NIHR HTA Programme

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1. Title of the project

Optical Coherence Tomography (OCT) for the diagnosis, monitoring, and guiding of treatment for neovascular Age-related Macular Degeneration (AMD): Systematic review and economic modelling evaluation.

2. Name of research team and contact details

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3 BACKGROUND

3.1 Importance of neovascular AMD as a health problem

Age-related Macular Degeneration (AMD) is the most common cause of sight impairment in the UK .[1] The prevalence of AMD, currently around 600,000 people in the UK, may rise by a quarter to nearly 756,000 by 2020.[1] There are two main forms: *neovascular ("exudative" or "wet") AMD,* in which patients' vision worsens rapidly (over weeks) as a consequence of the development of new, abnormal blood vessels that leak fluid and blood at the macula, and *atrophic ("dry") AMD* in which a slow and gradual loss of sight relates to the progressive demise of visual cells. Estimates of incidence of neovascular AMD in the UK suggest that there are between 13,000 and 37,000 new cases annually, many of whom will require monthly monitoring and treatment for several years.[1] Cases with sight loss due to neovascular AMD are expected to increase from 145,697 to 189,890 by the end of the decade.[2] As the incidence of AMD increases with age, the burden of disease to the NHS and the society is expected to increase with an ageing population. Furthermore, loss of vision contributes to a psychological ill-health (depression, emotional distress) and reduced quality of life.[1]

3.2 Diagnosis of neovascular AMD

Typically patients with possible AMD present to primary care (optometrists, GPs) or other health professionals with non-specific symptoms (such as blurred and distorted vision). Some patients may not report symptoms; in these patients the disease may be revealed on routine eye examination. Cases with suspected neovascular AMD will be referred to secondary care, where ophthalmologists will assess their vision and undertake fundus examination with slit-lamp biomicroscopy. Clinical examination reveals typical changes associated with AMD such as drusen and irregularities in the appearance of the retinal pigment epithelium, most commonly in both eyes. The presence of a neovascular component may not be easy to be detected clinically; under these circumstances, imaging tests such as Fluorescein Angiography (FA or FFA) and Optical Coherence Tomography (OCT) are commonly used to confirm the diagnosis of neovascular AMD. These tests also provide a baseline reference for future comparisons during the follow-up of the patient, particularly if treatment is performed at a later stage. Additional technologies are used at presentation in some units, e.g. Fundus Autofluorescence (FAF) imaging, to evaluate the status of the retinal pigment epithelium (RPE) which may have prognostic implications.

According to current guidelines from the Royal College of Ophthalmologists, [1] FA interpreted by an ophthalmologist is the method of choice and reference standard test to diagnose neovascular AMD. Occasionally, Indocyanine Green Angiography (ICG) is obtained in addition to FA as part of the reference standard when particular phenotypes of neovascular AMD are suspected, including retinal angiomatous proliferation and idiopathic polypoidal choroidal vasculopathy. FA is an invasive and time-consuming procedure, entailing the injection of a dye into a peripheral vein by a nurse and a trained photographer undertaking the test to obtain images while the dye goes through the retina; this test also needs to subsequently be interpreted by an ophthalmologist with knowledge on this procedure. In addition to FA, the current Royal College of Ophthalmologists' guidelines recommend using OCT at diagnosis.[1] Due to recent developments in technology, it is possible that in some cases OCT might be superior to FA in detecting neovascular AMD. When active neovascular AMD is confirmed, treatment with anti-vascular endothelial growth factor (anti-VEGF) therapy is initiated.

