National Institute for Health and Care Excellence

Final

Tinnitus: assessment and management

[C-D] Evidence reviews for symptoms and features for urgent and non-urgent referral

NICE guideline NG155

Diagnostic evidence review

March 2020

Final

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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1 Symptoms and features for urgent and non-urgent referral

People affected with tinnitus can present to health care professionals at different levels of care. The aetiology of tinnitus can vary from causes such as ear wax and hypertension which can be managed in general practice, noise induced or age related hearing loss which may require referral for audiological assessment, to causes such as vestibular schwannoma or multiple sclerosis (MS) which require specialist assessment and management. The majority presenting with tinnitus have benign symptoms and do not need onward referral as they can be supported in general practice or audiology services. Tinnitus may present as the main complaint or with additional symptoms and or signs such as hearing loss.

This review question aims to help general practice healthcare professionals and audiologists determine which symptoms and signs indicate further specialist clinical assessment following an assessment of clinical history and physical examination. The review question will also aim to identify whether their referral needs to be immediate, urgent or non-urgent. This will enable people presenting with tinnitus to receive the care they require, depending on their symptoms. This has potential to cut down unnecessary referrals and to identify those that may have underlying pathology or psychosocial effects who need to be seen and managed sooner, thus preventing potential disabling effects on functioning and quality of life.

1.1 Review question: Which symptoms and features should indicate the need for urgent investigation and/or management?

1.1.1 Introduction

The objective of this review question is to determine the diagnostic accuracy of specific symptoms and features of tinnitus for diagnosis of conditions such as skull base tumours, neoplasm or glomus tumours or symptoms amenable to urgent investigation and or/ management.

1.1.2 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People presenting to a healthcare setting with tinnitus
Index test (symptoms and features)	Symptoms and features • Sudden onset pulsatile tinnitus. • Tinnitus in association with sudden onset of significant neurological symptoms and/or signs (for example facial weakness). • Tinnitus associated with acute vertigo. • Tinnitus secondary to recent head trauma. • Sudden onset unilateral tinnitus • Tinnitus associated with a sudden onset hearing loss • Tinnitus associated with suicidal ideations • Tinnitus associated with significant mental health impact • Tinnitus associated with marked distress • Tinnitus associated with self-harm

Reference standard(s)	• Cerebrovascular disease • Hypertension • Neoplasm • Skull base tumours • Vascular lesions • Vestibular schwannoma (Acoustic Neuroma) • Cerebellopontine angle tumour • Glomus tumour • Mental health conditions
Outcomes	• Sensitivity • Specificity • Positive predictive value • Negative predictive value • ROC curve or area under the curve • Adjusted odds ratios
Study design	• Diagnostic accuracy study (2-gate studies will be excluded unless no other data are available from single gate-studies) • Systematic reviews of diagnostic accuracy studies

1.1.3 Clinical evidence

No relevant diagnostic accuracy studies investigating the symptoms and features of tinnitus for diagnosis of conditions or symptoms amenable to urgent investigation and/or management were identified.

See also the study selection flow chart in appendix C.

1.1.4 Excluded studies

No full-text papers were assessed for eligibility for the evidence review questions. See details in appendix G.

1.2 Which symptoms and features should indicate the need for non-urgent specialist treatment?

1.2.1 Introduction

The objective of this review question is to determine the diagnostic accuracy of specific symptoms and features of tinnitus for diagnosis of conditions such as otitis externa, Meniere's disease or symptoms amenable to non-urgent specialist treatment.

1.2.2 PICO table

For full details see the review protocol in appendix A.

Table 2: PICO characteristics of review question

Population	People presenting to a healthcare setting with tinnitus
Index test (symptoms and features)	• Tinnitus associated with persistent otalgia or otorrhoea that doesn't resolve with routine treatment • Tinnitus with vestibular symptoms (for example dizziness, vertigo). • Tinnitus that is bothersome or causing distress

