National Institute for Health and Care Excellence

Final

Addendum to Clinical Guidelines 79, Rheumatoid arthritis: the management of rheumatoid arthritis in adults

Clinical Guideline Addendum 79.1

Methods, evidence and recommendations

December 2015

Final version

Developed by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Contents

Clinical guidelines update

The NICE Clinical Guidelines Update Team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the new surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. When a new guideline is allocated to a standing Committee, the core members of the Committee are complemented by topic expert members. They have specialist knowledge of the topic and may include providers, commissioners and practitioners, and should include at least 1 lay member.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic expert members.

Where 'standing Committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the Committee.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

The NICE guideline on rheumatoid arthritis (NICE clinical guideline CG79) was reviewed in 2015 as part of NICE's routine surveillance programme to decide whether it required updating. The surveillance report identified new evidence that supported the need for an update as since the publication of the guideline a large trial has completed and been published relating to an exercise programme of strengthening and stretching hand exercises. This area is not specifically included in the current guidance and the surveillance review considered that updating the guideline to consider in this area was warranted. The full surveillance report can be found here.

The review question for this guideline update is;

What is the clinical and cost effectiveness of hand exercises in adults with rheumatoid arthritis?

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

1.2 Recommendations

1. **Consider a tailored strengthening and stretching hand exercise programme for people with rheumatoid arthritis with pain and dysfunction of the hands or wrists if:**
   - they are not on a drug regimen for rheumatoid arthritis, or
   - they have been on a stable drug regimen for rheumatoid arthritis for at least 3 months. [new 2015]
2. **The tailored hand exercise programme for people with rheumatoid arthritis should be delivered by a practitioner with training and skills in this area. [new 2015]**

1.3 Patient-centred care

This guideline offers best practice advice on the care of adults with rheumatoid arthritis.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have the capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

1.4 Methods

The scoping phase of this update (including development of the review protocol) was conducted based on the process and methods described in the guideline manual 2012. The development and validation phases of this update followed The Manual 2014. Where there are deviations from the process and methods, these are clearly stated in the interim process and methods guide for updates pilot programme 2013.

2 Evidence review and recommendations

2.1 Introduction

Rheumatoid arthritis (RA) is a chronic condition involving persistent synovial inflammation and associated damage to articular cartilage and underlying bone. RA typically affects the small joints of the hands and feet, though any joint can be affected. Uncontrolled active RA can cause pain, joint damage, disability, decreased quality of life, fatigue, and cardiovascular and other comorbidities.

The cause of RA is unknown, though environmental factors are known to have a role and several genes have been identified as linked to an increased risk. RA affects 0.5% to 1.0% of adults in the UK, prevalence increases with age and RA is 3 times more frequent in females than males.

Early recognition and rapid referral to rheumatology are important in the management of RA and prevention of joint damage. Treatment for RA includes disease-modifying antirheumatic drugs (DMARDs), analgesia, glucocorticoids, biological drugs and surgery. Non-drug treatments include exercise, joint protection, foot care and psychological support.

The NICE guidance in CG79 does not specifically include recommendations on hand exercises. A recent, large, UK-based study considered both the clinical and cost effectiveness of usual care compared with usual care and an individualised programme of strengthening and stretching exercises. Following the NICE surveillance review, the decision was made that the publication of this trial warranted an update to the guideline.

2.2 Review question

What is the clinical and cost effectiveness of hand exercises in adults with rheumatoid arthritis?

2.3 Clinical evidence review

A systematic search was conducted (see appendix D) which identified 1032 articles. The titles and abstracts were screened and 35 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 29 were excluded as they did not meet the criteria and 6 met the criteria and were included.

The included studies used varying hand exercise programmes and comparators, had participants who were at differing stages of their disease and the interventions involved varying levels of input from the therapists involved in the interventions. For a summary of included studies, please see Table 1.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

2.3.1 Methods

The population included adults with rheumatoid arthritis, excluding those who have had hand or upper limb surgery within the previous 6 months. Where studies included mixed populations they would be included if at least 75% of participants had an RA diagnosis. Outcomes were prioritised by the topic experts and reviewed by core Committee members before the review was undertaken. The following outcomes were chosen as important for the decision-making for this review question:

- hand function (including hand strength and range of motion)
- pain measurement (general, resisted and non-resisted, interference of pain with function)
- quality of life
- adverse events
- adherence

Due to the heterogeneity of the 6 included studies, a meta-analytic approach was not considered to be appropriate in this review.

All of the included studies were randomised controlled trials where the intervention had been delivered by a therapist (physiotherapist, occupational therapist or hand therapist). All the studies included a hand exercise based programme for adults with RA. In all of the studies both participants and therapist were not blinded. It would not have been possible to blind participant or therapist in these studies as they involved hand exercise interventions, blinding of the assessor was used in some of the included studies. There were a number of scales/tools used within these studies; a summary of these is included in Appendix I. The quality of evidence for each outcome was considered using the approach recommended by the Grading Recommendations, Assessment, Development and Evaluation (GRADE) working group.

A search in relation to rheumatoid arthritis of the Core Outcome Measures in Effectiveness Trials (COMET Initiative) database did not yield information on accepted minimum clinically important difference thresholds (MIDs) for most of the outcomes in this review. Consideration of reviews of the measures used in some of the included studies found MIDs for some of the sections of the Michigan Hand Outcomes Questionnaire. However these were only applicable after surgery. No MIDs were identified for the other measures used (Poole, 2011; Gignac 2011; Maska 2011). It was agreed with the topic expert members of the Committee that the use of these post-surgical MIDs to consider imprecision for this review question would not be appropriate. For pain outcomes, in those with chronic conditions (including rheumatoid arthritis), there has been some consideration given to identifying the magnitude of pain reduction that could be considered to be clinically significant. Consensus from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has considered changes in pain scores in trials of patients with chronic pain (Dworkin, 2008). Where visual analogue scales have been used to assess pain, the IMMPACT consensus recommends that reductions of pain at least 10% to 20% from baseline appear to reflect minimally important changes. There were many types of measures for the continuous outcomes in the included studies. For the included continuous outcomes the default sample size of at least 400 was used to determine imprecision where published or consensus MIDs were not available (as suggested by the GRADE Working Group).

Each included study used a varying hand exercise intervention and comparator/s. Due to this and the varying ways in which the outcomes data were reported it was agreed with the Committee that the evidence statements would be presented by intervention/study not by outcome. This would enable a more succinct presentation of the evidence.

For full evidence tables and GRADE profiles please see Appendices G and H.

Table 1: Summary of included studies

Study reference (including study design)	Study population	Intervention & comparator (intervention duration)	Outcomes reported	Therapist input to the programme
Cima et al. (2013) RCT Brazil	N=20 RA Deformity in at least 1 finger of each hand	To increase the muscle force of handgrip via exercises with both free and motor-coordination tasks; strengthening exercises Comparator: no treatment for handgrip (2months study period, no further follow-up)	• Handgrip strength • Pinch strength	20 sessions (x2/week), for an average of 35minutes, 2 consecutive months
Delhag et al. (1992) RCT Sweden	N=52 RA Functional class I to II Hand problems; decreased range of motion (ROM)and/or grip strength	Active hand exercise, 8 different movement exercises of the hands; rotation, flexion and abduction of the shoulders Comparators: wax bath treatment, wax bath and hand exercise, control (4weeks study period, no further follow-up)	• ROM • Grip function • Grip strength • Pain with resisted motion • Pain with non-resisted motion • Stiffness of hands	Included in regular treatment groups in occupational therapy department x3/week, for 4weeks
Dogu et al. (2013) RCT Turkey	N=52 RA Disease >1year, stage 1 to 3	Isotonic exercises Comparator: isometric exercises (6weeks study period, no further follow-up)	• Pain • Hand function • Dexterity • Quality of life • Handgrip strength • Disease activity	For the first 2weeks of the study exercises performed under guidance of a therapist, x5days/week
Hoeing et al. (1993) RCT USA	N=57 RA Functional class II or III	ROM exercises; tendon gliding exercises, thumb and fingers Resistive hand exercises; finger abduction and adduction, metacarpophalangeal (MCP) extended, gross grip	• Articular index (painful joints) • Ulnar deviation • MCP extension • Proximal interphalangeal (PIP) extension	All exercise demonstrated by an OT, written explanations, individually contacted to

Study reference (including study design)	Study population	Intervention & comparator (intervention duration)	Outcomes reported	Therapist input to the programme
		ROM and resistive exercises Comparator; control (12weeks study period, no further follow-up)	• Dexterity • Adherence • Adverse effects	ensure that they understood their exercise assignment
Lamb et al. (2015) RCT UK	N=490 RA Reported active pain and dysfunction of hands	SARAH trial Usual care and a programme to improve strength, mobility and dexterity (4 strength exercises of the hand, 7 mobility exercises of the upper limb joints) Comparator; usual care (12weeks study period 12month follow-up)	Primary outcome; • Overall hand function Secondary outcomes; • Activities of daily living, work performance, satisfaction, aesthetics • Pain • Physical ability measures • Self-efficacy • Modified tender and swollen joint counts • Changes in disease activity • Quality of life • Self-assessment of compliance • Adverse events	x5, 30 to 45minute exercise sessions with a therapist over 12weeks
O'Brien et al. (2006) RCT UK	N=67 RA	8 simple strengthening and mobilising tendon gliding exercises, radial finger walking, pinch grip exercises, strengthening eminence muscles and wrist extensor muscles with a resistive band Comparator; 8 stretching exercises, global flexion abduction of all finger joints, thumb opposition and interphalangeal flexion	Primary outcome; • Arthritis impact measurement scales Secondary outcomes; • Hand function tests • Power grip • Key pinch • Dominant hand index finger	30minute appointment with therapist, joint protection literature; 15minute appointment x2weeks later to monitor concordance

Study reference (including study design)	Study population	Intervention & comparator (intervention duration)	Outcomes reported	Therapist input to the programme
		(6months study period, no further follow-up)	flexion • Disease activity	

2.4 Health economic evidence review

2.4.1 Methods

Evidence of cost effectiveness

The Committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits rather than the total implementation cost.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline update was sought. The health economist undertook a systematic review of the published economic literature.

A systematic literature search was undertaken to identify health economic evidence within published literature relevant to the review question. The evidence was identified by conducting a broad search relating to rheumatoid arthritis in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA). The search also included Medline and Embase databases using an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 27 May 2015. The health economic search strategies are detailed in appendix J. The health economist also sought out relevant studies identified by the surveillance review and Committee members.

Economic literature review

The health economist:

- Identified potentially relevant studies for the review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies.
- Critically appraised relevant studies using the economic evaluations checklist as specified in *Developing NICE Guidelines: the manual 2014*.
- Extracted key information about the studies' methods and results into a full economic evidence table (appendix L).
- Generated summaries of the evidence in an economic evidence profile.

Inclusion and Exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that address the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported burden of disease or cost of illness were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of *Developing NICE Guidelines: the manual 2014*.

Economic evidence profile

The economic evidence profile summarises cost-effectiveness estimates. It shows an assessment of the applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from *Appendix H* of *Developing NICE Guidelines: the manual 2014*. It also shows the incremental cost, incremental effect and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty. Table 2 explains the information contained in the economic evidence profile.

Table 2: Explanation of fields used in the economic evidence profile

Item	Description
Study	This field is used to reference the study and provide basic details on the included interventions and country of origin.
Applicability	Applicability refers to the relevance of the study to specific review questions and the NICE reference case. Attributes considered include population, interventions, healthcare system, perspective, health effects and discounting. The applicability of the study is rated as: • Directly applicable – the study meets all applicability criteria or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	This field provides an assessment of the methodological quality of the study. Attributes assessed include the relevance of the model's structure to the review question, timeframe, outcomes, costs, parameter sources, incremental analysis, uncertainty analysis and conflicts of interest. The methodological quality of the evaluation is rated as having: • Minor limitations – the study meets all quality criteria or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	This field contains particular issues that should be considered when interpreting the study, such as model structure and timeframe.
Incremental cost	The difference between the mean cost associated with one strategy and the mean cost of a comparator strategy.
Incremental effect	The difference between the mean health effect associated with the intervention and the mean health effect associated with the comparator. This is usually represented by quality-adjusted life years (QALYs) in accordance with the NICE reference case.
Incremental cost effectiveness ratio (ICER)	The incremental cost divided by the incremental effect which results in the cost per quality-adjusted life year gained (or lost). Negative ICERs are not reported as they could represent very different conclusions: either a decrease in cost with an increase in health effects; or an increase in cost with a decrease in health effects. For this reason, the word 'dominates' is used to represent an intervention that is associated with decreased costs and increased health effects compared to the comparator, and the word 'dominated' is used to represent an intervention that is associated with an increase in costs and

Item	Description
	decreased health effects.
Uncertainty	A summary of the extent of uncertainty about the ICER. This can include the results of deterministic or probabilistic sensitivity analysis or stochastic analyses or trial data.

Cost-effectiveness criteria

NICE's report *Social value judgements: principles for the development of NICE guidance* sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the Committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'evidence to recommendations' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in *Social value judgements: principles for the development of NICE guidance*.

2.4.2 Results of the economic literature review

353 articles were identified by the initial search. 351 were excluded based on their title and abstract alone. Two full papers were obtained relating to the same study and subsequently included in the review. Table 3 contains the economic evidence profile for this review question summarising the results of the study included in the systematic review. Full economic evidence tables are contained in appendix L.

The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in appendix K. The one trial obtained was subsequently included so no excluded economic studies list is provided.

The single included study (Williams et al. 2015) was a within-trial economic evaluation of the SARAH trial. It investigated the cost effectiveness of usual care plus a tailored strengthening and stretching hand exercise programme compared with usual care only. The authors found that the hand exercise programme was likely to be cost effective with an incremental cost-effectiveness ratio of £17,941 per quality-adjusted life year based on their primary analysis. This is based on differences in costs and effects that are not statistically significant. The incremental cost of the hand exercise programme compared with usual care was £206.40 (95% CI -495.12 to 907.53). The incremental effect was 0.012 QALYs (95% CI -0.017 to 0.040). Therefore, there was a high degree of uncertainty around the estimated incremental cost-effectiveness ratio. Four alternative analyses were conducted by the authors using various statistical methods. The estimated incremental cost-effectiveness ratios of these analyses ranged from £8,564 to £9,572 per QALY. This study was directly applicable to the review question with minor methodological limitations.

Table 3: Economic evidence profile

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	Effect	ICER	
Williams et al. (2015) SARAH hand exercise programme vs. usual care United Kingdom	Directly applicable	Minor limitations	Within-trial analysis	£206.40 (-495.12 to 907.53)	0.012 (-0.017 to 0.040) QALYs	£17,941 per QALY	52% probability that the incremental cost-effectiveness ratio is less than £20,000 per QALY

Acronyms: QALY: quality adjusted life year

2.5 Evidence statements

2.5.1 Clinical evidence statement

Usual care and a hand exercise programme to improve strength, mobility and dexterity compared with usual care only

One large multicentre UK-based trial, with 490 participants, found a significant mean difference, at 4 months, favouring the intervention in overall hand function measured via the Michigan Hand Questionnaire (mean difference, 4.71 (95%CI 2.32 to 7.11)) and in grip strength, in Newtons (9.29 (95%CI, 2.01 to 16.57)). The same trial also found a significant mean difference, at 12 months follow-up, favouring the intervention in overall hand function (4.28 (95%CI, 1.49 to 7.06)), pinch strength in Newtons (3.01 (95%CI, 0.13 to 5.88)), and dexterity (-1.19 (95%CI, -2.15 to -0.23)) (moderate quality evidence).