3.3 Monitoring of neovascular AMD

For all patients with this condition it is common practice to initiate treatment with three consecutive (monthly) injections of anti-VEGF therapy, and then the patient is reassessed to evaluate whether or not the disease is active (i.e. neovascularisation leaking fluid/blood at the macula) or inactive. For this purpose, both FA and OCT may be used, according to the guidelines of the Royal College of Ophthalmologists.[1] Studies that have a large influence in current practice[3, 4] used visual acuity and OCT at monthly intervals and FA at quarterly intervals to decide on the need for re-treatment. In some units OCT is the only test utilised for this purpose. Indications for FA are highly variable, and one of them is when the functional results are not at the level expected. Alternative technologies such as FAF may also be used at variable intervals during the follow-up of these patients as areas of atrophy in the retinal pigment epithelium (difficult to detect clinically but easily observed on autofluorescence images) could be associated with fluid in the retina, in the absence of active neovascular AMD. If fluid is not seen intraretinally or subretinally, further treatment is not given and the patient is followed thereafter regularly. The timing of follow-up visits is variable; results of RCTs strongly suggest that it should be every 4 weeks for the first year when treatment with anti-VEGF has to be delivered. Given the great burden of this approach, other intervals have been used in clinical practice. "Treat and extend" strategy is the most successful strategy, consists of anti-VEGF monthly basis treatment to patients with nAMD until no intraretinal or subretinal fluid

is observed on OCT. Treatment intervals are sequentially lengthened by 2 weeks until signs of exudation recur. The intervals are individualized for each patient in an attempt to maintain an exudation-free macula. [5] If, during the patient's follow-up, the disease is judged to be active, further injections of anti-VEGF are given; either a single or three injections (one every month) and then the patient is followed as explained above (4 weeks monitoring scheme).

3.4 Optical Coherence Tomography (OCT)

OCT is a light-wave based technology producing cross sectional images of the retina with scan rates and resolution parameters that have greatly improved over the last 10 years. OCT is a non-invasive, non-contact visual test that requires around 5-10 minutes to assess both eyes.[6] It is user friendly, typically undertaken by trained medical photographers and interpreted by ophthalmologists. Automated analysis can also be used.

There are two main types of OCT system. The earlier time domain (TD) system, available from 1995, had an image rate of 100 to 400 scans per second and provided information for a limited view of the retina with a resolution in the range of 10 to 20 µm.[7] The newer system, spectral domain (SD) OCT, has been available since 2006. Improvements with this system include (i) a faster scan speed of approximately 27,000 scans per second; (ii) the ability to scan larger areas of the retina by taking six scans radially-oriented 30 degrees from each other, and (iii) increased resolution at 5 µm; and (iv) 'real time registration' which was not previously available with TD OCT.[7] The real-time registration feature enables the identification of specific anatomical locations on the retina, against which subsequent tests may be evaluated, which is of particular importance in the monitoring of patients.[7] Compared with TD OCT, the faster scan speed of SD OCT enables the collection of additional information on larger regions of the retina and eliminates image distortion arising from patient movement, while the improved resolution allows for a clearer and more distinguishable view of retinal layers, with the possibility of detecting earlier signs of disease.[7]

OCT is now widely used.[1] It may help clinicians to provide a more cost-effective service for people with neovascular AMD by potentially replacing the current reference standard of FA and helping to distinguish between those patients with active disease requiring treatment and those whose disease is not active at a particular point and who do not require treatment. OCT might also lead to

efficiencies by allowing other categories of health professionals to become involved in the diagnosis and monitoring of patients.

4 RESEARCH OBJECTIVES

The overall review objective is to determine "What is the optimal role of OCT in (i) the diagnosis of people newly presenting with suspected neovascular AMD and (ii) monitoring of those previously diagnosed with the disease?"

Specifically the research objectives are:

1. Determine the diagnostic performance of OCT, alone or in combination with alternative tests, in detecting neovascular AMD, including accuracy, interpretability, and acceptability.
2. Determine the performance of OCT and/or other alternative tests in the monitoring of the disease post-diagnosis, specifically in detecting activity of the disease and the need for further treatment.
3. Determine the performance of other health professionals (e.g. medical photographers, nurses) compared with ophthalmologists interpreting OCT findings.
4. Model the effects of using OCT and/or other alternative tests in the diagnosis and management of the disease and estimate the relative cost-effectiveness of alternative diagnostic and monitoring strategies, including determination of an optimal cut-off point for sensitivity and specificity for use in practice, and the alternative timing between tests during monitoring
5. Identify future research needs.

