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Current reported outcome domains in studies of adults with a focus on the treatment of tinnitus: protocol for a systematic review

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Current reported outcome domains in studies of adults with a focus on the treatment of tinnitus: protocol for a systematic review

Full names, institutional addresses and email addresses for all protocol authors

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Abstract

Introduction In Europe alone, over 70 million people experience tinnitus. Despite its considerable socioeconomic relevance, progress in developing successful treatments has been limited. Clinical effectiveness is judged according to change in primary outcome measures, but because tinnitus is a subjective condition, the definition of outcomes is challenging and it remains unclear which distinct aspects of tinnitus (i.e. 'domains') are most relevant for assessment. The development of a minimum outcome reporting standard would go a long way to addressing these problems. In 2006, a consensus meeting recommended using one of four questionnaires for tinnitus severity as an outcome in clinical trials in part because of availability in different language translations. Our initiative takes an approach motivated by clinimetrics; first by determining what to measure before seeking to determine how to measure it. Agreeing the domains that contribute to tinnitus severity (i.e. '*what*') is the first step towards achieving a minimum outcome reporting standard for tinnitus that has been reached via a methodologically rigorous and transparent process.

Methods and analysis Deciding what should be the core set of outcomes requires a great deal of discussion and so lends itself well to international effort. This protocol lays out the methodology to be implemented by the COMiT initiative (Core Outcome Measures in Tinnitus) to define a Core Domain Set for clinical trials of tinnitus. The review described here will establish existing knowledge and practice with respect to which outcome domains have been measured and which instruments used in recent registered and published clinical trials.

Ethics and dissemination No ethical issues are foreseen. Findings will be reported at national and international ENT and audiology conferences and in a peer-reviewed journal, using PRISMA guidelines.

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3 **Registration details** The systematic review protocol is registered on PROSPERO
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5 (International Prospective Register of Systematic Reviews): CRD42015017525.
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9 **Strengths and limitations of this study**

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- 12 • The protocol addresses important questions relevant to weaknesses in the design of
13 controlled trials assessing clinical efficacy of treatments for tinnitus.
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 - 15 • Review contributors span a number of European countries, bringing an international
16 point of view.
17
 - 18 • Clearly established purpose and well defined methods for data collection and
19 synthesis.
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 - 21 • Review will generate independent evidence from professional stakeholder groups.
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 - 23 • Limitations include anticipated heterogeneity across studies and low-quality reporting
24 which may pose challenges for the data synthesis.
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Introduction

Tinnitus is a common symptom arising from a range of otological and non-otological conditions, affecting 10-20% of the adult population, and rising with age.¹ Tinnitus is described as a ringing, buzzing or hissing sound heard in the ears or head. Most forms of tinnitus have no physically identifiable source of the sound and so they cannot be objectively measured. This is the condition known as subjective tinnitus which throughout this article will be referred to simply as 'tinnitus'. The tinnitus experience can be characterised by the perceptual properties of the sound percept, namely its pitch, timbre and loudness. Yet these perceptual attributes relate poorly to the degree of self-reported functional impact on daily life.² Instead, disability arising from tinnitus can be described as a multi-dimensional concept relating to impairments, activity limitations, and participation restrictions that people with tinnitus may experience, not forgetting the environmental factors which affect these experiences.³⁻⁵ In this sense, tinnitus is construed within the biopsychosocial model of disability proposed by the World Health Organisation.

General practitioners and Ear, Nose and Throat (ENT) consultants play an important role in the clinical assessment and management of tinnitus, but across countries patients may be referred to a range of other clinical stakeholders including neurologists, radiologists, audiologists, psychologists and psychiatrists.⁶ Given the inter-disciplinary approach, it is unsurprising that there are a number of different strategies for managing tinnitus in adults. These include, but are not restricted to psychoeducation and advice, provision of hearing aids, sound generators or other acoustic devices, physical therapy, psychological counselling, and complementary therapies.^{7,8} There are no current drugs that are licensed for alleviating tinnitus, but for managing some of the co-morbid symptoms such as depression and insomnia, pharmacological approaches are prescribed.^{8,9} Generally speaking, choice of clinical intervention is a multi-factorial decision based on the experience of the treating clinicians, their assessment of patient needs, and the broader healthcare

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3 context.⁶ Few professional bodies work to specific clinical practice guidelines or protocols for
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5 tinnitus (but see Tunkel *et al*¹⁰ for an example from the USA).
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9 It is good clinical practice that treatment decisions between health care professionals and
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11 their patients should be supported by informed conversations about the evidence for
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13 treatment efficacy. The best quality evidence for treatment effectiveness is drawn from
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15 randomised controlled trials and systematic reviews that synthesise the findings from those
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17 studies.¹¹ Where it is not possible to design a trial that has random allocation to intervention
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19 groups, certain types of controlled trials may also be considered.¹² Of the numerous
20
21 systematic reviews of tinnitus treatments have been published over recent years, many of
22
23 them reach the conclusion that few high quality trials are available for inclusion and for those
24
25 trials that are included, a range of different outcome measures preclude the pooling of
26
27 findings.^{9,12,13} There is a growing recognition that consistency between academic centres and
28
29 clinics engaged in tinnitus research in the way that treatment outcomes are measured would
30
31 facilitate more meaningful evaluation and comparison of trial findings.^{3,14,15} There is also
32
33 agreement that the heterogeneous nature of tinnitus complaints and impact can also make
34
35 clinical research and outcome measurement difficult. Moreover, there is increasing evidence
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37 for co-operative working to address these challenges. The creation of a comprehensive and
38
39 a brief core set for hearing loss (Danermark *et al*¹⁶) is an example of the successful product
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41 of international collaboration in hearing.
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46 In 2006, a meeting in Regensburg of 29 tinnitus professionals sought consensus for tinnitus
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48 patient assessment and treatment outcome measurement. They recommended using one of
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50 four standard questionnaires (Tinnitus Handicap Inventory, Tinnitus Handicap Questionnaire,
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52 Tinnitus Reactions Questionnaire or Tinnitus Questionnaire) as an outcome instrument in
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54 therapeutic trials.¹⁴ Part of the rationale for this choice was motivated by pragmatism (e.g.
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56 availability in different language translations). These are all multi-item questionnaires that
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58 purport to measure tinnitus severity, but do so using different questions, rating scales and
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3 subscales. Moreover, the design of the four recommended questionnaires was optimised for
4 intake assessment of tinnitus, rather than for evaluation of treatment-related change.^{3,17}