This trial did not find differences between the intervention and usual care in grip strength (12 months), pinch strength (4 months), range of motion (4 and 12 months), dexterity (4 months), pain via troublesomeness questionnaire (4 and 12 months), and quality of life (4 and 12 months) (moderate quality evidence).

Exercises with both free and motor-coordination tasks, strengthening exercises compared with no treatment

One single-centre trial, with 20 participants, found patients in the intervention group performed significantly better on grip strength and pinch strength (both hands, no detailed data reported) from baseline to the end of the trial, there was no comparison made between the intervention and no treatment group (very low quality evidence).

Active hand exercise compared with no treatment

One single-centre trial, with 52 participants, found patients in the intervention group had significantly decreased pain with non-resisted motion of the dominant hand, from baseline to the end of the trial. The same trial did not find a difference between the intervention and no treatment groups, on grip strength, pinch strength, range of motion, and in pain with resisted motion of the dominant hand (in either hand) from baseline to the end of the trial (very low quality evidence).

Isotonic exercises compared with isometric exercises

One single-centre trial (within-subject design), with 52 participants, found a significant difference from baseline to the end of the trial in; hand function (both interventions), grip strength of the non-dominant hand (isotonic exercises), grip strength of the dominant hand (isometric exercises), dexterity (both interventions), and quality of life (both interventions) (very low quality evidence).

The same trial did not find a difference with the intervention from baseline to the end of the trial in; grip strength in the dominant hand (isotonic exercises), grip strength of the non-dominant hand (isometric exercises), and pain (very low quality evidence).

Range of motion and/or resistive exercises compared with no treatment

One single-centre trial, with 57 participants, found a significant difference with any of the interventions (range of motion and/or resistive exercises) compared with the control group in; grip strength in the left hand. This trial found a significant difference with the range of motion intervention compared with the control group in range of motion of the left hand and in painful joints of the right hand. This trial also found a significant difference with the range of motion and resistive exercise intervention compared with the control group in dexterity of the left hand.

This trial did not find a significant difference with any of the interventions compared with the control group in grip strength, right hand. This trial did not find a significant difference with the range of motion/resistive or the resistive intervention groups compared with the control group in range of motion of the right hand and in painful joints of the left hand. This trial did not find a significant difference with the range of motion or resistive exercise intervention groups compared with the control group in dexterity of the right hand (very low quality evidence).

Strengthening and mobilising exercises compared with stretching exercises or no exercise

One single-centre trial, with 67 participants, found a significant difference in improvements from baseline, in key pinch, for the strengthening and mobilising exercise group compared with stretching exercises or no exercise groups.

This trial did not find a difference between any of the groups in changes from baseline to the end of the trial in hand function and in grip strength (very low quality evidence).

2.5.2 Health economic evidence statements

One within-trial economic evaluation found that a structured programme of strengthening and stretching hand exercises was likely to be cost effective. This study was directly applicable to the review question with minor methodological limitations.

2.6 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The Committee noted that for those with rheumatoid arthritis (RA) where their hand joints are affected, any treatment that can help preserve joint function, prevent further deterioration or have an impact on joint pain may have a considerable impact on quality of life. Consequently the Committee noted the importance of patient reported outcomes and quality of life outcomes. The Committee acknowledged that they cannot assume measurements made by a clinician are equally important to patients. The standing Committee members questioned the topic experts about the current methods used to assess outcomes in RA and whether the scales/tools used in the research studies would be used in practice. The topic experts noted that there is not standardisation in assessment methods used and these may vary between practitioners. The Committee noted that this may make the applicability of the study outcomes to current clinical practice more difficult to assess. The Committee noted the importance of the individualised nature of the intervention; while a programme of exercises may be used this should be tailored to the individual. This includes exercises that may potentially provide the most benefit and minimise risks to the patient. Therefore, the Committee agreed the need for a practitioner with training and skills in the area to be involved in the delivery of any hand exercise intervention programme. The Committee agreed the importance of the following outcomes to patients and to clinical decision making. These were hand function, hand impairment, pain (including resisted and non-resisted motion, interference with function), quality of life measures, adverse events, and adherence.
Quality of evidence	The Committee noted that there was a range of quality of evidence presented. This included 1 large, UK-based, multi-centred trial that yielded outcomes where the GRADE assessment considered the quality to be moderate (the SARAH trial, Lamb, 2015) and 5 smaller single-centred trials

	Committee discussions
	where the GRADE assessment of the included outcomes was very low quality. The Committee therefore agreed that the data that were reported from the larger trial should be given more weight in the discussion of the evidence and the development of the recommendation. The Committee agreed that no subgroup analysis was possible with the evidence presented, particularly in relation to recent onset RA. Though they did note that, predominantly, the participants within the included studies did not include those with recent-onset RA. The Committee discussed that there may be potential benefits from hand exercises in patients with earlier stage disease. The Committee discussed the applicability of the programmes included in the trials to current UK based practice. The topic experts noted that the comparator element of the SARAH trial of usual care had included up to 1.5 hours of therapist intervention. They noted that this may be more therapist time than would be generally available within current UK practice. The Committee noted that many of the included studies had not reported adherence data. The Committee acknowledged that the adherence of patients with exercise programmes, which may currently be offered in practice, is not known.
Trade-off between benefits and harms	The Committee discussed the lack of agreed minimal clinical important differences that had been identified for the scales/tools used within the included studies. The topic experts confirmed the lack of agreed minimal clinical important differences (MIDs) for the measures used within the studies. The Committee agreed on the MIDs for the pain outcomes and agreed that there were no published MIDs that could be applied for other outcomes. The Committee noted that the scales/tools that had been used were appropriate for the outcomes in the studies. The Committee discussed this lack of a clinically meaningful interpretation of the outcomes data and noted that this made it more difficult to determine the applicability to patients. The committee further noted that a number of the studies had not included between group comparisons and had provided data only on differences from baseline. While significant differences in important outcomes with the hand exercise interventions were seen across the included studies the clinical difference that these confer is not known. The Committee concluded that accepting the unclear clinical significance of the outcome data it did consistently show a benefit to patients with hand exercise programmes. The Committee agreed that with a chronic condition, such as RA, where hand function can be affected any improvement in the included outcomes could have significance to the individual patient involved. They further noted that in the SARAH trial which provided the only longer-term data, the follow-up at 12months continued to show improvements with the intervention. The Committee noted that the interventions delivered across the evidence base had varied. They considered the strength of the evidence across the studies and concluded that, while the evidence did not support a detailed recommendation on a specific hand exercise programme, it did support the use of strengthening and stretching exercises. The Committee noted that the recommendations within CG79 had considered specialist physiotherapy and specialist occupational therapist input. They also noted specialist hand therapists are common within UK practice and concluded that the intervention could be delivered by these healthcare professionals.

	Committee discussions
	The Committee noted the lack of adverse effects data reported in the included trials. The Committee discussed whether there may be patients with rheumatoid arthritis where a hand exercise programme may be contraindicated. They noted that as the interventions are delivered by a therapist this would include an initial assessment of the patient for suitability to undertake the intervention. Therefore they concluded that in any recommendation relating to hand exercise programmes no further clarification on this would be needed. The Committee noted that the included studies had included participants with RA that could be considered stable, where there had not been recent medication changes or surgery. In recognition of the difficulty with defining stable disease they agreed to use the criteria from the SARAH trial of patients having been on a stable drug regimen for 3 months or not being on a current drug regimen.
Trade-off between net health benefits and resource use	One study was included in the economic literature review. This within-trial economic evaluation investigated the cost effectiveness of usual care plus a tailored strengthening and stretching hand exercise programme compared with usual care only. The main results of the analysis were (hand exercise programme vs. usual care): • The incremental cost effectiveness ratio (ICER) was £17,941. This is below the £20,000 per QALY cost-effectiveness threshold, indicating that the hand exercise programme is likely to be cost effective. • The incremental net monetary benefit was £24 based on a cost-effectiveness threshold of £20,000 per QALY. A positive figure indicates that the hand exercise programme is cost effective because it adds net value, taking into account both cost consequences and health benefits. • The probability that the incremental cost-effectiveness ratio was below £20,000 per QALY was 52%. The probability that the incremental cost-effectiveness ratio was below £30,000 was 59%. The Committee considered that there was a high degree of uncertainty due to the small magnitude of QALY gain and wide variation in costs. The Committee considered an alternative scenario based on the SF-6D to represent health benefits. Based on the SF-6D, The ICER was £23,288 per QALY, suggesting that the hand exercise programme was borderline cost ineffective. However, this was still within the upper cost-effectiveness threshold of £30,000 per QALY and there was a 56% probability that it was below the £30,000 per QALY threshold. The primary analysis based on the EQ-5D (resulting in an ICER of £17,941) was better aligned with the NICE reference case. The base case analysis accounted for baseline utility, correlation between costs and QALYs, used non-parametric bootstrapping and imputed for missing cost and QALY data. Four alternative analyses were provided using alternative statistical techniques resulting in far lower ICERs ranging from £8,564 to £9,364 per QALY. This was likely due to the finding that people excluded from the complete case analysis were different from those included. 92 people, evenly divided between arms, could not be included in the EQ-5D based analysis because one or more cost or utility observations were missing. At baseline, those excluded tended to be younger, with worse hand function, more troublesome pain, poorer confidence in self-efficacy , lower EQ-5D scores and higher daily drug costs. The Committee noted that all ICERs based on the EQ-5D were below £20,000 per QALY regardless of analytic technique used. Overall, this was a high quality economic evaluation. The Committee concluded that the hand exercise programme was likely to

	Committee discussions
	be a cost-effective addition to usual care.
Other considerations	The Committee noted the difficulties with applying the data that were reported in the included evidence to current practice as minimal clinical important differences are not available and there is no uniformity in the assessment methods used in current practice. The Committee considered that the included evidence supported the development of a recommendation to consider a therapist delivered hand exercise programme.

2.7 Recommendations

1. Consider a tailored strengthening and stretching hand exercise programme for people with rheumatoid arthritis with pain and dysfunction of the hands or wrists if:
   - they are not on a drug regimen for rheumatoid arthritis, or
   - they have been on a stable drug regimen for rheumatoid arthritis for at least 3 months. [new 2015]
2. The tailored hand exercise programme for people with rheumatoid arthritis should be delivered by a practitioner with training and skills in this area. [new 2015]

3 References

Cima SR, Barone A, Porto JM et al. (2013) Strengthening exercises to improve hand strength and functionality in rheumatoid arthritis with hand deformities: a randomized, controlled trial. Rheumatoid Int 33:725-732

Delhag B, Wollersjo I, Bjelle A (1992) Effect of active hand exercise and wax bath treatment in rheumatoid arthritis patients. Arthritic Care & Research 5:87-92

Dogu B, Sirzai H, Yilmaz F et al. (2013) Effects of isotonic and isometric hand exercises on pain, hand functions, dexterity and quality of life in women with rheumatoid arthritis. Rheumatol Int 33:2625-2630

Gignac M, Cao X, McAlpine J et al. (2011) Measures of disability. Arthritis Care & Research 63:S308-S324

Hoeing H, Groff G, Pratt K et al. (1993) A randomized controlled trial of home exercise on the rheumatoid hand. The Journal of Rheumatology 20:785-789

Lamb SE, Williamson EM, Heine PJ et al. (2015) Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 385:421-429

Maska L, Anderson J, Michaud K. (2011) Measures of functional status and quality of life in rheumatoid arthritis. Arthritis Care & Research 63:S4-S13

O'Brien AV, Jones P, Mullis R et al. (2006) Conservative hand therapy treatments in rheumatoid arthritis – a randomized controlled trial. Rheumatology 45:577-583

Poole JL. (2011) Measures of hand function. Arthritis Care & Research 63:S189-S199

Williams MA, Williamson EM, Heine PJ et al. (2015) Strengthening And stretching for Rheumatoid Arthritis of the Hand (SARAH). A randomised controlled trial and economic evaluation. Health Technology Assessment (Winchester, England): 1-222

4 Glossary and abbreviations

Please refer to the NICE glossary.

Additional terms used in this document are listed below

DMARDs: Disease modifying anti-rheumatic – treatment that can reduce or prevent joint damage

Established RA: Rheumatoid arthritis disease duration of longer than 2 years

Recent-onset RA: Rheumatoid arthritis disease duration of up to 2 years. Within recent-onset RA, categories of suspected persistent synovitis or suspected RA refer to patients in whom a diagnosis is not yet clear, but in whom referral to specialist care or further investigation is required.

ROM: Range of motion

MCP: metacarpophalangeal

PIP: proximal interphalangea

Appendices

Appendix A: Committee members and NICE teams

A.1 Core members

Name	Role
Damien Longson (Chair)	Consultant Liaison Psychiatrist, Manchester Mental Health and Social Care Trust
Catherine Briggs	GP Principal, Bracondale Medical Centre, Stockport
John Cape	Director of Psychological Therapies Programme, University College London
Alun Davies	Professor of Vascular Surgery and Honorary Consultant Surgeon, Charing Cross & St Mary's Hospital & Imperial College NHS Trust
Alison Eastwood	Senior Research Fellow, Centre for Reviews and Dissemination, University of York
Sarah Fishburn	Lay Member
Jim Gray	Consultant Medical Microbiologist, The Birmingham Children's Hospital NHS Foundation Trust
Kath Nuttall	Director, Lancashire & South Cumbria Cancer Network (- April 2013)
Tilly Pillay	Consultant Neonatologist, Staffordshire, Shropshire and Black Country Newborn Network, Royal Wolverhampton Hospitals Trust
Nick Screaton	Radiologist, Papworth Hospital NHS Foundation Trust
Lindsay Smith	Principal in General Medical Practice, Somerset
Philippa Williams	Lay Member
Sophie Wilne	Paediatric Oncologist, Nottingham Children's Hospital

A.2 Topic expert Committee members

Name	Role
Kate Betteridge	Lay member
Will Gregory	Specialist Rheumatology Physiotherapist, Salford Royal Hospital
Wendy Holden	Consultant Rheumatologist, North Hampshire Hospitals NHS Foundation Trust
Donna Kennedy	Hand Therapist, Imperial College London
Sue Oliver	Nurse Consultant in Rheumatology
Mark Williams	Research Physiotherapist

A.3 NICE project team

Name	Role
Mark Baker	Clinical Advisor
Steven Barnes	Technical Lead
Christine Carson	Guideline Lead
Anne-Louise Clayton	Editor
Jessica Fielding	Public Involvement Advisor
Ross Maconachie	Technical Lead (Health Economics)
Louise Shires	Guideline Commissioning Manager

Trudie Willingham	Guideline Co-ordinator

A.4 Clinical guidelines update team

Name	Role
Phil Alderson	Clinical Advisor
Emma Banks	Co-ordinator
Jane Birch	Project Manager
Paul Crosland	Health Economist
Nicole Elliott	Associate Director
Jenny Kendrick	Information Specialist
Nick Lowe	Administrator
Roberta Richey	Technical Analyst
Toni Tan	Technical Adviser
Lorraine Taylor	Associate Director