5 METHODS

5.1 Systematic review to address objective 1-3

5.1.1 Inclusion criteria

5.1.1.1 Population

The types of participants to be considered are people suspected or previously diagnosed with neovascular AMD.

5.1.1.2 Clinical scenario

People presenting with the suspected diagnosis of neovascular AMD or those who have been previously diagnosed with the disease and are under monitoring.

5.1.1.3 *Types of studies*

Diagnostic studies:

- Direct (head-to head) comparisons (index test and comparator test(s) are evaluated in the same study population):
  - Fully paired (all study participants receive the index test, comparator test(s) and the reference standard)
  - Not fully paired (participants receive only a subset of the tests (e.g. randomised direct comparison in which study participants are randomly allocated to receive the index test or the comparator and all receive the reference standard)
- Indirect comparisons (estimates of the accuracy of the respective tests are obtained in different study groups):
  - e.g. two-gate or 'case-control' type studies (different sets of criteria are used for those with and without the target condition). Indirect comparisons will be considered if there is insufficient evidence from direct comparisons.

Studies reporting clinical effectiveness:

- RCTs evaluating outcomes when treatment is based on OCT or FA findings.

Qualitative studies evaluating patients' and/or clinicians/healthcare professionals' acceptability and/or interpretability of the OCT tests.

5.1.1.4 Types of outcomes

The following outcomes will be evaluated for the use of OCT at presentation and during follow-up of patients with neovascular AMD:

- Diagnostic accuracy (e.g. sensitivity, specificity, likelihood ratios, diagnostic odds ratio)
- Clinical effectiveness (e.g. visual acuity, anatomical control of the disease, patient reported outcomes)
- Interpretability of the test – to be defined as in included studies, considering the ability to acquire a quality image that can be interpreted or analysed.
- Acceptability of the test – to be defined as in included studies, considering users and healthcare providers' perspective.
- Proportion of participants not able to receive the diagnostic test (due to an eye condition e.g. lens or other media opacity, or personal circumstances e.g. wheelchair bound).

The evidence for the use of OCT will be considered separately for the purposes of diagnosis and monitoring.

5.1.2 Exclusion criteria

We may exclude case-control studies that compare severely diseased people with very healthy controls or studies excluding people with other ophthalmological disease or conditions where it is likely that the spectrum of disease and non-disease is unlike that to be encountered in practice. However case-control studies that apply their exclusion criteria equally to the cases and controls and otherwise meet the review's inclusion criteria will be included.

Studies in which FA has been interpreted by junior doctors will be excluded as this does not follow the reference standard definition.

5.1.3 Index test

The index test considered will be OCT, alone or in combination with alternative tests as described below. We will include both time domain OCT (TD OCT) and spectral domain OCT (SD OCT).

5.1.4 Alternative test(s)

The alternative tests to be considered will include the following examinations:

- Clinical Evaluation (with slit-lamp biomicroscopy with or without use of diagnostic contact lens and evaluation of patients' symptoms)
- Visual Acuity (for monitoring)
- Amsler Chart
- Colour Fundus Photographs
- Infra-red Reflectance (IR)
- Red-free Images (RF) or Blue Reflectance
- Fundus Autofluorescence Imaging (FAF)
- Indocyanine Green Angiography (ICGA), Dynamic High- Speed or digital subtraction ICGA Angiography (DS-ICGA)
- Preferential Hyperacute Perimeter (PHP)
- Microperimetry

5.1.5 Reference standard

The reference standard considered will be ophthalmologist interpreted FA. FA is generally acknowledged as being the recognised reference standard test for

detecting neovascular AMD. The Royal College of Ophthalmologists states in its guidelines for management of AMD that FA is currently the reference standard for diagnosing exudative disease.[1]

It may be possible that OCT might be superior to FA in some cases. We will address this issue following the methodology described by Glasziou and colleagues.[8]

Studies with unclear information about healthcare staff involved in the interpretation of FA will be included.