	• Objective or pulsatile tinnitus. • Unilateral tinnitus • Tinnitus associated with unilateral or asymmetric hearing loss. • People with tinnitus and normal peripheral hearing, but difficulty hearing in noisy backgrounds, or with sound localisation, or difficulty following complex auditory directions; • People with tinnitus associated with non-otological conditions: – systemic, e.g. cardiovascular, endocrine or metabolic disorders – neurological, e.g. multiple sclerosis, head injury, whiplash
Reference standard(s)	Reference standard: Conditions or symptoms amenable to specialist treatment e.g.: • Meniere's disease • Middle ear infection • Otitis externa • Cholesteatoma • Cochlear, retrocochlear or other central nervous system disorders • Tinnitus that is causing distress
Outcomes	• Sensitivity • Specificity • Positive predictive value • Negative predictive value • ROC curve or area under the curve • Adjusted odds ratios
Study design	• Diagnostic accuracy study (2-gate studies will be excluded unless no other data are available from single gate-studies) • Systematic reviews of diagnostic accuracy studies

1.2.3 Clinical evidence

No relevant diagnostic accuracy studies investigating the symptoms and features of tinnitus for diagnosis of conditions or symptoms amenable to non-urgent specialist treatment were identified.

See also the study selection flow chart in appendix C.

1.2.4 Excluded studies

No full-text papers were assessed for eligibility for the evidence review questions. See details in appendix G.

1.3 Economic evidence

1.3.1 Included studies

No relevant health economic studies were identified.

1.3.2 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 F.

1.4 Evidence statements

1.4.1 Clinical evidence statements

- No relevant published evidence was identified.

1.4.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.5 The committee's discussion of the evidence

1.5.1 Interpreting the evidence

1.5.1.1 The diagnostic measures that matter most

Diagnostic accuracy of symptoms indicating medical conditions requiring urgent or non-urgent investigation and management was prioritised for this review. Diagnostic accuracy outcomes included: sensitivity, specificity, positive predictive value, negative predictive value, ROC curve or area under the curve adjusted odds ratios.

No evidence was identified for any of the outcomes in the review.

1.5.1.2 The quality of the evidence

No evidence was identified for this review.

1.5.1.3 Benefits and harms

The committee noted that whilst no evidence was identified this is a crucial part of the management pathway and therefore consensus recommendations were made. There is generally inconsistency in how referrals are made in the UK, whereby people with tinnitus are referred from general practice to ENT services or audiology services. The consequences of not appropriately referring people presenting with tinnitus can be catastrophic, impacting on physical and mental well-being. Tinnitus can be also associated with numerous other symptoms and features that have not been explicitly mentioned in the recommendations. The committee highlighted the most commonly reported symptoms and features.

The committee discussed that the investigation and/or management pathway associated with tinnitus should be categorised into immediately, to be seen within 24 hours, seen within 2 weeks and non-urgent. These categories are similar to those adopted in the hearing loss guideline (NG98). The committee discussed that hearing loss is a clinical manifestation commonly associated with tinnitus. The committee wished to cross-refer readers to NG98 (recommendations 1.1.2-1.1.4).

There is a high prevalence of depression in the tinnitus population.[1] Severe depression may be associated with suicidal ideations. A small number of people with tinnitus do die by suicide; however, the committee acknowledged assessing suicide risk is very difficult and complex. In discussing the balance between levels of risk and duty of care to a patient the committee concluded that people who present to any healthcare setting (for example, general practice) with tinnitus and symptoms and features that indicate a high risk of suicide (e.g. suicidal ideation with an expression of intent) should be red flags that trigger onward referral to a crisis mental health management team (including children and adolescent mental health services (CAMHS) immediately for assessment to preserve life. The committee also agreed that healthcare professionals should ensure that these individuals are kept safe whilst waiting for an assessment.

If tinnitus is associated with a sudden onset of significant neurological symptoms such as facial weakness, a referral to be seen within 24 hours (e.g. to accident and emergency (A&E) should be made as such symptoms can indicate stroke, cerebrovascular event or rapid tumour enlargement which can be life-threatening and increase morbidity. Similarly if an individual with tinnitus presents with a first episode of uncontrolled vestibular symptoms they should be referred immediately. The committee noted that this will ensure that underlying neurological causes are diagnosed. This should be in line with the NICE guideline on suspected neurological conditions and/or NICE guideline on stroke and transient ischaemic attack in over 16s. The committee noted that it is important that assessment and management for tinnitus is provided following onward referral for other co-morbidities (for example suspected stroke). The committee agreed that it was appropriate for the tinnitus referral recommendations from the NICE guideline on hearing loss and NICE guideline on stroke and TIAs to also apply to children and young people, even though the guidelines apply to adults. This is because the same clinical manifestations will be considered for referral. However, children would be seen in child-friendly settings.