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7 Clearly, there is more work to be done, and recommendations for outcome measurement do
8 not necessarily need to be restricted to questionnaires.
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13 ** insert Figure 1 here **
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17 Building on the 2006 consensus approach, a COST Action network for tinnitus (TINNET) is
18 promoting the international coordination of nationally-funded research across Europe
19 (<http://tinnet.tinnitusresearch.net/>). The network has five working groups, one of which
20 Working Group 5 has the goal to establish an international standard for outcome
21 measurements in clinical trials of tinnitus. Our activity is conducted as the COMiT initiative
22 (Core Outcome Measures in Tinnitus) which is part of Working Group 5. In a recent article,
23 we promoted a step-wise roadmap (Hall *et al*¹⁵) (see Figure 1) for developing a core
24 outcome set. This approach is inspired by the work of the COMET (Core Outcome Measures
25 in Effectiveness Trials) Initiative.¹⁸ The first output will be a consensus on what outcome
26 domains are essential (i.e. core) to be captured in all controlled trials. A domain is defined as
27 a distinct element (or topic) of tinnitus such as how loud or how emotionally distressing a
28 patient may find his or her tinnitus. These core domains will be identified as being important
29 for characterising tinnitus and will reflect the perspectives of professionals and lay people,
30 alike. This article describes a systematic review protocol to be implemented within Stage 1 of
31 that roadmap. It relates to current reported outcome domains in studies of adults with a
32 focus on the treatment of tinnitus. International agreement on a core outcome domain set
33 would drive up the quality and relevance of research by ensuring that the most relevant
34 outcomes are consistently measured and reported in trials relating to tinnitus.
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56 The aim of the first systematic review is to contribute to the development of a core domain
57 set for future controlled trials on tinnitus treatment effectiveness using *quantitative* data
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3 collected from ongoing registered or published trials since the 2006 consensus meeting.¹⁴
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5 This represents the professional perspective on outcome domains in clinical trials of tinnitus.
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7 The objective of the review is to conduct a world-wide search of the recent published
8
9 literature of clinical trials of interventions for tinnitus, as well as those ongoing trials that are
10
11 publicly registered. More specifically, this objective will answer the research question: 'What
12
13 are the current reported outcome domains in studies of adults with a focus on the treatment
14
15 of tinnitus?'

16 17 18 19 **Methods and Analysis**

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23 Methods are reported according to the Preferred Reporting Items for Systematic reviews and
24
25 Meta-analyses for Protocols 2015 (PRISMA-P^{19,20}). Subheadings correspond to some of the
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27 items in the PRISMA-P checklist. The allocation of specific roles to named authors of the
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29 review will be made at a later date, and this information will clearly be acknowledged in any
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31 subsequent dissemination of findings.
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35 **Eligibility criteria** We have defined our inclusion criteria according to PICOS (Patient,
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37 Intervention, Comparison, Outcome, Setting) guidelines as follows:
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41 *Participants* For maximum inclusivity, we will include all human participants with the only
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43 restrictions being adults (≥ 18 year) who report tinnitus as one of their primary complaints.
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45 To be confident that our review does not include trials recruiting participants younger than
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47 18 years old, any trials specifying an age range with a lower limit than this will be
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49 excluded. We will include both men and women.
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54 *Intervention* Again for maximum inclusivity, we will include any intervention irrespective of
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56 whether it is a clinical intervention or a novel experimental intervention. The key criterion
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3 is that the main aim of the intervention is to achieve a therapeutic benefit for people with
4 tinnitus, not those in which the impact on tinnitus might be of secondary benefit.
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9 *Comparison* The following types of study comparisons will be eligible for inclusion:
10 randomised controlled trials, before and after studies, non-randomised controlled trials or
11 case controlled studies and cohort studies. We will also include published meta-analysis
12 and systematic reviews that have considered such studies. However, we will exclude
13 articles reporting expert opinions, practice guidelines, case reports, case series,
14 conference abstracts and book chapters due to their more limited clinical and scientific
15 value. In accordance with this rationale, the search strategy will also exclude those trials
16 either recruiting fewer than 20 participants with tinnitus, or having fewer than 20 at the
17 end of follow up. This cut-off is somewhat arbitrarily selected, but follows Needleman *et al*
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3 2006. However, by doing so, we acknowledge the potential limitation of this strategy
4 which is that included study designs may have been approved and open for recruitment
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6 before the Regensburg consensus meeting in July 2006.
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11 **Information sources** Intended information sources are the following electronic research
12 databases: PubMed (National Center for Biotechnology Information), Embase (OVID) and
13 Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCO), and trial
14 registers: ClinicalTrials.gov, the International Standard Randomised Controlled Trial
15 Number registry (ISRCTN, BioMed Central), International Clinical Trials Registry Platform
16 (ICTRP, World Health Organisation), and the Cochrane Database of Systematic Reviews
17 (CDSR). We will also search the Cochrane Central Register of Controlled Trials
18 (CENTRAL) which contains a highly concentrated source of reports of randomized
19 controlled trials. With the exception of trial registers, we will not use databases that are
20 specialised in grey literature.
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33 Additional information will be identified by a manual search of the registered clinical trials
34 to identify any additional registers of the trial and to identify any published protocols or
35 study findings that are indexed to a particular trial by its unique study identifier, but that
36 have not already been identified by the electronic research database search.
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39 Furthermore, we will manually search all the systematic review articles found in order to
40 seek any further trials for inclusion. This will be restricted to those studies that met
41 eligibility for inclusion in the corresponding review publication.
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49 Following title exclusion, the next phase will assess eligibility based on the full text,
50 accessing hard-to-reach records via the British Library where necessary. Contact with
51 study authors will be permitted.
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3 The database search was conducted soon after registration in PROSPERO (12-13
4 March, 2015). The manual search and personal author contact will be ongoing up to the
5 end of the data collection phase.
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11 **Search strategy** The systematic review attempts to collate all relevant evidence that fits
12 pre-specified eligibility criteria to answer our specific research question. The electronic
13 database search strategy will use a combination medical subject headings (MeSH) and
14 relevant text words wherever possible. The search terms for PubMed, Embase and
15 CINAHL are: (tinnitus) AND (stud* OR clinical trial* OR therap* OR treatment* OR
16 intervention). For example, the search strategy for Embase will be: (((((((("tinnitus" and
17 "stud*") or "Tinnitus") and "clinical trial*") or "Tinnitus") and "Therap*") or "Tinnitus") and
18 "Treatment*") or "Tinnitus") and "Intervention*").mp. [mp=title, abstract, subject headings,
19 heading word, drug trade name, original title, device manufacturer, drug manufacturer,
20 device trade name, keyword]. Limit to (english language and (embase or medline) and
21 yr="2006 -Current" and (article or "review") and (adult <18 to 64 years> or aged <65+
22 years>)). This will be adapted to the syntax and subject headings of the other databases.
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24 The authors do not have access to a health information specialist with database
25 searching skills, and so the most experienced researchers will conduct the search.
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41 **Data management** DAH (author) will be responsible for data management and will have
42 editorial rights. All identified records will be saved into an excel master file where records
43 can be tracked through the screening and data collection process. A simple system of
44 record annotation will be implemented to capture reasons for exclusion. Included records
45 will be allocated a study ID code to link each record in the master file with its
46 corresponding full text and data collection sheet.
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56 **Selection process** Endnote will be used to remove duplicate records from the PubMed,
57 Embase and CINAHL searches. One of the review authors will then manually screen all
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3 records for duplicates using author names, study title and trial registration number. A two-
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5 step process will then be implemented to decide eligibility according to the inclusion and
6
7 exclusion criteria: first by reading the title, and second by reading the full text. The full text
8
9 will be obtained for all potentially relevant records appearing to meet the inclusion criteria
10
11 or for which there is insufficient information in the title to make a clear decision. We will
12
13 adopt the principle that two review authors will always perform each key step
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15 independently for every record (i.e. title screening, full text screening, and data
16
17 collection). However, the individuals conducting each step may differ. If any discrepancies
18
19 cannot be resolved, then the primary review author will make a judgement on the data
20
21 entered and act as an arbitrator. Inter-rater agreement will not be calculated.
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25 We will piece together data from multiple reports of the same study by manually
26
27 screening all included records using author names, study title and trial registration
28
29 number.
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33 **Data collection process** Data collection will be guided by an electronic form (excel
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35 spreadsheet) that will also be used to collate all responses. To ensure consistency across
36
37 reviewers, a full set of guidance notes will be produced for the data collection procedure
38
39 and calibration exercises will be conducted with new members of the review team prior to
40
41 any individual contribution to this review. Both the sheet and the guidance notes will be
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43 developed and revised through two iterations of piloting across several review authors.
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45 Data collection will be conducted independently and in duplicate (two people) for every
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47 included record. For any studies where insufficient detail is given to determine eligibility
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49 (e.g minimum age of enrolment or sample size), we will contact the corresponding author
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51 by email (without a reminder) to seek clarification.
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3 Many of the review authors will not have English as their native language and so DAH will
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5 sample a subset (<5%) of data collection sheets for each author performing this step,
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7 again in order to confirm consistency of approach.
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11 **Data items** The data collection sheet will include a list of fields relating to trial design and
12
13 methodology. These are given in Table 1. If any information is not reported, then 'not
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15 stated' will be recorded in the corresponding field. For those records in which several
16
17 pieces of information are consolidated into a single record, we will seek to detect any
18
19 modifications to the methods and any selective reporting in the completed reports of the
20
21 study findings.
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25 ** insert Table 1 here **
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27