5.1.6 Search strategy for the identification of studies

Published, unpublished and ongoing studies will be identified from literature searches of electronic databases (from 1995 onwards) and appropriate websites. The evidence for the two systems (TD OCT and SD OCT) will be considered separately. The search strategies will be designed to be highly sensitive, including appropriate subject headings and text word terms that reflect both the clinical content and type of study required for each component of the research project and there will be no language restriction. Databases to be searched will include MEDLINE, MEDLINE In-Process, EMBASE, CINAHL, Biosis and Science Citation Index (SCI) for all reviews. The Cochrane Controlled Trials Register (CENTRAL) will be searched for additional reports of RCTs for the effectiveness review and PsycINFO and ASSIA for patient acceptability data. The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effectiveness (DARE), MEDION and HTA database will be searched for relevant systematic reviews and HTA reports. Abstracts and presentations from national and international meetings to be searched such as AAO, ARVO, the USA Macula Society, the Retina Society, American Society of Retina Specialists, Euretina and EVER. WHO International Clinical Trials Registry, Clinical Trials and EU Clinical Trials Register will be searched for ongoing studies. The websites of key journals will also be searched. Websites of professional organisations and manufacturers of OCTs will also be consulted. Search strategy will also scan for OCT safety reports (if available). Reference lists of all included studies will be scanned and experts contacted for details of additional reports.

5.1.7 Study selection and data extraction

Two reviewers will screen the titles (and abstracts if available) of all reports identified by the search strategy. Full-text copies of all studies deemed to be potentially relevant will be obtained and two reviewers will independently assess them for inclusion. Disagreements will be resolved by consensus or arbitration by a third reviewer.

A data extraction form will be developed, piloted and standardised. One reviewer will extract details of study design, participants, index, comparator and reference standard tests and outcome data, and a second reviewer will check the data extraction. Disagreements will be resolved by consensus or arbitration by a third reviewer.

5.1.8 Assessment of risk of bias

The quality assessment of studies deemed to meet the inclusion criteria will be undertaken by two reviewers independently. The methodological quality of the studies will be assessed using QUADAS-2, a quality assessment tool developed for use in systematic reviews of diagnostic studies.[10] QUADAS-2 (see appendix A) was developed through a formal consensus method and was based on empirical evidence. The research team will adapt the tool to make it applicable to this specific review, and will discuss and agree by consensus in the advisory group.

The methodological quality of any RCTs that meet our inclusion criteria will also be assessed using the Cochrane risk of bias tool.[11] This tool addresses six specific domains relating to methodological quality (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'). Disagreements will be resolved by consensus or arbitration by a third reviewer.

5.1.9 Data analysis

The results of the individual diagnostic studies will be tabulated and sensitivity, specificity, predictive values, likelihood ratios and diagnostic odds ratios calculated.

Summary receiver operating characteristic (SROC) curves will be produced for each test where two or more diagnostic studies report sufficient data. Where studies report 2x2 data for a number of different cut off values then the most frequently used cut off value across studies will be chosen. If considered appropriate, meta-analysis models will be fitted using the hierarchical summary receiver operating characteristic (HSROC) model[12] in SAS version 9.1. A symmetric SROC model will be used. This model takes proper account of the diseased and non-diseased sample sizes in each study, and allows estimation of random effects for the threshold and accuracy effects. The SROC curves from the HSROC models will be produced on the corresponding SROC plots. Summary sensitivity, specificity, positive and negative likelihood ratios

and diagnostic odds ratios (DORs) for each model will be reported as point estimate and 95% confidence interval (CI).

