National Institute for Health and Care Excellence

Draft for consultation

Tinnitus: assessment and management

Imaging to investigate the cause of pulsatile tinnitus

NICE guideline

Diagnostic test and treat evidence review

September 2019

Draft for Consultation

This evidence review was developed by the National Guideline Centre

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN

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1.1 Review question: What is the most clinical and cost-effective imaging method to investigate the cause of pulsatile tinnitus?

1.2 Introduction

In certain groups of individuals with tinnitus, it is important to image the head and neck to exclude an organic cause for their symptoms. The role of imaging is to detect specific pathology that is treatable. A variety of imaging modalities may be considered depending on the type of tinnitus and/or associated symptoms reported, particularly if the tinnitus is considered to be pulsatile in nature. Imaging modalities include ultrasound, computerised tomography, magnetic resonance imaging and angiography. A thorough history and clinical examination can direct the decision for imaging and the type of imaging.

Pulsatile tinnitus is heard as a regular rhythmical noise. It can occur at the same time as the heart beat (synchronous) or at a different interval (non-synchronous). Synchronous pulsatile tinnitus can be caused by a number of different causes such as irregular blood vessels, high blood pressure, raised intracranial pressure, anaemia and atherosclerosis. Vascular causes may be systemic, for example anaemia, or due to a vascular anomalies or pathology, for example arteriovenous malformation or fistula. Non-vascular pulsatile causes include paragangliomas, intracranial hypertension, osseous pathology and somatic causes. Middle ear pathology such as glomus tumours can also give rise to synchronous tinnitus. Non-synchronous pulsatile tinnitus may be caused by palatal myoclonus. If these conditions are identified they can then be treated, which should also improve the tinnitus.

Whilst it is crucial not to miss significant pathology, it is also important not to over-scan people where significant pathology is unlikely. Not only is this cost unnecessary, it maybe unpleasant and stressful for the person and possibly expose them to an unnecessary dose of ionising radiation or risk of adverse effects from the contrast agent.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Children, young people and adults with suspected or confirmed pulsatile tinnitus. Strata: People presenting with isolated pulsatile tinnitus People presenting with pulsatile tinnitus plus other conditions Synchronous and non-synchronous (including somatic) pulsatile tinnitus Unilateral and bilateral
Intervention(s)	• CT/A scan • MRI/A scan • Angiography • Ultrasound scan

Comparison(s)	• CT/A scan • MRI/A scan • Angiography • Ultrasound • No imaging
Outcomes	• Mortality (critical) • Tinnitus severity (critical) Impact of tinnitus (critical): • Tinnitus distress • Tinnitus annoyance Health related QoL(critical): • QoL (tinnitus) • QoL Tinnitus percept (important): • Tinnitus loudness Other co-occurring complaints (important): • Depression • Anxiety • Anxiety and depression • Sleep Adverse events (important): • Safety • Tolerability • Side effects
Study design	• Systematic review of RCTs • RCT • If there is an inadequate amount of RCT data, non-randomised comparative studies will be considered.

1.4 Clinical evidence

1.4.1 Included studies

No relevant randomised controlled trial evidence comparing imaging methods with other imaging methods or with no imaging method were identified. Consequently, non-randomised comparative studies were also assessed. However, no relevant studies were identified for inclusion.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.6 Unit Costs

Table 2: Unit costs of imaging techniques for non-pulsatile tinnitus

Imaging Modality[(a)]	Contrast	Number of areas[(b)]	Code	Costs
Computerised Tomography	With Contrast	Two areas	RD24Z	£106
Magnetic Resonance Imaging	Without Contrast	Two areas	RD04Z	£152
Magnetic Resonance Imaging	With Contrast	Two Areas	RD05Z	£202

(a) The committee provided the names of the key imaging techniques used for people with pulsatile tinnitus and the required contrast for each test. The costs were subsequently sourced from NHS reference costs.[6]

1.7 Evidence statements

1.7.1 Clinical evidence statements

- No relevant published evidence was identified.