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The committee agreed that objective tinnitus that is persistent should be investigated as a non-urgent referral in services such as ENT or audiology. In most cases, persistent tinnitus is less likely to be associated with severe medical conditions. However, as this is not always the case (e.g. vestibular schwannoma), the committee agreed that investigations are needed. Non-urgent referrals for persistent pulsatile tinnitus and persistent unilateral tinnitus are in line with the NICE guideline on hearing loss in adults. These types of tinnitus may be associated with vascular or neurological abnormalities. Detection of these abnormalities may prevent the development of significant pathologies such as vestibular schwannoma.

Tinnitus can have a negative impact on mental health. Tinnitus can be particularly distressing and may impact on daily activities (for example, sleep). Adults, children and young people should be asked about their thoughts and feelings about the tinnitus and the impact on their daily life. When assessing tinnitus in children it is suggested to discuss this with both the child and their carers. When tinnitus-related distress is affecting mental wellbeing (for example distress that prevents them carrying out their usual daily activities such as leaving their house or going to work) even after receiving tinnitus support at first point of contact with a healthcare professional, urgent referrals should be made (to be seen within 2 weeks).

The committee recognised that the provision of information, reassurance and discussion about an individual's experiences with tinnitus are critical for the management of tinnitus, especially at the first contact with healthcare professionals (evidence reviews A and B). After receiving reassurance and tinnitus support, people with tinnitus may be able to cope with tinnitus better, leading to improved mental wellbeing. However, if individuals still find that their tinnitus is bothersome but does not significantly impact mental health, healthcare professionals in general practice should initiate a referral for non-urgent specialist treatment (such as a referral to a tinnitus informed psychology service). Some symptoms and features healthcare professionals should look out for when assessing children and young people for bothersome tinnitus include: listening difficulties, difficulties at school, sleep difficulties, emotional distress (moody, sad/depressed, angry, stressed and anxious), worried/cross/sad about or reluctant to talk about the tinnitus. Similar symptoms and features can be used for adults with tinnitus.

No referral was considered necessary for people with bilateral symmetrical tinnitus that is not bothering them.

It is important that a thorough assessment is undertaken, including an assessment of clinical history and physical examination. This will enable management of potential underlying pathology and to sign post accurately for further assessment and management. The overarching aim is to ensure a person suffering from tinnitus experiences a high standard of

care tailored to the individual's needs. Prognosis of their tinnitus or their underlying general medical problems can be greatly affected if delay occurs.

1.5.2 Cost effectiveness and resource use

There were no economic evaluations available for this review question. The recommendations would not result in an increase in expenditure because the committee agreed that everyone with the symptoms listed in these recommendations would currently eventually receive specialist assessment and care. However, the committee noted that it was important to consider the potential cost-consequences that may be placed on the NHS in the short term if there are too many unnecessary immediate referrals to be seen within 24 hours and urgent referrals (seen within two weeks). The decision framework the committee used to distinguish between these referrals was to establish whether failing to deal with the symptoms within particular time periods could result in increased morbidity, irreversible changes to a person's health status or even death. For example, the committee have limited immediate referrals to a crisis mental health management team for people with tinnitus associated with a high risk of suicide for assessment to preserve life. The committee also made recommendations for referrals within a maximum of 24 hours and urgent referrals (within 2 weeks) for groups where prompt referrals could lead to better long-term health outcomes and possibly reduced later expenditure associated with avoidable complications.

Finally, those symptoms which still warranted further specialist care, but where a longer delay in referral (beyond 2 weeks) would not result in changes to the final health outcomes, the committee opted for these people to be seen via the standard referral pathway. In summary, the recommendations will give rise to equivalent costs in specialist services, potentially reduce future costs to other services and result in the same if not better health outcomes. The committee therefore expect these recommendations to be cost neutral or even cost-saving over a longer time horizon compared with current practice.