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29 **Outcomes and prioritisation** The main aim of the review focuses on changes related to
30
31 tinnitus as a primary outcome and so the data relating to primary outcome domains and
32
33 instruments will be the priority for data synthesis and reporting of findings. These
34
35 outcomes link directly to the first two bullet points described in the section on data
36
37 synthesis.
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41 **Risk of bias in individual studies** Bias is typically considered to be a systematic error
42
43 that can lead to an overestimation or underestimation of the true intervention effect. Given
44
45 that the primary objective of this systematic review concerns methodology, not findings,
46
47 we have limited plans to assess risk of bias of individual studies. However, the data
48
49 collection for consolidated records will enable summary statistics and a narrative
50
51 synthesis about selective outcome reporting (reporting bias) either where original
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53 descriptions of outcomes as 'primary' or 'secondary' may have been altered
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55 retrospectively in the light of the findings, or where a subset of the original outcomes may
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3 have been selected, on the basis of the results, for inclusion in the publication of trial
4 findings.
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9 The potential for observer bias during data collection process will be reduced by avoiding
10 any instance where an individual will extract data relating to one of their own trials.
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15 **Data synthesis** The main purpose of this systematic review is to create new knowledge
16 around the outcome domains (and instruments) that are being used in clinical trials of
17 tinnitus by pooling together and critically evaluating these data. The identified domains
18 and instruments will be tabulated in such a way as to illustrate five patterns in the data
19 using all included records. The first two bullet points address the primary purpose of the
20 review, the subsequent three bullet points relate to secondary review aims.
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- 23
24
25 • *patterns across primary outcome domains* to determine the proportion of records
26 in which it is specified, and for those that do specify a domain what that domain is.
27 The same analysis will be conducted separately across secondary outcomes.
28
- 29
30 • *patterns across primary outcome instruments* to determine the proportion of
31 records in which it is specified, and for those that do specify an instrument what
32 that instrument is and what is the timing of the primary end-point for evaluating
33 treatment efficacy. The same analysis will be conducted separately across
34 secondary outcomes.
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37 • *patterns across continents* to determine whether there are geographical
38 preferences for using one primary outcome instrument over another,
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41 • *patterns across years* to determine changes over time in the uptake of outcome
42 instruments as a primary, especially the recent Tinnitus Functional Index²²,
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- 44
45 • *patterns across interventions* to determine whether particular classes of
46 intervention (e.g. neurophysiological, audiological, psychological etc) favour using
47 one primary outcome instrument over another.
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Four assessments of the quality of defining and reporting outcomes are planned:

- The first will consider whether the authors' specification of each primary outcome domain is adequate. For example, 'tinnitus severity' is not a domain, yet it is commonly presented as a complaint or an outcome.
- The second will consider the degree to which each primary outcome domain is appropriate and consistent with the authors' choice of primary outcome instrument. For example, 'tinnitus loudness' might be measured using a Visual Analogue Scale which should be specified for loudness.
- The third will examine the extent to which the trial design is informed by a sample size calculation based on previous data for the primary outcome instrument. This is informative because published information about the treatment-related sensitivity of particular instruments, necessary to determine the statistical power of the study, is often lacking.^{3,17}
- The fourth will consider how many *primary* outcomes are measured in each study. To avoid outcome reporting bias, it is preferable that one outcome measure and endpoint is specified¹⁸, but this is not always the case.

Table 2 provides an overview of the quality items to be synthesised and reported. In addition to these planned syntheses, the data collection for consolidated records will enable summary statistics and a narrative synthesis about selective outcome reporting (reporting bias).

** insert Table 2 here **

A final exploratory analysis of subgroups will address the question 'Is a particular outcome domain (or instrument) preferentially selected in trials that enrol a particular tinnitus sub-type, or when tinnitus presents with a particular co-morbid condition?' This final analysis will be conducted only if there is sufficient data.

Ethics and dissemination

No ethical issues are foreseen. The findings will be reported at national and international ENT and audiology conferences and in a peer-reviewed journal using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, www.prisma-statement.org/). Publication reporting will include both the checklist and the flow diagram to depict the flow of information through the different phases of the systematic reviews. All data collected according to the data items will be available on request to the extent that it is not included in the published systematic review article.

