Health Technology Assessment Programme

National Institute for Health Research

NETSCC, HTA
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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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National Institute for Health Research

PROGRESS REPORT

Report Type	Submit Updated Draft TAR Protocol
Due Date	30/01/2015
Submitted Date	30/01/2015

PROJECT DETAILS

Programme	**Research Type**
Technology Assessment Reports	HTA TAR (Full)
Project Reference Number	**Chief Investigator**
14/16/01	Simpson, Emma
Project Title	
Ultrasonography for monitoring of synovitis in rheumatoid arthritis	
Name and Address of Host Institution	
University of Sheffield	
Start Date (Current)	
End Date (Original)	**End Date (Current)**
Draft Final Report Due Date	
R&D Costs (Original)	**R&D Costs (Current)**

Details of Contract Variations Awarded

Requested Date	**Additional Time Granted (months)**	**Additional Funds Granted (£)**

Extension Totals		

UPLOADS

The following pages contain the following uploads:

Upload Name
Updated Protocol

HTA TAR –Draft Protocol

HTA no. 14/16/01

Ultrasonography for monitoring of synovitis in rheumatoid arthritis

Protocol date: 29.1.2015

1. Title of the project:

What is the added value of ultrasound joint examination for monitoring synovitis and can it beused to guide treatment decisions?

2. Name of TAR team and project 'lead'

TAR Team:

School of Health and Related Research (ScHARR), The University of Sheffield.

Contact details of the project lead:

Dr E. L. Simpson, Research Fellow
Health Economics and Decision Science, ScHARR, University of Sheffield
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3. Plain English Summary

Rheumatoid Arthritis (RA) is a disease that typically affects joints of the hands and feet but can affect many other joints in the body. It causes swelling, stiffness, pain and destroys the joint over time. RA limits the amount and the types of activities that individuals can perform. It can make them require additional help to perform everyday tasks. It can have a very substantial effect on quality of life. It is estimated that about one-third of people stop work within two years of onset because of the disease. Synovitis, which is inflammation of a synovial membrane, the soft tissue found in joint cavities, causes joint tenderness, and serious synovitis is usually a predictor of bone erosion.(1). In patients with established and aggressive disease, most joints will be affected over time.(2) Rheumatoid arthritis is usually a chronic relapsing condition that has a pattern of flare-ups followed by periods of lower disease activity; however, for some people, the disease is constantly progressive. It has a severe impact on quality of life. It has been estimated that approximately 1% of the population have rheumatoid arthritis.(3)

There is no cure. Treatment aims to improve quality of life and to prevent or reduce the amount of joint damage. There are a range of different drug treatments available including non-steroidal anti-inflammatory drugs (NSAIDS), which reduce pain, fever and joint swelling/inflammation; and "Disease Modifying Anti-Rheumatic Drugs" (DMARDs). Several of the DMARDs have been around for many years and are relatively inexpensive. Other newer drugs are called "biologic" DMARDs which are particularly expensive and generally used only in patients whose disease has not responded well to the cheaper conventional DMARDs.

Treatment attempts to achieve two things: first, the immediate goal is to control and relieve symptoms of the disease, particularly pain. A second goal is to slow or halt entirely the worsening of the underlying disease. However, there is no agreement on precisely how these aims should be best achieved. Treatment is complicated because there are many differences between patients and how they respond to the wide range of drugs and doses available.

Imaging techniques used in RA include ultrasound (US), conventional x-ray, magnetic resonance imaging (MRI) and computerised axial tomography (CT) scans. There is evidence to suggest that US scans are superior to clinical examination in the detection of synovitis, and that they are more sensitive to the presence of early signs of damage than x-rays, however, many clinicians have limited access to US, and so, as of their 2009 guidance, NICE considered clinician examination as the standard for the detection of synovitis.(2)

The purpose of this project is to consider the evidence relating synovitis to RA disease progression and whether the knowledge of the presence and severity of synovitis can aid the planned treatment of a patient. If so, whether the use of US represents a cost-effective use of resources will be explored.

4. Decision problem

Purpose of the decision to be made

The aim of this assessment is to systematically review the evidence on the use of ultrasound examination, as compared with clinical examination only, for monitoring synovitis in patients with rheumatoid arthritis, with an aim to address the question what is the added value of ultrasound joint examination for monitoring synovitis and can it be used to guide treatment decisions?

Definition of the intervention

The included intervention is ultrasound examination of joints in patients with rheumatoid arthritis, as used to assess synovitis. The review will investigate US at different joints.