1.5.3 Other factors the committee took into account

The committee noted that there is variation in tinnitus pathways across the UK and agreed to not recommend specific locations for urgent and non-urgent referrals. The recommendations should be followed in line with local pathways. The committee also noted that there are differences in the availability and composition of psychological services across the UK to support people with tinnitus that is causing distress. There are also differences in the availability of audiovestibular services; audiovestibular services are not available in Northern Ireland. Additionally, as per NHS values, multidisciplinary working particularly between psychology and audiology should be encouraged by organisations.

The committee noted that children should be seen in a paediatric environment by healthcare professionals used to managing the needs of children and working in the children's support services (in health, education and social care).

The Department of Health produced guidance on "Provision of Services for Adults with Tinnitus: A Good Practice Guide" which can be adapted to cover all people presenting with tinnitus where reasonable.[2] As a baseline, a person presenting with tinnitus should have their symptom clarified. Tinnitus is the perception of a sound such as ringing, buzzing, whishing or swooshing in either one or both ears or in the head in the absence of a concurrent external noise which might explain the perception [2].

The committee discussed the management of people in general practice whilst they are waiting to be seen by a specialist. The committee noted that general practice physicians are encouraged to conduct thorough consultations with people with tinnitus, including a medication review, management of earwax, measurement of blood pressure and assessment for underlying depression and anxiety.[4]

The committee discussed the importance of ensuring that general practice physicians are sufficiently trained during general practice training and medical school training on the management of tinnitus. This would enable overall better care for people with tinnitus.

References

1. Bhatt JM, Bhattacharyya N, Lin HW. Relationships between tinnitus and the prevalence of anxiety and depression. Laryngoscope. 2017; 127(2):466-469

2. Department of Health. Provision of services for adults with tinnitus: A good practice guide. Department of Health, 2009. Available from: https://webarchive.nationalarchives.gov.uk/20130124045237/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_093810.pdf

3. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [Updated October 2018] London. National Institute for Health and Care Excellence, 2014. Available from: https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview

4. National Institute for Health and Care Excellence. Tinnitus. NICE Clinical Knowledge Summary National Institute for Health and Care Excellence, 2017. Available from: https://cks.nice.org.uk/tinnitus#!scenario

Appendices

Appendix A: Review protocols

Table 3: Review protocol: Symptoms and features that indicate the need for urgent investigation and/or management

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	Symptoms and features that should indicate the need for urgent investigation and/or management
2.	Review question	Which symptoms and features should indicate the need for urgent investigation and/or management?
3.	Objective	The review aims to identify symptoms and features that should prompt onward referral for further investigation
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 Other searches: • None

		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: People presenting to a healthcare setting with tinnitus Exclusion: None
7.	Intervention/Exposure/Test	Symptoms and features • Sudden onset pulsatile tinnitus. • Tinnitus in association with sudden onset of significant neurological symptoms and/or signs (for example facial weakness). • Tinnitus associated with acute vertigo. • Tinnitus secondary to recent head trauma. • Sudden onset unilateral tinnitus • Tinnitus associated with a sudden onset hearing loss • Tinnitus associated with suicidal ideations • Tinnitus associated with significant mental health impact • Tinnitus associated with marked distress • Tinnitus associated with self-harm
8.	Comparator/Reference standard/Confounding factors	Reference standard: • Cerebrovascular disease • Hypertension • Neoplasm • Skull base tumours

		• Vascular lesions • Vestibular schwannoma (Acoustic Neuroma) • Cerebellopontine angle tumour • Glomus tumour • Mental health conditions
9.	Types of study to be included	• Diagnostic accuracy study (2-gate studies will be excluded unless no other data are available from single gate-studies) • Systematic reviews of diagnostic accuracy studies
10.	Other exclusion criteria	Studies that do not report sensitivity and specificity, or insufficient data to derive these values. Non-English language studies.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	• Sensitivity • Specificity • Positive predictive value • Negative predictive value • ROC curve or area under the curve • Adjusted odds ratios
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

