NETSCC, HTA

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Project Title:
(SARAH) Strengthening and stretching for people with Rheumatoid Arthritis of the Hands: The clinical and cost effectiveness of an exercise programme over and above usual care.

Planned Investigation

Research Objectives
(1) To estimate the clinical effectiveness of adding an optimised exercise programme for hands and upper limbs in addition to, standard care, joint protection in the reduction of hand dysfunction and pain for patients with rheumatoid arthritis.
(2) To estimate the cost-effectiveness of adding this programme to usual care.
(3) To describe, qualitatively, the experience on participants in the trial with a particular emphasis on patient expectation, exercise behaviours, and reasons for adherence / non-adherence.

Existing Research
Rheumatoid arthritis (RA) is the most common inflammatory polyarthritis. The prevalence is 1.16% in women and 0.44% in men[1]. This increases with age reaching 5% in those aged over 55[1]. (RA is a chronic unpredictable disorder that can cause persistent joint pain, joint damage (especially in the hands and feet) and long-term disability[2]. Five years after diagnosis, 40% of people with RA have relatively normal function (13% in remission), 44% have mild to moderate disability, and 16% have marked functional disability[2]. Although there are some effective drug treatments the condition has no known cure. The goals of management are to prevent or control joint damage, loss of function and decrease pain[3]. Particular problems for the hand are inflammation, deformity, pain, weakness and restricted mobility[4].

The American College of Rheumatology (ACR) clinical guidelines for RA recommend the use of physical therapy and occupational therapy as an adjunct to drug treatment[3]. These therapies do appear to be commonly utilised. An Irish survey of services used by RA patients (n=273), found that patients regularly attend physiotherapy (PT) and occupational therapy (OT) review appointments and may have contact with therapy departments over very long durations[5]. The three most common components of PT/OT for the hands of people with RA are exercise therapy, joint protection advice and functional splinting[6]. Therapists most commonly educate patients on how to protect the joints whilst performing functional activities and provide functional wrist splints followed by prescribing exercise programmes [5, 7, 8]. Thus current hand therapy is a balance between the provision of strategies to support and protect joints and exercising the hands to improve strength, maintain flexibility and increase functional ability.

Joint Protection and splinting: Conventional joint protection strategies include pain management advice, planning and pacing activities, regular rest, altering patterns of joint movement and the use of assistive devices[9]. Two approaches to wrist splinting may be used. Resting wrist splints are prescribed mainly to reduce pain and other signs of inflammation, and, to a lesser extent, to preserve function, although the evidence for their effectiveness is limited[10]. Functional wrist splints are used intermittently during functional activities in which resistance, weight, or protracted positioning are likely to stress the wrist. This type of 'intermittent support' splinting has more evidence of effectiveness than the 'immobilisation' resting splint approach[11]. A recent UK study found that an educational, behaviourally-based, method of providing joint protection advice in RA hands has a small positive effect in improving function[12]. However, it appears, from a survey of our collaborating sites (n=10), done to inform this application, that joint protection advice and functional splint provision is usual care in the UK rather than this method of providing joint protection education.

Exercise: Muscles act in a variety of ways. When shortening or lengthening they allow movement and generation of strength and power across a joint. In addition, and when acting statically, they provide protection and stability to a joint. In addition to 'rheumatoid cachexia'; loss of cell mass and destruction of muscle architecture due to the autoimmune, catabolic nature of the condition People with RA may develop disuse atrophy of muscle[13]. Muscle bulk, and thereby, strength, stability and protection are lost. Exercise programmes that

progressively increase the intensity of the exercise significantly increase the strength and size of muscles within twelve weeks, in the young people, older people and people with RA[14]. Additionally, the physiological benefits of exercising arthritic joints include reducing pain and improving sensori-motor function[15].

A systematic review [14], of six randomized controlled trials (RCTs) of the effectiveness of dynamic exercise programmes in hand RA, concluded that dynamic exercise was effective in improving muscular endurance and strength, without having detrimental effects on disease activity or pain. Stenstrom and Minor[16], systematically reviewed 15 RCTs, on the effectiveness of aerobic and strengthening exercises in RA and drew the same conclusion. Three RCTs have specifically studied the impact of exercise on radiological damage in RA patients[17-20]. These did not show any detrimental effect on radiological progression of the small joints of hands and feet from exercise. It should be noted however, that none of these studies specifically exercised the hands; rather the hands were used during general upper limb exercise activity. The number of RCTs that have specifically investigated the effects of exercise on RA hands is limited to three small studies (n= 44, 50, & 67 respectively)[21-23]. Each of these studies demonstrated small improvements in hand function with exercise with no increase in joint swelling, pain or disease activity. Unfortunately, the long term effectiveness of exercise has not been rigorously established as these studies were small and only had short follow-up limited to a few months.

