

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The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines will be used for the modelling.

### Candidate predictors

Candidate predictors will be based on the existing literature, clinical relevance and availability in the IPD set.

There is currently insufficient evidence and no consensus on potentially predictive factors of the effect of electrical stimulation with a CI on tinnitus impact. A few researchers have attempted to find predictive factors for the effect of cochlear implantation on tinnitus impact among individuals with bilateral severe-to-profound hearing loss. In these studies some pre-implantation tinnitus characteristics have been reported to predict a positive effect of cochlear implantation on tinnitus: unilateral localisation of tinnitus17 and higher pre-implantation tinnitus severity.15 16 Hearing characteristics such poorer pre-implantation hearing thresholds,15 poor pre-implantation speech perception15 and larger deterioration of residual hearing at 250 Hz (ie, the difference in hearing threshold before and after surgery at this frequency)17 were identified as potential predictive factors for tinnitus improvement after cochlear implantation.

| Study (authors, year) | N | Tinnitus questionnaires | Correlation coefficients | P value |
|-----------------------|---|-------------------------|--------------------------|---------|
| Baguley et al 200038  | 78 | TFI/TQ                  | 0.881                    | <0.001  |
| Zenner et al 200542   | 273| TQ/VAS-L                | 0.54                     | <0.001  |
|                       |    | TQ/VAS-A                | 0.66                     | <0.001  |
|                       |    | TQ/VAS-C                | 0.58                     | <0.001  |
| Huang et al 200645    | 20 | THI/VAS-L               | 0.64                     | 0.002   |
| Zeman et al 201239    | 1318| THI/TQ                 | 0.9                      | <0.05   |
| Müller et al 201646   | 260| TFI/THI                 | 0.85                     | <0.01   |
| Fackrell et al 201635 | 294| TFI/THI                 | 0.82                     | NI      |
|                       |    | TFI/VAS-L               | 0.46                     | NI      |
|                       |    | THI/VAS-L               | 0.41                     | NI      |
| Hoff and Kähäri 201740| 100| TFI/THI                 | 0.8                      | NI      |
|                       |    | TFI/VAS-D               | 0.69                     | NI      |
| Nascimento et al 201947| 148| THI/VAS-L               | 0.57                     | 0.001   |
| Jacquemin et al 201941| 100| TFI/TQ                  | 0.82                     | NI      |
| Boecking et al 202142 | 210| TFI/TQ                  | 0.78                     | NI      |
|                       |    | TFI/THI                 | 0.8                      | NI      |
|                       |    | THI/TQ                  | 0.83                     | NI      |

The rows with similar emphases (bold, italic and bolditalic) correspond to a comparison between two similar tinnitus questionnaires. N, sample size; NI, no information; TFI, Tinnitus Functional Index; THI, Tinnitus Handicap Inventory; TQ, Tinnitus Questionnaire; VAS-A, Visual Analogue Scale Tinnitus Annoyance; VAS-C, Visual Analogue Scale Tinnitus Comfort; VAS-D, Visual Analogue Scale Tinnitus Distress; VAS-L, Visual Analogue Scale Tinnitus Loudness.
Comorbidities such as a less severe depression state was found to be associated with better post-implantation tinnitus outcomes. In contrast, Kloostra et al were not able to find predictors for a positive tinnitus outcome, using speech comprehension scores and pre-operative tinnitus distress, personality characteristics, anxiety and depression, hearing handicap questionnaires, although they did find predictors that negatively influence tinnitus outcome in terms of lower pre-implantation tinnitus handicap and hearing handicap. None of the factors identified in the abovementioned studies were consistent among the various prediction models, which might be partly due to the small sample sizes of studies and high risk of bias of the presented models.

Based on these considerations and clinical reasoning, 31 potential candidate predictors can be found in table 2 organised in six domains: demographics, tinnitus characteristics, hearing characteristics, imaging, comorbidities and treatment.

### Subgroup analyses
Analyses will be conducted by subgroups of follow-up timelines and by subgroups of patients identified by previous tinnitus research on population data, if data permit.

### Further development of statistical analysis plan
The main analysis is planned as described above. Modification or additional analyses may be performed as the data collection progresses. Updated statistical analysis plans will be available in PROSPERO if required.

### Software
All analyses will be performed using R Studio V.1.3.1073 (R Studio). The IPD meta-analysis will be performed using RevMan.

### Ethics and dissemination
There will be no identifiable patient data in any of datasets. If any identifiable patient is available, it will be anonymised. Therefore, the Medical Research Involving Humans Subject Act (WMO) does not apply to this study. The Medical Research Ethics Committee Utrecht, the Netherlands, reviewed the study protocol and concluded that an official approval was not required.

All corresponding authors of the included studies will provide written confirmation that all participants included in the original studies had given full written informed consent. The paper data files will be stored in a locked cabin in a locked room. The data will be stored within a secured folder of the data management department of the University Medical Center Utrecht. Data will be stored for at least 15 years at a central drive of the data management department of the University Medical Center Utrecht and will be made available for the use by third parties on request and approval of the research team.