Appendix B: Declarations of interest

Standing Committee	Interest declared	Type of interest	Decision
Damien Longson	Family member employee of NICE.	Personal Non-financial Non-specific	Declare and participate
Damien Longson	Director of Research & Innovation, Manchester Mental Health & Social Care NHS Trust.	Personal Non-financial Non-specific	Declare and participate
Catherine Briggs	Husband is a consultant anaesthetist at the University Hospital of South Manchester.	Personal Non-financial Non-specific	Declare and participate
Catherine Briggs	Member of the Royal College of Surgeons, the Royal College of General Practitioners, the Faculty of Sexual and Reproductive Health and the BMA.	Personal Non-financial Non-specific	Declare and participate
Catherine Briggs	Chaired a discussion panel on urinary tract infections in women for Amco.	Personal Financial Non-specific	Declare and participate
John Cape	Trustee of the Anna Freud Centre, a child and family mental health charity which applies for and receives grants from the Department of Health and the National Institute for Health Research.	Personal Non-financial Non-specific	Declare and participate
John Cape	Member of British Psychological Society & British Association for Behaviour & Cognitive Psychotherapists who seek to influence policy towards psychology & psychological therapies.	Personal Non-financial Non-specific	Declare and participate
John Cape	Clinical Services Lead half-day a week to Big Health, a digital health company that has one commercial product; an online CBT self-help programme for insomnia with online support	Personal Non-financial Non-specific	Declare and participate
Alun Davies	Research grant funding – commercial: Vascular Insights; Acergy Ltd; Firstkind; URGO laboratoire; Sapheon Inc (terminated 2013). All administered by Imperial College London as Sponsor and Professor Davies as CI.	Non-personal Financial Non-specific	Declare and participate
Alun Davies	Research grant funding – non-commercial:	Non-Personal Financial	Declare and participate

Standing Committee	Interest declared	Type of interest	Decision
	National Institute for Health Research, British Heart Foundation, Royal College of Surgeons, Circulation Foundation, European Venous Forum.	Non-specific	
Alun Davies	Non-commercial: Attendance at numerous national & international meetings as an invited guest to lecture where the organising groups receive funding from numerous sources including device and pharmaceutical manufacturers. Organising groups pay expenses and occasionally honoraria - the exact source of funding is often not known.	Personal Financial Non-specific	Declare and participate
Alison Eastwood	Member of an independent academic team at Centre for Review & Dissemination, University of York commissioned by NICE through NIHR to undertake technology assessment reviews.	Non-personal Non-financial Non-specific	Declare and participate
Sarah Fishburn	Organises workshops for physiotherapists treating pelvic girdle pain. Paid for this work.	Personal Financial Non-specific	Declare and participate
Sarah Fishburn	Payment and expenses from the Nursing and Midwifery Council as a lay panellist of the Fitness to Practise Investigating Committee.	Personal Financial Non-specific	Declare and participate
Sarah Fishburn	Lay reviewer for the National Institute for Health Research; has reviewed a number of research proposals being considered for funding. Paid for carrying out these reviews.	Personal Financial Non-specific	Declare and participate
Sarah Fishburn	Chair of the Pelvic Partnership, a support group for women with pregnancy-related pelvic girdle pain (voluntary position).	Personal Non-financial Non-specific	Declare and participate
Sarah Fishburn	Trained as a chartered physiotherapist and qualified in 1988 but have not been in clinical practice since 1997. Remains a non-practicing member of the Chartered Society of Physiotherapy.	Personal Non-financial Non-specific	Declare and participate
Sarah Fishburn	Appointed by Mott	Personal	Declare and

Standing Committee	Interest declared	Type of interest	Decision
	MacDonald to carry out reviews as a lay reviewer on behalf to the Nursing and Midwifery Council of Local Supervising Authorities and Universities providing courses for nurses and midwives. This is paid work.	Financial Non-specific	participate
Jim Gray	Deputy Editor, Journal of Hospital Infection, funded by the Healthcare Infection Society (HIS pay the hospital for my time)	Personal Financial Non-specific	Declare and participate
Jim Gray	Co-investigator in four major trials (3 HTA-funded; 1 British Council funded. Two trials are about antibiotic prophylaxis on obstetrics and gynaecology to prevent pelvic infections, one is comparing different suture materials and the fourth is a diagnostic test accuracy study for use in woman in labour).	Non-personal Financial Non-specific	Declare and participate
Jim Gray	Associate Editor, International Journal of Antimicrobial Agents.	Personal Non-financial Non-specific	Declare and participate
Jim Gray	Associate Editor Journal of Pediatric Infectious Diseases.	Personal Non-financial Non-specific	Declare and participate
Jim Gray	Expert Advisor, British National Formulary for Children.	Personal Non-financial Non-specific	Declare and participate
Jim Gray	My Department is in receipt of an Educational Grant from Pfizer Ltd to develop improved diagnosis of invasive fungal infections in immunocompromised children	Non-personal Financial Non-specific	Declare and participate
Jim Gray	Small shareholding (under £2000) in Glaxo Smith Kline	Personal Financial Non-specific	Declare and participate
Kath Nuttall	None	Not applicable	Declare and participate
Tilly Pillay	None	Not applicable	Declare and participate
Nick Screaton	Clinical Commissioning Group stakeholder member	Personal Non-financial Non-specific	Declare and participate
Nick Screaton	Senior Editor British Journal of Radiology	Personal Non-financial Non-specific	Declare and participate

Standing Committee	Interest declared	Type of interest	Decision
Nick Screaton	Advisory Editor Clinical Radiology	Personal Non-financial Non-specific	Declare and participate
Nick Screaton	Chair East of England British Institute of Radiology	Personal Non-financial Non-specific	Declare and participate
Nick Screaton	Director – Cambridge Clinical Imaging LTD	Personal Non-financial Mon-specific	Declare and participate
Nick Screaton	British Thoracic Society Bronchiectasis Guidelines Group	Personal Non-financial Non-specific	Declare and participate
Nick Screaton	Specialised Imaging Clinical Commissioning Group stakeholder member	Personal Non-financial Non-specific	Declare and participate
Nick Screaton	Member of the Faculty Board for the Royal College of Radiologists	Personal Non-financial Non-specific	Declare and participate
Nick Screaton	Member of the Editorial Board of Pulmonary Circulation	Personal Non-financial Non-specific	Declare and participate
Lindsay Smith	None	Not applicable	Declare and participate
Philippa Williams	None	Not applicable	Declare and participate
Sophie Wilne	Recipient of NHS Innovation Challenge Award for clinical awareness campaign to reduce delays in diagnosis of brain tumours in children & young adults. Award will be used to develop the campaign.	Personal Financial Non-specific	Declare and participate
Sophie Wilne	Co-investigator for RFPB grant to undertake systematic reviews in childhood brain tumours.	Non-personal Financial Non-specific	Declare and participate
Sophie Wilne	Co-investigator for grant awards from charity to evaluate impact of brain tumour awareness campaign.	Non-personal Financial Non-specific	Declare and participate
Topic expert	**Interest declared**	**Type of interest**	**Decision**
Donna Kennedy	None	Not applicable	Declare and participate
Mark Williams	Study Lead and lead author – Stretching and Strengthening for Rheumatoid Arthritis of the Hand (SARAH) trial	Personal Non-financial Specific	Declare and participate (NOTE: provided factual clarifications in relation the

Standing Committee	Interest declared	Type of interest	Decision
			SARAH study and was involved in the general discussion of other evidence. Was not involved in the development of the recommendation).
Sue Oliver	Chair of European League Against Rheumatism Health Professionals Standing Committee	Personal Non-financial Non-specific	Declare and participate
Sue Oliver	Fellow and Member of the Royal College of Nursing	Personal Non-financial Non-specific	Declare and participate
Sue Oliver	Member of the British Society for Rheumatology International Strategy Group	Personal Non-financial Non-specific	Declare and participate
Sue Oliver	Training for nurses using Telephone advice link and other forms of communicating with patients (funded by Celegene)	Personal Financial Non-specific	Declare and participate
Sue Oliver	Delivered a lecture/workshop on service delivery and nursing leadership/change management (funded by Roche)	Personal Financial Non-specific	Declare and participate
Sue Oliver	Honorarium from AbbVie for 1 day participation in Connect Project Rheumatology Project	Personal Financial Non-specific	Declare and participate
Will Gregory	Carried out fee paid work (honorarium), an hour long presentation on ”the Role of the Rheumatology Physiotherapist” as part of an educational workshop to the physiotherapy department at South Manchester, funded for my work by Pfizer	Personal Financial Specific	Declare and participate
Will Gregory	Carried out fee paid work (honorarium), from Pfizer hour long talk about “IT services innovations in the management of ankylosing spondylitis”, plus facilitating discussions through the afternoon session. For rheumatology nurses, physios and doctors from the north-west area	Personal Financial Non-specific	Declare and participate

Standing Committee	Interest declared	Type of interest	Decision
Wendy Holden	None	Not applicable	Declare and participate
Kate Betteridge	Carry out consultancy work with healthcare industry companies, the NHS and other not for profit organisations. Work is of a patient representative/advisory nature	Personal Financial Non-specific	Declare and participate

Appendix C: Clinical review protocol

	Details
Review Question	What is the clinical and cost effectiveness of hand exercises in patients with rheumatoid arthritis?
Objectives	The current NICE guideline (CG79) recommends specialist physiotherapy and specialist occupational therapy. This guideline does not make specific recommendations on hand exercises. Since publication of this guideline an NIHR funded UK-based trial has considered best practice usual care with best practice usual care and an individualised exercise programme of strengthening and stretching hand exercises. Review during the NICE surveillance programme indicated that this study may impact on the current guideline and recommendations
Type of Review	Intervention
Language	English only
Study Design	Randomised controlled trials (RCTs), systematic reviews of RCTs (Systematic reviews must have the same inclusion and exclusion criteria as defined in this protocol, and meet the quality standards defined in the NICE clinical guidelines methods handbook)
Status	Published papers (full text only)
Population	Adults with confirmed rheumatoid arthritis Hand exercise programmes delivered via a specialist physiotherapist or specialist occupational therapist or hand therapist <u>Exclusions:</u> - <18years with RA - mixed population studies with <75% RA - hand surgery or upper limb surgery within the previous <6months <u>Subgroups:</u> - established RA (duration of longer than 2years) - recent-onset RA (duration of up to 2years – categories of suspected persistent synovitis or suspected RA refer to patients in whom a diagnosis is not yet clear) - exercise type (such as strengthening compared with stretching)
Intervention	Hand exercise programmes for those with confirmed RA with or without usual care (administered via physiotherapist, occupational therapist or hand therapist): - group or individual programmes
Comparator	Other hand exercise programmes, such as self-administered, or via information leaflets Usual care Electrotherapy (such as heat, ice, hot wax bath, therapeutic ultrasound) Manual therapy (massage, mobilisation or manipulation of joints)
Outcomes	Hand function (including hand strength and range of motion) Hand impairment (strength and movement) Pain measurement, general; resisted and non-resisted motion; interference of pain with function Quality of life Adverse events Adherence
Other criteria for	<u>Exclusions:</u>

	Details
inclusion / exclusion of studies	Other non-RCT study types; Non-randomised controlled studies Observational studies Narrative reviews, non-comparative studies, case series, case reports, editorials
Search strategies	No date limit
Review strategies	Data on all included studies will be extracted into evidence tables All agreed outcomes from evidence will be presented in GRADE profiles or modified profiles (where appropriate) and further summarised in evidence statements Where statistically possible, a meta-analytic approach will be used to give an overall summary effect

Appendix D: Clinical search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in table 4. The search strategy is shown in table 5. The same strategy was translated for the other databases listed.

Table 4: Clinical search summary

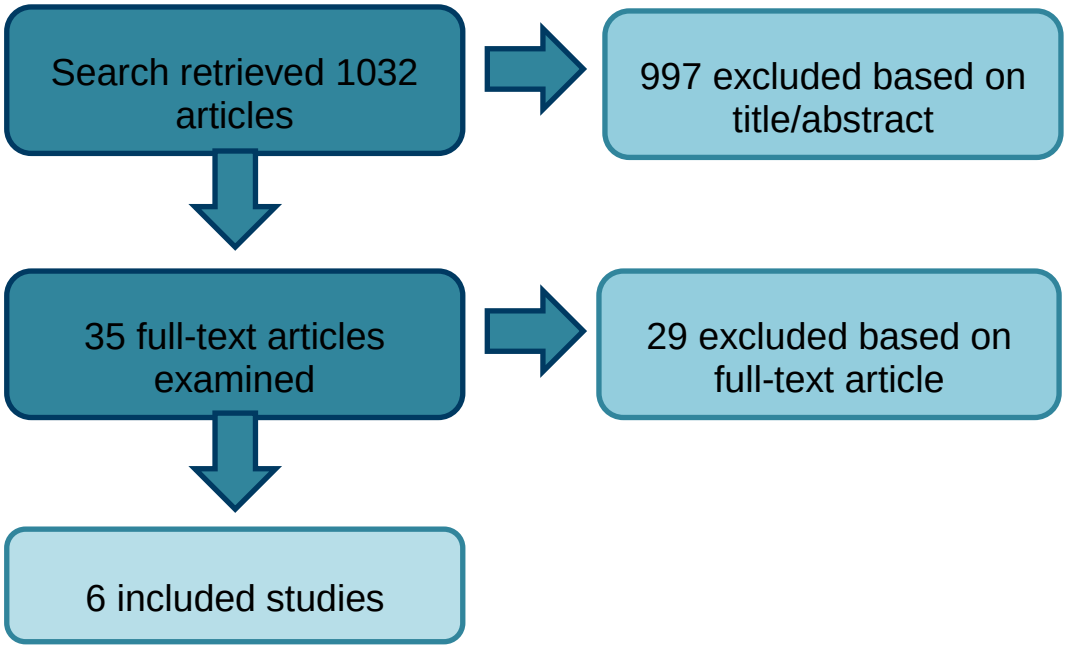
Database	Date searched	Number retrieved
MEDLINE (Ovid)	27/05/2015	496
MEDLINE In-Process (Ovid)	27/05/2015	38
EMBASE (Ovid)	27/05/2015	620
Cochrane Central Register of Controlled Trials (CENTRAL)	27/05/2015	336
Cochrane Database of Systematic Reviews (CDSR)	27/05/2015	68
Database of Abstracts of Reviews of Effectiveness (DARE)	27/05/2015	10
Health Technology Assessment (HTA)	27/05/2015	1
PubMed	27/05/2015	3

Table 5: Clinical search terms (Medline and Medline in Process)

Line number/Search term/Number retrieved
Search Strategy:
---
1 Arthritis, Rheumatoid/ (83803)
2 ((Rheumatoid* or rheumatic* or inflammat* or idiopathic* or deforman*) adj4 (arthrit* or arthros* or polyarthrit* or factor*)).tw. (104403)
3 (Chronic* adj4 (polyarthrit* or poly arthrit* or poly-arthrit* or rheumati*)).tw. (4304)
4 Rheumarthrit*.tw. (2)
5 (Beauvais* adj2 disease*).tw. (0)
6 ((Inflammat* or pain* or swell* or stiff*) adj4 (joint* or synovial*)).tw. (19420)
7 RA.tw. (49895)
8 or/1-7 (164535)
9 exp Hand/ (70980)
10 exp Hand Joints/ (15080)
11 (Hand* or finger* or thumb* or wrist* or digit* or metacarp* or carpal* or carpometacarpal* or metacarpophalangeal* or triangular* fibrocartilage*).tw. (619538)
12 or/9-11 (642173)
13 8 and 12 (10835)
14 Exercise/ or Exercise Therapy/ (95439)
15 Hand Strength/ (9695)
16 Movement/ or Exercise Movement Techniques/ (59589)
17 (Exercise* or strength* or move* or kinesiotherap*).tw. (654121)
18 (Finger* adj2 walk*).tw. (13)
19 "Range of Motion, Articular"/ (35234)
20 (Rang* adj2 (motion* or flex*)).tw. (19578)