Research Methods

Design: A pragmatic, multi-centre, randomised controlled trial. Participants will be recruited from referrals to, and from current patients of, Rheumatology units at **12** NHS Trusts (recruitment sites) across the England. Participants will be randomly allocated to one of two interventions. Participants in the control arm will receive usual care joint protection advice, simple mobility exercises for the hand and functional splinting. The intervention arm will consist of the same regimen, supplemented with an optimal exercise programme designed to reduce pain, improve strength, endurance and dexterity of the hand / upper limb delivered over six sessions of **approximately** thirty minutes spread over a 12 week period. Three hours of contact time with a therapist is representative of typical of annual NHS contact time and thus is generalisable to UK clinical practice. Adherence with the advice and exercises provided in the exercise arm will be enhanced with the incorporation of delivery strategies based on the Health Beliefs Model[24] and Gollwitzer's[25] concept of implementation intentions (IIs) model to enable the translation of intentions into behaviour. The participants will be followed up at **four** and 12 months with outcome assessments using self report questionnaires of disability and general health and objective tests of strength, endurance and dexterity. Medication history, surgical events and serious adverse events will be monitored during this period using hospital records, prescription records and self–report questionnaires with the clinical costs and benefits of the intervention being assessed with a full economic analysis. The flow of participants through the study is detailed in Figure 1.

Setting: Outpatient Rheumatology and PT/OT hand units in at **12** recruitment sites across England. These will be grouped into **three** hubs, Midlands, North-West England, and **Southern**. The Midlands hub consists of **three** large acute trusts in the region; their catchment areas are ethnically diverse. The **Southern** hub consists of **eight** NHS trusts that have previously participated in RA hand research[4].The North-West hub is made up of Wrightington hospital, a Centre of Excellence in the Treatment of Musculoskeletal disease and a Rheumatology centre for the region. All of the sites have dedicated PT/OT services for patients with hand complaints.

Identifying potential participants: Participants will come from direct referrals from Rheumatology clinics and from those referred to PT/OT**.** Participants will be contacted to assess their willingness to participate in the trial if they have been referred to PT/OT departments at participating Trusts with RA hands. Based on our recent survey we expect our

twelve sites will, in total, have around 80 new referrals of people with hand RA per month. Assuming 40% of these join the trial, we will recruit 480 participants over 15 months; just under 10 per site per quarter. The recruitment target is realistic and feasible. It contains an allowance for differences in case mix between departments, departments withdrawing or failing to recruit, for variations in the proportion of people who agree to participate in the trial. One factor, which can be over-looked in trials of this nature, is the capacity of the NHS to provide the trial treatments. We have considered this as a possibility particularly in the delivery of the PT/OT intervention. A target of 10 participants per quarter should be achievable without placing excessive strain on current PT/OT service provision. These referral figures represent usual clinical referral amounts. We will, in addition, encourage the rheumatologists at each site to refer eligible patients to the study, by having our recruitment therapists / nurses regularly attending outpatient clinics thus we are confident that referral levels should at least maintain or increase for the 15 month recruitment period.

In addition to the recruitment of newly referred patients, **all of the Rheumatology and some of the PT/OT departments** in our survey of practice, have a review register of 'chronic' patients, periodically called in for review appointments. These patients will be approached via postal questionnaires, with patients reporting hand pain and disability being asked to consider participation in the trial. Taking into account the numbers of patients on these review registers and using a conservative estimate of take up of 10% we expect to be able to recruit up to 100 participants from this source if recruitment of new referrals to PT/OT does not match targets. We are aware that referral numbers are traditionally lower in August due to the holiday period thus the review list patients may be targeted at this time. Participants recruited in this manner may respond differently than participants recruited from standard referrals and so recruitment method will be entered into the analysis as a covariate. We are confident that this trial will run and recruit well. Our group has been funded to undertake several clinical trials requiring recruitment across multiple sites. We have problem-solved effectively and efficiently on these trials, and have consistently delivered on our recruitment targets and timetable. Recent examples being the UKBEAM study (n=1335)[26], BeST study (n=705)[27], MOAT study (n=214)[28],CAST study (n=584) [29] and TOIB study(n=585)[30].