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**Table 2** Potential candidate predictors organised in domains.

| Domains       | Potential predictors                                                                 |
|---------------|--------------------------------------------------------------------------------------|
| Demographics  | 1. Age at implantation                                                               |
|               | 2. Gender                                                                             |
|               | 3. Social economic status                                                             |
|               | 4. Highest education level                                                             |
| Tinnitus      | 5. Pre-implantation tinnitus impact multi-item or single-item validated questionnaire |
| characteristics| 6. Tinnitus duration at the time of the implantation                                  |
|               | 7. Tinnitus localisation                                                               |
|               | 8. Tinnitus pitch-matched                                                             |
|               | 9. Tinnitus loudness-matched                                                          |
|               | 10. Tinnitus temporal pattern (constant or intermittent)                              |
| Hearing       | 11. Pre-implantation speech perception scores in quiet                                 |
| characteristics| 12. Pre-implantation speech perception scores in noise                                 |
|               | 13. Pre-implantation hearing level in the future implanted ear (including means and per frequencies ranging from 125 Hz to 20 kHz) |
|               | 14. Pre-implantation hearing level in the contralateral ear (including means and per frequencies ranging from 125 Hz to 20 kHz) |
|               | 15. Pre-implantation subjective hearing disability measure (total score) assessed by a multi-item or single-item validated questionnaire, holding outcomes on one or multiple domains covering body function, activity limitations and participation restrictions, environmental factors and personal factors |
|               | 16. Pre-implantation electrophysiological outcomes (ABR or ECochG)                    |
| Imaging       | 17. Cochlear anatomy limiting cochlear implant performance based on imaging (eg, cochlear ossification, cochlear dysplasia) |
| Comorbidities | 18. Hyperacusis presence                                                               |
|               | 19. Depression symptoms assessed by a multi-item or single-item validated questionnaire |
|               | 20. Anxiety symptoms assessed by a multi-item or single-item validated questionnaire   |
|               | 21. Stress symptoms assessed by a multi-item or single-item validated questionnaire    |
|               | 22. Personality assessed by a multi-item or single-item validated questionnaire        |
|               | 23. Coping strategies assessed by a multi-item or single-item validated questionnaire  |
|               | 24. Measure of general health assessed by a multi-item or single-item validated questionnaire |
|               | 25. Measure of quality of life assessed by a multi-item or single-item validated questionnaire |
|               | 26. Measure of sleep quality assessed by a rating                                     |
|               | 27. Cardiovascular disease presence diagnosed by a clinician                          |
|               | 28. Metabolic disease presence diagnosed by a clinician                                |
|               | 29. Neurological disease presence diagnosed by a clinician                            |
| Treatment     | 30. Hearing aid use in the future implanted ear                                       |
|               | 31. Hearing aid use in the contralateral ear                                          |
The IPD meta-analysis will be published in a peer-review international journal.

**Review registration and anticipated end date of study**

The protocol of the IPD meta-analysis has been registered in PROSPERO with the registration number CRD42022319367. The anticipated date of data collection is May 2022 and the anticipated end date of the study is May 2023.

**DISCUSSION**

The IPD meta-analysis is complementary to the systematic review of 2020 in which seven studies were included investigating the effect of electrical stimulation with a CI for tinnitus as a primary complaint. This systematic review reported a high degree of heterogeneity among included studies and therefore a meta-analysis could not be performed. In IPD meta-analysis, data from several trials are standardised and analysed in a uniform way, which is useful to tackle heterogeneity between studies. Pooling IPD together increases power and enables to investigate interaction and subgroups effect. In this IPD meta-analysis, we aim to assess the effect of electrical stimulation with a CI on tinnitus impact and second predict the effect of cochlear implantation for individual adult patients with tinnitus.

Multiple tinnitus questionnaires are available to assess tinnitus impact and treatment responsiveness. Due to a lack of method standardisation, interventional studies often differ in the questionnaires used. Therefore, literature on convergence between different tinnitus questionnaires has been reviewed by authors before drafting the protocol (table 1). High convergence between validated multi-items questionnaires was shown in several studies. Based on these findings, multi-item tinnitus questionnaires will be analysed together, if enough data are available. In a second stage, a sensitivity analysis will be performed to differentiate scores from each type of tinnitus multi-item validated questionnaires. Due to missing evidence on the convergence between multi-items and single-item tinnitus questionnaires, individual meta-analysis will be performed for each type of single-item tinnitus questionnaires.

This IPD meta-analysis is an efficient way to investigate whether the effect of electrical stimulation with a CI varies by patient characteristics. For this purpose, authors reviewed the current literature on predictive models of the effect of cochlear implantation on tinnitus and organised brainstorming sessions to discuss the clinical relevance of potential candidate predictors. This resulted in the selection of 31 candidate predictors classified in six domains (demographics, tinnitus characteristics, hearing characteristics, imaging, comorbidities and treatment) that could be used for future research studies on the same topic.

The main limitation of the project is missing data. It is likely that some potential candidate predictors will not be available in data of included studies and could not be included in our predictive models due to missing data in more than 50% of the studies. However, using available candidate predictors and using multiple imputation when applicable, the large sample size available in the IPD set will provide a unique opportunity to identify potential predictors explaining the variance of effect on tinnitus impact.

Despite additional efforts spent to gather and standardise the IPD, an IPD meta-analysis is the best way to estimate the overall effect on understudied populations, such as patients seeking help for tinnitus. We hope that this study will lead to a higher level of evidence and a better understanding of the effect of electrical stimulation as an effective treatment option for tinnitus.

**Contributors** KA, ALS and IS conceptualised, designed the study and developed the protocol. All authors (KA, ALS and IS) critically revised the draft of the protocol. IS provided statistical expertise in clinical trial design. KA drafted the manuscript. All other authors revised the manuscript. All authors read and approved the final version.

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**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

**Patient consent for publication** Not applicable.

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