		The full text of these potentially eligible studies will be retrieved and assessed in line with the criteria outlined above. A standardised form will be used to extract data from the included studies (see Developing NICE guidelines: the manual section 6.4). Data extraction will be independently quality assured by a second reviewer, discrepancies will be identified and resolved through discussion (with a third party where necessary).
15.	Risk of bias (quality) assessment	Risk of bias quality assessment will be assessed using QUADAS-2. Assessment will be independently quality assured by a second reviewer. Disagreements between the reviewers will be resolved by discussion, with involvement of a third party where necessary.
16.	Strategy for data synthesis	Where possible data will be meta-analysed where appropriate (if at least 3 studies reporting data at the same diagnostic threshold) in WinBUGS. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. Particular attention will be placed on specificity determined by the committee to be the primary outcome for decision making. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.
17.	Analysis of sub-groups	None
18.	Type and method of review	☐ Intervention ☒ Diagnostic

		☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	27/06/2018		
22.	Anticipated completion date	11/03/2020		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) 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. [Add in any additional agree dissemination plans.]
32.	Keywords	Tinnitus, symptoms, features, referral, investigation, management
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

Table 4: Review protocol: Symptoms and features that indicate the need for non-urgent specialist treatment

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	Symptoms and features that should indicate the need for non-urgent specialist treatment
2.	Review question	Which symptoms and features should indicate the need for non-urgent specialist treatment?
3.	Objective	The review aims to identify symptoms and features that should prompt onward referral for specialist treatment
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language Other searches: • None The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Tinnitus

6.	Population	Inclusion: People presenting to a healthcare setting with tinnitus Exclusion: None
7.	Intervention/Exposure/Test	Symptoms and features • Tinnitus associated with persistent otalgia or otorrhoea that doesn't resolve with routine treatment • Tinnitus with vestibular symptoms (for example dizziness, vertigo). • Tinnitus that is bothersome or causing distress • Objective or pulsatile tinnitus. • Unilateral tinnitus • Tinnitus associated with unilateral or asymmetric hearing loss. • People with tinnitus and normal peripheral hearing, but difficulty hearing in noisy backgrounds, or with sound localisation, or difficulty following complex auditory directions; • People with tinnitus associated with non-otological conditions: – systemic, e.g. cardiovascular, endocrine or metabolic disorders – neurological, e.g. multiple sclerosis, head injury, whiplash
8.	Comparator/Reference standard/Confounding factors	Reference standard: Conditions or symptoms amenable to specialist treatment e.g.: • Meniere's disease • Middle ear infection • Otitis externa • Cholesteatoma

		• Cochlear, retrocochlear or other central nervous system disorders • Tinnitus that is causing distress
9.	Types of study to be included	• Diagnostic accuracy study (2-gate studies will be excluded unless no other data are available from single gate-studies) • Systematic reviews of diagnostic accuracy studies
10.	Other exclusion criteria	Studies that do not report sensitivity and specificity, or insufficient data to derive these values. Non-English language studies.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	• Sensitivity • Specificity • Positive predictive value • Negative predictive value • ROC curve or area under the curve • Adjusted odds ratios
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of these potentially eligible studies will be retrieved and assessed in line with the criteria outlined above.

		A standardised form will be used to extract data from the included studies (see Developing NICE guidelines: the manual section 6.4). Data extraction will be independently quality assured by a second reviewer, discrepancies will be identified and resolved through discussion (with a third party where necessary).
15.	Risk of bias (quality) assessment	Risk of bias quality assessment will be assessed using QUADAS-2. Assessment will be independently quality assured by a second reviewer. Disagreements between the reviewers will be resolved by discussion, with involvement of a third party where necessary.
16.	Strategy for data synthesis	Where possible data will be meta-analysed where appropriate (if at least 3 studies reporting data at the same diagnostic threshold) in WinBUGS. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. Particular attention will be placed on specificity determined by the committee to be the primary outcome for decision making. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.
17.	Analysis of sub-groups	None
18.	Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery

		☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	27/06/2018		
22.	Anticipated completion date	11/03/2020		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) 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 reviewer] • 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. [Add in any additional agree dissemination plans.]
32.	Keywords	Tinnitus, symptoms, features, referral, investigation, management
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

Table 5: 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). [3] **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.

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.[3]

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 6: 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

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

Cochrane Library (Wiley) search terms

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

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 7: 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)

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.