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Authors' contributions

DAH is the guarantor of the first review (CRD42015017525). DAH and AJS lead on the development of the information sources, search strategy, and data management. AJS created the search strategies. DAH developed the risk of bias assessment strategy and data synthesis plan. DAH and HH produced and approved the manuscript. VK and AJS contributed to the development of the eligibility criteria, selection process, data collection, definition of data items, read, provided feedback and approved the final manuscript.

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Competing interests statement

The author(s) declare that they have no competing interests.

Figure 1

The proposed step-wise roadmap (Hall *et al*¹⁵) for developing a core outcome set. This figure is taken from a SAGE article published under the Creative Commons Attribution-Non-Commercial 3.0 License that permits reproduction without further permission (Attribution: Hall et al. Toward a global consensus on outcome measures for clinical trials in tinnitus: report from the first international meeting of the COMiT initiative, November 14, 2014, Amsterdam, The Netherlands. Trends in Hearing. DOI:10.1177/2331216515580272. Vol 19:1-7. 14 April 2015).

Table 1 Data items for the systematic review of trials on treatment effectiveness

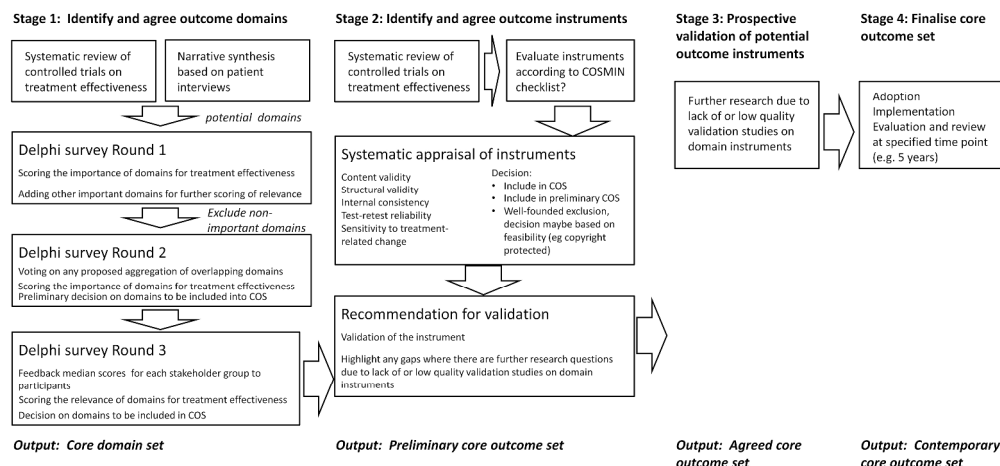
Descriptive checklist

- Study ID code
- Study title
- Name and contact details of corresponding author
- Country where study is conducted
- Date of publication (month, year)
- Date of study start (month, year)
- Study design
 - randomised controlled trials
 - before and after studies
 - non-randomised controlled trials or case control studies
 - cohort study
 - other
- Aim of study
- Type of intervention (all arms)
- Duration of intervention
- Sample size calculation (if 'yes' give details)
- Sample size
- Age range
- Inclusion criteria relating to tinnitus
 - duration
 - intermittent or constant
 - pulsatile or non-pulsatile
 - severity
 - any other subtypes
- Exclusion criteria relating to tinnitus

- Inclusion criteria relating to other health-related co-morbidities
- Exclusion criteria relating to other health-related co-morbidities
- Primary outcome domain(s)
- Primary outcome instrument(s)
- Time-frame: primary outcome(s)
- Secondary outcome domain(s)
- Secondary outcome instrument(s)
- Time-frame: secondary outcome(s)
- Description of any modifications to the methods, particularly any information that might be interpreted as reporting bias
- Notes (this optional field will be used to record any further comments that may be deemed informative. In particular whether a clinical interpretation of outcome instrument scores was defined and whether adverse events or side effects were reported as study findings).

Table 2 Quality items for the systematic review of trials on treatment effectiveness

Quality checklist	Count of records			
Adequate specification of primary outcome domains	<i>Proportion adequately specified in each record</i>			
	76-100%	51-75%	<50%	not stated
	(n=)	(n=)	(n=)	(n=)
Appropriate mapping between primary domain and instrument	<i>Proportion appropriately specified in each record</i>			
	76-100%	51-75%	<50%	not stated
	(n=)	(n=)	(n=)	(n=)
Sample size calculated for primary instrument	Yes (n=)	No (n=)	not stated (n=)	
Number of primary outcomes	<i>Number in each record</i>			
	1	2-3	4-5	>5
	(n=)	(n=)	(n=)	(n=)



The proposed step-wise roadmap (Hall et al 15) for developing a core outcome set. This figure is taken from a SAGE article published under the Creative Commons Attribution-Non-Commercial 3.0 License that permits reproduction without further permission (Attribution: Hall et al. Toward a global consensus on outcome measures for clinical trials in tinnitus: report from the first international meeting of the COMiT initiative, November 14, 2014, Amsterdam, The Netherlands. Trends in Hearing. DOI:10.1177/2331216515580272. Vol 19:1-7. 14 April 2015). 390x190mm (300 x 300 DPI)

Review only

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PRISMA-P 2015 checklist: recommended items to include in a systematic review protocol^a			
Section/topic	Item #	Checklist item	Page number in manuscript
ADMINISTRATIVE INFORMATION			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number	3
Authors			
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	18
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support			
Sources	5a	Indicate sources of financial or other support for the review	18
Sponsor	5b	Provide name for the review funder and/or sponsor	18
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	18

INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
METHODS			
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	7-9
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	9-10
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10
Study records			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	10-11
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any	11-12

		processes for obtaining and confirming data from investigators	
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	12 and Table 1
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	12
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12-13
Data	15a	Describe criteria under which study data will be quantitatively synthesized	13-14 Table 2
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	N/A
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	14
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	14

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Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	N/A
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PRISMA-P Preferred Reporting Items for Systematic review and Meta-Analysis Protocols.

