NETSCC, HTA

31 March 2010

09/68/01 HTA TAR

Revised Protocol

February 2010

1. Title of the project:
Routine echocardiography in the management of stroke and transient ischemic attack (TIA)

2. Name of TAR team and project 'lead'
TAR team: ScHARR Technology Appraisal Group, University of Sheffield

Project lead: Rachel Jackson, Research Fellow, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA
Email: R.Jackson@Sheffield.ac.uk, Tel: 0114 222 0793, Fax: 0114 272 4095

Address for correspondence
All correspondence should be sent to the project lead (R.Jackson@Sheffield.ac.uk), the project administrator (Gill Rooney, G.Rooney@Sheffield.ac.uk) and the managing director of ScHARR-TAG (Eva Kaltenthaler, E.Kaltenthaler@Sheffield.ac.uk).

3. Plain English Summary
Stroke is a serious medical condition in which the blood supply to the brain is disrupted, potentially resulting in disability and mortality. The World Health Organisation defined stroke as 'rapidly developing clinical signs of focal (sometimes global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin' (Hatano, 1976). Symptoms of stroke include numbness, disrupted vision, slurred speech, confusion and headache (Stroke Association, 2009). There are two major types of stroke: ischaemic stroke, in which the blood supply is disrupted due to a narrowing or blockage of the circulatory system; and haemorrhagic stroke, in which blood loss in the brain causes neurological damage. Transient ischaemic attack (TIA) has been defined as 'a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia, without acute infarction' (Easton *et al.*, 2009). In a transient ischaemic attack, symptoms typically subside within a few hours (Stroke Association, 2009). However, people who have experienced a TIA have a high risk of stroke following the event (Coull *et al.*, 2004) and therefore should receive prompt medical attention.

It is estimated that approximately 110,000 people experience a stroke and a further 20,000 individuals have a TIA in England each year (National Audit Office, 2005). It has been reported that 10-15% of TIA patients experience a stroke within 3 months (Easton *et al.*, 2009). Over 56,000 deaths were attributable to stroke in England and Wales in 1999, representing 11% of total deaths for this period (Mant *et al.*, 2004). Stroke places a considerable burden on the economy in England, resulting in direct costs to the NHS of £2.8 billion (Mant *et al.*, 2004).

The identification of the origin of a stroke or TIA can inform treatment and secondary prevention strategies. Embolism of cardiac origin has been estimated to account for approximately 20% of ischaemic strokes (Palacio & Hart, 2002). Imaging technologies such

as transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE) facilitate the detection of potentially-treatable cardiac sources of stroke and TIA. Of the two methods, transthoracic echocardiography is less invasive. Both of these imaging methods are capable of detecting a number of potential cardiac sources of stroke and TIA, including left ventricular/left atrial thrombus (which can be treated by anticoagulation with warfarin), cardiomyopathy (treatable with warfarin or antiplatelet therapy), and patent foramen ovale / atrial septal aneurysm (treatable by anticoagulation, surgical closure, antiplatelet therapy, or by observation) (Yu *et al.*, 2009).

No recommendations relating to the use of echocardiography in the assessment of newly diagnosed stroke and TIA patients were made within the national clinical guidelines for stroke published by the Royal College of Physicians (2004), the NICE stroke clinical guideline (NICE, 2008) or the National Stroke Strategy (Department of Health, 2007). The use of this technology in the management of stroke and TIA patients in the UK appears to be variable. The British Society of Echocardiography stated that echocardiography was indicated in adult cases of neurological disease in several instances including: a) unexplained stroke or TIA without evidence of prior cerebrovascular disease or without significant risk factors for other cause (with the suggestion that saline contrast echocardiography by TTE or TOE be used), and b) in patients for whom a therapeutic decision will depend on the outcome of echocardiography (eg. anticoagulation). This guidance also stated that echocardiography was not indicated in patients in whom echocardiography would not affect the decision to begin anticoagulation (eg. patients in atrial fibrillation with cerebrovascular event and no suspicion of structural heart disease).

McNamara *et al.* (1997) found in their US-specific cost effectiveness analysis that transthoracic echocardiography (either alone or in sequence with transoesophageal echocardiography) was not cost effective compared with transoesophageal echocardiography. The 2007 update of the 2002 Agency for Healthcare Research and Quality (AHRQ) assessment (Meenan *et al.*, 2007) found that current cost effectiveness evidence was insufficient to justify widespread use of echocardiography in stroke patients in the United States.