Line number/Search term/Number retrieved
21 Splints/ or Splint*.tw. (14115)
22 Physical Therapists/ (470)
23 Physical Therapy Modalities/ (28792)
24 Physiotherapist/ (470)
25 Occupational Therapy/ (10535)
26 ((Physio* or physical* or Occ or Occupation* or Hand*) adj2 (therap* or treat* or service* or train* or program* or manage* or techni* or educat*)).tw. (59905)
27 or/14-26 (825497)
28 13 and 27 (2089)
29 Meta-Analysis.pt. (55570)
30 Meta-Analysis as Topic/ (14250)
31 Review.pt. (1953807)
32 exp Review Literature as Topic/ (8019)
33 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (65885)
34 (review$ or overview$).ti. (280419)
35 (systematic$ adj5 (review$ or overview$)).tw. (60868)
36 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4629)
37 ((studies or trial$) adj2 (review$ or overview$)).tw. (26028)
38 (integrat$ adj3 (research or review$ or literature)).tw. (5781)
39 (pool$ adj2 (analy$ or data)).tw. (14922)
40 (handsearch$ or (hand adj3 search$)).tw. (5515)
41 (manual$ adj3 search$).tw. (3265)
42 or/29-41 (2119681)
43 Randomized Controlled Trial.pt. (394882)
44 Controlled Clinical Trial.pt. (89465)
45 Clinical Trial.pt. (494303)
46 exp Clinical Trials as Topic/ (289367)
47 Placebos/ (32969)
48 Random Allocation/ (83416)
49 Double-Blind Method/ (130391)
50 Single-Blind Method/ (20469)
51 Cross-Over Studies/ (36041)
52 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (768399)
53 (random$ adj3 allocat$).tw. (21501)
54 placebo$.tw. (157160)
55 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (127859)
56 (crossover$ or (cross adj over$)).tw. (58382)
57 or/43-56 (1429225)
58 42 or 57 (3299791)
59 28 and 58 (609)
60 Animals/ not Humans/ (3947089)
61 59 not 60 (600)
62 limit 61 to english language (496)

Appendix E: Clinical review flowchart



Appendix F: Clinical excluded studies

Clinical excluded studies table

Reference	Reason for exclusion
Adams J, Bridle C, Dosanjh S, et al. (2012) Strengthening and stretching for rheumatoid arthritis of the hand (SARAH): design of a randomised controlled trial of a hand and upper limb exercise intervention. BMC Musculoskeletal Disorders 13:230	Study protocol
Bearne LM, Manning VL, Scott DL, et al. (2012) A brief exercise and self-management programme improves upper limb disability in people with early rheumatoid arthritis. Arthritis and Rheumatism 64:S1027	Abstract
Bergstra SA, Murgia A, Te Velde AF, et al. (2014) A systematic review into the effectiveness of hand exercise therapy in the treatment of rheumatoid arthritis. Clinical Rheumatology 33:1539-1548	Insufficient details on included studies
Bromley J, Unsworth A, Haslock I. (1994) Changes in stiffness following short- and long-term application of standard physiotherapeutic techniques. British Journal of Rheumatology 33:555-561	Not an RCT
Brorsson S, Thorstensson C, Nilsdotter A, et al. (2014) Two different sets of handexercises improved grip strength after eight weeks in patients with arthritis.	Abstract
Biljina AI, Taljanovic MS, Avdic DM, et al. (2001) Physical and exercise therapy for treatment of the rheumatoid hand. Arthritis Care & Research 45:392-397	Combined intervention (exercise and thermal baths, therapeutic heat or cold)
Chadwick A. (2004) A review of the history of the hand exercises in rheumatoid arthritis. Musculoskeletal Care 2:29-39	Review
Dogu B, Sirzai H, Yilmaz F, et al. (2012) Comparison of effects of isotonic and isometric hand exercises on pain, hand functions, dexterity and quality of life in patients with rheumatoid arthritis. International Journal of Rheumatic Diseases 15:142	Abstract
Ellegaard K, Torp-Pederson S, Lund H, et al. (2013) The effect of isometric exercise of the hand on the synovial blood flow in patients with rheumatoid arthritis measured by color Doppler ultrasound. Rheumatol Int 33:65-70	Not an RCT
Hawkes J, Care G, Dixon JS, et al. (1985) Comparison of three physiotherapy regimens for hands with rheumatoid arthritis. British Medical Journal of Clinical Research 291:1016	Brief research report, no relevant comparison group
Hawkes J, Care G, Dixon JS, et al. (1986) A comparison of three different physiotherapy treatments for rheumatoid arthritis of the hands. Physiotherapy Practice 2:155-160	No relevant comparison group
Heine P, Williams MA, McConkey C, et al. (2013) Sarah: strengthening and stretching for people with rheumatoid arthritis of the hands: a randomised controlled trial.	Abstract
Henning T, Haehre L, Hornburg VT, et al. (2013) Hand exercises significantly improved activity performance, grip strength and pain in women with hand osteoarthritis – results from a randomised controlled trial. Arthritis and Rheumatism S892-893	Abstract
Hoogeboom TJ, Dopp CM, de Jong S, et al. (2014) Meta-analysis on the effectiveness of exercise therapy in people with rheumatoid arthritis: time to account for therapeutic validity? Annals of Rheumatic Diseases Conference 73:201	Abstract

Reference	Reason for exclusion
Linekar SC, Bell MJ, Wilkins AL, et al. (2001) Improvements following short term home based physical therapy are maintained at one year in people with moderate to severe rheumatoid arthritis. The Journal of Rheumatology 28:165-168	Not an RCT
March L. (2015) An exercise program for hands and arms improved hand function in RA controlled with medication. Annals of Internal Medicine 162:JC9	Commentary
Mathieux R, Marotte H, Battistini L, et al. (2009) Early occupational therapy programme increases hand grip strength at 3 months: results from a randomised, blind, controlled study in early rheumatoid arthritis. Ann Rheum Dis 68:400-403	Not relevant intervention (full OT programme)
Nichols VP, Williamson EM, Toye F, et al. (2013) Factors affecting adherence to the sarah trial hand exercise programme for rheumatoid arthritis: an interview study. Rheumatology i100	Abstract
Opava C. (2015) Towards evidence-based hand exercises in rheumatoid arthritis. Lancet 385:396-398	Commentary
Porter BJ, Brittain A. (2012) Splinting and hand exercise for three common hand deformities in rheumatoid arthritis: a clinical perspective. Curr Opin Rheumatol 24:215-221	Review
Ronningen A, Kjeken I (2008) Effect of an intensive hand exercise programme in patients with rheumatoid arthritis. Scandinavian Journal of Occupational Therapy 15:173-183	Not an RCT
Singh H, Kumar S, Talapatra P, et al. (2012) Assessment of hand functions in rheumatoid arthritis using SF-SACRAH (short form score for the assessment and quantification of chronic rheumatoid affections of the hands) and its correlation to disease activity. Rheumatol Int 32:3413-3419	Nor an RCT
Wessel J. (2004) The effectiveness of hand exercises for persons with rheumatoid arthritis: a systematic review. Journal of Hand Therapy 17:174-180	Systematic review, insufficient detail on methods, included not RCT studies
Williams MA, Heine PJ, McConkey C, et al. (2013) Sarah: strengthening and stretching for people with rheumatoid arthritis of the hands: a randomized controlled trial. Rheumatology i31-i32	Abstract
Williams MA, Heine PJ, Bruce J, et al. (2012) Exercise therapy for the rheumatoid hand. Cochrane Database of Systematic Reviews. 4:DOI 10.1002/14651858	Protocol
Wilson RL. (1986) Rheumatoid arthritis of the hand. Orthopedic Clinics of North America 17:313-343	Clinical review

Appendix G: Clinical evidence tables

Table 6: Evidence tables

<table>
<tr><td>Bibliographic reference</td><td>Cima et al (2013) Strengthening exercises to improve hand strength and functionality in rheumatoid arthritis with hand deformities: a randomized, controlled trial. Rheumatol Int 33:725-732</td></tr>
<tr><td>Study type</td><td>RCT (randomisation by computer-generated programme, evaluator and research therapists not blinded)</td></tr>
<tr><td>Aim</td><td>To evaluate the effects of an exercise programme aimed at improving the force of intrinsic and extrinsic hand muscles of individuals with RA hand deformities as well as to analyse the impact of the exercises on hand functionality</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion:
- RA with deformity in at least one of the fingers of each hand

Deformities;<table><tr><td>Deformity</td><td>Description</td></tr><tr><td>Swan neck</td><td>Hyperextension of the proximal interphalangeal joint with flexion of distal interphalangeal joint</td></tr><tr><td>Boutonniere finger</td><td>Flexion of the proximal interphalangeal joint with hyperextension of distal interphalangeal joint</td></tr><tr><td>Z-shaped thumb</td><td>Flexion of the metacarpophalangeal joint and hyperextension of the interphalangeal joint</td></tr><tr><td>Ulnar deviation</td><td>Ulnar deviation of the metacarpophalangeal joints</td></tr></table>
Exclusion:
- Other RA-related diseases and/or had entered the exacerbation phase during the experimental time

All participants were female, intervention group mean age 53years, control mean age 60.4years</td></tr>
<tr><td>Number of Patients</td><td>N=20</td></tr>
<tr><td>Intervention</td><td>N=13
Rehabilitation programme aimed at increasing the muscle force of handgrip; 20 sessions x2/week for an average of 35minutes, 2 consecutive months;
- Series of exercises with both free and motor-coordination tasks
- Strengthening exercises with both hands by means of Digiflex hand exerciser, modelling mass and elastics
- Intensity and load of strengthening increased every 3weeks by adding repetitions to each series and adjusting the Digiflex load depending on the individual capacity of the patient</td></tr>
</table>

Bibliographic reference	Cima et al (2013) Strengthening exercises to improve hand strength and functionality in rheumatoid arthritis with hand deformities: a randomized, controlled trial. Rheumatol Int 33:725-732
	Also given a primer showing how to do exercises at home, x1/day for 3days/week Instructed to keep habitual daily activities
Comparison	N=7 No type of treatment for improving handgrip Instructed to keep habitual daily activities
Length of follow up	Intervention group evaluated at 10 and 20 sessions Control group evaluated at 2months
Location	Brazil
Outcomes measures and effect size	Health Assessment Questionnaire (HAQ), considered validated and useful for the assessment and functionality capacity of RA patients (applied in a single day) Handgrip and pinch strength by using a pinch gauge (B&L, model PG-30) and handgrip dynamometer (JAMAR, model 5030J1) at (Kgf) scale Pinch strength; PS1 (index finger and thumb), PS2 (third finger and thumb), PS3 (fourth finger and thumb), PS4 (fifth finger and thumb) N=17 (N=10 intervention and N=7 control) completed the study **Results:** **Average scores HAQ;** Intervention group: baseline mean 1.28 (SD 0.82), 10 sessions 1.11 (0.78), 20 sessions 0.85 (0.7), after 20 sessions internally compared, p=0.016 Control group: baseline 1.23 (0.67), 2months 1.29 (0.29); no difference between initial and final values Handgrip strength; At baseline no differences between intervention and control groups Intervention group; - increase in grip strength at 10sessions p<0.05 vs baseline for both dominant and non-dominant hands - increase in grip strength at 20sessions p<0.05 vs baseline for both dominant and non-dominant hands - increase in grip strength at 20sessions p<0.05 vs at 10sessions for non-dominant hand Control group; no difference at 2months vs baseline Pinch strength;

Bibliographic reference	**Cima et al (2013) Strengthening exercises to improve hand strength and functionality in rheumatoid arthritis with hand deformities: a randomized, controlled trial. Rheumatol Int 33:725-732**
	At baseline no differences between intervention and control groups Intervention group; - PS1 increase in strength at 10sessions p<0.05 vs baseline for both dominant and non-dominant hands - PS2 increase in strength at 10sessions p<0.05 vs baseline for both dominant and non-dominant hands - PS4 increase in strength at 10sessions p<0.05 vs baseline for non-dominant hand - PS1 increase in strength at 20sessions p<0.05 vs baseline for both dominant and non-dominant hands - PS2 increase in strength at 20sessions p<0.05 vs baseline for both dominant and non-dominant hands - PS3 increase in strength at 20sessions p<0.05 vs baseline for both dominant and non-dominant hands - PS4 increase in strength at 20sessions p<0.05 vs baseline for both dominant and non-dominant hands - PS2 increase in strength at 20sessions p<0.05 vs at 10sessions for dominant hand - PS3 increase in strength at 20sessions p<0.05 vs at 10sessions for non-dominant hand Control group; no difference at 2months vs baseline
Source of funding	Research Foundation of Sao Paulo, National Counsel of Technological and Scientific Development
Comments	

Bibliographic reference	**Delhag et al (1992) Effect of active hand exercise and wax bath treatment in rheumatoid arthritis patients. Arthritis Research and Care 5:87-92**
Study type	RCT (randomised using sequential allocation according to age, sex, duration of disease and/or previous hand surgery)
Aim	To evaluate the effects in RA patients of active hand exercise and wax bath treatment alone and in combination
Patient characteristics	From a questionnaire survey of all seropositive RA patients of the university hospital, January 1987 to June 1988 Inclusion; - Resident of Gothenberg, <70years, duration of disease 6 to 10years - Functional class I-II - Hand problems defined as decreased ROM and/or grip strength Exclusion;

Bibliographic reference	Delhag et al (1992) Effect of active hand exercise and wax bath treatment in rheumatoid arthritis patients. Arthritis Research and Care 5:87-92
	- Seropositive RA patients with other diagnoses N=33 female, N=19 male, between 29 and 69years, mean duration of disease 7.7years (male), 7.5years (female) No differences between variables at baseline
Number of Patients	N=52 (Initially N=65 N=13 dropped out before the start of the study)
Intervention	Patients included in the regular treatment groups in the OT department x3/week for 4weeks N=15 Wax-bath treatment; - Both hands slowly dipped x5 in 47 to 50ºC wax bath, wrapped in paper and fitted in quilt mittens, kept on for 20minutes N=11 Hand exercise; - Standard written programme including 8 different movement exercises (flexion, extension and radial deviation of fingers, dorsal flexion, palmar flexion and ulnar deviation of wrists, opposition and abduction of thumbs), repeated x5/session - Rotation, flexion and abduction movements of shoulders added to the programme - Soft exercise dough used to obtain slight resistance to facilitate the performance of exercises - Programme took about 20minutes N=13 Wax bath and hand exercise
Comparison	N=13 Control
Length of follow up	2 to 5days after the 4week treatment period
Location	Sweden
Outcomes measures and effect size	Range of motion, bilaterally; - Flexion deficits of digits II-V - Extension deficits of digits II-V Grip function, dominant hand;

Bibliographic reference	Delhag et al (1992) Effect of active hand exercise and wax bath treatment in rheumatoid arthritis patients. Arthritis Research and Care 5:87-92

- Measured by Sollerman test (7 different grips combined within 20 different tasks (graded from 4, best, to 0, worst)

Grip strength, bilaterally;

- By electronic instrument, Groppit (AB Detektor, Gotherberg, Sweden)

Pain with resisted motion, dominant hand;

- During grip function tests, measured on a 10-point scale (o is described as no pain, 9 as maximal pain), mean score calculated

Pain with nonresisted motion, both hands;

- 100mm vertical VAS, lowest point was no pain, highest point was maximal pain

Stiffness of both hands;

- 100mm vertical VAS, lowest pain was no stiffness, highest point was maximal stiffness

Results;