For peer review only

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BMJ Open

Current reported outcome domains in studies of adults with a focus on the treatment of tinnitus: protocol for a systematic review

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Primary Subject Heading:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Research methods
Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult otolaryngology < OTOLARYNGOLOGY, Audiology < OTOLARYNGOLOGY, Clinical trials < THERAPEUTICS

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Title of the article

Current reported outcome domains in studies of adults with a focus on the treatment of tinnitus: protocol for a systematic review

Full names, institutional addresses and email addresses for all protocol authors

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Keywords

Protocols and guidelines, adult otolaryngology, audiology, clinical trials

Abstract

Introduction In Europe alone, over 70 million people experience tinnitus. Despite its considerable socioeconomic relevance, progress in developing successful treatments has been limited. Clinical effectiveness is judged according to change in primary outcome measures, but because tinnitus is a subjective condition, the definition of outcomes is challenging and it remains unclear which distinct aspects of tinnitus (i.e. 'domains') are most relevant for assessment. The development of a minimum outcome reporting standard would go a long way to addressing these problems. In 2006, a consensus meeting recommended using one of four questionnaires for tinnitus severity as an outcome in clinical trials in part because of availability in different language translations. Our initiative takes an approach motivated by clinimetrics; first by determining what to measure before seeking to determine how to measure it. Agreeing the domains that contribute to tinnitus severity (i.e. '*what*') is the first step towards achieving a minimum outcome reporting standard for tinnitus that has been reached via a methodologically rigorous and transparent process.

Methods and analysis Deciding what should be the core set of outcomes requires a great deal of discussion and so lends itself well to international effort. This protocol lays out the first-step methodology in defining a Core Domain Set for clinical trials of tinnitus by establishing existing knowledge and practice with respect to which outcome domains have been measured and which instruments used in recent registered and published clinical trials.

Ethics and dissemination No ethical issues are foreseen. Findings will be reported at national and international ENT and audiology conferences and in a peer-reviewed journal, using PRISMA guidelines.

Registration details The systematic review protocol is registered on PROSPERO (International Prospective Register of Systematic Reviews): CRD42015017525.

Strengths and limitations of this study

- The protocol addresses important questions relevant to weaknesses in the design of controlled trials assessing clinical efficacy of treatments for tinnitus.
- Review contributors span a number of European countries, bringing an international point of view.
- Clearly established purpose and well defined methods for data collection and synthesis.
- Review will generate independent evidence from professional stakeholder groups.
- Limitations include anticipated heterogeneity across studies and low-quality reporting which may pose challenges for the data synthesis.

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Introduction

Tinnitus is a common symptom arising from a range of otological and non-otological conditions, affecting 10-20% of the adult population, and rising with age.¹ Tinnitus is described as a ringing, buzzing or hissing sound heard in the ears or head. Most forms of tinnitus have no physically identifiable source of the sound and so they cannot be objectively measured. This is the condition known as subjective tinnitus. Throughout this protocol, we will refer simply to 'tinnitus', without limiting our question to one subtype or another. The tinnitus experience can be characterised by the perceptual properties of the sound percept, namely its pitch, timbre and loudness. Yet these perceptual attributes relate poorly to the degree of self-reported functional impact on daily life.² Instead, disability arising from tinnitus can be described as a multi-dimensional concept relating to impairments, activity limitations, and participation restrictions that people with tinnitus may experience, not forgetting the environmental factors which affect these experiences.³⁻⁵ In this sense, tinnitus is construed within the biopsychosocial model of disability proposed by the World Health Organisation.

General practitioners and Ear, Nose and Throat (ENT) consultants play an important role in the clinical assessment and management of tinnitus, but across countries patients may be referred to a range of other clinical stakeholders including neurologists, radiologists, audiologists, psychologists and psychiatrists.⁶ Given the inter-disciplinary approach, it is unsurprising that there are a number of different strategies for managing tinnitus in adults. These include, but are not restricted to psychoeducation and advice, provision of hearing aids, sound generators or other acoustic devices, physical therapy, psychological counselling, and complementary therapies.^{7,8} There are no current drugs that are licensed for alleviating tinnitus, but for managing some of the co-morbid symptoms such as depression and insomnia, pharmacological approaches are prescribed.^{8,9} Generally speaking, choice of clinical intervention is a multi-factorial decision based on the experience of the treating clinicians, their assessment of patient needs, and the broader healthcare

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3 context.⁶ Few professional bodies work to specific clinical practice guidelines or protocols for
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5 tinnitus (but see Tunkel *et al*¹⁰ for an example from the USA).
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9 It is good clinical practice that treatment decisions between health care professionals and
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11 their patients should be supported by informed conversations about the evidence for
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13 treatment efficacy. The best quality evidence for treatment effectiveness is drawn from
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15 randomised controlled trials and systematic reviews that synthesise the findings from those
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17 studies.¹¹ Where it is not possible to design a trial that has random allocation to intervention
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19 groups, certain types of controlled trials may also be considered.¹² Of the numerous
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21 systematic reviews of tinnitus treatments have been published over recent years, many of
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23 them reach the conclusion that few high quality trials are available for inclusion and for those
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25 trials that are included, a range of different outcome measures preclude the pooling of
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27 findings.^{9,12,13} There is a growing recognition that consistency between academic centres and
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29 clinics engaged in tinnitus research in the way that treatment outcomes are measured would
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31 facilitate more meaningful evaluation and comparison of trial findings.^{3,14,15} There is also
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33 agreement that the heterogeneous nature of tinnitus complaints and impact can also make
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35 clinical research and outcome measurement difficult. Moreover, there is increasing evidence
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37 for co-operative working to address these challenges. The creation of a comprehensive and
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39 a brief core set for hearing loss (Danermark *et al*¹⁶) is an example of the successful product
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41 of international collaboration in hearing.
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46 In 2006, a meeting in Regensburg of 29 tinnitus professionals sought consensus for tinnitus
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48 patient assessment and treatment outcome measurement. They recommended using one of
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50 four standard questionnaires (Tinnitus Handicap Inventory, Tinnitus Handicap Questionnaire,
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52 Tinnitus Reactions Questionnaire or Tinnitus Questionnaire) as an outcome instrument in
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54 therapeutic trials, although most were developed for intake assessment. Part of the rationale
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56 for this choice was motivated by pragmatism (e.g. availability in different language
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58 translations). These are all multi-item questionnaires that purport to measure tinnitus
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3 severity, but do so using different questions, rating scales and subscales. Moreover, the
4 design of the four recommended questionnaires was optimised for intake assessment of
5 tinnitus, rather than for evaluation of treatment-related change.^{3,17} Clearly, there is more work
6 to be done. We keep our minds open that recommendations for outcome measurement do
7 not necessarily need to be restricted to questionnaires. For example in chronic pain,
8 biological markers and clinician ratings of global improvement are proposed as supplemental
9 domains for clinical trials.¹⁸