1.7.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

Tinnitus distress, annoyance and tinnitus severity were critical outcomes as they were thought to be common complaints for those with tinnitus and impact their quality of life. Quality of life (tinnitus-related) and general quality of life were also critical outcomes due to their impact on the person with tinnitus. Mortality was another critical outcome.

Tinnitus loudness, anxiety, depression, sleep, safety, tolerability and side effects were thought to be important outcomes.

The committee did not prioritise diagnostic accuracy outcomes such as sensitivity and specificity because they felt it was more useful to know about the effect on tinnitus outcomes and cost effectiveness of including these scans in the pathway compared to each other or no scanning.

There was no outcome data for any of the outcomes.

1.8.1.2 The quality of the evidence

Randomised controlled trials (RCTs) and systematic reviews of RCTs were searched for and assessed for eligibility but no relevant RCT evidence was identified which matched the review protocol. Consequently, non-randomised comparative studies were also searched for and assessed for eligibility. No relevant non-randomised comparative studies were identified.

1.8.1.3 Benefits and harms

The committee noted that whilst no evidence was identified, the use of imaging to investigate pulsatile tinnitus is a crucial part of the management pathway and therefore consensus recommendations were made. The committee discussed that there is a risk of anxiety with any scan and healthcare professionals should take this into consideration when offering scans to people with tinnitus. Pulsatile tinnitus may be due to a benign cause, but it can also be due to a vascular malformation or abnormal intracranial pressure that can be potentially significant or life-threatening. Therefore, the committee agreed that imaging should be offered to all age groups with pulsatile tinnitus in order to detect significant and treatable lesions.

Synchronous pulsatile tinnitus

Synchronous pulsatile tinnitus can originate from a number of different causes such as raised intracranial pressure, irregular blood vessels, high blood pressure, anaemia and atherosclerosis. If these conditions are identified they can then be treated which should also improve the tinnitus.

Contrast-enhanced CT scan is more effective at detecting osseous pathology, while MR imaging is more suitable for detecting soft tissue or intracranial pathology. Therefore, the choice of initial imaging method will depend on the clinical suspicion of underlying pathology. For example, middle ear pathology or osseous abnormality such as glomus tumours can give rise to synchronous tinnitus. If this is suspected at examination and audiological assessment, a contrast enhanced CT scan was considered by the committee to be the best next step to identify the cause.

Magnetic resonance angiography (MRA) can be used to identify or exclude significant and/or treatable disease such as vascular problems. The committee noted that it can also be used to assess the risk of stroke as well as other serious vascular and neurological complications. MRA does not involve ionising radiation, unlike CT scans, and therefore the committee considered this to be the first choice of investigation. Some people may not be able to have or to tolerate an MRA due to metal implants such as pacemakers, or claustrophobia. In these cases, contrast enhanced CT scans should be considered. CT scans are however associated with a risk from the radiation dose and a risk of sustaining a reaction from the contrast medium. The committee agreed that MRI with contrast should also be considered and noted that MRI with contrast could be digital. The selection of MRA or MRI with contrast is based on experience and equipment available.

There may be instances (e.g. glomus tumour) when both CT and MR imaging can be helpful in improving diagnostic accuracy as they can be complementary in diagnosing and assessing the extent of the medical condition.

Angiography was not recommended by the committee because the committee considered that angiography is associated with a risk of stroke or heart attack, a risk of allergic reaction to the contrast medium and risk from the radiation dose.

Non-synchronous pulsatile tinnitus

Non- synchronous pulsatile tinnitus may be caused by palatal myoclonus. The committee considered that where this is a suspected pathology, an MRI could be considered. MRI provides the most accurate method for investigating non-synchronous pulsatile tinnitus to exclude significant and/or treatable disease. The committee noted that the incidence of this medical condition is very low. Again, where MRI is not suitable, contrast enhanced CT should be considered, although the risk from radiation dose and potential for adverse reaction to the contrast media means that MRI is preferred where possible.