	Wax bath/exercise		Exercise		Wax bath		Control		Test of changes scores
	Baseline	4wks	Baseline	4wks	Baseline	4wks	Baseline	4wks	
ROM deficit (mm)									
Flexion, dominant hand	62.3	52.1	56.1	43.8	43.0	42.9	59.4	62.0	8.4, p<0.05
Flexion, non dominant hand	77.0	55.4*	46.6	39.8	26.1	36.5	43.9	42.5	6.7, NS
Extension, dominant hand	42.4	32.9	25.8	24.1	21.3	21.6	39.4	33.5	6.0, NS
Extension, non dominant hand	24.9	15.8*	15.2	14.5	6.8	9.2	21.5	19.2	7.0, NS
Grip function (0-80points)	72.3	74.8*	74.8	76.1	75.5	75.0	75.2	75.0	6.9, NS
Pinch function (0-32points)	27.4	29.3*	29.2	29.3	29.3	28.3	29.5	29.2	8.9, NS
Grip strength (Newton)									
Maximum dominant hand	93.9	98.8	117.1	126.2	90.9	96.5	107.4	105.9	1.8,NS
Maximum non dominant hand	106.8	107.4	135.3	145.1	120.5	99.7	128.3	120.3	3.2,NS
Average dominant hand	72.4	79.2	90.7	109.7	72.9	75.9	82.6	85.4	2.9,NS
Average non dominant hand	88.2	86.9	100.8	108.0	97.3	80.0	101.0	99.9	3.9,NS
Pain									
Resisted motion dominant hand (0-9points)	1.4	0.8	1.1	1.3	1.5	1.6	1.3	1.5	7.4,NS
Non resisted motion dominant	29.3	22.1	28.8	17.0*	20.3	25.9	27.7	33.1	10.5, p<0.05

Bibliographic reference	**Delhag et al (1992) Effect of active hand exercise and wax bath treatment in rheumatoid arthritis patients. Arthritis Research and Care 5:87-92**
	hand (0-9points) | | | | | | Stiffness, both hands (0-100points) | 39.3 24.9 | 42.1 31.1 | 23.7 27.0 | 36.0 30.2 | 2.6,NS *p<0.05 between baseline and end of treatment
Source of funding	Riksforbundet mot Reumatism, Stockholm
Comments	

Bibliographic reference	**Dogu et al (2013) Effects of isotonic and isometric hand exercises on pain, hand functions, dexterity and quality of life in women with rheumatoid arthritis. Rheumatol Int 33:2625-2630**
Study type	RCT (parallel, single-blinded, randomisation by a random number sequence, blinded physician undertook evaluations)
Aim	To evaluate the effect of a 6-week-long isotonic and isometric hand exercises on pain, hand functions, dexterity and quality of life in women with RA
Patient characteristics	Rheumatology out-patient clinic Inclusion: - fulfilling the American College of Rheumatology criteria for RA - disease >1year, age 40 to 70years, stage 1 to 3 based on Steinbrocker's functional evaluation scale Exclusion: - carpel tunnel and cubital tunnel syndromes, polyneuropathies, pregnancy - having undergone hand surgery, active arthritis of the hand joints All participants were female, mean age isotonic group (54.91±9.27years), isometric group (50.38±9.32years), disease duration isotonic group (10.65±7.64years), isometric group (8.17±6.51years) – no differences between the groups, similar for other characteristics
Number of Patients	N=52 (N=47 completed study)
Intervention	All patients received instructions for exercises via printed material. For the first 2weeks of the study exercises performed under guidance of a therapist, x5days/week N=23

Bibliographic reference	Dogu et al (2013) Effects of isotonic and isometric hand exercises on pain, hand functions, dexterity and quality of life in women with rheumatoid arthritis. Rheumatol Int 33:2625-2630
	Isotonic, at least x1/day with x10 repetitions - flexion and extension of the wrist - supination and pronation of the hand and the forearm - fingers flexed to form a fist and extended back - touch the tips of other fingers with the thumb - abduction and adductions of the fingers (Isotonic exercises are active exercises in which muscles contract and cause movement, there is not significant resistance throughout the movement)
Comparison	N=24 Isometric, at least x1/day with x10 repetitions – movement to last 5s with 15s pause in between the movements - push the hands by facing the palms towards each other - ulnar deviation against pressure while the fingers are in flexion - pushing the lid of the perfume bottle while the IP joint of the thumb is in flexion - abduction and adduction by placing the hands of the physician in between the fingers - while the fingers are at 90º flexion at the MP joint , flexion and extension of the fingers against pressure - gripping the water glass placed into the palm (Isometric exercises are active exercises in which muscle tension is increased while pressure is applied against resistance)
Length of follow up	6weeks of exercises
Location	Turkey
Outcomes measures and effect size	Pain; - VAS ranging from 0 to 10 (0= no pain, 10=highest pain tolerance) Hand function; - Duruoz Hand Index (DHI) - self-reporting questionnaire of 18 questions to evaluate the limitations in hand function of RA patients, scored 0 (not difficult) to 5 (impossible to perform) Dexterity; - Nine hole peg test – time to complete Quality of life; - Rheumatoid Arthritis Quality of Life (RAQoL) Handgrip strength;

Bibliographic reference	Dogu et al (2013) Effects of isotonic and isometric hand exercises on pain, hand functions, dexterity and quality of life in women with rheumatoid arthritis. Rheumatol Int 33:2625-2630

- Handheld dynamometer (JAMAR dynamometer) in kgs – measured x3, means calculated

Disease activity;

- Disease activity score (DAS 28)

N=47 completed study

Results:

Pain, hand function, dexterity, QoL, handgrip strength, disease activity changes

Medians (IQR)

	Isotonics, N=23	Isometrics, N=24	P value
Pain			
Pre treatment	5(0-8)	3.5(2-6.75)	0.636
6weeks	3(0-5)	4(0-4.75)	0.931
P value	0.036	0.021	
Hand function			
Pre treatment	15(5-40)	16.5(5.25-30.5)	0.823
6weeks	11(3-33)	12(3.5-25.25)	0.814
P value	0.002	0.002	
Dexterity			
Pre treatment	30(25-45)	30(20-38.75)	0.158
6weeks	28(20-40)	23.5(20-30)	0.276
P value	0.0001	0.005	
RA QoL			
Pre treatment	19(15-24)	18(11.5-22.75)	0.572
6weeks	15(14-21)	14.32(7.25-21)	0.502
P value	0.003	0.001	
Dominant hand strength			
Pre treatment	10(6-18)	10.5(8-13.75)	0.991
6weeks	11(8-20)	14(8.5-18)	0.572

Bibliographic reference	Dogu et al (2013) Effects of isotonic and isometric hand exercises on pain, hand functions, dexterity and quality of life in women with rheumatoid arthritis. Rheumatol Int 33:2625-2630

P value	0.372	0.029	
Non-dominant hand strength			
Pre treatment	9(4-16)	10.5(6-17)	0.363
6weeks	10(6-18)	10(6.5-17.5)	0.616
P value	0.013	0.138	
Disease activity			
Pre treatment	3.99(3.49-4.81)	4.06(2.77-5.08)	0.632
6weeks	3.2(2.5-4.02)	3.03(2.27-3.56)	0.425
P value	0.002	0.0001	

Differences in improvements;

	Isotonics, N=23	Isometrics, N=24	Differences
Pain			
Mean±SD	1.26±2.68	1.04±2.13	0.22, p=0.711
Median (IQR)	1(0-3)	0(0-2.75)	
Hand function			
Mean±SD	2.83±3.71	3.06±3.60	0.23, p=0.847
Median (IQR)	2(0-7)	2(0.25-6)	
Dexterity			
Mean±SD	5.17±5.19	4.12±6.92	-1.05, p=0.123
Median (IQR)	5(2-5)	2(0-8.75)	
RA QoL			
Mean±SD	4.09±5.14	6.04±8.76	1.95, p=0.748
Median (IQR)	3(0-9)	2(0-13.75)	
Dominant hand strength			
Mean±SD	0.56±2.62	2.04±4.28	1.48, p=0.136
Median (IQR)	0(-1to2)	2(-0.75to4)	

Bibliographic reference	**Dogu et al (2013) Effects of isotonic and isometric hand exercises on pain, hand functions, dexterity and quality of life in women with rheumatoid arthritis. Rheumatol Int 33:2625-2630**
	Non-dominant hand strength | | | | Mean±SD | 1.30±3.39 | 1.00±2.84 | -0.30, p=0.327 Median (IQR) | 2(0-2) | 0(-1to2) | **Disease activity** | | | | Mean±SD | 0.70±1.08 | 0.78±0.80 | 0.08, p=0.856 Median (IQR) | 0.7(0.2-1.24) | 0.68(0.21-1.27) |
Source of funding	Not reported
Comments	

Bibliographic reference	**Hoenig et al (1993) A randomized controlled trial of home exercise on the rheumatoid hand. The Journal of Rheumatology 20:785-789**
Study type	RCT (randomisation in blocks of 4 using random number tables, OT evaluator blinded)
Aim	To study differing home hand exercise interventions to determine effects on grip strength
Patient characteristics	All patients at the hospital with a diagnosis of RA and the first 50 alphabetical patients on a rheumatologist outpatient list Inclusion; - Met American Rheumatism Association criteria for definite or classical RA - ARA functional class II or III Exclusion; - Changes medication in the last 6weeks Groups similar for age, sex, years since diagnosis (mean years since diagnosis 11.3), global assessment, morning stiffness, pain scale, prior involvement in exercise, employment and performance of housework, significant difference in left and right MCP extension and in left ulnar deviation Protocol permitted changes in NSAID or decreases in either corticosteroids or DMARDs
Number of Patients	N=57 enrolled (N=44 completed the study)
Intervention	All 3 exercise regimens demonstrated by an OT

Bibliographic reference	Hoenig et al (1993) A randomized controlled trial of home exercise on the rheumatoid hand. The Journal of Rheumatology 20:785-789
	Received written explanations of their particular exercises Contacted individually to ensure that they understood their exercise assignment Therapy was continued for 12weeks N=15 Range of motion (ROM); - Tendon gliding exercises (thumb and fingers) N=14 Resistive; - Used therapy putty, performed balanced resistive hand exercises, included finger abduction and adduction exercises with the metacarpophalangeal (MCP) extended and gross grip - x10 repetitions of each exercise, 10-20minutes to complete, x2/day N=15 Resistive and ROM
Comparison	N=13 Control; - Encouraged to maintain an active lifestyle
Length of follow up	3months post-intervention – follow-up evaluation
Location	USA
Outcomes measures and effect size	Follow-up evaluation; - Grip strength, modified aneroid mamometer - ROM of the MCP and proximal interphalangeal (PIP) joints - Hand articular index - PIP joint circumference, arthrocircometer - Degrees of ulnar deviation of the 3rd digit, goniometer with the fingers voluntarily adducted on a flat surface - Clinical impression of hand deformities (MCP subluxation, boutonniere and swan neck deformities) - Dexterity with a timed 9 hole peg test - Questionnaire, including number of min of morning stiffness, numerical analog scale of hand pain, and global assessment of the severity of their arthritis

Bibliographic reference	Hoenig et al (1993) A randomized controlled trial of home exercise on the rheumatoid hand. The Journal of Rheumatology 20:785-789

N=16 dropouts (did not return, discontinued exercise and/or were protocol violations
N=1 left-handed

Results:
Comparison of measured hand indices pre and post exercise left (L), right (R), hands;

	Articular index (painful joints)		Ulnar deviation (cm/hand)		MCP extension (º)		PIP extension (º)		Dexterity	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
ROM (N=11)										
ROM, L	2.3	2.7	1.7#	-0.4	1.7#	1.3	-2.1	-2.0	23.9	23.6
ROM,R	2.6	2.2*	3.2	1.7	4.5#	1.6	-1.3	-0.5	23.2	23.3
Res (N=9)										
Res, L	2.0	3.3	17.8	15.9	19.2#	20.6	2.9	-1.4*	29.2	28.0
Res, R	3.0	3.4	18.6	14.7	30.3#	34.4.	1.2	0.4	32.3	30.1
Res/ROM (N=10)										
Res/ROM, L	2.5	2.4	6.5	4.0	5.3	7.8	7.3	8.1	29.5	24.4*
Res/ROM, R	3.5	3.2	12.8	9.9	9.9	10.1.	6.6	8.2	26.4	28.8
Control (N=11)										
Control, L	1.6	2.6	9.9	10.5	7.7	7.1	1.4	2.1	26.2	26.5
Control, R	1.5	2.7	11.8	11.8	13.5	16.6	0.8	3.9	24.3	25.0

#difference between groups at baseline, p<0.05
*compared with control groups for change over time, p<0.05

Duration of RA in those who completed the study compared with those who did not;
- Completed (N=41) 9.8years, dropouts (N=16) 15.1years, p<0.05

Mean grip strength;

	Left hand mmHg		Right hand mmHg	

Bibliographic reference	**Hoenig et al (1993) A randomized controlled trial of home exercise on the rheumatoid hand. The Journal of Rheumatology 20:785-789**

	(SD)		(SD)	
	Pre	Post	Pre	Post
ROM (N=11)	70.4 (44.0)	84.0 (47.5)	93.4 (58.0)	85.5 (43.8)
Res (N=9)	62.0 (32.8)	87.4 (44.6)	69.3 (43.3)	82.1 (43.0)
Res/ROM (N=10)	83.2 (62.1)	96.8 (71.6)	84.2 (61.5)	97.6 (68.4)
Any hand exercise (N=30)	72.1 (48.9)	89.3* (56.3)	83.1 (56.1)	90.0 (53.4)
Control (N=11)	83.0 (64.9)	81.1 (64.7)	68.2 (36.7)	81.1 (60.1)

* compared with control groups for change over time, $p<0.05$

Adherence;

- 87.5% of those in the exercise portion of the study returned log sheets, these showed 79.9% of the recommended exercises were performed

Adverse events;

Problems with upper extremities;

- ROM (N=4/15), Resistive (N=12/14), ROM and resistive (N=10/15)
- For 70% of those involved – occurred within 1 week of starting exercise

Decreased the frequency of sessions and/or number of repetitions;

- ROM (N=1/15), Resistive (N=5/14), ROM and resistive (N=5/15), $X^2 = 0.017$
- 87% of those who tried reducing frequency and/or repetitions were able to continue exercising

Source of funding	The Bassett Research Foundation, Fred Sammons Inc
Comments	Not ITT analysis

Bibliographic reference	**Lamb et al (2015) Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 385:421-429**
Study type	RCT (investigator blinded, stratification by centre, allocation computer generated and unmasked to participants and therapists delivering treatment after allocation)
Aim	To estimate for those with RA controlled by drugs, the effectiveness and cost effectiveness of adding an individually tailored, progressive exercise programme for the hands and arms to best practice usual care

Bibliographic reference	**Lamb et al (2015) Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 385:421-429**
Patient characteristics	17 NHS hospital trusts, October 2009 to May 2011, recruited from outpatient clinics and mailing patients on consultant and therapy review lines Inclusion; - RA meeting American College of Rheumatology clinical and immunological criteria - Reported active pain and dysfunction of hands - Not on a DMARD regimen or on a stable DMARD regimen (including biologics if used) for ≥3months Exclusion; - Upper limb surgery or fracture in previous 6months, pregnancy, waiting for upper limb surgery Groups similar at baseline; both 76% female, years since diagnosis (intervention median 10 (IQR 4, 22); usual care 10 (4,21))
Number of Patients	N=490 (N=4 withdrew before treatment)
Intervention	N=246 (N=2 withdrew before treatment) usual care and intervention; Assessment and advice session plus x5 30 to 45minute exercise sessions over 12weeks Content of usual care arm treatment An exercise programme aiming to improve strength, mobility and dexterity (including 4 strength exercises for the hand and 7 mobility exercises of all upper limb joints) A home exercise plan with exercises performed daily A standardised protocol for progression or regression Strategies to improve programme adherence including exercise diaries No resting splints No manual therapy or electrotherapy To standardise treatment all therapists had a training session and were provided with treatment manuals – none of the interventions are beyond the scope of normal therapy practice
Comparison	N=244 (N=2 withdrew before treatment) usual care; Individual appointments with a therapist (number dependent on clinical need, maximum of x3 sessions (1.5hours in total) Joint protection advice