Intervention protocols:

Control Arm: Usual Care - Joint protection education, mobility exercises and functional splinting.

The control intervention will consist of joint protection advice, provided in **a maximum of 3 sessions (maximum duration one and a half hours)** with a PT/OT. Participants will be given **information sheets** that will explain the advice and include simple exercises used to maintain mobility of the hand. The participants will be advised to continue the exercises at home. The participant will not be reviewed by the treating therapist again. This practice represents usual care for joint protection across the UK[31]. The provision of functional wrist splints is common practice in the UK[6]. Resting splints will not be provided, however, we will not restrict the provision of functional splinting as we expect its use to be similar in both arms of the study. Provision of functional splinting will be recorded and incorporated into the analysis of treatment effect

Intervention Arm: Usual Care supplemented with an optimal exercise Programme

In addition to the participants receiving conventional care we are proposing to implement a programme of exercise therapy to increase hand function using functional exercises to stretch and strengthen the muscles and tendons, also to mobilise the joints of the hand and wrist and improve dexterity. The programme will entail six half-hour appointments spread over 12 weeks. This number of contacts, spread over this epoch, will allow sufficient progression of the intensity of exercise and physiological response in the neuromuscular system to significantly improve function[32]. The programme is based on the programme developed by a collaborator on the bid[23]. This exercise programme was developed following a professional consensus of UK PT/OTs and has some evidence of short-term effectiveness. We are proposing a number of additional elements designed to increase long-term effectiveness.

The intervention will use a standardised protocol of progression and reduction of exercise intensity[33].

i) Specific Functional Exercise: A fundamental principle of exercise training is the specificity of response to exercise[32] . Exercising muscles and joints in a particular direction or with a particular type of muscle contraction will lead to benefit specifically during functional activities that mimic the movement performed during training. Our exercise programme will use sound exercise principles to improve strength, mobility and dexterity whilst performing functional tasks.

ii) Progressive Resistance Training: A crucial requirement in increasing muscle strength is the use of adequate intensity of resistance. Unless muscles are contracting at a high proportion of their maximum capacity (>60%) muscle hypertrophy will not occur and thus as the muscle strengthens, during the course of treatment, resistance must be increased correspondingly[34]. Participants will be provided with elastic resistance **materials** that provide this resistance and can progressively increase demand. These **materials** are inexpensive and commonly used in PT/OT departments. Participants will be educated on the need for progression of exercise and will be taught how to increase their own exercises.

iii) Mobility and Dexterity Exercise: The tendon sheaths of patients with RA hands are known to suffer from adhesions and consequently specific 'tendon sliding' exercises have been developed that target movements of the wrist and fingers in combination to maintain full mobility of the flexor and extensor tendons[35] and will be incorporated into the programme. People with hand RA frequently have deformity of the hands and wrists that make the placement of their hands into positions for efficient function difficult. Additionally, people with RA can develop restriction of movement of the elbows and shoulders as well as the hands. Thus, as the function of the hand is associated with the ability to position and maintain the hand in space, the exercise programme will also include mobility exercise of all the upper limbs joints.

iv) Home Exercise: Exercise and stretching should be repeated regularly and with increasing demand to stimulate psychomotor or muscular adaptation[10]. This is one of the reasons that exercise programmes incorporating a home exercise programme, mimicking the exercise programme practiced in the clinic, are more effective than those where no home exercise is performed[33]. The number of home exercises and the demand of dexterity tasks will be progressively increased to ensure the intensity of home exercise is adequate to overload the muscular system and challenge sensori-motor control. Targets for home exercise will be **progressed or regressed** based on individual assessment of performance.

v) Adherence with Home Exercise: Adherence with any exercise programme is vital to ensure the regular overload required to strengthen muscle is achieved. There is a dose-response between those patients who are adherent to prescribed home exercise and improvement in strength and pain in arthritis studies[36, 37]. We aim to maximise adherence to the prescribed exercise regimen through a two-stage mechanism that distinguishes between motivational and volitional phases of behaviour. The motivational phase is concerned with strengthening the intention to adhere to the exercise regimen, whereas the volitional phase is concerned with enabling the translation of the behavioural intention into actual behaviour. Distinguishing between motivational and volitional phases is necessary because behavioural intentions account for about a quarter of the variance in actual behaviour, thus demonstrating an intention-behaviour gap[38, 39]. The Health Belief Model (HBM)[40] will be used to strengthen intention to adhere to the exercise regimen. According to the HBM the adoption of a health behaviour depends on one's perception of a threat to personal health and a belief that the recommended action will reduce that threat. The intervention will target the antecedent beliefs of perceived threat (susceptibility and severity) and perceived efficacy (benefits and barriers) in order to strengthen behavioural intention and increase motivation.