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23 Building on the 2006 consensus approach, a COST Action network for tinnitus (TINNET) is
24 promoting the international coordination of nationally-funded research across Europe
25 (<http://tinnet.tinnitusresearch.net/>). The network has five working groups, one of which
26 Working Group 5 has the goal to establish an international standard for outcome
27 measurements in clinical trials of tinnitus. Our activity is conducted as the COMiT initiative
28 (Core Outcome Measures in Tinnitus) which is part of Working Group 5. In a recent article,
29 we promoted a step-wise roadmap (Hall *et al*¹⁵) (see Figure 1) for developing a core
30 outcome set. This approach is inspired by the work of the COMET (Core Outcome Measures
31 in Effectiveness Trials) Initiative.¹⁹ The first output will be a consensus on what outcome
32 *domains* are essential (i.e. core) to be captured in all controlled trials. A domain is defined as
33 a distinct element (or topic) of tinnitus such as how loud or how emotionally distressing a
34 patient may find his or her tinnitus. These core domains will be identified as being important
35 for characterising tinnitus and will reflect the perspectives of professionals and lay people,
36 alike. This article describes a systematic review protocol to be implemented within Stage 1 of
37 that roadmap. It relates to current reported outcome domains in studies of adults with a
38 focus on the treatment of tinnitus. International agreement on a core outcome domain set
39 would drive up the quality and relevance of research by ensuring that the most relevant
40 outcomes are consistently measured and reported in trials relating to tinnitus.
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5 The aim of the first systematic review is to contribute to the development of a core domain
6 set for future controlled trials on tinnitus treatment effectiveness using *quantitative* data
7 collected from ongoing registered or published trials since the 2006 consensus meeting.¹⁴
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9 This represents the professional perspective on outcome domains in clinical trials of tinnitus.
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11 The objective of the review is to conduct a world-wide search of the recent published
12 literature of clinical trials of interventions for tinnitus, as well as those ongoing trials that are
13 publicly registered. More specifically, this objective will answer the research question: 'What
14 are the current reported outcome domains in studies of adults with a focus on the treatment
15 of tinnitus?'

26 **Methods and Analysis**

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29 Methods are reported according to the Preferred Reporting Items for Systematic reviews and
30 Meta-analyses for Protocols 2015 (PRISMA-P^{20,21}). Subheadings correspond to some of the
31 items in the PRISMA-P checklist. The allocation of specific roles to named authors of the
32 review will be made at a later date, and this information will clearly be acknowledged in any
33 subsequent dissemination of findings.
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41 **Eligibility criteria** We have defined our inclusion criteria according to PICOS (Patient,
42 Intervention, Comparison, Outcome, Setting) guidelines as follows:
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47 *Participants* For maximum inclusivity, we will include all human participants with the only
48 restrictions being adults (≥18 year) who report tinnitus as one of their primary complaints.
49 To be confident that our review does not include trials recruiting participants younger than
50 18 years old, any trials specifying an age range with a lower limit than this will be
51 excluded. We will include both men and women.
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3 *Intervention* Again for maximum inclusivity, we will include any intervention irrespective of
4 whether it is a clinical intervention or a novel experimental intervention. The key criterion
5 is that the main aim of the intervention is to achieve a therapeutic benefit for people with
6 tinnitus, not those in which the impact on tinnitus might be of secondary benefit.
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13 *Comparison* The following types of study comparisons will be eligible for inclusion:
14 randomised controlled trials, before and after studies, non-randomised controlled trials or
15 case controlled studies and cohort studies. We will also include published meta-analysis
16 and systematic reviews that have considered such studies. However, we will exclude
17 articles reporting expert opinions, practice guidelines, case reports, case series,
18 conference abstracts and book chapters due to their more limited clinical and scientific
19 value. In accordance with this rationale, the search strategy will also exclude those trials
20 either recruiting fewer than 20 participants with tinnitus, or having fewer than 20 at the
21 end of follow up. This cut-off is somewhat arbitrarily selected, but follows Needleman *et al*
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Outcomes Since the research question has a focus on the treatment of tinnitus, studies
will be restricted to any changes related to tinnitus as a primary outcome, irrespective of
how these are measured.

Settings Any research settings will be included, notably both clinical and academic sites.
This is consistent with our approach to include all participants and interventions for
tinnitus, including exploratory therapies recruiting non-clinical groups.

Two review eligibility characteristics are specified. First, articles will be in the English
language. Second, articles must be published (in print copy, not epub ahead of print) on
or after July 2006. This date is selected to follow from the first international consensus
meeting for tinnitus patient assessment and treatment outcome measurement (cf.

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3 Langguth *et al*¹⁴). For registered clinical trials, we will apply the same publication date
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5 criteria so that our search will include only those studies that are first received after July
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7 2006. However, by doing so, we acknowledge the potential limitation of this strategy
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9 which is that included study designs may have been approved and open for recruitment
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11 before the Regensburg consensus meeting in July 2006.
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15 **Information sources** Intended information sources are the following electronic research
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17 databases: PubMed (National Center for Biotechnology Information), Embase (OVID) and
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19 Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCO), and trial
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21 registers: ClinicalTrials.gov, the International Standard Randomised Controlled Trial
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23 Number registry (ISRCTN, BioMed Central), International Clinical Trials Registry Platform
24
25 (ICTRP, World Health Organisation), and the Cochrane Database of Systematic Reviews
26
27 (CDSR). We will also search the Cochrane Central Register of Controlled Trials
28
29 (CENTRAL) which contains a highly concentrated source of reports of randomized
30
31 controlled trials. With the exception of trial registers, we will not use databases that are
32
33 specialised in grey literature.
34
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36
37 Additional information will be identified by a manual search of the registered clinical trials
38
39 to identify any additional registers of the trial and to identify any published protocols or
40
41 study findings that are indexed to a particular trial by its unique study identifier, but that
42
43 have not already been identified by the electronic research database search.
44

45
46 Furthermore, we will manually search all the systematic review articles found in order to
47
48 seek any further trials for inclusion. This will be restricted to those studies that met
49
50 eligibility for inclusion in the corresponding review publication.
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54 Following title exclusion, the next phase will assess eligibility based on the full text,
55
56 accessing hard-to-reach records via the British Library where necessary. Contact with
57
58 study authors will be permitted.
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5 The database search was conducted soon after registration in PROSPERO (12-13
6
7 March, 2015) by authors DAH and AJS. The manual search and personal author contact
8
9 will be ongoing up to the end of the data collection phase.
10