<table>
<tr><th>Bibliographic reference</th><th>Lamb et al (2015) Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 385:421-429</th></tr>
<tr><td></td><td>Provision of Arthritis Research Campaign booklets
Functional splinting as required
Assistive devices as required
No resting splints provided
No explicit exercise prescription
No manual therapy (joint mobilisations) or electrotherapy</td></tr>
<tr><td>Length of follow up</td><td>4 and 12months after randomisation</td></tr>
<tr><td>Location</td><td>UK</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Primary outcome;
- Overall hand function subscale of the Michigan Hand outcome Questionnaire (MHQ) at 12months (scale 0to100, high score indicates great function)
Secondary outcomes;
- Other subscales of the MHQ; activities of daily living, work performance, satisfaction, aesthetics, summed MHQ score
- Pain – via Troublesomeness questionnaire (range 0to20, high score indicates greater pain), self-reported global change, benefit or harm, and treatment satisfaction questions
- Physical ability measures; isometric pinch and grip strength, dexterity, hand and wrist range of motion, and metacarpophalangeal joint alignment
- Self-efficacy; Arthritis Self-efficacy scale (7 items, high score indicates great self-efficacy)
- Modified tender and swollen joint counts of the hands and wrist (22 joints in total)
- Changes in disease activity
- Health related quality of life (SF-12) and EuroQoL EQ-5D
- Self-assessment of exercise compliance via 5 item questionnaire
- Adverse events

Used complier-average casual effect analysis (CACE) to estimate the effects of patient compliance on the primary outcome

Results:
Treatments delivered;
<table>
<tr><td>Treatments delivered</td><td>Usual care</td><td>Exercise intervention</td></tr>
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</td></tr>
</table>

Bibliographic reference	Lamb et al (2015) Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 385:421-429

Median number of sessions	1 (1 to 2)	6 (5 to 6)
Did not attend any sessions	7/242 (3%)	8/246 (3%)
Attended assessment session only*	135/242 (56%)	8/246 (3%)
Part completion of treatment	10/242 (4%)	46/246 (19%)
Full completion of treatment	225/242 (93%)	184/246 (75%)
Self-reported exercise[#] at 4months	137/222 (62%)	174/216 (81%)
Self-reported exercise[#] at 4months	123/216 (57%)	128/206 (62%)

*no follow-up sessions attended, usual care were expected to have between 1 and 3 sessions
[#]≥1 to 2 sessions/week

Primary outcome and patient-reported secondary outcome measures;

	Mean change from baseline (95%CI)		**Mean treatment difference (95%CI)**	**P value**
Overall hand function (MHQ)	**Usual care**	**Exercise**		
4 months (N=449)	4.04 (2.17 to 5.91)	8.73 (6.83 to 10.64)	4.71 (2.32 to 7.11)	0.0001
12 months (N=438)	3.56 (1.45 to 5.68)	7.93 (5.98 to 9.88)	4.28 (1.49 to 7.06)	0.0028
MHQ ADL (both hands)				
4 months (N=448)	2.57 (-0.40 to 4.74)	7.86 (5.44 to 10.28)	5.66 (2.64 to 8.69)	0.0003
12 months (N=436)	2.27 (-0.04 to 4.59)	5.89 (3.66 to 8.13)	3.48 (0.31 to 6.66)	0.0321
MHQ work				
4 months (N=445)	5.27 (2.62 to 7.92)	6.12 (3.68 to 8.56)	1.04 (-2.39 to 4.48)	0.5518
12 months (N=436)	3.11 (0.23 to 5.98)	8.12 (5.36 to 10.87)	4.62 (0.82 to 8.42)	0.0175
MHQ satisfaction (both hands)				
4 months (N=445)	6.66 (4.01 to 9.31)	9.59 (6.86 to 12.32)	3.61 (0.12 to 7.09)	0.0430
12 months (N=436)	7.06 (4.16 to 9.95)	10.36 (7.53 to 13.18)	3.38 (-0.37 to 7.13)	0.0784
MHQ pain				
4 months (N=445)	-5.11 (-7.58 to -2.63)	-7.60 (-9.94 to -5.26)	-3.30 (-6.50 to -0.11)	0.0433

Bibliographic reference	Lamb et al (2015) Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 385:421-429				
	12 months (N=437)	-6.01 (-8.74 to -3.29)	-8.26 (-10.83 to -5.70)	-2.40 (-5.92 to 1.12)	0.1814
	MHQ aesthetics (both hands)				
	4 months (N=442)	2.84 (0.27 to 5.41)	3.52 (0.89 to 6.14)	0.9 (-2.96 to 3.74)	0.8209
	12 months (N=437)	3.37 (0.42 to 6.33)	4.70 (1.81 to 7.59)	1.01 (-2.70 to 4.72)	0.5933
	MHQ summed score				
	4 months (N=451)	4.34 (2.67 to 6.00)	7.28 (5.65 to 8.91)	3.17 (0.91 to 5.43)	0.0063
	12 months (N=438)	4.22 (2.23 to 6.21)	7.59 (5.75 to 9.43)	3.21 (0.53 to 5.89)	0.0195
	SF12 mental component score				
	4 months (N=443)	0.58 (-0.56 to 1.73)	0.46 (-0.66 to 1.59)	-0.16 (-1.58 to 1.27)	0.8299
	12 months (N=423)	0.41 (-0.89 to 1.71)	2.19 (0.75 to 3.63)	1.59 (-0.06 to 3.23)	0.0593
	SF12 physical component score				
	4 months (N=443)	0.91 (0.03 to 1.80)	2.04 (1.01 to 3.08)	1.18 (-0.11 to 2.46)	0.0743
	12 months (N=423)	0.03 (-0.96 to 1.03)	1.19 (0.23 to 2.14)	0.93 (-0.35 to 2.22)	0.1555
	EQ-5D health state				
	4 months (N=448)	0.01 (-0.03 to 1.80)	0.04 (0.01 to 0.07)	0.02 (-0.02 to 0.06)	0.3813
	12 months (N=434)	0.02 (-0.01 to 0.06)	0.03 (0.00 to 0.06)	0.00 (-0.03 to 0.04)	0.8714
	Troublesomeness				
	4 months (N=439)	-4.64 (-7.23 to -2.05)	-5.44 (-7.91 to -2.97)	-2.70 (-5.91 to 0.50)	0.0993
	12 months (N=423)	-4.54 (-7.35 to -1.73)	-4.32 (-7.15 to -1.49)	-1.61 (-5.21 to 1.99)	0.3810
	Self-efficacy				
	4 months (N=49)	2.04 (-0.10 to 4.19)	5.78 (3.40 to 8.17)	3.38 (0.45 to 6.30)	0.0244
	12 months (N=438)	1.11 (-1.44 to 3.66)	5.19 (2.45 to 7.92)	3.21 (-0.19 to 6.62)	0.0651

Physical performance and secondary outcome measures;

	Mean change from baseline (95%CI)		**Mean treatment difference (95%CI)**	**P value**

Bibliographic reference	Lamb et al (2015) Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 385:421-429				
	Full-hand grip force (Newtons)	**Usual care**	**Exercise**		
	4 months (N=400)	7.35 (2.43 to 12.28)	15.55 (10.17 to 20.93)	9.29 (2.01 to 16.57)	0.0129
	12 months (N=355)	9.57 (3.66 to 15.48)	15.77 (10.11 to 21.42)	6.41 (-1.87 to 14.70)	0.1303
	Pinch grip force (Newtons)				
	4 months (N=396)	3.15 (1.60 to 4.70)	4.92 (2.74 to 5.4)	1.57 (-0.59 to 3.73)	0.1547
	12 months (N=351)	2.35 (0.63 to 4.06)	5.33 (2.99 to 7.68)	3.01 (0.13 to 5.88)	0.0411
	Active wrist ROM score (º)				
	4 months (N=401)	2.75 (0.63 to 4.87)	4.84 (2.65 to 7.02)	1.58 (-1.25 to 4.41)	0.2750
	12 months (N=356)	4.21 (1.73 to 6.68)	4.56 (2.13 to 7.00)	0.27 (-2.72 to 3.26)	0.8587
	Combined finger flexion (mm)				
	4 months (N=398)	-3.39 (-4.54 to -2.25)	-4.45 (-5.82 to -3.07)	-0.93 (-2.43 to 0.58)	0.2281
	12 months (N=355)	-3.20 (-4.51 to-1.89)	-3.92 (-5.48 to -2.36)	-0.64 (-2.40 to 1.13)	0.4793
	Composite finger extension (mm)				
	4 months (N=390)	1.45 (-0.17 to 3.07)	4.04 (1.98 to 6.09)	2.55 (0.05 to 5.04)	0.0462
	12 months (N=346)	1.45 (-0.76 to 3.65)	4.81 (2.77 to 6.84)	4.05 (1.13 to 6.96)	0.0068
	Thumb opposition score				
	4 months (N=403)	0.18 (0.00 to 0.35)	0.31 (0.13 to 0.50)	0.13 (-0.10 to 0.37)	0.2725
	12 months (N=359)	0.12 (-0.07 to0.33)	0.16 (-0.04 to 0.37)	0.10 (-0.16 to 0.36)	0.4416
	Dexterity				
	4 months (N=403)	-0.74 (-1.50 to 0.03)	-1.39 (-1.97 to -0.81)	-0.64 (-1.53 to 0.26)	0.1643
	12 months (N=358)	-0.09 (-0.92 to 0.74)	-1.33 (-1.86 to -0.80)	-1.19 (-2.15 to -0.23)	0.0156
	Swollen joint count (both hands)				
	4 months (N=405)	-0.12 (-0.73 to 0.48)	-1.05 (-1.58 to -0.53)	-0.87 (-1.50 to -0.23)	0.0077
	12 months (N=360)	-1.02 (-1.71 to -0.34)	-1.13 (-1.69 to -0.56)	-0.07 (-0.74 to 0.61)	0.8844
	Tender joint count (both hands)				

Bibliographic reference	Lamb et al (2015) Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 385:421-429

4 months (N=405)	-0.38 (-1.02 to 0.27)	-1.27 (-1.86 to -0.68)	-1.03 (-1.77 to -0.29)	0.0069
12 months (N=360)	-1.15 (-1.86 to -0.43)	-0.96 (-1.69 to -0.23)	0.12 (-0.77 to 1.00)	0.7955
MCP joint deformity (º)				
4 months (N=398)	-0.59 (-1.32 to 0.15)	-0.92 (-1.57 to -0.27)	-0.66 (-1.53 to 0.21)	0.1357
12 months (N=355)	-0.32 (-1.01 to 0.36)	-0.70 (-1.41 to 0.01)	-0.56 (-1.50 to 0.37)	0.2369

Subgroups;

	Treatment effect (95%CI)	P (interaction)
Time since diagnosis		
<5years (N=115) ≥5years (N=276)	-6.08 (0.22 to 11.94) -3.72 (0.21 to 7.22)	0.4822
Baseline medication		
Biological DMARD only Combination non-biological DMARD Single non-biological DMARD No DMARD	4.70 (-1.12 to 10.52) 6.20 (-0.09 to 12.49) 4.20 (0.10 to 8.50) -1.84 (-12.04 to 8.37)	0.6261

Adverse events;
N=103 serious AEs – none considered related to treatment
N=2 in the intervention group had transient arm pain

Source of funding	NIHR HTA project, funder stated to have no role in data analysis, interpretation or publication decisions
Comments	SMD of 0.3 based on previous study and nature of this trial, for this difference and 80% power, 5% significance, needed a total of 352 participants, allowing for 25% drop-out needed 469 ITT analysis Estimated therapist effects from a random effect nested within each centre

Bibliographic reference	**O'Brien et al (2006) Conservative hand therapy treatments in rheumatoid arthritis – a randomized controlled trial. Rheumatology 45:577-583**
Study type	RCT (single-blind, outcomes assessors blinded, computer-generated randomisation list with permuted blocks within strata, research physiotherapist phoned a blinded third party , this person identified treatment allocation)
Aim	To evaluate the clinical effectiveness of three different hand therapy approaches on changes in impairment in patients with RA over a 6-month period
Patient characteristics	Out-patient rheumatology clinics, February 1999 to January 2001 Inclusion; - >18years - Diagnosis of RA as defined by the American College of Rheumatology criteria Exclusion; - Recent changes in drug regime (including a change in DMARDs) in the previous 3months - On oral corticosteroids >7.5mg/day or had received a corticosteroid intra-articular or intramuscular injection in the previous month - Surgery to the wrist, hand, elbow or shoulder in previous 6months - Sensory impairment to the hand, uncontrolled pain affecting the joints of the wrist or hand - Pregnancy Mean age for participants 59.6years, 69% female; mean disease duration (mobilising and strengthening exercises 17.7years (SD14.21), mobilising exercises 13.2years (SD11.63), leaflet alone 9.7years (SD7.59) – differences not statistically significant
Number of Patients	N=67
Intervention	The content of the hand exercise interventions was defined following a survey of 60 senior hand therapists All participants had a 30minute appointment with an experienced musculoskeletal therapist who delivered the intervention and discussed relevant issues from the leaflet 15minute appointment x2weeks later to monitor concordance N=21 Joint protection literature Additional instruction from a therapist on how to perform a total of 8 simple strengthening and mobilising (stretching) tendon gliding exercises. These encouraged a maximum range of movement of all small joints of the fingers, thumb and wrist, as well as radial finger walking (fingers moving toward the radius only avoiding exacerbating ulnar deviation), pinch grip exercises, strengthening the intrinsic and thenar eminence muscles (using a towel) and wrist

Bibliographic reference	O'Brien et al (2006) Conservative hand therapy treatments in rheumatoid arthritis – a randomized controlled trial. Rheumatology 45:577-583
	extensor muscle groups with a 'Theratubes' resistive band (Promedics, UK) Graduated programme – increasing repetitions from 5 at baseline, 10 at 1month, 20 at 3months onwards – x2/day over the 6month study period
Comparison	N=24 Joint protection literature Set of 8 stretching exercises, without any specific strengthening exercises; included wrist flexion, extension and circumduction, pronation and supination, radial deviation as well as global flexion and abduction of all finger joints, thumb opposition and interphalangeal flexion to the end of the possible range. Graduated programme – increasing repetitions from 5 at baseline, 10 at 1month, 20 at 3months onwards – x2/day over the 6month study period
Comparison	N=22 Joint protection literature alone
Length of follow up	6months
Location	UK
Outcomes measures and effect size	Primary outcome; - Arthritis Impact Measurement Scales II (AIMS II) – asks 5 functional questions relating to the previous month – normalised score gives 0 to 10 where higher scores indicate more problems Secondary outcomes; - Jebson-Taylor hand function test, in seconds - Power grip (in pounds) – Jamar dynamometer - Key pinch (in pounds) – using pinch gauge (B&L Engineering, Tustin, CA, USA - Dominant hand index finger flexion goniometry measured in degrees - Disease activity – measured with swollen and tender joint scores as well as patients' perceptions of their disease activity Lost to follow-up at 6months; - N=52/67 (78%) - N=3 strengthening and mobilising exercises - N=8 mobilising exercises - N=4 leaflet alone Results:

Bibliographic reference	O'Brien et al (2006) Conservative hand therapy treatments in rheumatoid arthritis – a randomized controlled trial. Rheumatology 45:577-583
	Change scores from baseline at 6months; (AIMS upper limb function, not extracted, outcome not in review protocol) AIMS hand and finger function (0-10), mean (SD); - Strengthening and mobilising exercises 0.97(1.72); mobilising exercises 0.18(2.07); leaflet alone 0.38(1.68), p=0.414 (0.729, adjusted using ANCOVA) Jebsen-Taylor (right hand, s), median (IQR); - Strengthening and mobilising exercises 7.92(16.56); mobilising exercises 3.38(15.26); leaflet alone 3.46(13.73), p=0.627 Right index finger flexion (degrees), mean (SD); - Strengthening and mobilising exercises 8.97(10.17); mobilising exercises 7.47(12.02); leaflet alone 4.25(18.07), p=0.599 (0.761, adjusted using ANCOVA) Dominant gross grip (lbs), median (IQR); - Strengthening and mobilising exercises 9.70(11.50); mobilising exercises 6.70(17.35); leaflet alone 3.40(21.32), p=0.300 Dominant key grip (lbs), median (IQR); - Strengthening and mobilising exercises 1.00(2.97); mobilising exercises 0.30(2.60); leaflet alone -1.00(2.45), p=0.014 Disease activity; - No differences between the groups at 6months - Strengthening and mobilising exercises mean 4.25(SD 2.41); mobilising exercises 3.41(2.52); leaflet alone 4.31(2.71)
Source of funding	Promedics UK, Birmingham Branch of the Chartered Society of Physiotherapy, Arthritis Research Campaign
Comments	No previous data on primary outcomes, sample size based on interim analysis after 15 participants had completed all 3 arms of the study, based on a 0 to 6month, sample size of 20/arm to estimate a large effect size with 80% power 5% significance ITT analysis