The HBM has been shown to be an effective behaviour change framework for a range of health behaviours, including exercise for rheumatoid arthritis[41], whilst the concept of implementation intentions(IIs)[42] will be used to enable the translation of intentions into behaviour. While behavioural intentions state that 'I intend to perform X', IIs state that 'I

intend to perform X when Y conditions are encountered'. In other words, IIs involve the planning of 'when', 'where', and 'how' to perform a specific behaviour. Using the recommended procedure[42], intervention participants will be asked to decide when and where they will perform the prescribed exercise regimen (the how is the prescribed regimen), and to write down the precise timing and location for doing so. Use of implementation intentions has been shown to significantly increase the performance of a wide range of health behaviours over and above mere intention, including breast self-examination[43], and increasing attendance for screening[44].

The exercise programme will incorporate a strong emphasis on encouraging adherence with the home exercise component of the programme. Training on the practical delivery of the health beliefs and implementation intentions models will be provided to the treating therapists by the trial's clinical research fellow and Dr Bridle (Health Psychologist). Training in the principles of progression and regression of exercise will be provided by the clinical research fellow and will build on and formalise the existing knowledge of the PT/OTs, providing the treatment interventions. A comprehensive handbook with descriptions of protocols – assessment procedures, target setting and progression and regression protocols will be produced. This handbook will be made freely available at the end completion of the trial to aid dissemination and replication of the programme, nationally and internationally if the intervention is shown to be effective. The treating therapists will provide both the usual care intervention and the exercise intervention, thereby reducing the influence of therapist effects.

Pilot study: Before starting the main study we will pilot the recruitment procedures, the assessments, both intervention packages and follow-up systems. The intervention that we are testing has already been developed (with this process including an element of qualitative evaluation (AO'B)), and we anticipate, only a minor amount of revision will be required before implementation in the main study. We will undertake qualitative studies during the pilot study and will test the acceptability of the intervention in a representative group of patients. We will interview up to 20 individuals, and explore a range of issues including barriers and beliefs about exercise, acceptability of the intervention, the content and presentation of the programme, and the expectations of and satisfaction with the programme. Issues regarding motivation, adherence, safety, acceptability and perceived effectiveness of treatment will be covered. The interview schedule will be developed by the trial investigators, and the study will be supported by senior researchers with proven track record in qualitative and mixed methods (MU).

Planned inclusion /exclusion criteria

Inclusion Criteria:

People with RA, meeting the American College of Rheumatology clinical and immunological criteria, with pain and dysfunction of the hands and or wrist joints[3] who are either not on a disease modifying medication (DMARD), or who have been on a stable DMARD regimen, for three months or more.

Exclusion Criteria:

Patients recovering from upper limb joint surgery, or fracture, in the previous six months.
Patients on a waiting list for upper limb orthopaedic surgery.
Patients who are pregnant.
Aged less than 18 years

Ethical Considerations

Ethics and R&D Committee approval: An application to the national allocation for MREC approval will be made in the pre-funding phase. The LREC and R&D committees of each participating hospital will approached to approve local involvement in the trial. We do not anticipate major ethical concerns with this study other than the possibility of participants may suffer some increased discomfort as a consequence of the exercise and the unlikely possibility that increased exercise might precipitate tendon rupture.

Blinding and allocation issues: It will be impossible to blind the treating therapists and participants, however the study will undertake blinded outcome assessment and analysis. Participants will be offered one of two management plans involving 'joint protection and exercise' although little detail will be given regarding the specific content of the exercise programmes. It will be necessary to provide detail on the number of appointments needing to be attended. Thus, participants will be blind to the specific differences in the exercise programme provided, reducing the potential for resentful demoralisation after allocation into non-preferred intervention arm.

Method of randomisation: The unit of randomisation will be the individual. We will use the Warwick Medical School Clinical Trials Unit (WMSCTU) telephone randomisation service to ensure allocation concealment. Randomisation will be stratified by centre to control for any confounding factors evident at local recruitment sites, such as therapist effects or local contamination of intervention. No other stratification is proposed.

Risks and benefits: The risks to participants are small. The available evidence suggests that both exercise and joint protection interventions are not harmful for the hands of RA patients whilst the available evidence suggests that exercising the hands may reduce disability and reduce pain.