The aim of this assessment is to explore the use of transthoracic echocardiography in the assessment of stroke and TIA patients in a UK context.

A related assessment is currently being undertaken by the TAR team in Sheffield entitled ‘Echocardiography in newly diagnosed atrial fibrillation patients’ (08/45/01).

4. Decision problem

4.1 Purpose of assessment

The aim of this assessment is to answer the following research question: What is the clinical and cost effectiveness of the addition of an echocardiogram to the routine assessment of patients who have had a stroke or transient ischaemic attack (TIA) in the UK?

4.2 Clear definition of the intervention

Transthoracic echocardiography (TTE) is an ultrasound imaging technique utilising beams of sound transmitted at frequencies of 2.5-5 MHz. A transducer is placed on the chest, allowing the structures of the heart and velocity of blood flow to be visualised (Patient UK, 2009). TTE may be used to determine cardiac sources of stroke or TIA and facilitate treatment and secondary prevention strategies.

4.3 Place of the intervention in the treatment pathway(s)

The assessment will investigate the effects of undertaking TTE in the routine assessment of all newly diagnosed stroke and TIA patients in secondary care. Typically, once a stroke has been established as being ischaemic in nature via brain imaging (CT or MRI scanning),

further imaging technologies may then be employed to determine the underlying aetiology of the episode and inform patient management. If data are available, the cost effectiveness of performing TTE in specific population subgroups will be determined.

4.4 Relevant comparators

Current UK diagnostic protocol (to be identified by researchers). As data available on current practice within the UK from clinical guidelines and the existing literature are limited, we propose to collect information on current UK diagnostic protocols. Managing staff at stroke units across the UK will be approached and a copy of any current stroke diagnostic protocol(s) will be requested. Clinical advisors to the team will be involved in the identification of an appropriate sample. If necessary, professional bodies may be requested to further advise on recruitment. Following collection of diagnostic protocols, the comparator will then be selected in conjunction with clinical advisors. Comparators may include transoesophageal echocardiography, 24 hour Holter monitoring or cardiac monitoring via telemetry (used alone or in combination with TTE and each other).

4.5 Population and relevant subgroups

Patients who have had an ischaemic stroke or TIA (but have no other indication for a TTE) (NB: Echocardiography in newly diagnosed atrial fibrillation patients is being considered in a separate Health Technology Assessment). If data are available, the effectiveness of performing TTE in specific population subgroups (eg. by age, ethnicity) will be described. Such subgroups are to be defined following the completion of Review 1.

4.6 Key factors to be addressed

The objectives of the review are:

1) To investigate by systematic review the prevalence of cardiac sources of stroke and TIA (limited to those detectable by TTE) (Review 1)

2) To investigate by systematic review the diagnostic accuracy of TTE for these cardiac sources (Review 2)

3) To estimate the potential benefits and harms arising from the alteration of treatment based on results of TTE

4) To estimate the incremental cost effectiveness of providing routine TTE to all newly diagnosed stroke and TIA patients in secondary care

5) To estimate the incremental cost effectiveness of providing routine TTE to subgroups within the newly diagnosed stroke and TIA patient population in secondary care (where data are available). Subgroups are to be defined based on the findings of Review 1.

5. Report methods for synthesis of evidence of clinical effectiveness

5.1 Description of reviews

Two systematic evidence reviews (Review 1: Prevalence of cardiac sources of stroke and TIA; Review 2: Diagnostic accuracy of TTE for cardiac sources of stroke and TIA) will be undertaken informed by the general principles recommended in the PRISMA (formerly QUOROM) statement (Moher *et al.,* 2009).

<u>Review 1: Prevalence of cardiac sources of embolism in stroke and TIA</u>

Prevalence of cardiac sources of embolism in stroke and TIA will be investigated using epidemiological studies. Cardiac sources will be restricted to those identifiable by TTE. These include left ventricular/left atrial thrombus, patent foramen ovale and atrial septal aneurysm (Yu *et al.,* 2009). It is proposed that conditions that may be associated with cardioembolic stroke such as recent myocardial infarction, dilated cardiomyopathy, infective endocarditis and atrial fibrillation be excluded since they are typically clinically apparent without echocardiography or are present with symptoms that represent other indications for echocardiography (as per Meenan *et al.,* 2007).