Appendix H: GRADE profiles

For intervention question

Table 7: Hand function

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference from baseline difference (95% CI)	
Outcome: hand function (Duruoz Hand Index)										
Dogu (2013)	RCT	Serious[5]	Very serious[6]	N/A	Serious[9]	No serious	23	24	Isotonic exercise group baseline median 15 (IQR 5 to 40), 6wks 11 (3 to 33), p=0.002; isometric exercise group baseline median 16.5 (IQR 5.25 to 30.5), 6wks 12 (3.5 to 25.25), p=0.002	Very low
Outcome: overall hand function (Michigan Hand outcome Questionnaire. MHQ)										
Lamb (2015)	RCT	Serious[7]	No serious	N/A	No serious	No serious	246	244	Mean difference At 4mths; 4.71 (2.32 to 7.11), p=0.0001 At 12mths; 4.28 (1.49 to 7.06), p=0.0028	Moderate
Outcome: hand function questions (Arthritis Impact measurement Scale, AIMS II)										
O'Brien (2006)	RCT	Serious[7]	Serious[8]	N/A	Serious[9]	No serious	21 (strengthening/mobilising) 24 (mobilising	22	Changes from baseline, dominant hand; strengthening/mobilising mean 0.97 (SD 1.72), mobilising 0.18 (2.07), control 0.38	Very low

Quality assessment							No of patients		Effect estimate	Quality
							)		(1.68), p=0.414	

1 *No blinding, unclear allocation concealment*
2 *Unclear recruitment of participants, no sample size consideration (small sample), single centre*
3 *No blinding, unclear allocation concealment, insufficient randomisation*
4 *No sample size consideration, single centre*
5 *Single blinded, unclear allocation concealment*
6 *No sample size consideration, single centre, high drop-out rate*
7 *Single blinded*
8 *Single centre*
9 *Unable to use MID, default of <400 sample size used*

Table 8: Grip strength

Quality assessment							No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**Treatment (T)**	**Comparator (C)**	**Mean difference from baseline difference (95% CI)**	
Outcome: grip strength (handgrip dynamometer, follow-up 20 sessions or 2months)										
Cima (2013)	RCT	Very serious[1]	Very serious[2]	N/A	Serious[9]	No serious	13	7	At 10 and 20 sessions increase for both dominant and non-dominant hands compared with baseline for intervention group, p<0.05, control group, no difference	Very low
Outcome: grip strength (by Groppit (in Newton), follow-up 4weeks)										
Delhag (1991)	RCT	Very serious[3]	Very serious[4]	N/A	Serious[9]	No serious	11	13	Average dominant hand; baseline 90.7; 4wks 109.7, NS difference Average non-dominant hand; baseline 100.8; 4wks 108.0, NS difference Control group, no	Very low

Quality assessment							No of patients		Effect estimate	Quality
									difference	
Outcome: grip strength (JAMAR dynamometer)										
Dogu (2013)	RCT	Serious[5]	Very serious[6]	N/A	Serious[9]	No serious	23	24	Dominant hand; isotonic exercise group baseline median10(IQR 6 to 18), 6wks 11 (8 to 20), p=0.372; isometric exercise group baseline 10.5(8 to 13.75) 6wks 14 (8.5 to 18), p=0.029 Non-dominant hand; isotonic baseline 9(4 to 16), 6wks 10 (6 to 18), p=0.013; isometric baseline 10.5(6 to 17) 6wks 10 (6.5 to 17.5), p=0.138	Very low
Outcome: grip strength (modified aneroid manometer, mmHg)										
Hoenig (1993)	RCT	Serious[5]	Very serious[6]	N/A	Serious[9]	No serious	30 (any hand exercise, includes ROM, resistive and ROM/resistive groups)	13	Left hand; any exercise, pre 72.1mmHg(SD, 48.9), post 89.3 (56.3), p<0.05 compared with control Right hand; any exercise, pre 83.1mmHg(SD, 56.1), post 90.0 (53.4)	Very low
Outcome: grip force (in Newtons)										
Lamb (2015)	RCT	Serious[7]	No serious	N/A	No serious	No serious	246	244	At 4mths; 9.29 (2.01 to 16.57), p=0.0129 At 12mths; 6.41 (-1.87 to 14.70), p=0.1303	Moderate
Outcome: power grip (in lbs)										

Quality assessment							No of patients		Effect estimate	Quality
O'Brien (2006)	RCT	Serious[7]	Serious[8]	N/A	Serious[9]	No serious	21 (strengthening/mobilising) 24 (mobilising)	22	Changes form baseline, dominant hand; strengthening/mobilising median 9.70 (IQR 11.50), mobilising 6.70 (17.35), control 3.40 (21.32), p=0.300	Very low

01 No blinding, unclear allocation concealment
02 Unclear recruitment of participants, no sample size consideration (small sample), single centre
03 No blinding, unclear allocation concealment, insufficient randomisation
04 No sample size consideration, single centre
05 Single blinded, unclear allocation concealment
06 No sample size consideration, single centre, high drop-out rate
07 Single blinded
08 Single centre
09 Unable to use MID, default of <400 sample size used

Table 9: pinch strength

Quality assessment							No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**Treatment (T)**	**Comparator (C)**	**Mean difference from baseline difference (95% CI)**	
Outcome: pinch (pinch gauge)										
Cima (2013)	RCT	Very serious[1]	Very serious[2]	N/A	Serious[9]	No serious	13	7	At 10 and 20 sessions increase for both dominant and non-dominant hands compared with baseline for 3 of the pinch strength measures for the intervention group, p<0.05, control group, no difference	Very low
Outcome: pinch function (0-32 points)										
Delhag	RCT	Very	Very serious[4]	N/A	Serious[9]	No serious	11	13	Exercise intervention,	Very low

Quality assessment							No of patients		Effect estimate	Quality
(1991)		serious[3]							baseline 29.2; 4wks 29.3 Control group; baseline 29.5; 4wks 29.2	
Outcome: pinch grip force (in Newtons)										
Lamb (2015)	RCT	Serious[7]	No serious	N/A	No serious	No serious	246	244	At 4mths; 1.57 (-0.59 to 3.73), p=0.1547 At 12mths; 3.01 (0.13 to 5.88), p=0.0411	Moderate
Outcome: key pinch (in lbs)										
O'Brien (2006)	RCT	Serious[7]	Serious[8]	N/A	Serious[9]	No serious	21 (strengthening/mobilising) 24 (mobilising)	22	Changes form baseline, dominant hand; strengthening/mobilising median 1.00 (IQR 2.97), mobilising 0.30 (2.60), control -1.00 (2.45), p=0.014	Very low

01 No blinding, unclear allocation concealment
02 Unclear recruitment of participants, no sample size consideration (small sample), single centre
03 No blinding, unclear allocation concealment, insufficient randomisation
04 No sample size consideration, single centre
05 Single blinded, unclear allocation concealment
06 No sample size consideration, single centre, high drop-out rate
07 Single blinded
08 Single centre
09 Unable to use MID, default of <400 sample size used

Table 10: range of motion (ROM)

Quality assessment							No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**Treatment (T)**	**Comparator (C)**	**Mean difference from baseline difference (95% CI)**	
Outcome: Range of motion (flexion and extension deficits, mm, follow-up 4weeks)										
Delhag	RCT	Very	Very serious[4]	N/A	Serious[9]	No serious	11	13	Flexion dominant	Very low

Quality assessment							No of patients		Effect estimate	Quality
(1991)		serious[3]							hand; baseline 56.1; 4wks 43.8, NS difference Control group, baseline 59.4; 4wks 62.0, NS difference Extension dominant hand; baseline 25.8; 4wks 24.1, NS difference Control group, baseline 39.4; 4wks 33.5, NS difference	
Outcome: ROM of MCP and PIP joints (extension, º)										
Hoenig (1993)	RCT	Serious[5]	Very serious[6]	N/A	Serious[9]	No serious	11 (ROM) 9 (resistive) 10 (Rom/resistive)	11	ROM, MCP, left; pre 1.7, post 1.3 Resistive, MCP, left; pre 19.2, post 20.6 ROM/Resistive, MCP, left; pre 5.3, post 7.8 Control, MCP, left; pre 7.7, post 7.1 ROM, PIP, left; pre -2.1, post -2.0 Resistive, PIP, left; pre 2.9, post -1.4, p<0.05 compared with control group ROM/Resistive, PIP, left; pre 7.3, post 8.1 Control, MCP, left; pre 1.4, post 2.1	Very low
Outcome: ROM (Active wrist score º)										
Lamb	RCT	Serious[7]	No serious	N/A	No serious	No serious	246	244	At 4mths; 1.58 (-1.25	Moderat

Quality assessment							No of patients		Effect estimate	Quality
(2015)									to 4.41), p=0.2750 At 12mths; 0.27 (-2.72 to 3.26), p=0.8587	e

01 No blinding, unclear allocation concealment
02 Unclear recruitment of participants, no sample size consideration (small sample), single centre
03 No blinding, unclear allocation concealment, insufficient randomisation
04 No sample size consideration, single centre
05 Single blinded, unclear allocation concealment
06 No sample size consideration, single centre, high drop-out rate
07 Single blinded
08 Single centre
09 Unable to use MID, default of <400 sample size used

Table 11: Pain

Quality assessment							No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**Treatment (T)**	**Comparator (C)**	**Mean difference from baseline difference (95% CI)**	
Outcome: pain (resisted motion, during grip function tests, VAS 10-point scale, follow-up 4weeks)										
Delhag (1991)	RCT	Very serious[3]	Very serious[4]	N/A	Serious[10]	No serious	11	13	Resistive motion, dominant hand (0-9 points); baseline mean 1.1; 4wks 1.3 Control group; baseline mean1.3; 4wks 1.5	Very low
Outcome: pain (VAS 10-point scale)										
Dogu (2013)	RCT	Serious[5]	Very serious[6]	N/A	Serious[10]	No serious	23	24	Isotonics, pre-treatment; difference in improvements 1.26±2.68 (SD) Isometrics, pre-treatment; difference in improvements 1.04±2.13 (SD), p=0.711	Very low
Outcome: painful joints (Hand articular index)										

Quality assessment							No of patients		Effect estimate	Quality
Hoenig (1993)	RCT	Serious[5]	Very serious[6]	N/A	Serious[9]	No serious	11 (ROM) 9 (resistive) 10 (ROM/resistive)	11	ROM, right; pre 2.6, post 2.2, p<0.05 compared with control group Resistive, right; pre 3.0, post 3.4 ROM/Resistive, right; pre 3.5, post 3.2 Control, MCP, left; pre 1.5, post 2.7	Very low
Outcome: pain (Troublesomeness questionnaire, range 0 to 20)										
Lamb (2015)	RCT	Serious[7]	No serious	N/A	No serious	No serious	246	244	Mean treatment difference At 4mths; -2.70 (-5.91 to 0.50), p=0.0993 At 12mths; -1.61 (-5.21 to 1.99), p=0.3810	Moderate

01 No blinding, unclear allocation concealment
02 Unclear recruitment of participants, no sample size consideration (small sample), single centre
03 No blinding, unclear allocation concealment, insufficient randomisation
04 No sample size consideration, single centre
05 Single blinded, unclear allocation concealment
06 No sample size consideration, single centre, high drop-out rate
07 Single blinded
08 Single centre
09 Unable to use MID, default of <400 sample size used
10 95% CI unreported (or unable to calculate)crossed MID

Table 12: Dexterity

Quality assessment							No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**Treatment (T)**	**Comparator (C)**	**Mean difference from baseline difference (95% CI)**	
Outcome: dexterity (timed 9 hole peg test)										
Dogu (2013)	RCT	Serious[5]	Very serious[6]	N/A	Serious[9]	No serious	23	24	Isotonics, pre-treatment; median 30 (IQR, 25 to 45), 6wks	Very low

Quality assessment							No of patients		Effect estimate	Quality
									28 (20 to 40), p=0.0001 Isometrics, pre-treatment; median 30 (IQR, 20 to 38.75), 6wks 23 (20 to 30), p=0.005	
Outcome: dexterity (timed 9 hole peg test)										
Hoenig (1993)	RCT	Serious[5]	Very serious[6]	N/A	Serious[9]	No serious	11 (ROM) 9 (resistive) 10 (Rom/resistive)	11	ROM, left; pre 23.9, post 23.6, right; pre 23.2, post 23.3 Resistive, left; pre 29.2, post 28.0, right; pre 32.3, post 30.1 ROM/Resistive, left; pre 29.5, post 24.4, p<0.05 compared with control group over time, right; pre 26.4, post 28.8 Control, left; pre 26.2, post 26.5, right; pre 24.3, post 25.0	Very low
Outcome: dexterity (9 hole peg test)										
Lamb (2015)	RCT	Serious[7]	No serious	N/A	No serious	No serious	246	244	At 4mths; -0.64 (-1.53 to 0.26), p=0.1643 At 12mths;-1.19 (-2.15 to -0.23), p=0.0156	Moderate

01 No blinding, unclear allocation concealment
02 Unclear recruitment of participants, no sample size consideration (small sample), single centre
03 No blinding, unclear allocation concealment, insufficient randomisation
04 No sample size consideration, single centre
05 Single blinded, unclear allocation concealment
06 No sample size consideration, single centre, high drop-out rate
07 Single blinded
08 Single centre
09 Unable to use MID, default of <400 sample size used

Table 13: Quality of life

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference from baseline difference (95% CI)	
Outcome: QoL (RA QoL)										
Dogu (2013)	RCT	Serious[5]	Very serious[6]	N/A	Serious[9]	No serious	23	24	Isotonics, pre-treatment; median 19 (IQR, 15 to 24), 6wks 15 (14 to 21), p=0.003 Isometrics, pre-treatment; median 18 (IQR, 11.5 to 22.75), 6wks 14.32 (7.25 to 21), p=0.001	Very low
Outcome: QoL (Eq-5D)										
Lamb (2015)	RCT	Serious[7]	No serious	N/A	No serious	No serious	246	244	At 4mths; 0.02 (-0.02 to 0.06), p=0.3813 At 12mths; 0.00 (-0.03 to 0.04), p=0.8714	Moderate

01 No blinding, unclear allocation concealment
02 Unclear recruitment of participants, no sample size consideration (small sample), single centre
03 No blinding, unclear allocation concealment, insufficient randomisation
04 No sample size consideration, single centre
05 Single blinded, unclear allocation concealment
06 No sample size consideration, single centre, high drop-out rate
07 Single blinded
08 Single centre
09 Unable to use MID, default of <400 sample size used