Sensitivity and specificity will be pooled using the weighted average method[13] if numerical difficulties are encountered with the HSROC model and there is no evidence of a threshold effect. Pooled likelihood ratios and DOR will be calculated using the DerSimonian and Laird random effects method.[14] These analyses will be carried out using Metadisc software.[15] Heterogeneity will be assessed using the I^2 statistic, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error.[16]

For relevant clinical efficacy outcomes reported resulting from use of the tests, where appropriate, meta-analysis will be employed to estimate a summary measure of effect. Dichotomous outcome data will be combined using the Mantel-Haenszel relative risk (RR) method and continuous outcomes will be combined using the inverse-variance weighted mean difference (WMD) method. For the estimates of RR and WMD 95% confidence intervals (CIs) and p-values will be calculated. The results will be reported using a fixed effect model in the absence of heterogeneity. Chi-squared tests and I-squared statistics will be used to explore statistical heterogeneity across studies. Possible reasons for heterogeneity will be explored using sensitivity analysis. Where there is no obvious reason for heterogeneity, the implications will be explored using random effects methods.

Where a quantitative synthesis is considered to be inappropriate (e.g. acceptability of tests studies) or not feasible a narrative synthesis of results will be provided.

6 ECONOMIC EVALUATION

6.1 Systematic review to address objective 4

6.1.1 Systematic review of economic evaluations

We will assess efficiency as well as efficacy as health technologies adopted within the NHS should be cost-effective. We will assess cost-effectiveness by systematically searching for and reviewing the literature. Sensitive electronic searches for economic evaluations will be undertaken in the Health Management Information Consortium Database, NHS Economic Evaluations Database (NEED) and the HTA Database as well as general health care databases (MEDLINE, EMBASE and SCI) from 1995 onwards. Reference lists of all included studies will be scanned and experts contacted for details of additional reports.

Studies that compare, in terms of cost and outcomes, strategies that include OCT for diagnosis and/or monitoring individuals with AMD, will be included. Studies will be included even if no formal attempt to relate cost to outcome data in a cost-effectiveness or cost-utility analyses is available. One reviewer will assess all abstracts for relevance and full papers will be obtained for those that appear potentially relevant. One economist will assess included studies following the NHS-EED guidelines for reviewers.[17]

These guidelines address all the important issues that should be reported when conducting an economic evaluation in health care. No attempt will be made to synthesise quantitatively the primary studies. Data from included studies will be summarised and appraised in order to identify common results, variations and weaknesses between studies. If a study does not report incremental cost effectiveness ratios (ICERs) but provides sufficient data then, where possible, these will be reanalysed to provide estimates of ICERs.

6.1.2 Economic Evaluation

An economic evaluation[18] will also be part of this study. The decision analytic modelling will be used to assess the cost effectiveness of alternative diagnostic strategies with subsequent monitoring strategies using OCT compared with strategies that do not use it. The economic model will include a decision tree structure to model the diagnostic elements and a Markov model structure to capture the consequences of correct and incorrect diagnoses and follow up. The structure of the economic model will describe different care pathways for AMD patients from the moment of diagnosis. These care pathways and hence model structure, while informed by existing research, will also be determined in consultation with the project steering and advisory committee that will include clinical experts as well as patient representatives. If data permit model strategies will probably include alternative monitoring intervals. The perspective of the analyses will be that of the UK NHS. Data to populate these models will be obtained from the review of diagnostic accuracy/clinical effectiveness and from other structured searches of the literature. Two recent Health Technology Assessment studies provide important insights and potentially relevant data for the economic model.[18,19] With regard to the former,[19] Professor Clegg has indicated that in principle they would be happy to share their model with us. Although the question we will be addressing in our project is substantially different from the one addressed by the SHTAC group and we believe that a new economic model will be necessary to answer the cost-effectiveness