Potential side effects and monitoring: Based on previous literature evaluating the overall safety of exercise in RA[18, 45] and specific trials of exercise in RA hands[21-23] there are unlikely to be any serious side effects in relation to the interventions. Any adverse events will be reported to the DMEC. A serious adverse event will be defined as one that requires hospitalisation as a result of the intervention. Serious adverse events (SAEs) will be reported to the chief investigator in the first instance. Expected side effects of exercise, considered to be normal with any form of exercise therapy such as delayed onset muscle soreness, temporary increases in pain (<1 week) or increase in stiffness (<1 week) will be not be recorded as adverse events, however increases in pain (>1 week) or increase in stiffness (>1 week) will be. Participants will be given clear instructions on how and when to contact the local investigator to report serious and non-serious adverse events. Whilst we consider it highly unlikely that tendon rupture will occur as a result of the intervention, tendon rupture can spontaneously occur in this patient group. Specific questions regarding tendon rupture and joint dislocation will be included in the outcome assessments.

Participant confidentiality*:* All approaches to potential participants will be made through their PT/OT departments. The research team will only know the identity of those who have agreed to participate. All study paper work will identify participants by study number only.

Inclusion of people from ethnic minorities: Some of the localities we will be using include a large proportion of people of South Asian origin. We consider that it is feasible (based on the availability of interpretation services) to recruit non-English speaking participants into the study.

Sample Size:

Typically positive trials of physical interventions for musculoskeletal disorders, at best, show a small to moderate standardised mean effect size. Thus, if we can demonstrate a standardised mean effect size of 0.3 or greater then we can conclude that we have demonstrated a worthwhile clinical effect. A standardised mean effect size of 0.3 is thought to represent a clinically important difference in hand function in this group[46]. A previous small study, of a similar intervention, found a mean benefit of 0.7 in the AIMS2 with a standard deviation of 1.81; a standardised effect size of 0.39[23] . **This suggests that in this larger more rigorous multi-centre trial a standardised effect size of 0.3 in the similar function score using the Michigan Hand Questionnaire is realistic and meaningful. To show this difference with 80% power at the 5% significance level we require data on 352 participants (using SAS procedure GLMPOWER)**. Over 15 months we expect 1,200 people with hand RA to be referred to our participating centres. If half of these assessed for study entry and 80% of these join the study we will have 480 participants (1,200*0.5*0.8) with 25% loss to follow up we will have data on 360 participants at one year.

Statistical Analysis

Primary outcome: The difference in scores from baseline for the **Michigan Hand Outcomes Questionnaire** will be analysed by repeated measures mixed models with a treatment effect (control and exercise groups), a time effect (**4** and 12 months follow-up) and a treatment*time interaction. The estimated mean difference from baseline to the 12-month time-point for the treatment groups will be compared (the primary treatment effect hypothesis) and 95% confidence intervals given. The overall time effect will be modelled. As a sensitivity analysis the primary treatment effect will also be tested with the stratification variables used at randomisation in the model. This analysis will provide data regarding time, group and group*time effects. Where non-parametric methods are used then the primary hypothesis will be tested by Wilcoxon tests.
Secondary endpoints: Pain, hand strength, dexterity, adherence with exercise, will be analysed in a similar manner. Numbers of surgical and serious adverse event data will be analysed using the relative risk or Hazard rates, and survival methods.
We will utilise hierarchical models to evaluate whether therapists effects are important in the quantifying the effectiveness, and understanding the mechanism of effect. We have developed methods to do this in previous studies, although have found that therapist effects are weaker than had been supposed.

Economic analysis
The economic analysis will be conducted alongside the trial and thus will make use of trial data but additionally will model beyond the trial using a decision analytic model[47]. Resource use data will be collected to estimate the health sector and patient costs associated with the intervention and management of such participants. We shall prospectively collect data on resource use alongside the clinical trial. The main resources to be monitored include: training costs, primary care consultations, use of drugs, use of secondary care services, and patient costs, including time costs. Data will be collected using self-completed patient questionnaires, based upon those used by the investigators in other similar trials. Evidence of good patient recall with respect to health care appointments provides support for the plan to collect some data directly from participants[48]. Information on unit costs or prices will then be required to attach to each resource item in order that an overall cost per patient can be calculated. Such data will be collected from relevant routine sources, NHS reference costs and hospital finance departments.