1.8.1.4 Cost effectiveness and resource use

There were no economic evaluations available for this review question. The view of the committee was that all people with pulsatile tinnitus should be offered a scan because pulsatile tinnitus can occur due to serious causes such as irregular blood vessels, high blood pressure, raised intracranial pressure, anaemia and atherosclerosis, paragangliomas, osseous pathology and glomus tumours. A scan would be able to help identify the underlying cause of tinnitus and avoid later expenditure and morbidity that might occur if these conditions were left untreated. The committee judged that a scan was imperative for the pulsatile tinnitus population but they were also mindful of the potential resource impact. One way that the committee considered cost-effectiveness in its recommendations is by ensuring clinicians are directed towards the most appropriate tests and thereby limiting unnecessary use of more expensive imaging modalities such as an MRI with contrast (see Table 2).

Synchronous pulsatile tinnitus

The committee noted that examinations and audiological assessments may indicate suspicion of osseous or middle ear abnormality in people with synchronous pulsatile tinnitus. In these cases, the committee formed a consensus view that a CT scan would be the preferred and more sensitive imaging modality for this abnormality. The committee were of the view that this recommendation would aid in preventing clinicians immediately opting for the more expensive MRI scan and thus help generate cost-savings.

In those instances where there are no such suspicions but a person has synchronous pulsatile tinnitus, the committee formed a consensus view that an MRA or MRI should be provided. This is because in these cases, MRI and MRA imaging techniques are more able to pick up soft tissue, vascular and other abnormalities and are associated with less harm than CT. The committee suggested that a CT should however be used if MRI or MRA is not possible or cannot be tolerated. While a CT scan would be less sensitive than the MRA, the committee noted that it was still important for clinicians to rule out significant pathology as this would reduce later expenditure and avoidable complications.

The committee noted that the consensus recommendations on imaging modalities for synchronous tinnitus has the potential to be cost saving because it will limit the unnecessary use of more expensive imaging modalities (e.g. MRA or MRI).

Non-synchronous pulsatile tinnitus

Current practice for investigating non-synchronous pulsatile tinnitus is for an MRI to be performed in cases where palatal myoclonus is thought to be the cause of the tinnitus. Therefore, the recommendation is not a change to practice and is expected to be cost-neutral to the NHS. Again, the committee noted that it was important all people with non-synchronous tinnitus are considered for imaging (preferably an MRI or CT if an MRI is contraindicated) to prevent avoidable complications and later expenditure.

1.8.2 Other factors the committee took into account

Whilst individuals may become anxious whilst waiting for scans and results, the clinician can minimise this anxiety by discussing openly the reasons for the scan, the risks and benefits of the scan and the possible outcomes. Most people with pulsatile tinnitus will appreciate having an investigation which will either indicate a condition to be treated or rule out any serious underlying cause for the tinnitus.

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Appendices

Appendix A: Review protocols

Table 3: Review protocol: Imaging method to investigate the cause of pulsatile tinnitus

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	The most clinical and cost effective imaging method to investigate the cause of pulsatile tinnitus
2.	Review question	What is the most clinical and cost effective imaging method to investigate the cause of pulsatile tinnitus?
3.	Objective	People with pulsatile tinnitus will generally undergo medical imaging following a medical examination. There are various imaging methods that can be used including ultrasound, CT scans, MRI and MRA. The objective of the review is to evaluate the clinical effectiveness and cost-effectiveness of different imaging methods to investigate the cause of pulsatile tinnitus. These imaging methods would be followed up by appropriate treatments for the cause of pulsatile tinnitus and the resulting patient outcomes assessed.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE

		• CINAHL, Current Nursing and Allied Health Literature Searches will be restricted by: • English language • Human studies • Letters and comments are excluded. Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Tinnitus
6.	Population	Inclusion: Children, young people and adults with suspected or confirmed pulsatile tinnitus. Strata: • People presenting with isolated pulsatile tinnitus • People presenting with pulsatile tinnitus plus other conditions • Synchronous and non-synchronous (including somatic) pulsatile tinnitus • Unilateral and bilateral Exclusion: None