question in our project, nevertheless having access to the SHTAC economic model will help us in developing our own economic model. The main outputs of the model will be NHS costs for diagnosis, total NHS costs (modelled up to the lifetime of patients), diagnostic performance, QALYs, and incremental cost per QALY. In addition to diagnostic performance, data will be required on the natural history of treated or untreated AMD and the relative effectiveness of treatments (versus each other and no treatment), costs and health state utilities. These data will be assembled from structured reviews of UK relevant literature. Costs will be obtained from typical public sources (e.g. Personal Social Services Research Unit (PSSRU) [20] for staff unit costs, British National Formulary (BNF)[21] for cost of medicines, Scottish Health Care Costs (SHSC)[22] for health interventions. Results will be reported in terms of incremental cost-effectiveness ratios using a suitable measure of effectiveness (e.g. number of AMD cases detected, number of blinded individuals avoided, QALYs). Uncertainty in the model will be dealt with using sensitivity analyses[23]. Parameter uncertainty will be addressed by conducting deterministic and probabilistic sensitivity analyses. For the latter, probability distributions will be attached to model parameters and Monte Carlo simulation conducted. Whenever possible, heterogeneity will be tackled by running models for different sub-groups. Other sources of uncertainty due, for instance, to the assumptions made in the models (e.g. structural uncertainty) will be explored if considered necessary. Probabilistic results will be presented using scatter plots and/or cost-effectiveness acceptability curves –CEACs–. Finally, value of information analyses will be performed in order to identify priority areas for future research. [24]

6.2 Research methods to address objective 5

The economic model will be used to identify gaps in the evidence base leading to uncertainty surrounding estimated costs and effects. A value of information analysis will be considered if it proves feasible to identify and fit appropriate distributions to all model parameters. This would aim to identify the expected value of perfect information of the diagnostic performances and consequences strategies considered, and the value of further research to identify more precise and reliable estimates for key parameters of the economic model.

A project expert advisory group, comprising the applicants, a leading UK expert in AMD (Mr. Winfried Amoaku), Professor Andrew Lotery representative from the Royal College of Ophthalmologists, representatives from patient organisations (North East Sensory Services, Macular Diseases Society) will assist in the identification of

research needs, and in the interpretation of evidence from the systematic reviews, their views on acceptability of tests and determination of plausible care pathways, including timing between visits and role of different health professionals.

7 PROJECT TIMETABLE AND MILESTONES

- *February - August 2012:* Develop protocol, care pathways, develop and run literature searches, develop tools for data abstraction and quality assessment, screen search results
- *28 June 2012:* First project expert advisory group meeting
- *July - August 2012:* Assess full text papers for inclusion
- *September- October 2012:* Data abstraction and quality assessment
- *November 2012 – December 2013:* Statistical analyses completed
- *January 2013:* Second project expert advisory group meeting
- *May 2012 – February 2013:* Economic modelling
- *January - April 2013:* Report writing

8 EXPERTISE

The project will be led from the Health Services Research Unit (HSRU), University of Aberdeen. Mayret Castillo, systematic reviewer will be responsible for the day-to-day running of the review as well as undertaking the reviews of diagnostic accuracy/ clinical effectiveness, and will be supervised by Graham Mowatt (co-principal investigator), senior research fellow and lead for the Evidence Synthesis Theme, with extensive experience in conducting systematic reviews. Augusto Azuara-Blanco (co-principal investigator), Professor in Health Services Research and ophthalmologist with extensive experience in diagnostic studies, will act as clinical lead to the project. Craig Ramsay, programme director and senior health services research methodologist within HSRU, will advise on methodological and statistical aspects of the study. Noemi Lois, consultant ophthalmologist who leads the AMD services in NHS Grampian (and has done so for the past 12 years) and has extensive experience with retinal imaging, will provide clinical expertise. Jennifer Burr is a senior research fellow and an ophthalmologist with experience in systematic reviews of diagnostic technologies, and former lead of the Evidence Synthesis Theme at HSRU. Rodolfo Hernandez, Research Council UK fellow in modelling, with considerable experience of economic modelling of diagnostic and screening interventions, will supervise the Health Economist Research Fellow, Olatunde Aremu, who will undertake the economic evaluations review and will be able to draw

upon the support of experienced colleagues from the Assessment of Technologies theme within the Health Economics Research Unit (HERU), University of Aberdeen. Andrew Elders, Statistician from HSRU, will provide statistical advice and support.