Within trial analysis: The data available for this analysis will be patient-specific resource use and costs, and patient-specific outcome and quality of life data. An incremental economic analysis will be conducted. The base-case analysis will be framed in terms of cost-consequences, reporting data in a disaggregated manner on the incremental cost, and the important consequences (including data on quality of life, etc.). If this convincingly identifies a situation of dominance (i.e. one arm is associated with both better outcomes and a lower cost) then further analysis will not be required. If no dominance is found then cost-utility analysis (i.e. cost per quality-adjusted life year [QALY]) will be employed over a 12 month time frame. QALYs will be calculated using EQ-5D data collected as part of the clinical study. The EQ-5D is a generic utility-based measure of health-related quality of life that has been widely used in economic analyses of health care interventions. The EQ-5D is a widely-used brief measure of health utility[49]. It measures quality of life using questions in five domains. Previous work suggests that it is better at picking up serious illness and has fewer floor effects in groups like this than other measures, such as the SF-6D. It is included in this study in order that improvements in overall quality of life can be estimated and measured in terms of the strength of preference for such improvements. The instrument is designed to be self-completed and so, where possible, the patient will provide the data. Missing data due to non-completion of self-report questionnaires may be a problem for the economic analysis. If this turns out to be the case then imputation will be employed using multiple imputation methods.

Model-based analysis: A longer-term projection of costs and benefits will be obtained through decision analytic modeling work that will allow extrapolation beyond the trial. The

model will likely be of a Markov type, given the lack of interaction between individuals in this clinical area but the need to consider the timing of key clinical events[47], and will build on our previous modeling in the RA field[50].

Presentation of results and sensitivity analysis: The results of these economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. We shall also use both simple and probabilistic sensitivity analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results. For example, if the use of such exercise therapies appears cost-effective on the basis of the data collected as part of this study, we shall explore the extent to which the results are likely to hold in other centres and other settings.

Outcome Measurement

Our first follow-up at **four** months is timed to be at the end of the treatment phase of the trial. All treatment sessions thus need to be completed within **four** months of randomisation. Our clinical collaborators in PT/OT do not anticipate this to be a problem and consider this additional work to be practicable. The total outcome measurement package that trial participants will have to complete includes **will** take between 15 and 20 minutes to complete. At each assessment, a series of physical impairment tests will be conducted to quantify the effect of the interventions on hand strength, flexibility, alignment and coordination. Included in the outcome assessment battery will be specific questions regarding any incidence of adverse or serious adverse events, including specific questions on tendon rupture, hospitalisation or alteration in DMARD use.

We will reduce loss to follow up by

- Providing training in compliance issues to all staff in contact with participants
- Utilising an established and effective reminder system for appointments that utilises letters and telephone contact, used previously by WMSCTU.
- Providing funding for travel costs, to enable taxi's for participants, and if necessary to allow therapists to travel to participants homes.
- Keeping face to face appointments down to a minimum (three attendances).
- Re-enforce in the importance of follow up visits to participants, regardless of their response to treatment or their exercise behaviour.
- Use the National Strategic Tracking Service

Primary Outcome: Michigan Hand Outcomes Questionnaire (MHQ).

Hand and wrist Function: This self-report questionnaire has been shown to be a reliable, valid and responsive measure for an RA population (Massy-Westropp et al, 1996; van der Giesen et al, 2008). The MHQ contains 6 domains: (1) overall hand function, (2) ADL, (3) pain, (4) work performance, (5) aesthetics, and (6) patient satisfaction. Scores range from 0 to 100, with higher scores indicating better performance, except for the pain scale. For the pain scale, a higher score indicates more pain.

Table 1: The Study Outcome Measures

Domain		Measures	Details	Time points
Function	***Primary***	Michigan Hand Outcomes Questionnaire (MHOQ)	Self-completed questionnaire	0, 4, 12
Pain	***Secondary***	'Troublesomeness' rating and from Pain sub-scale of MHOQ	Self-completed questionnaire	0, 4, 12
Impairment	***Secondary***	Grip and Pinch Strength Dexterity Range of motion (hand and wrist only) Joint alignment (MCPJ only)	Observed test using a dynamometer Observation of timed 9 hole peg test Observed test using a goniometer Observed test using a goniometer	0, 4, 12
Disease Activity	***Secondary***	Disease Activity Joint Tenderness and swelling (hand and wrist joints only)	Erythrocyte sedimentation rate (ESR) and/or C-Reactive protein (CRP) blood test results from notes Observation and palpation of each joint	0, 4, 12
Health-related Quality of Life	***Secondary***	SF-12	Self-completed questionnaire	0, 4, 12
Self-efficacy	***Secondary***	7 item questionnaire	Self-completed questionnaire	0, 4, 12
Satisfaction	***Secondary***	Treatment satisfaction item and satisfaction sub-scale of MHOQ	Self-completed questionnaire	0, 4, 12
Global Change	***Secondary***	Global change question 7 point Likert scale	Self-completed questionnaire	4, 12
Adherence	***Secondary***	5 item questionnaire	Self-completed questionnaire	0, 4, 12
Economics	***Secondary***	Resource use questionnaire EQ-5D (health utility)	Self-completed questionnaire Self-completed questionnaire	0, 4, 12 0, 4, 12

