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

| ID | Field | Content |
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| 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.<br><br>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:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE |

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

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

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| | | • Tolerability<br>• 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.<br><br>The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above.<br><br>10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.<br><br>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.<br><br>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.<br><br>For Intervention reviews the following checklist will be used according to study design being assessed:<br><br>• Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)<br>• Randomised Controlled Trial: Cochrane RoB (2.0) |

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| | | 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.<br><br>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.<br><br>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.<br><br>Publication bias is tested for when there are more than 5 studies for an outcome.<br>Other bias will only be taken into consideration in the quality assessment if it is apparent.<br><br>Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.<br><br>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<br>• Hearing loss<br>• Neurological features (e.g. double vision, |

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| | | dysarthria, ataxia, vertigo/dizziness, facial palsy)<br>• Vascular risks (e.g. hypertension and hypercholesterolaemia) | | |
| 18. | Type and method of review | ☐ Intervention<br>☐ Diagnostic<br>☐ Prognostic<br>☐ Qualitative<br>☐ Epidemiologic<br>☐ Service Delivery<br>☒ Other – diagnostic test and treat | | |
| 19. | Language | English | | |
| 20. | Country | England | | |
| 21. | Anticipated or actual start date | 27/06/18 | | |
| 22. | Anticipated completion date | 11/03/20 | | |
| 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) | ☐ | ☑ |

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| | | assessment | | |
| | | Data analysis | ☐ | ☑ |
| 24. | Named contact | 5a. Named contact<br>National Guideline Centre<br><br>5b Named contact e-mail<br>Tinnitus@nice.org.uk<br><br>5e Organisational affiliation of the review<br>National Institute for Health and Care Excellence (NICE) and the National Guideline Centre | | |
| 25. | Review team members | From the National Guideline Centre:<br>• Dr Jennifer Hill [Guideline lead]<br>• Ms Sedina Lewis/Ms Julie Neilson [Senior systematic reviewers]<br>• Dr Richard Clubbe [Systematic reviewer]<br>• Mr David Wonderling [Health economist lead]<br>• Mr Emtiyaz Chowdhury [Health economist]<br>• Ms Jill Cobb [Information specialist]<br>• 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. | | |

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| 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:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• 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<br>☒ Completed but not published<br>☐ Completed and published<br>☐ Completed, published and being updated<br>☐ Discontinued |
| 35.. | Additional information | N/A |
| 36. | Details of final publication | www.nice.org.uk |