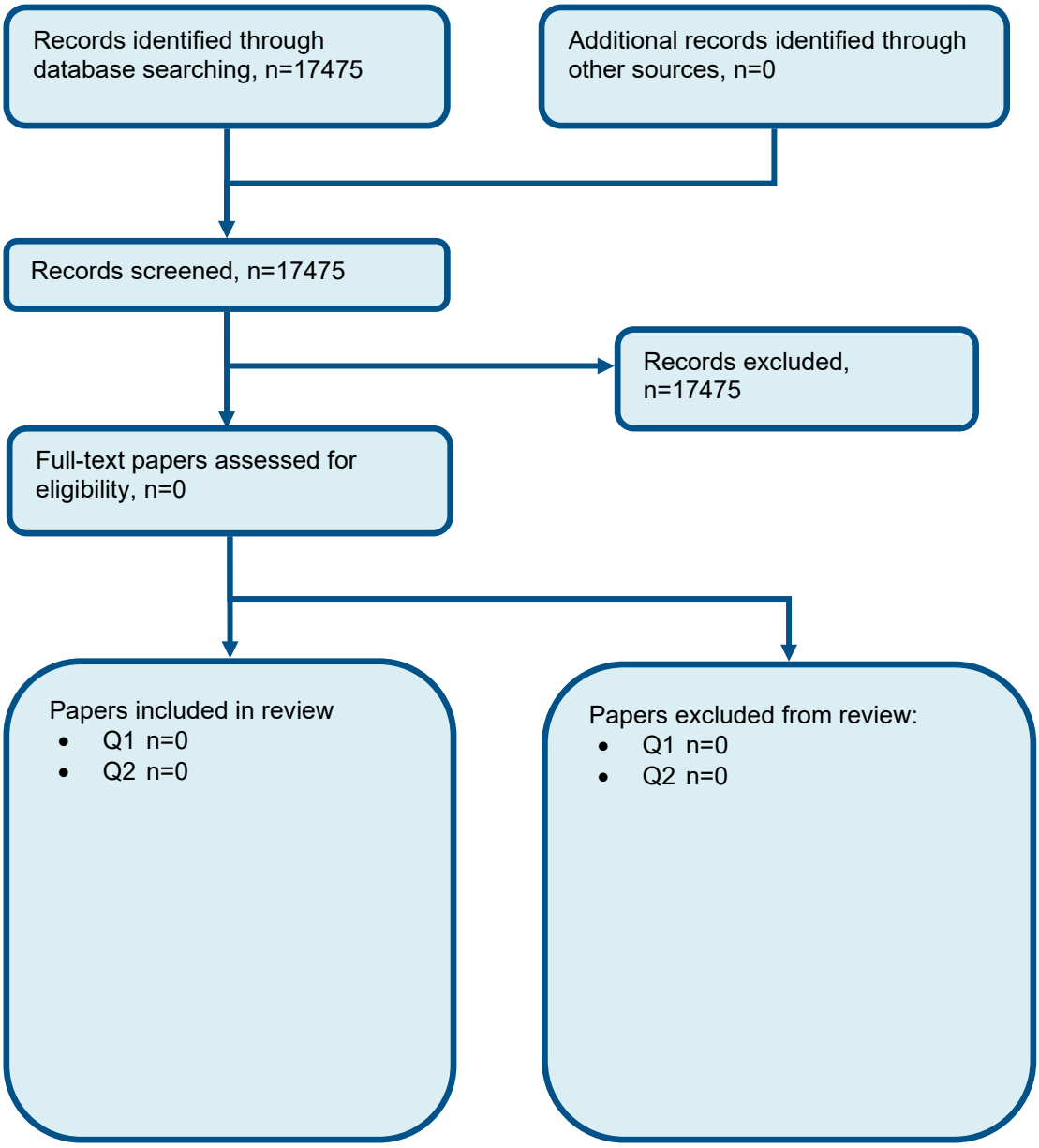
47.	(health* year* equivalent* or hye or hyes).ti,ab.
48.	discrete choice*.ti,ab.
49.	rosser.ti,ab.
50.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
51.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
52.	(sf20 or sf 20 or short 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

NHS EED and HTA (CRD) search terms

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

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of (1) which symptoms and features should indicate the need for urgent investigation and/or management (2) which symptoms and features should indicate the need for non-urgent specialist treatment