Secondary outcomes:
Pain: We will use the MHQ pain section; two items that grade severity and frequency of pain. This section has been shown to correlate well with other measures of pain (Chung et al, 1998). We will also use the 'Troublesomeness' scale which has previously been used in other areas of chronic pain and has been shown have good psychometric properties (Parsons et al, 2006).

Upper Limb, Hand and Wrist Impairment: Data will be collected on isometric pinch and grip strength and endurance using the reliable MIE Digital Grip analyser (Medical Research Ltd, Leeds, UK)[4], as both types of grip have been shown to be strong indices of hand function[4].
Joint swelling, tenderness and alignment scores will be taken **for the hand and wrist** using standardised methods **(Adams et al, 2004; Wolfe et al, 2001)** to monitor any deformity development or progression. **Composite finger and wrist movement will be measured by linear measurement (Ellis and Bruton, 2000) and goniometry (LaStayo and Wheeler, 1994) respectively**. Dexterity of the hand will be measured using 9 hole peg board, as this component of the Arthritis Hand Function Test has demonstrable measurement validity and responsiveness[4] and is an inexpensive 'off the shelf test' (Homecraft-Roylan, UK).
Adherence to the exercise advice: In light of the difficulties in acquiring accurate recordings of adherence behaviour we plan to use self-report measure of adherence, at **4** and 12 months follow up. Whilst self report measures are notoriously unrepresentative of actual behaviour, in the absence of a 'gold standard' measure we will use a five item self report questionnaire[59]. However, it has been suggested that self-report should not be automatically dismissed as unreliable Individuals who admit to being non-adherent are virtually always being truthful, and self-report is likely to identify at least 50% of non-adherent individuals[60].
Medication: We will estimate participants' medication use over the duration of the study period using data on their regular medications collected at baseline, three and twelve months after randomisation,. At each follow up appointment we will ascertain participants' current regular medication. Starting from their hospital records and their general practice repeat prescription request slip we will ask participants to confirm their current regular medication. In addition, we will ascertain their use of 'as required' medication, mainly pain killers and anti-inflammatory drugs, in the previous week. We anticipate that in this group of patients with a chronic disease requiring regular treatment that, in discussion with our assessors that we will be able to get accurate data on both regular and as required drug use. We will use

these data to estimate their total use of medication over the study period. Daily DMARD dosage will be calculated and entered as a covariate in our analysis of effect. We will estimate total cost of prescription medication using the prescribing and cost analysis database (http://www.ic.nhs.uk/pubs/prescostanalysis2005). We have used this general approach successfully in a previous HTA-funded study[30]. We will collect these data on all of those from whom we obtain consent/assent to examine their hospital records. Numbers of shoulder, elbow, wrist and hand intra-articular steroid injections received, will be monitored using hospital records.

Hospital admissions: This data will be collected as part of the health economic analysis. Firstly we will identify these from participant self report at each follow-up assessment, including data on duration and reason for the admission. We will then obtain the copies of the discharge letters after each admission from the hospital concerned. We will obtain copies of hospital discharge letters for each admission to confirm details of the admission. Two medical members of the study team will extract data on cause and duration of these admission blind to treatment allocation, conferring on any disagreements with a third member of the team to arbitrate in the case of disagreements. We will code these admissions into Diagnosis Related Groups and use standard costs derived from these for our economic analysis. We will specifically report on any differences between the groups in upper limb surgery. In the event that a participant dies during the study period we will seek to identify hospital admissions directly from their hospital and general practice records.