11
12
13 **Search strategy** The systematic review attempts to collate all relevant evidence that fits
14
15 pre-specified eligibility criteria to answer our specific research question. The electronic
16
17 database search strategy will use a combination medical subject headings (MeSH) and
18
19 relevant text words wherever possible. The search terms for PubMed, Embase and
20
21 CINAHL are: (tinnitus) AND (stud* OR clinical trial* OR therap* OR treatment* OR
22
23 intervention). For example, the search strategy for Embase will be: (((((((("tinnitus" and
24
25 "stud*") or "Tinnitus") and "clinical trial*") or "Tinnitus") and "Therap*") or "Tinnitus") and
26
27 "Treatment*") or "Tinnitus") and "Intervention*").mp. [mp=title, abstract, subject headings,
28
29 heading word, drug trade name, original title, device manufacturer, drug manufacturer,
30
31 device trade name, keyword]. Limit to (english language and (embase or medline) and
32
33 yr="2006 -Current" and (article or "review") and (adult <18 to 64 years> or aged <65+
34
35 years>)). This will be adapted to the syntax and subject headings of the other databases.
36
37 The authors do not have access to a health information specialist with database
38
39 searching skills, and so the most experienced researchers will conduct the search.
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44 **Data management** DAH (author) will be responsible for data management and will have
45
46 editorial rights. All identified records will be saved into an excel master file where records
47
48 can be tracked through the screening and data collection process. A simple system of
49
50 record annotation will be implemented to capture reasons for exclusion. Included records
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52 will be allocated a study ID code to link each record in the master file with its
53
54 corresponding full text and data collection sheet.
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3 **Selection process** Endnote will be used to remove duplicate records from the PubMed,
4 Embase and CINAHL searches. One of the review authors will then manually screen all
5 records for duplicates using author names, study title and trial registration number. A two-
6 step process will then be implemented to decide eligibility according to the inclusion and
7 exclusion criteria: first by reading the title, and second by reading the full text. The full text
8 will be obtained for all potentially relevant records appearing to meet the inclusion criteria
9 or for which there is insufficient information in the title to make a clear decision. Screening
10 steps will be carried out by a pool of three authors (DAH, AJS and HH), while data
11 collection will be conducted by a pool of 20 project team members. We will adopt the
12 principle that two project team members will always perform each key step independently
13 for every record (i.e. title screening, full text screening, and data collection).
14 Discrepancies will be resolved by DAH or one other designated project team member (in
15 cases when DAH is the screener or data extractor), acting as an arbitrator. Inter-rater
16 agreement will not be calculated.
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33 We will piece together data from multiple reports of the same study by manually
34 screening all included records using author names, study title and trial registration
35 number.
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42 **Data collection process** Data collection will be guided by an electronic form (excel
43 spreadsheet) that will also be used to collate all responses. To ensure consistency across
44 reviewers, a full set of guidance notes will be produced for the data collection procedure
45 and calibration exercises will be conducted with new members of the review team prior to
46 any individual contribution to this review. Both the sheet and the guidance notes will be
47 developed and revised through two iterations of piloting across several review authors.
48 Data collection will be conducted independently and in duplicate (two people) for every
49 included record. For any studies where insufficient detail is given to determine eligibility
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3 (e.g minimum age of enrolment or sample size), we will contact the corresponding author
4
5 by email (without a reminder) to seek clarification.
6
7

8
9 Many of the review authors will not have English as their native language and so DAH will
10
11 sample a subset (<5%) of data collection sheets for each author performing this step,
12
13 again in order to confirm consistency of approach.
14

15
16
17 **Data items** The data collection sheet will include a list of fields relating to trial design and
18
19 methodology. These are given in Table 1. If any information is not reported, then 'not
20
21 stated' will be recorded in the corresponding field. For those records in which several
22
23 pieces of information are consolidated into a single record, we will seek to detect any
24
25 modifications to the methods and any selective reporting in the completed reports of the
26
27 study findings.
28

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31 ** insert Table 1 here **
32
33

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36 **Outcomes and prioritisation** The main aim of the review focuses on changes related to
37
38 tinnitus as a primary outcome and so the data relating to primary outcome domains and
39
40 instruments will be the priority for data synthesis and reporting of findings. These
41
42 outcomes link directly to the first two bullet points described in the section on data
43
44 synthesis.
45

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48 **Risk of bias in individual studies** Bias is typically considered to be a systematic error
49
50 that can lead to an overestimation or underestimation of the true intervention effect. Given
51
52 that the primary objective of this systematic review concerns methodology, not findings,
53
54 we have limited plans to assess risk of bias of individual studies. However, the data
55
56 collection for consolidated records will enable summary statistics and a narrative
57
58 synthesis about selective outcome reporting (reporting bias) either where original
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3 descriptions of outcomes as 'primary' or 'secondary' may have been altered
4 retrospectively in the light of the findings, or where a subset of the original outcomes may
5 have been selected, on the basis of the results, for inclusion in the publication of trial
6 findings.
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12 The potential for observer bias during data collection process will be reduced by avoiding
13 any instance where an individual will extract data relating to one of their own trials.
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18 **Data synthesis** The main purpose of this systematic review is to create new knowledge
19 around the outcome domains (and instruments) that are being used in clinical trials of
20 tinnitus by pooling together and critically evaluating these data. The identified domains
21 and instruments will be tabulated in such a way as to illustrate five patterns in the data
22 using all included records. The first two bullet points address the primary purpose of the
23 review, the subsequent three bullet points relate to secondary review aims.
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 - *patterns across primary outcome domains* to determine the proportion of records
33 in which it is specified, and for those that do specify a domain what that domain is.
34 The same analysis will be conducted separately across secondary outcomes.
35
 - *patterns across primary outcome instruments* to determine the proportion of
36 records in which it is specified, and for those that do specify an instrument what
37 that instrument is and what is the timing of the primary end-point for evaluating
38 treatment efficacy. The same analysis will be conducted separately across
39 secondary outcomes.
40
 - *patterns across continents* to determine whether there are geographical
41 preferences for using one primary outcome instrument over another,
42
 - *patterns across years* to determine changes over time in the uptake of outcome
43 instruments as a primary, especially the recent Tinnitus Functional Index²³,
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- *patterns across interventions* to determine whether particular classes of intervention (e.g. neurophysiological, audiological, psychological etc) favour using one primary outcome instrument over another.

Four assessments of the quality of defining and reporting outcomes are planned:

- The first will consider whether the authors' specification of each primary outcome domain is adequate. For example, 'tinnitus severity' is not a domain, yet it is commonly presented as a complaint or an outcome.
- The second will consider the degree to which each primary outcome domain is appropriate and consistent with the authors' choice of primary outcome instrument. For example, 'tinnitus loudness' might be measured using a Visual Analogue Scale which should be specified for loudness.
- The third will examine the extent to which the trial design is informed by a sample size calculation based on previous data for the primary outcome instrument. This is informative because published information about the treatment-related sensitivity of particular instruments, necessary to determine the statistical power of the study, is often lacking.^{3,17}
- The fourth will consider how many *primary* outcomes are measured in each study. To avoid outcome reporting bias, it is preferable that one outcome measure and endpoint is specified¹⁹, but this is not always the case.

Table 2 provides an overview of the quality items to be synthesised and reported. In addition to these planned syntheses, the data collection for consolidated records will enable summary statistics and a narrative synthesis about selective outcome reporting (reporting bias).