Review 2: Diagnostic accuracy of TTE for cardiac sources of embolism in stroke and TIA

Diagnostic accuracy of TTE will be investigated using studies comparing the identification of cardiac sources of stroke or TIA by TTE with other diagnostic tools. Outcomes relating to screening performance will be described. TTE may be compared against a diagnostic gold standard or alternative imaging method for the detection of cardiac sources of stroke or TIA (eg. transoesophageal echocardiography) within the literature. To inform the economic evaluation, these will need to be synthesised into a consistent evidence base. Studies relating to the prognostic value of TTE (ie. the ability of TTE results to predict subsequent stroke or TIA outcomes) will also be identified. A structured search defined on ad hoc criteria will be undertaken to identify adverse events as a result of the tests under study. Whilst no physical harms appear to be associated with the use of transthoracic echocardiography, there is the potential for the occurrence of adverse events as a result of local anaesthetic or sedation procedures used during the insertion of the transducer probe in transoesophageal echocardiography. Furthermore, patient harms may result as a consequence of diagnostic inaccuracies and resulting inappropriate care.

5.2 Identifying and systematically reviewing clinical effectiveness evidence

Population

The population will be the same for both reviews

Inclusion

Newly diagnosed ischaemic stroke and TIA patients

Interventions

Transthoracic echocardiography (TTE) in the routine assessment of newly diagnosed stroke and TIA patients in secondary care

Comparators

Current UK diagnostic protocol (to be identified by researchers). Clarification of the care pathway and current UK diagnostic practice is required. As data available on current practice within the UK from clinical guidelines and the existing literature are limited, we propose to collect information on current UK diagnostic protocols. Managing staff at stroke units across the UK will be approached and a copy of any current stroke diagnostic protocol(s) will be requested. Clinical advisors to the team will be involved in the identification of an appropriate sample. If necessary, professional bodies may be requested to further advise on recruitment. Following collection of diagnostic protocols, the comparator will then be selected in conjunction with clinical advisors. Comparators may include transoesophageal echocardiography, 24 hour Holter monitoring or cardiac monitoring via telemetry (used alone or in combination with TTE and each other).

Search strategy

The search strategy for both reviews will comprise the following main elements: searching of electronic databases; contact with experts in the field; scrutiny of bibliographies of retrieved papers. The electronic databases to be searched will include MEDLINE; Medline in Process (for latest publications); EMBASE; Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, CINAHL, DARE, NHS EED and HTA databases; NHS EED; NIHR Clinical Research Network Portfolio database, NRR (National Research Register) Archive, Web of Science Proceedings, Science Citation Index; Current Controlled Trials, Clinical Trials.gov, FDA website, EMEA website, and relevant conference proceedings.

The draft search strategy is presented in Appendix 1.

Study selection

In both reviews, citations will be imported into reference management software and screened for inclusion. The following publication types will be excluded: studies which are only published in languages other than English; studies based on animal models; preclinical and biological studies; narrative reviews, editorials, opinions; and reports published as meeting abstracts only (where insufficient methodological details are reported to allow critical appraisal of study quality). Titles and abstracts will be examined for inclusion by one reviewer. Two reviewers will independently make decisions on inclusion of studies at full text stage and any discrepancies resolved by discussion.

Data extraction strategy

In both reviews, data will be extracted independently by one reviewer (with no blinding to authors or journal) using a standardised form and checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Quality assessment strategy

Quality assessment will be subject to the types of studies identified but will be undertaken using appropriate and established tools (eg. checklists specifically designed for quality assessment of diagnostic studies such as the QUADAS checklist (QUality Assessment of Diagnostic Accuracy Studies; Whiting *et al.*, 2003, see Appendix 2)). The quality assessment of epidemiological studies is likely to be based on the STROBE statement (Elm *et al.*, 2007) (see Appendix 2). Quality assessment will be confirmed by a second reviewer.

Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. For the review of diagnostic accuracy of TTE in the detection of cardiac sources of stroke or TIA, we will combine data to provide pooled estimates of diagnostic performance where appropriate.