Ultrasound technologies to be included will be determined by scoping searches and recommendations from clinical advisors. These are likely to include power Doppler US and greyscale US. Scoping searches will not exclude any methods of US. Where evidence allows results will be presented by ultrasound technology and by the joint examined.

Population/setting

The population will be adult patients with confirmed diagnosis of RA, at any point in the disease pathway. For the purposes of cost-effectiveness analyses, populations will be considered separately according to decision of whether to commence biologic DMARDS, or patients on biologic DMARDs considering dose adjustment. The setting will be secondary care.

Relevant comparators

The comparator will be assessment of synovitis without ultrasound technology by clinical examination. This may include assessment of inflammatory biomarkers and disease activity scoring tools.
As of their 2009 guidance, NICE considered clinician examination as the standard for the detection of synovitis.(2) However, as later studies have considered MRI as the gold standard, studies that also include MRI will not be excluded for the purposes of the review.

Key factors to be addressed

The review aims to address the clinical value of ultrasound to detect synovitis at different joints and at different points in disease pathway, compared with clinical examination alone, and to investigate performance monitoring strategies and influence on treatment decisions, exploring the cost-effectiveness of ultrasound to inform decisions around commencement of, or of dose adjustments of, biologic DMARDs.

5. Report methods for synthesis of evidence of clinical effectiveness

There will be two phases in the searches: phase I scoping searches; phase II comprehensive searches. Scoping searches will determine whether evidence is available on US for monitoring synovitis in RA. Assuming these do not indicate that the full project is of limited value then we will proceed to a full systematic review.
If scoping searches indicate uncertainty in the project's value this will be flagged to the HTA for a decision to be made.

Scoping searches

Phase I: scoping searches using keywords and specific study design filters will determine evidence available on US monitoring synovitis in RA. This will include diagnostic and prognostic data, and data regarding the ability to predict response to treatment, or influence on treatment decisions. This will also identify studies available on different types of US, and the different joints assessed. If scoping searches indicate uncertainty in the project's value, HTA will be contacted. However, where the full project value is not reduced, we will proceed to phase II where comprehensive searches will be carried out for the full systematic review. A draft scoping review search strategy is shown in the Appendix 1.

Phase II: Comprehensive searches will be carried out to identify clinical effectiveness studies comparing ultrasound examination, with clinical examination without ultrasound, for monitoring synovitis in patients with rheumatoid arthritis. This will include diagnostic accuracy and prognostic studies. The search strategy will be developed based on the results of the Phase I search.

Potential monitoring strategies and influence on treatment decisions, with emphasis on conventional and biologic DMARD treatment, will be explored in the literature. If evidence

is not available in published literature, it may be necessary to explore databases or survey relevant clinicians.

Systematic review

A review of the evidence for clinical effectiveness of ultrasound for monitoring synovitis will be undertaken systematically following the general principles recommended in the PRISMA statement (http://www.prisma-statement.org/).

Inclusion criteria:

Population

Adult patients diagnosed with rheumatoid arthritis.(4) Subgroups will be considered according to different joints evaluated by ultrasound. If evidence allows patients on biologic DMARDs will be considered separately from those on conventional DMARDs being considered for biologic therapy.

Intervention

The intervention will be ultrasound examination of joints in patients with rheumatoid arthritis, as used to assess synovitis. Ultrasound technologies to be included will be determined by scoping searches and recommendations from clinical advisors and where evidence allows results will be presented by different US technologies.

Comparators

The comparator will be assessment of synovitis by clinical examination without ultrasound technology. This may include assessment of inflammatory biomarkers and disease activity scoring tools.

Outcomes

Comparison of US and clinical examination in: synovitis detection rate; sensitivity; specificity and diagnostic accuracy; responsiveness to change in inflammation; and prediction of response to treatment. Different joints and US technologies will be considered separately.

Study design

Systematic reviews will be sought, and used to identify studies meeting the inclusion criteria for the review. Studies of robust design will be sought, but in their absence other study types will be accepted into the review.

For studies of diagnostic accuracy, study designs will be accepted into the review according to the hierarchy of evidence published by Merlin *et al*.(5) For this, level 1 evidence is considered to be systematic reviews of level 2 evidence, with level 2 being diagnostic test accuracy studies with an independent, blinded comparator of a valid reference standard, tested on consecutive patients. Level 3 evidence includes comparative studies with either non-consecutive patients, a comparator that has not been validated or is not blinded, or a case-control design. Level 4 refers to studies of diagnostic yield that do not compare with a reference standard. For studies investigating monitoring strategies and prediction of response to treatment, cohort studies will be sought.(5)

Exclusion criteria

Ultrasound used for RA diagnosis only (for example, differentiating between types of arthritis).