** insert Table 2 here **

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3 A final exploratory analysis of subgroups will address the question 'Is a particular
4 outcome domain (or instrument) preferentially selected in trials that enrol a particular
5 tinnitus sub-type, or when tinnitus presents with a particular co-morbid condition?' This
6
7 final analysis will be conducted only if there is sufficient data.
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11 12 13 14 15 **Ethics and dissemination**

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19 No ethical issues are foreseen. The findings will be reported at national and international
20 ENT and audiology conferences and in a peer-reviewed journal using the Preferred
21 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, [www.prisma-](http://www.prisma-statement.org/)
22 [statement.org/](http://www.prisma-statement.org/)). Publication reporting will include both the checklist and the flow diagram to
23 depict the flow of information through the different phases of the systematic reviews. All data
24 collected according to the data items will be available on request to the extent that it is not
25 included in the published systematic review article.
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Authors' contributions

DAH is the guarantor of the first review (CRD42015017525). DAH and AJS lead on the development of the information sources, search strategy, and data management. AJS created the search strategies. DAH developed the risk of bias assessment strategy and data synthesis plan. DAH and HH produced and approved the manuscript. VK and AJS contributed to the development of the eligibility criteria, selection process, data collection, definition of data items, read, provided feedback and approved the final manuscript.

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Competing interests statement

The author(s) declare that they have no competing interests.

For peer review only

Figure 1

The proposed step-wise roadmap (Hall *et al*¹⁵) for developing a core outcome set. This figure is taken from a SAGE article published under the Creative Commons Attribution-Non-Commercial 3.0 License that permits reproduction without further permission (Attribution: Hall et al. Toward a global consensus on outcome measures for clinical trials in tinnitus: report from the first international meeting of the COMiT initiative, November 14, 2014, Amsterdam, The Netherlands. Trends in Hearing. DOI:10.1177/2331216515580272. Vol 19:1-7. 14 April 2015).

Table 1 Data items for the systematic review of trials on treatment effectiveness

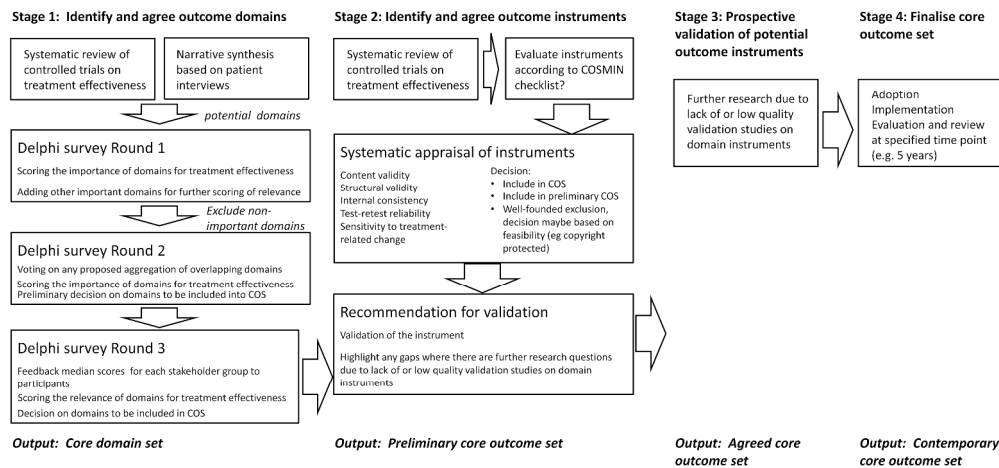
Descriptive checklist

- Study ID code
- Study title
- Name and contact details of corresponding author
- Country where study is conducted
- Date of publication (month, year)
- Date of study start (month, year)
- Study design
 - randomised controlled trials
 - before and after studies
 - non-randomised controlled trials or case control studies
 - cohort study
 - other
- Aim of study
- Type of intervention (all arms)
- Duration of intervention
- Sample size calculation (if 'yes' give details)
- Sample size
- Age range
- Inclusion criteria relating to tinnitus
 - duration
 - intermittent or constant
 - pulsatile or non-pulsatile
 - severity
 - any other subtypes
- Exclusion criteria relating to tinnitus

- Inclusion criteria relating to other health-related co-morbidities
- Exclusion criteria relating to other health-related co-morbidities
- Primary outcome domain(s)
- Primary outcome instrument(s)
- Time-frame: primary outcome(s)
- Secondary outcome domain(s)
- Secondary outcome instrument(s)
- Time-frame: secondary outcome(s)
- Description of any modifications to the methods, particularly any information that might be interpreted as reporting bias
- Notes (this optional field will be used to record any further comments that may be deemed informative. In particular whether a clinical interpretation of outcome instrument scores was defined and whether adverse events or side effects were reported as study findings).

Table 2 Quality items for the systematic review of trials on treatment effectiveness

Quality checklist	Count of records			
Adequate specification of primary outcome domains	<i>Proportion adequately specified in each record</i>			
	76-100%	51-75%	<50%	not stated
	(n=)	(n=)	(n=)	(n=)
Appropriate mapping between primary domain and instrument	<i>Proportion appropriately specified in each record</i>			
	76-100%	51-75%	<50%	not stated
	(n=)	(n=)	(n=)	(n=)
Sample size calculated for primary instrument	Yes (n=)	No (n=)	not stated (n=)	
Number of primary outcomes	<i>Number in each record</i>			
	1	2-3	4-5	>5
	(n=)	(n=)	(n=)	(n=)



The proposed step-wise roadmap (Hall et al 15) for developing a core outcome set. This figure is taken from a SAGE article published under the Creative Commons Attribution-Non-Commercial 3.0 License that permits reproduction without further permission (Attribution: Hall et al. Toward a global consensus on outcome measures for clinical trials in tinnitus: report from the first international meeting of the COMiT initiative, November 14, 2014, Amsterdam, The Netherlands. Trends in Hearing. DOI:10.1177/2331216515580272. Vol 19:1-7. 14 April 2015). 390x190mm (300 x 300 DPI)

Review only

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PRISMA-P 2015 checklist: recommended items to include in a systematic review protocol^a			
Section/topic	Item #	Checklist item	Page number in manuscript
ADMINISTRATIVE INFORMATION			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number	3
Authors			
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	18
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support			
Sources	5a	Indicate sources of financial or other support for the review	18
Sponsor	5b	Provide name for the review funder and/or sponsor	18
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	18

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INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any

		processes for obtaining and confirming data from investigators	
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	12 and Table 1
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	12
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12-13
Data	15a	Describe criteria under which study data will be quantitatively synthesized	13-14 Table 2
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	N/A
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	14
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	14

Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	N/A
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PRISMA-P Preferred Reporting Items for Systematic review and Meta-Analysis Protocols.

For peer review only

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