Appendix D: Clinical evidence tables

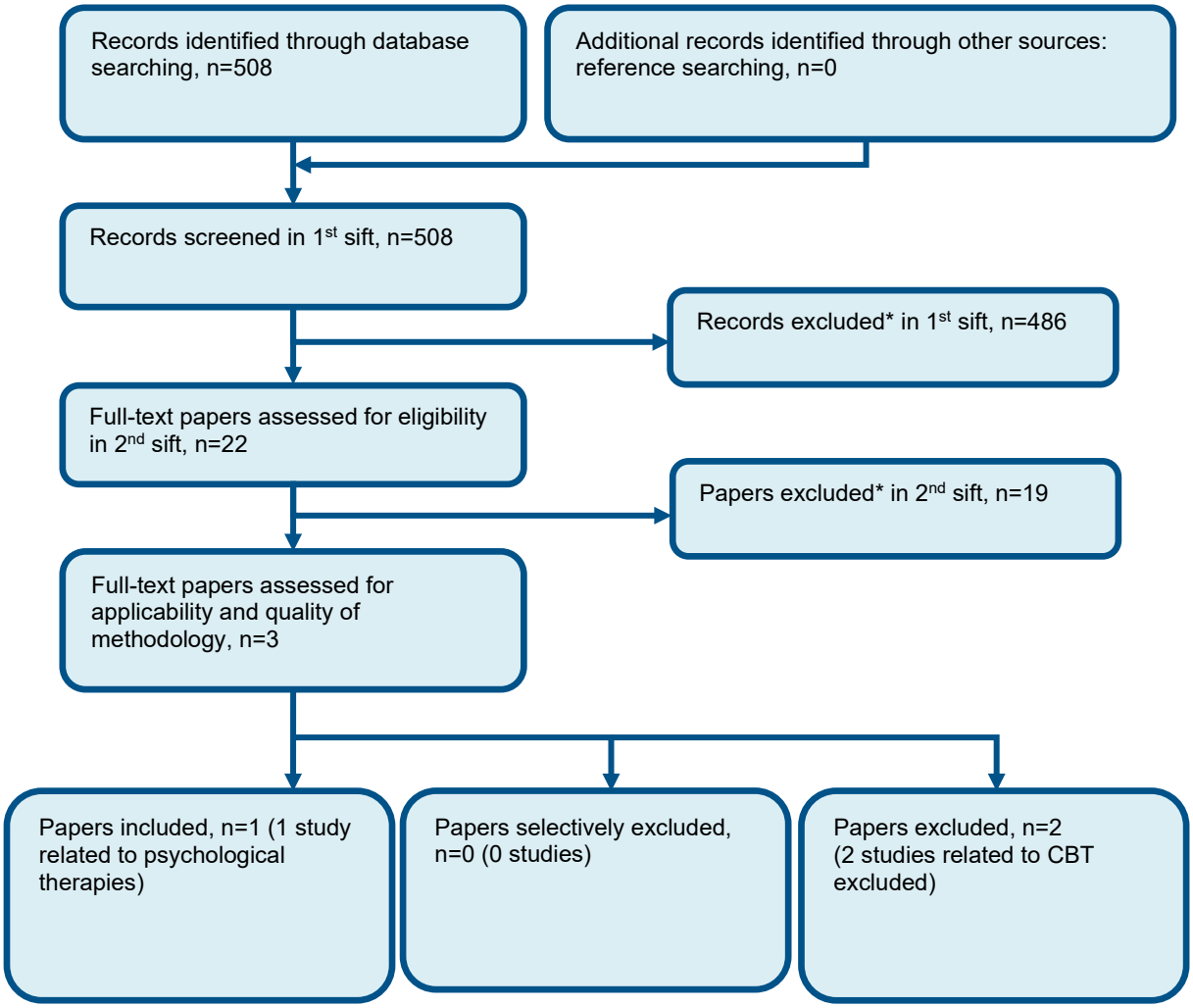
No evidence identified.

Appendix E: Coupled sensitivity and specificity forest plots and ROC curves

No evidence identified.

Appendix F: 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 G: Excluded studies

G.1 Excluded clinical studies

Whilst screening the records, the reviewer did not identify any papers that were suitable for review. No full-text papers were assessed for eligibility for both of the evidence review questions in this chapter.

G.2 Excluded health economic studies

None.