Further information needed

Further clinical data needed for economic modelling will be sought from clinical guidelines and advice from clinical experts. If a large group of data are required, non systematic searches may be undertaken. If studies of prognostic accuracy (ie. the ability of TTE to predict later outcomes in stroke and TIA) are not available, it may be necessary to find data on the risk of later events arising from each clinically important pathology. In considering how each clinically important pathology is treated, details of current NHS practice and data on the benefits and harms of these treatments in the relevant population will be required.

6. Report methods for synthesising evidence of cost effectiveness

6.1 Identifying and systematically reviewing published cost effectiveness studies

The sources detailed in section 5 will be used to identify studies of the cost effectiveness of TTE in the management of newly diagnosed stroke and TIA patients. An economic search filter will be incorporated into the search strategy to identify relevant studies. Identified economic literature will be critically appraised and quality assessed using the critical appraisal checklist for economic evaluations proposed by Drummond *et al.* (2005). Existing cost effectiveness analyses will also be used to identify sources of evidence to inform structural modelling assumptions and parameter values for the economic model.

6.2 Development of a health economic model

A *de novo* economic evaluation of the cost effectiveness of TTE in the assessment of newly diagnosed stroke and TIA patients in secondary care will be conducted. A model will be developed to identify whether the routine testing of all patients (who do not already have an indication for TTE) would result in more cost effective treatment of patients with stroke and TIA compared with current practice. Cost effectiveness modelling will take account of

potential benefits and harms of altered treatment, and (if data allow) will identify any subgroups of patients in whom TTE is most likely to be cost effective.

The primary outcome from the model will be an estimate of the incremental cost per additional quality-adjusted life year (QALY) gained associated with the use of TTE in the assessment of newly diagnosed stroke and TIA patients. A lifetime time horizon will be used in order to reflect the chronic effects of stroke and the ongoing risk of further cerebrovascular events and potential mortality. The perspective used will be that of the National Health Services and Personal Social Services. Costs and QALYS will be discounted at 3.5% as recommended in current guidelines (NICE, 2008). Modelling assumptions will be taken from the literature, supplemented by clinical expert opinion where required.

The ScHARR modelling team have published papers using different modelling techniques (such as discrete event simulation (Stevenson *et al.,* In press a; Stevenson *et al.,* In press b; Michaels *et al.,* 2009), transition state modelling (Wardlaw *et al.,* 2009) and meta-modelling (Stevenson *et al.,* 2004)). The model structure and software used to construct the model will be determined following data collection in order that the most appropriate technique is used for this particular assessment. Clinical experts will be consulted at the conceptual stage to ensure that the structure of the model is appropriate to clinical practice. The model will include estimates of the effects of TTE on the management of different types of stroke and TIA patients, as well as costs of intervention and subsequent downstream costs associated with appropriate and inappropriate care. If data allow, this approach will enable an analysis of whether the cost effectiveness of the use of TTE in the routine assessment of stroke and TIA patients differs between patient groups.

Ideally, health related quality of life evidence will be available directly from the review literature. In the absence of such evidence, the mathematical model may use indirect evidence on quality of life from alternative sources. Quality of life data will be reviewed and used to generate the quality adjustment weights required for the model. In addition to the reviewed literature, national sources (eg. NHS reference costs (Department of Health), national unit costs (Curtis, 2008), British National Formulary (http://bnf.org)) will be used to estimate resource use and costs for use in the economic model.

It is anticipated that there may be limited evidence for some of the parameters that will be included in the economic model. Therefore, the uncertainty around the parameter estimates will be modelled to take this into account. The uncertainty in the central value for each required parameter will be represented by a distribution, enabling probabilistic sensitivity analysis to be undertaken. This will allow an assessment of the uncertainty to be made. If resources allow, the cost effectiveness of collecting further information will be explicitly explored using Expected Value of Sample Information techniques (Stevenson *et al.,* In Press; Stevenson & Lloyd-Jones, In Press).

7. Expertise in this TAR team

TAR centre

The School of Health and Related Research (ScHARR) is one of the four Schools that comprise the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical and health-related disciplines, including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research, and information science. The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the effectiveness and cost effectiveness of healthcare interventions for the NHS R&D Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Clinical Excellence.

Team members' contributions

Rachel Jackson (Research Fellow, ScHARR) has experience in systematic reviews of health technologies. She will act as the project lead and lead reviewer on this assessment. She has compiled the study protocol.

Sophie Whyte (Research Associate, ScHARR) has experience in cost-effectiveness analysis. She will undertake the review of cost effectiveness evidence and development of the cost effectiveness model.