Studies with a low proportion of patients diagnosed with RA, unless outcome data are reported separately for the RA subgroup.

Animal models

Preclinical and biological studies

Narrative reviews, editorials, opinions

Non-English language papers

Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality

Search strategy

The search strategy will comprise the following main elements:

- Searching of electronic databases, registers and websites;
- Contact with experts in the field;
- Scrutiny of bibliographies of retrieved papers.

Databases and trials registers:

Electronic databases: including MEDLINE and Medline in Process (Ovid); EMBASE; The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, DARE, NHS EED and HTA databases; Web of Science Conference Proceedings and websites (e.g. The European League Against Rheumatism, the American College of Rheumatology); Clinical Trials.gov; metaRegister of Controlled Trials; FDA website; and EMEA website; society and professional organisation websites: Arthritis Research UK; British Society for Rheumatology; National Rheumatoid Arthritis Society; OMERACT Task Force; Royal College of Pathologists; Royal College of Physicians; Royal College of Radiologists; and Royal College of Surgeons.

Study selection

Titles and abstracts will be examined by one reviewer. Study selection based on full texts will be decided by two reviewers, with discrepancies resolved by discussion, with involvement of a third team member if necessary.

Data extraction strategy

Data will be extracted from all studies by one reviewer using a standardised data extraction form piloted on at least one study (initial draft in Appendix 2). All extractions will be checked thoroughly by a second reviewer. Discrepancies will be resolved by discussion, and with reference to a third team member if necessary.

Quality assessment strategy

Diagnostic studies will be assessed by criteria based on the QUADAS tool.(6) Critical appraisal will be performed by one reviewer and double-checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third team member if necessary.

Methods of analysis/synthesis

Data will be tabulated and discussed.

Where appropriate, evidence will be combined across studies to generate a summary estimate of effect.

Where evidence allows, different joints will be investigated separately, as will different types of US.

Patient or public involvement

The National Rheumatoid Arthritis Society has been contacted for suitable patient or public involvement. Should this not be possible, other avenues will be explored to obtain the necessary input.

6. Report methods for synthesising evidence of cost-effectiveness

Methods for estimating qualify of life

The time horizon of our analysis will be a patient's lifetime in order to reflect the chronic nature of the disease. The perspective will be that of the National Health Services and Personal Social Services. Both costs and QALY will be discounted at 3.5%.

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 ultrasound examination for patients either i) that are candidates for starting treatment with biologic therapies or ii) that are currently being managed with biologic DMARDs. Stand alone cost analyses based in the UK NHS will also be sought. An economic/cost search filter will be incorporated into the search strategy to identify relevant studies. Identified studies will be critically assessed using a critical appraisal checklist for economic evaluations. An example is that of Drummond *et al*.(7)

Evaluation of costs and cost-effectiveness, which may include development of a de novo economic model

A new economic evaluation will be carried out from the perspective of the UK NHS using an individual sampling modelling approach. The model will be based on the Sheffield Rheumatoid Arthritis model that has been applied to assess the cost effectiveness of treatment strategies at various points in the RA treatment pathway,(8) including substantial attention given to the population of UK patients on biologic therapies and the course of disease from that point onwards. This model has been extensively updated for use in the recent NICE appraisal of biologic DMARDs. The model simulates individual patients, considers responses to therapies in terms of EULAR categories, and then estimates the course of disease over a patient lifetime in terms of HAQ. HAQ is used to drive estimates of health state utility values and costs. The mapping function used to estimate the relationship between HAQ and utility is the most robust both in terms of statistical method and the characteristics of the estimating sample, and the model has capability to include other methods through sensitivity analysis. We believe that the general structure provided by the model provides an appropriate approach to the modelling of rheumatoid arthritis and to capturing the costs and benefits of different information in guiding decisions about patients and their use of high cost biologic therapies. The model complies fully with the current NICE Reference Case.

7. Expertise in this TAR team

TAR Centre

The ScHARR Technology Assessment Group (ScHARR-TAG) undertakes reviews of 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 Care Excellence. A list of publications can be found at: http://www.sheffield.ac.uk/scharr/sections/heds

E.L. Simpson, Research Fellow, has extensive experience in undertaking systematic reviews of health technologies.

M.D. Stevenson (Professor of Health Technology Assessment, ScHARR) is a mathematical modeller and Technical Director of ScHARR-TAG. He led the Assessment Group on the ongoing multiple technology appraisal of biologic DMARDs in RA. Matt is a member of NICE Appraisal Committee C and has published in excess of 70 peer-reviewed papers.