An expert advisory group will be convened at the start and towards the end of the project. The members on the advisory group are all the co-applicants previously mentioned along with patient representatives (service users) and professional organisation representation. Helen Jackman, Chief Executive, Macular Disease Society and Graham Findlay, Chief Executive, North East Sensory Services (formerly Grampian Society for the Blind) will help provide patient perspectives and insights. Dr David Findlay Clark (retired clinical psychologist) will provide the perspective of a service user with the condition. Professional organisation representation will be provided by Professor Andrew Lotery, representative from the Royal College of Ophthalmologists. In addition, Winfried Amoaku, a leading UK expert in AMD will provide the perspective of a clinical expert in AMD. Malcolm McPherson, Chairman of the Grampian Area Optometric Committee and representative of the College of Optometrists on the Optometry Scotland Council and Executive Committee, will provide a community optometrist perspective to the project.

Jennifer Burr and Augusto Azuara-Blanco are both editors of the Cochrane Eyes and Vision Group (CEVG), and will provide a linkage with the group. The CEVG, through Richard Wormald (Co-ordinating Editor) and Gianni Virgili (Editor), who is Associate Professor of Ophthalmology, University of Florence, Italy, has expressed support for the project and an interest in preparing a Cochrane diagnostic test accuracy review in conjunction with the HTA project.

Role of the Advisory group:

- confirm reference standard test*
- confirm alternative tests*
- adapt QUADAS 2*
- participate in the care pathway development for the economic model
- review and edit report results
- determine future research needs

*specific tasks for the expert research team such as clinicians, methodologists, statisticians, health economists, research fellows.

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10 APPENDIX A – Quadas 2 (Risk of bias tool)

DOMAIN 1: PATIENT SELECTION			
A. RISK OF BIAS			
Signalling questions:	**Yes**	**No**	**Unclear**
1. Was a consecutive or random sample of patients enrolled?			
2. Was a case-control design avoided?			
3. Did the study avoid inappropriate exclusions?			
4. Were the participants pre-selection avoided?			
	RISK		
	LOW	**HIGH**	**UNCLEAR**
Could the selection of patients have introduced bias?			
B. CONCERNS REGARDING APPLICABILITY	**CONCERN**		
	LOW	**HIGH**	**UNCLEAR**
Is there concern that the included patients do not match the review question?			
DOMAIN 2: INDEX TEST(S)			
A. RISK OF BIAS			
Signalling questions:	**Yes**	**No**	**Unclear**
5. Were the index test results interpreted without knowledge of the results of the reference standard?			
6. If a threshold was used, was it pre-specified?			
	RISK		
	LOW	**HIGH**	**UNCLEAR**
Could the conduct or interpretation of the index test have introduced bias?			
B. CONCERNS REGARDING APPLICABILITY	**CONCERN**		
	LOW	**HIGH**	**UNCLEAR**
Is there concern that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: REFERENCE STANDARD			
A. RISK OF BIAS			
Signalling questions:	**Yes**	**No**	**Unclear**
7. Is the reference standard likely to correctly classify the target condition?			
8. Were the reference standard results interpreted without knowledge of the results of the index test?			
	RISK		
	LOW	**HIGH**	**UNCLEAR**
Could the reference standard, its conduct, or its interpretation have introduced bias?			
B. CONCERNS REGARDING APPLICABILITY	**CONCERN**		
	LOW	**HIGH**	**UNCLEAR**
Is there concern that the target condition as			

defined by the reference standard does not match the review question?			
DOMAIN 4: FLOW AND TIMING			
A. RISK OF BIAS			
Signalling questions:	**Yes**	**No**	**Unclear**
9. Was there an appropriate interval between index test(s) and reference standard?			
10. Did all patients receive a reference standard?			
11. Did patients receive the same reference standard?			
12. Were all patients included in the analysis?			
	RISK		
	LOW	**HIGH**	**UNCLEAR**
Could the patient flow have introduced bias?			