Munira Essat (Research Associate, ScHARR) will assist in the systematic reviewing of clinical evidence.

Angie Rees (Information Specialist, ScHARR) is experienced in conducting searches for health technology assessments. She will develop the search strategy and undertake the electronic literature searches.

Matt Stevenson (Senior Research Fellow, ScHARR) assisted in the drafting of the study protocol. He will provide support to the cost effectiveness modelling where appropriate and will oversee the project.

Clinical advisors (including echocardiography and stroke specialists) have been approached by the research team and are to be confirmed.

8. Competing interests of authors

None

9. Timetable/milestones

Milestone	Date
Draft protocol	30th October 2009
Final protocol	5h February 2010
Progress report	29th April 2011
Assessment report	31st May 2011

10. Appendices

Appendix 1. Draft search strategy

Review 1: Prevalence of cardiac sources of stroke and transient ischaemic attack

1. Stroke
2. Cerebrovascular accident
3. Cerebrovascular event
4. Transient ischaemic attack
5. TIA
6. vascular accident.mp.
7. cva.mp.
8. stroke.mp.
9. or/1-8
10. Cardiac source$
11. Cardiac origin$

12. Cardioemboli$
13. Cardiogenic
14. Patent foramen ovale
15. Atrial thromb$/clot$
16. Ventricular thromb$/clot$
17. Cardiac thromb$/clot
18. Cardiac embol$
19. Cardiomyopath$
20. Hypertroph$
21. Atrial sept$
22. Cardiac mass$
23. Cardiac vegetation$
24. Endocarditis
25. or/10-24
26. 9 and 25
27. Exp Epidemiologic studies
28. Exp Epidemiology
29. epidemiology.tw
30. Exp Prevalence
31. prevalence.ti
32. Exp Incidence
33. incidence.ti
34. ep.fs
35. or/27-34
36. 26 and 35

Review 2: Diagnostic accuracy of TTE for cardiac sources of embolism in stroke and TIA

1. Stroke$
2. Cerebrovascular accident$
3. Cerebrovascular event$
4. Transient ischaemic attack$
5. TIA$
6. vascular accident.mp.
7. cva.mp.
8. stroke.mp.
9. or/1-8
10. Echocardiography

11. Transthoracic echocardiography
12. TTE
13. Transoesophageal echocardiography
14. Transesophageal echocardiography
15. TOE
16. TEE
17. 24/Twenty four h$ Holter
18. Telemetr$
19. Secondary prevention
20. Cardiac imag$
21. or/10-20
22. Exp sensitivity and specificity
23. Sensitivity.tw
24. Specificity.tw
25. ((pre-test ot pretest) adj probability).tw
26. Post-test probability
27. Predictive value$.tw
28. Likelihood ratio$
29. exp diagnosis/
30. di.fs.
31. diagnos$.tw.
32. exp predictive value of tests/
33. value.ti.
34. accuracy.ti.
35. correlat$.ti.
36. or/22-35
37. 9 and 21 and 36

Appendix 2. Draft data extraction
Forms are to be adapted from the following tools:

QUADAS (quality assessment of studies of diagnostic accuracy) (Whiting *et al.*, 2003)

Was the spectrum of patients described in the paper and was it chosen adequately?
Were selection criteria described clearly?
Was the method of population recruitment consecutive?
Was the setting of the study relevant?
In light of current technology, was the reference standard chosen appropriate to verify test results?
Was there an abnormally long time period between the performance of the test under evaluation and the confirmation of the diagnosis with the reference standard?

Was the execution of the index test described in sufficient detail to permit replication of the test?
Was the execution of the reference standard described in sufficient detail to permit replication of the test?
Did the whole sample, or a random selection of the sample, receive verification using a reference standard of diagnosis?
Did all patients receive the same reference standard regardless of the index test result?
Were the results of the index test incorporated in the results of the reference standard?
Were the index test results interpreted blind to the results of the reference standard?
Were the reference standard results interpreted blind to the results of the index test?
Was clinical data available when test results were interpreted?
Were uninterpretable/indeterminate/ intermediate results reported and included in the results?
Were reasons for drop-out from the study reported?

STROBE (Strengthening the reporting of observational studies in epidemiology) (Elm *et al.*, 2007)

Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures

Main results	16	*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

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