Appendix I: Tools/scales used in the included studies

Tool/scale used	Brief details
Sollerman Hand Function Test	Designed to measure the grips needed for certain activities of daily living, ADLs (eating, driving, personal hygiene, writing), 20 items Clinician-administered standardised performance test Subtests the represent common handgrips and activities Scoring takes into account the time taken, level of difficulty displayed, the quality of the performance using the correct pinch or grip position 5-point scales from 0 (task cannot be performed at all) to 4 (task completed without any difficulty within the time frame, 20secs, and with the prescribed hand-grip of normal quality) Total sum score (0-80) by adding up the scores from the different subtests
Cochin Hand Function Scale (Duruoz's hand index)	Self-report scale to measure functional ability in the hand Patient or clinician completed self-report Questions on difficulty with performing 18 tasks without assistive device; - Kitchen tasks (8 items) - Dressing items (2 items) - Hygiene items (2 items) - Office items (2 items) - Other (4 items) 7-point scale from 0 (without difficulty) to 5 (impossible)
Arthritis Impact Measurement Scales 2 (AIMS 2)	Arthritis specific health status measure, to assess physical functioning, pain, psychological status, social interactions and support, health perceptions and demographic and treatment information, 78 questions Self-administered

	Questions; - Physical function, 28 items capture the 6 domains; mobility (5 items), walking and bending (5 items), hand and finger function (5 items), arm function (5 items), self-care tasks (4 items), household tasks (4 items) - Other domains; symptoms (pain), role (work), social interaction (social activity, family support), affect (tension, mood) Physical function; 5-point Likert scale with 1=all days, 2=most days, 3=some days, 4=few days, 5=no days Subscales measuring self-care and household tasks are assessed with 1=always, 2=very often, 3=sometimes, 4=almost never, 5=never
Michigan Hand Outcomes Questionnaire (MHQ)	To measure the perception of their hands in terms of function, appearance, pain and satisfaction – 6 subscales (37 items). Intended for those with hand and wrist conditions and injuries, including arthritis Patient or clinician completed self-report 6 subscales; - Overall hand function - ADL - Pain - Work performance - Aesthetics - Patient satisfaction with hand function 5-point Likert scale from 1 (very good/not at all difficult/always/very mild/very satisfied) to 5 (very poor/very difficult/never/severe/very dissatisfied) – scores converted to scale from 0-100 according to a scoring algorithm
RA QoL	Disease specific measure to assess self-reported quality of life in those with RA Self-assessment Questions to assess specific activities of daily living and quality of life – 30 items, each answered with a yes or no Score range of 0-30, higher scores indicate worsening quality of life

Jebsen-Taylor Hand Function Test	To assess broad aspects of hand function commonly used in activity of daily living using standardised tasks, for children (>6yrs) and adults with impairments in the hands Performance based test Tasks simulate ADLs 7 items (subscales); - Writing - Turning over 3x5-inch cards - Picking up small common objects - Simulated feeding - Stacking checkers - Picking up large light cans - Picking up large heavy cans Measured in seconds, each item is timed, score range variable, the longer the time to complete the subscales, the more the disability

Appendix J: Economic search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 14. The search strategy is shown in Table 15. The same strategy was translated for the other databases listed.

Table 14: Economic search summary

Databases	Version/files	No. retrieved
MEDLINE (Ovid)	1996 to May Week 3 2015	91
MEDLINE In-Process (Ovid)	May 26, 2015	13
EMBASE (Ovid)	1980 to 2015 Week 21	330
NHS Economic Evaluation Database - NHS EED (Wiley)	Issue 2 of 4, April 2015	0
Health Technology Assessment Database	Issue 2 of 4, April 2015	1

Table 15: Economic search strategy

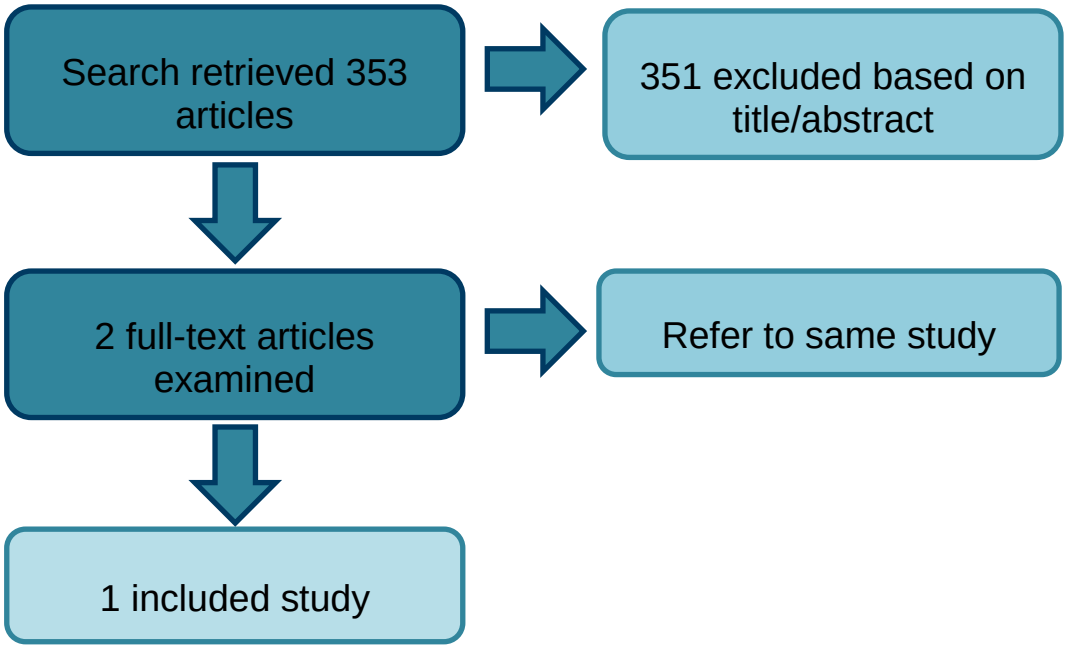
Database: Medline and Medline in Process
Search Strategy: --- 1 Arthritis, Rheumatoid/ (83803) 2 ((Rheumatoid* or rheumatic* or inflammat* or idiopathic* or deforman*) adj4 (arthrit* or arthros* or polyarthrit* or factor*)).tw. (104403) 3 (Chronic* adj4 (polyarthrit* or poly arthrit* or poly-arthrit* or rheumati*)).tw. (4304) 4 Rheumarthrit*.tw. (2) 5 (Beauvais* adj2 disease*).tw. (0) 6 ((Inflammat* or pain* or swell* or stiff*) adj4 (joint* or synovial*)).tw. (19420) 7 RA.tw. (49895) 8 or/1-7 (164535) 9 exp Hand/ (70980) 10 exp Hand Joints/ (15080) 11 (Hand* or finger* or thumb* or wrist* or digit* or metacarp* or carpal* or carpometacarpal* or metacarpophalangeal* or triangular* fibrocartilage*).tw. (619538) 12 or/9-11 (642173) 13 8 and 12 (10835) 14 Exercise/ or Exercise Therapy/ (95439) 15 Hand Strength/ (9695) 16 Movement/ or Exercise Movement Techniques/ (59589) 17 (Exercise* or strength* or move* or kinesiotherap*).tw. (654121) 18 (Finger* adj2 walk*).tw. (13) 19 "Range of Motion, Articular"/ (35234) 20 (Rang* adj2 (motion* or flex*)).tw. (19578) 21 Splints/ or Splint*.tw. (14115) 22 Physical Therapists/ (470) 23 Physical Therapy Modalities/ (28792) 24 Physiotherapist/ (470) 25 Occupational Therapy/ (10535) 26 ((Physio* or physical* or Occ or Occupation* or Hand*) adj2 (therap* or treat* or service* or train* or program* or manage* or techni* or educat*)).tw. (59905) 27 or/14-26 (825497) 28 13 and 27 (2089)

Database: Medline and Medline in Process

29 Economics/ (26620)
30 exp "Costs and Cost Analysis"/ (187805)
31 Economics, Dental/ (1859)
32 exp Economics, Hospital/ (20266)
33 exp Economics, Medical/ (13536)
34 Economics, Nursing/ (3914)
35 Economics, Pharmaceutical/ (2572)
36 Budgets/ (9961)
37 exp Models, Economic/ (10750)
38 Markov Chains/ (10446)
39 Monte Carlo Method/ (20992)
40 Decision Trees/ (9097)
41 econom$.tw. (162830)
42 cba.tw. (8855)
43 cea.tw. (16718)
44 cua.tw. (809)
45 markov$.tw. (12233)
46 (monte adj carlo).tw. (21720)
47 (decision adj3 (tree$ or analys$)).tw. (8720)
48 (cost or costs or costing$ or costly or costed).tw. (319509)
49 (price$ or pricing$).tw. (23911)
50 budget$.tw. (17825)
51 expenditure$.tw. (36252)
52 (value adj3 (money or monetary)).tw. (1388)
53 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (2898)
54 or/29-53 (677369)
55 "Quality of Life"/ (125771)
56 quality of life.tw. (145860)
57 "Value of Life"/ (5440)
58 Quality-Adjusted Life Years/ (7554)
59 quality adjusted life.tw. (6367)
60 (qaly$ or qald$ or qale$ or qtime$).tw. (5242)
61 disability adjusted life.tw. (1277)
62 daly$.tw. (1248)
63 Health Status Indicators/ (20519)
64 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (15995)
65 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1022)
66 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2814)
67 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (21)
68 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (336)
69 (euroqol or euro qol or eq5d or eq 5d).tw. (4189)
70 (qol or hql or hqol or hrqol).tw. (26201)
71 (hye or hyes).tw. (53)
72 health$ year$ equivalent$.tw. (38)
73 utilit$.tw. (117072)
74 (hui or hui1 or hui2 or hui3).tw. (886)
75 disutili$.tw. (227)

Database: Medline and Medline in Process	
76	rosser.tw. (71)
77	quality of wellbeing.tw. (5)
78	quality of well-being.tw. (337)
79	qwb.tw. (175)
80	willingness to pay.tw. (2368)
81	standard gamble$.tw. (665)
82	time trade off.tw. (768)
83	time tradeoff.tw. (208)
84	tto.tw. (614)
85	or/55-84 (333942)
86	54 or 85 (965909)
87	28 and 86 (122)
88	Animals/ not Humans/ (3947089)
89	87 not 88 (121)
90	limit 89 to english language (102)

Appendix K: Economic review flowchart



Appendix L:Economic evidence tables

Bibliographic reference	**Williams MA, Williamson EM, Heine PJ et al. (2015) Strengthening And stretching for Rheumatoid Arthritis of the Hand (SARAH). A randomised controlled trial and economic evaluation. Health Technology Assessment (Winchester, England): 1-222** **Lamb SE, Williamson EM, Heine PJ et al. (2015) Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 385(9966): 421-429**
Evaluation design	

Intervention	Individualised hand exercise programme (as per SARAH trial: 6 sessions of strengthening and stretching exercises with a hand therapist, daily home exercises and strategies to maximise adherence)
Comparators	Usual care (joint protection education, general exercise advice and functional splinting if required)
Base-line cohort characteristics	Adults with rheumatoid arthritis who had pain and dysfunction of the hands or wrists and had been on stable medication for at least 3 months.
Type of Analysis	Within-trial analysis based on healthcare resource use and utility data collected alongside the clinical data over the 12 month trial period
Structure	Not applicable
Cycle length	Not applicable
Time horizon	12 months
Perspective	NHS and PSS
Country	United Kingdom
Currency unit	£
Cost year	2011
Discounting	Not applicable
Other comments	Nil

Bibliographic reference	**Williams MA, Williamson EM, Heine PJ et al. (2015) Strengthening And stretching for Rheumatoid Arthritis of the Hand (SARAH). A randomised controlled trial and economic evaluation. Health Technology Assessment (Winchester, England): 1-222** **Lamb SE, Williamson EM, Heine PJ et al. (2015) Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 385(9966): 421-429**
Results	

Comparison	Hand exercise programme vs. usual care
Incremental cost	£206.40 (-495.12 to 907.53)
Incremental effects	0.012 QALYs (-0.017 to 0.040)
Incremental cost effectiveness ratio	£17,941 per QALY
Conclusion	Analysis of the costs and effects of the hand exercise programme over the 12 month trial period indicates, on balance, this is likely to be a cost-effective use of NHS resources.

Data sources

Base-line data	Not applicable (within-trial comparison of 2 groups)
Effectiveness data	EQ-5D and SF-6D data collected alongside clinical outcome measures (within-trial)
Cost data	Resource use obtained by patient self-report at 4 and 12 months (within-trial) Prescribed medication usage reported by participants at baseline, 4 and 12 months (within-trial) Cost of hospital presentations from NHS Reference Costs Cost of staff time from NHS Reference Costs or Personal Social Services Research Unit, Unit Costs of Health and Social Care 2011 Cost of diagnostic tests from NHS Reference Costs Cost of medicines from BNF
Utility data	EQ-5D and SF-6D data collected alongside clinical outcome measures (within-trial)

Uncertainty

Alternative methods of data analysis	Five different methods were used. They differed in assumptions about the distributions of costs and QALYs, whether or not correlations between costs and QALYs were accounted for, adjusted for baseline utility values and the handling of missing data. 'Analysis E' was the preferred analysis for reporting in the main results because it accounted for a range of potential biases and sources of uncertainty. Analysis A used simple, large sample methods to estimate differences in mean costs and mean QALYs between the groups with no adjustment for baseline utility. Analysis B used a regression approach to better reflect the nature of the data. Baseline utility was included as a covariate. Analysis C used a

Bibliographic reference	Williams MA, Williamson EM, Heine PJ et al. (2015) Strengthening And stretching for Rheumatoid Arthritis of the Hand (SARAH). A randomised controlled trial and economic evaluation. Health Technology Assessment (Winchester, England): 1-222 Lamb SE, Williamson EM, Heine PJ et al. (2015) Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 385(9966): 421-429	
		seemingly unrelated regression approach to estimate the costs and QALYs simultaneously to allow for the likely correlation of costs and QALYs. Baseline utility was included as a covariate. Analysis D repeated the approach of Analysis C but used non-parametric bootstrapping. Analysis E combined the bootstrap seemingly unrelated regression approach and multiple imputation of missing cost and QALY data. ICERs based on the EQ-5D: • Analysis A: £8,564 per QALY • Analysis B: £9,572 per QALY • Analysis C: £9,549 per QALY • Analysis D: £9,364 per QALY • Analysis E: £17,941 per QALY (preferred) ICERs based on the SF-6D: • Analysis A: £5,986 per QALY • Analysis B: £7,455 per QALY • Analysis C: £7,440 per QALY • Analysis D: £6,823 per QALY • Analysis E: £23,288 per QALY
	One-way sensitivity analysis	• Half the training costs that were incurred in the trial (£6.77 per patient vs. £13.54): ICER for Analysis E was £17,395 • Best-case scenario for cost of consumables (£24.75; base case £43.42): ICER for Analysis E was £16,361 • Worst-case scenario for cost of consumables (£106.34; base case £43.42): ICER was £23,453
	Probabilistic sensitivity analysis	Probability that the incremental net benefit is greater than 0 based on a cost-effectiveness threshold of £20,000 per QALY: • Analysis A: 66% • Analysis B: 63% • Analysis C: 53% • Analysis D: 60%

Bibliographic reference	**Williams MA, Williamson EM, Heine PJ et al. (2015) Strengthening And stretching for Rheumatoid Arthritis of the Hand (SARAH). A randomised controlled trial and economic evaluation. Health Technology Assessment (Winchester, England): 1-222** **Lamb SE, Williamson EM, Heine PJ et al. (2015) Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 385(9966): 421-429**
	• Analysis E: 52%
Applicability	**Directly Applicable**
Limitations	**Minor Limitations**
Conflicts	Funded by the National Institute for Health Research Health Technology Assessment programme

Acronyms: QALY: quality adjusted life year; BNF: British National Formulary; EQ-5D: European Quality of Life 5 Dimensions; SF-6D: Short Form questionnaire 6Dimensions