J.W. Stevens, Reader in Decision Science has extensive experience in the application of Bayesian statistics and methods of evidence synthesis for the National Institute for Health and Clinical Excellence (NICE), and the National Institute for Health Research (NIHR) Health Technology Assessment programme.

A. Wailoo (Professor, ScHARR) is a health economist and director of the NICE Decision Support Unit. He has worked on several NICE appraisals of biologic therapies for RA, led a project modelling similar issues in the US for the Agency for HealthCare Research and Quality, won funding to provide health economics support to the development of NICE RA Clinical Guidelines (CG79) and has published several papers on the health state utility values in RA.

R. Wong, Information Specialist, has experience of undertaking literature searches for the ScHARR Technology Assessment Group systematic reviews and other external projects.

8. Competing interests of authors

ScHARR authors: none

Clinical advisors

R.J. Wakefield – personal pecuniary interest (consulting advice and speaker fees for GE, and speaker fees from Abbvie, in regards to ultrasound related projects.)

Other clinical advisors – none.

9. Timetable/milestones

Milestone	
Draft protocol	1st July 2014
Final protocol	30th January 2015
Progress report	Estimate 2nd November 2015
Assessment report	Estimate 30th November 2015

10. Appendices

10.1. Appendix 1 Draft search strategy

10.1. Appendix 1 Draft scoping review search strategy

1 exp Arthritis, Rheumatoid/
2 rheumatoid arthritis.tw.
3 or/1-2 (120775)
4 exp Synovitis/
5 synovitis.tw.
6 ((synovial or synovium) adj5 inflam$).tw.
7 or/4-6
8 exp Ultrasonography/
9 ultrasound.tw.
10 ultrason$.tw.
11 sonography.tw.
12 echography.tw.
13 or/8-12
14 3 and 7 and 13

A specific study design filter will be included at the end of the strategy and combined with statement 14 of the scoping search strategy.

10.2.Appendix 2 Draft data extraction form

Table: Characteristics of included studies

Study Author, date, country	**Study design**	**Eligibility criteria (including how RA diagnosed)**	**Follow-up**	**Sample size and baseline characteristics**	**Intervention detail (type of ultrasound, clinician delivering ultrasound)**	**Comparator detail**

Table: Study outcomes

Study	**Joint(s) examined**	**Intervention detection of synovitis**	**Clinical evaluation detection of synovitits**	**Diagnostic accuracy, sensitivity, specificity (intervention compared with clinical evaluation)**	**Prediction of response to treatment**

10.3 Team members' contributions

E. L. Simpson, Research Fellow, will lead the project and undertake the review of clinical effectiveness.

M. D. Stevenson, Professor of Health Technology Assessment, will conduct the economic modelling.

Allan Wailoo, Professor of Health Economics , will work with Professor Stevenson on the economic model, help with the collection and analysis of any additional parameter estimates required for the model and comment on the assessment throughout.

Ruth Wong, Information Specialist, ScHARR will be involved in developing the search strategy and undertaking the electronic literature searches.

J. W. Stevens, Senior Lecturer, will plan and conduct statistical analyses.

Gill Rooney, Project Administrator, will assist in the retrieval of papers and in preparing and formatting the report.

Clinical advisors

Professor Philip Conaghan, Professor of Musculoskeletal Medicine, University of Leeds

Dr Cristina Estrach, Consultant Rheumatologist, Aintree University Hospital

Dr Richard Wakefield, Senior Lecturer and Honorary Consultant in Rheumatology, University of Leeds

Dr Chris Edwards (to be confirmed), Consultant Rheumatologist, University Hospital Southampton NHS Foundation Trust

References

Reference List

(1) Bugatti S, Manzo A, Caporali R, Montecucco C. Assessment of synovitis to predict bone erosions in rheumatoid arthritis. Therapeutic Advances in Musculoskeletal Disease 2012 Aug 1;4(4):235-44.

(2) National Institute for Health and Clinical Excellence. Rheumatoid arthritis. 2009. Report No.: Clinical Guidance 79.

(3) Symmons D, Turner G, Webb R, Asten P, Barrett EM, Lunt M, et al. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. Rheumatology (UK) 2002;41(7):793-800.

(4) Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010 Sep;69(9):1580-8.

(5) Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. BMC Medical Research Methodology 2009;9(1):34.

(6) Whiting P, Rutjes A, Reitsma J, Bossuyt P, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Medical Research Methodology 2003;3(1):25.

(7) Drummond MF, Sculpher MJ, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Oxford University Press; 2005.

(8) Tosh J, Brennan A, Wailoo A, Bansback N. The Sheffield rheumatoid arthritis health economic model. Rheumatology (UK) 2011;50(Suppl 4):iv26-iv31.