7.	Intervention/Exposure/Test	• CT/A scan • MRI/A scan • Angiography • Ultrasound scan
8.	Comparator/Reference standard/Confounding factors	• CT/A scan • MRI/A scan • Angiography • Ultrasound • No imaging
9.	Types of study to be included	• Systematic reviews • RCTs • If there is an inadequate amount of RCT data, non-randomised comparative studies will be considered
10.	Other exclusion criteria	• Non-English language studies • Studies will only be included if they report one or more of the outcomes listed above. • Descriptive (non-comparative) studies will be excluded
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	• Mortality • Tinnitus severity Impact of tinnitus: • Tinnitus distress • Tinnitus annoyance Health related QoL: • QoL (tinnitus) • QoL
13.	Secondary outcomes (important outcomes)	Tinnitus percept: • Tinnitus loudness Other co-occurring complaints: • Depression • Anxiety • Anxiety and depression • Sleep Adverse events: • Safety

		• Tolerability • Side effects
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)

		Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
17.	Analysis of sub-groups	• Sudden onset tinnitus • Hearing loss • Neurological features (e.g. double vision,

<table>
<tr><td></td><td></td><td colspan="3">dysarthria, ataxia, vertigo/dizziness, facial palsy)
• Vascular risks (e.g. hypertension and hypercholesterolaemia)</td></tr>
<tr><td>18.</td><td>Type and method of review</td><td colspan="3">☐ Intervention
☐ Diagnostic
☐ Prognostic
☐ Qualitative
☐ Epidemiologic
☐ Service Delivery
☒ Other – diagnostic test and treat</td></tr>
<tr><td>19.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3">27/06/18</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">11/03/20</td></tr>
<tr><td rowspan="6">23.</td><td rowspan="6">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☑</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☑</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☑</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☑</td></tr>
<tr><td>Risk of bias (quality)</td><td>☐</td><td>☑</td></tr>
</table>

		assessment		
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail Tinnitus@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: • Dr Jennifer Hill [Guideline lead] • Ms Sedina Lewis/Ms Julie Neilson [Senior systematic reviewers] • Dr Richard Clubbe [Systematic reviewer] • Mr David Wonderling [Health economist lead] • Mr Emtiyaz Chowdhury [Health economist] • Ms Jill Cobb [Information specialist] • Dr Giulia Zuodar [Project manager]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		

28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	N/A
30.	Reference/URL for published protocol	N/A
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Tinnitus, pulsatile tinnitus, imaging, MRI, CT, scans,
33.	Details of existing review of same topic by same authors	N/A
34.	Current review status	☐ Ongoing ☒ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

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1 **Table 4: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[5] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland).

	• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[5]

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 5: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 02 April 2019	Exclusions
Embase (OVID)	1974 – 02 April 2019	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 4 of 12 CENTRAL to 2019 Issue 4 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception – 02 April 2019	Exclusions

Medline (Ovid) search terms

1.	Tinnitus/
2.	tinnit*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case report/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/

19.	exp Rodentia/
20.	(rat or rats or mouse or mice).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language

1 **Embase (Ovid) search terms**

1.	tinnitus/
2.	tinnit*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	Case report/ or Case study/
8.	(letter or comment*).ti.
9.	or/4-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animal/ not human/
13.	Nonhuman/
14.	exp Animal Experiment/
15.	exp Experimental animal/
16.	Animal model/
17.	exp Rodent/
18.	(rat or rats or mouse or mice).ti.
19.	or/11-18
20.	3 not 19
21.	limit 20 to English language

2 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Tinnitus] explode all trees
#2.	tinnit*:ti,ab
#3.	#1 or #2

3 **CINAHL (EBSCO) search terms**

S1.	(MH "Tinnitus")
S2.	(MH "Tinnitus Retraining Therapy")
S3.	tinnit*
S4.	S1 OR S2 OR S3
S5.	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website
S6.	S4 NOT S5

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the tinnitus population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

Table 6: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2002 – 02 March 2019	Exclusions Health economics studies Quality of life studies
Embase	2002 – 02 March 2019	Exclusions Health economics studies Quality of life studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 Mar 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	Tinnitus/
2.	tinnit*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case report/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	Economics/
25.	Value of life/

26.	exp "Costs and Cost Analysis"/
27.	exp Economics, Hospital/
28.	exp Economics, Medical/
29.	Economics, Nursing/
30.	Economics, Pharmaceutical/
31.	exp "Fees and Charges"/
32.	exp Budgets/
33.	budget*.ti,ab.
34.	cost*.ti.
35.	(economic* or pharmaco?economic*).ti.
36.	(price* or pricing*).ti,ab.
37.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38.	(financ* or fee or fees).ti,ab.
39.	(value adj2 (money or monetary)).ti,ab.
40.	or/24-39
41.	quality-adjusted life years/
42.	sickness impact profile/
43.	(quality adj2 (wellbeing or well being)).ti,ab.
44.	sickness impact profile.ti,ab.
45.	disability adjusted life.ti,ab.
46.	(qal* or qtime* or qwb* or daly*).ti,ab.
47.	(euroqol* or eq5d* or eq 5*).ti,ab.
48.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
49.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
50.	(hui or hui1 or hui2 or hui3).ti,ab.
51.	(health* year* equivalent* or hye or hyes).ti,ab.
52.	discrete choice*.ti,ab.
53.	rosser.ti,ab.
54.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
55.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
56.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
57.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
58.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
59.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
60.	or/41-59
61.	23 and (40 or 60)

1 **Embase (Ovid) search terms**

1.	tinnitus/
2.	tinnit*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.

7.	Case report/ or Case study/
8.	(letter or comment*).ti.
9.	or/4-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animal/ not human/
13.	Nonhuman/
14.	exp Animal Experiment/
15.	exp Experimental animal/
16.	Animal model/
17.	exp Rodent/
18.	(rat or rats or mouse or mice).ti.
19.	or/11-18
20.	3 not 19
21.	health economics/
22.	exp economic evaluation/
23.	exp health care cost/
24.	exp fee/
25.	budget/
26.	funding/
27.	budget*.ti,ab.
28.	cost*.ti.
29.	(economic* or pharmaco?economic*).ti.
30.	(price* or pricing*).ti,ab.
31.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
32.	(financ* or fee or fees).ti,ab.
33.	(value adj2 (money or monetary)).ti,ab.
34.	or/21-33
35.	quality adjusted life year/
36.	"quality of life index"/
37.	short form 12/ or short form 20/ or short form 36/ or short form 8/
38.	sickness impact profile/
39.	(quality adj2 (wellbeing or well being)).ti,ab.
40.	sickness impact profile.ti,ab.
41.	disability adjusted life.ti,ab.
42.	(qal* or qtime* or qwb* or daly*).ti,ab.
43.	(euroqol* or eq5d* or eq 5*).ti,ab.
44.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
45.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
46.	(hui or hui1 or hui2 or hui3).ti,ab.

47.	(health* year* equivalent* or hye or hyes).ti,ab.
48.	discrete choice*.ti,ab.
49.	rosser.ti,ab.
50.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
51.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
52.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
53.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
54.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
55.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
56.	or/35-55
57.	20 and (34 or 56)
58.	limit 57 to English language

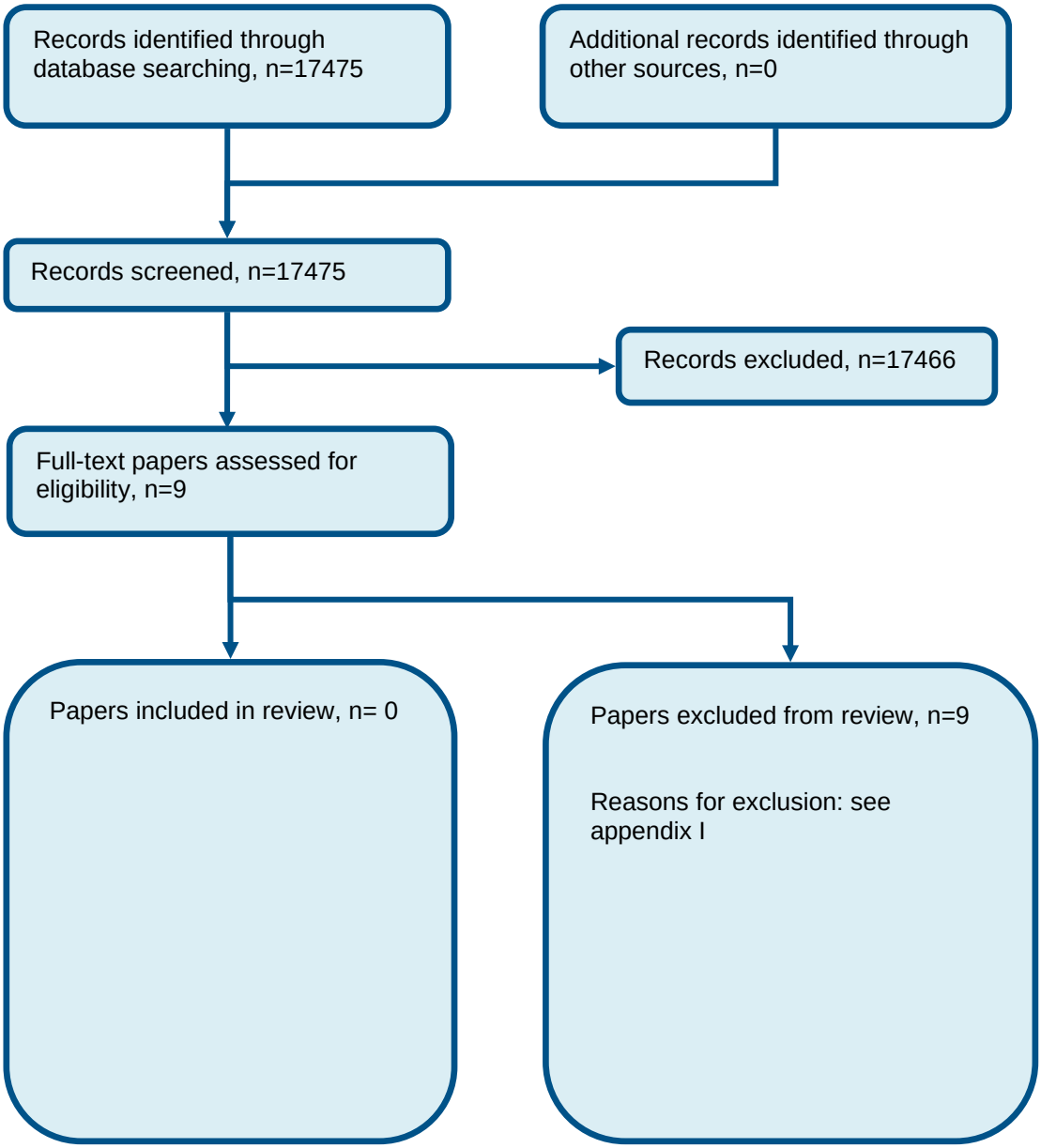
1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Tinnitus EXPLODE ALL TREES
#2.	(tinnit*)
#3.	#1 OR #2

2

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of imaging method to investigate the cause of pulsatile tinnitus



Appendix D: Clinical evidence tables

No evidence identified.

Appendix E: Forest plots

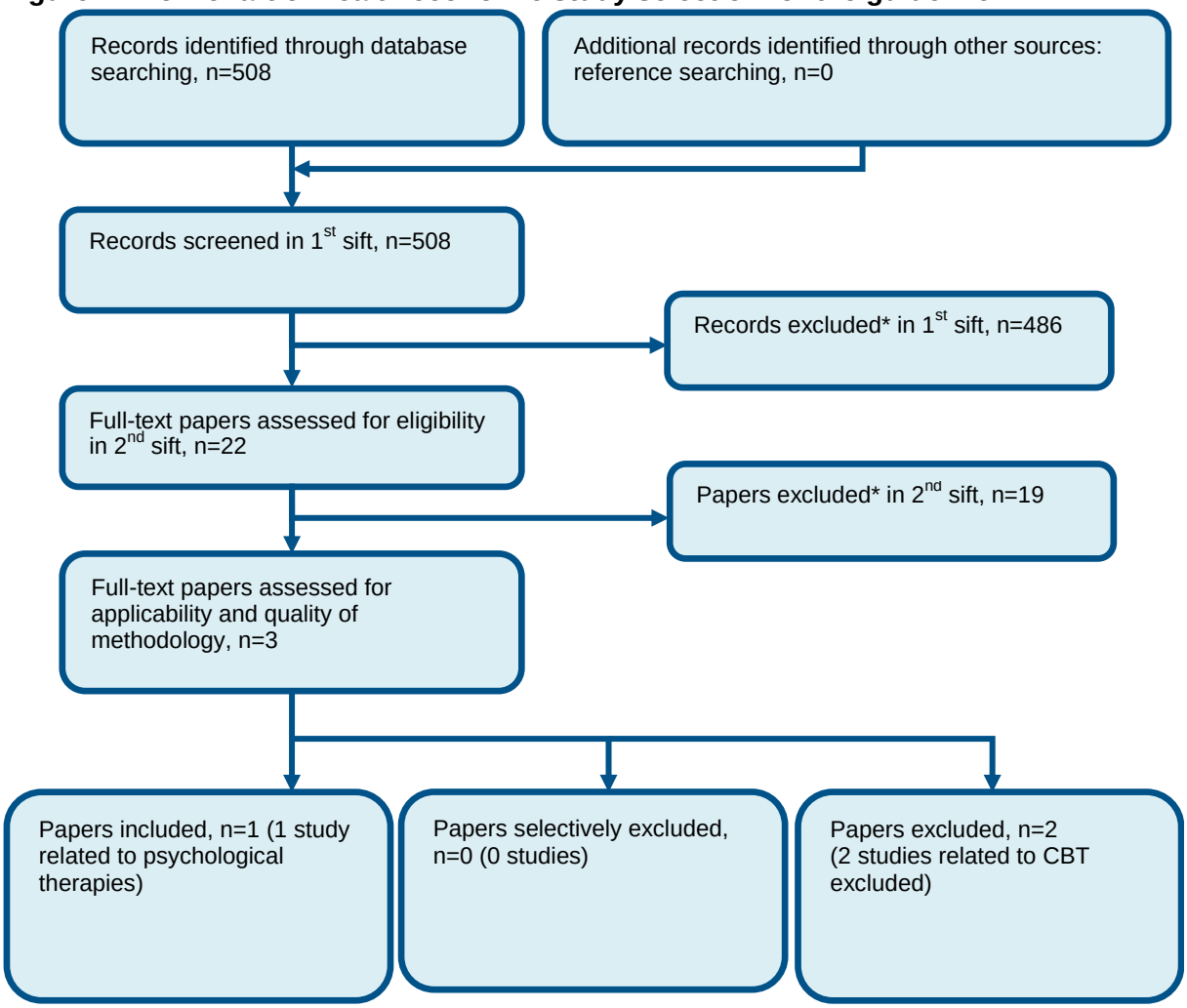
No evidence identified.

Appendix F:GRADE tables

No evidence identified.

Appendix G: Health economic evidence selection

Figure 2: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 7: Studies excluded from the clinical review

Reference	Reason for exclusion
Dawes 1999[1]	No relevant outcomes (details of diagnoses reported)
De Ridder 2005[2]	Incorrect comparison (MRI for pulsatile versus non-pulsatile tinnitus); no relevant outcomes
Fortnum 2009[3]	Systematic review of non-RCTs
Mundada 2015[4]	No relevant outcomes (details of diagnoses reported)
Remley 1990[7]	No relevant outcomes (details of diagnoses reported)
Seemann 2005[8]	No relevant outcomes (details of diagnoses reported)
Simonetti 2015[9]	Systematic review; incorrect comparisons (functional studies comparing people with tinnitus versus people without tinnitus)
Song 2012[10]	Meta-analysis; incorrect comparison (people with tinnitus versus people without tinnitus)
Waldvogel 1998[11]	No relevant outcomes (details of diagnoses reported)

H.2 Excluded health economic studies

None.