Embedded qualitative study of adherence, expectations and development of the exercise intervention: This study is of a complex intervention and we propose to utilize mixed methods to develop a greater understanding of the efficacy and effectiveness of components of the intervention[61]. Qualitative interviews will be undertaken to explore patient expectations, their experience through the course of the trial, and to optimize the intervention package during piloting. Adherence with exercise is notoriously low in patients with arthritic conditions[37]. A number of authors have implemented strategies to increase adherence with exercise programmes with only marginal effect[16]. The use of an educational behavioural model has been shown to increase adherence with joint protection advice[12] and we intend to utilise this model supplemented with the other strategies to increase adherence to exercise. As part of the pilot study and main study we will undertake a qualitative study to explore the acceptability and expectations of the exercise programme to participants, the content and presentation of the programme, and the expectations of and satisfaction with the programme.

A researcher experienced in social science methodology will conduct in-depth interviews using a purposively diverse sample of up to 20 individuals (10 from each intervention arm). These data will be collected on two occasions: after randomisation, and after treatment. These interviews will be recorded, transcribed and analysed using the principles of theory informed qualitative analysis[62]. The data will be managed in the first instance by mapping key concepts (charting) and extracting emergent themes from the transcripts. Transcripts will be analysed iteratively and emergent themes and concepts will be revisited and refined. Particular attention will be paid to discordant voices or dissonant cases, i.e. elements of the transcript that do not readily accommodate a theme but which are notable for future analysis. The emergent themes will form the basis of the analytical interpretation[63]. Prior to the interviews a topic guide will be developed to structure the content.

Research Governance: A Trial Steering Committee (TSC) will be formed with an independent chair, two other independent members and the principle investigators. There will be an independent Data Monitoring and Ethics Committee (DMEC) will be chaired by a statistician. This study will be fully compliant with the research governance framework and MRC Good Clinical Practice Guidance. Data will be securely stored for 10 years after completion of the trial. WMSCTU has well established processes for ensuring adherence with good clinical practice in research.

This proposal is lead by a group with considerable experience of satisfactorily completing large community-based pragmatic trials. We are therefore closely familiar with the process management methods needed for trials of this nature.

Trial management: The framework for the collaboration for this study is well established. Prof Lamb will assume overall responsibility for the trial. The trial will be managed on a day to day basis by a Clinical Trial Co-ordinator, supported by WMSCTU administrative staff. A senior physiotherapist who is experienced in RA management will be appointed to undertake the training of, and interface with clinicians at each of the sites and be responsible for recruiting participants. We will employ clinical staff on temporary contracts at remote sites to undertake recruitment, assessment and treatment. Trial meetings will be held at monthly intervals with the principal investigators to monitor progress and provide support. The responsibilities of each of the applicants are specified in the application form. The trial statistician and economist will be closely involved in setting up data capture systems, design of data bases, protocols for data entry and cleaning, trial steering committee meetings.

Quality control: We will institute a rigorous programme of quality control. We will employ a clinical research fellow (Chartered Physiotherapist/ Occupational Therapist), to be based at WMSCTU. Part of his/her duties will be to ensure adherence to the study protocols at the sites. To achieve this s/he will periodically observe the consent process and baseline and follow-up assessments. The clinical research fellow based at Warwick and the local site coordinating therapist will share responsibility for quality control of the interventions. The clinical research fellow will periodically make quality control visits to observe the exercise sessions and the control treatments. Quality assurance checks will be undertaken by the WMSCTU to ensure the integrity of randomisation, study entry procedures and data collection. The WMSCTU has a quality assurance officer who will monitor this trial, as with all trials that run at WMSCTU. The WMSCTU Quality Assurance Manager will conduct an annual inspection of the Trial Master File. A written report will be produced for the TSC, informing them if any corrective action is required and the timeframe in which it should be completed. The Quality Assurance Manager will be available to answer any questions at any time during the trial. A monitoring plan will be set in place that will consider the trial procedures and Standard Operating Procedures (SOPs). Consent taking, randomisation, registration, provision of information, provision of treatment will be monitored. Likewise all activities relating to SOPs on data management will be audited and quality controlled. Databases for the trial will be set up using the SQLSERVER and MACRO trial management system, which allows programming of audit trails for data input.

Project Timetable and Milestones: We propose a three-and-a-half year study starting in **November 2009**. In the pre-funding stage we will obtain MREC approval and LREC and research governance approval in our participating host Trusts. In the event that we experience delays in obtaining these approvals we will defer the start of the project until they are in place, however, we have considerable experience in obtaining research ethics and research governance approvals.

Our proposed study milestones are:

- Month **0-9** R&D approval, contracting and piloting of interventions
- Month **10** Recruitment of first participants
- Month **14** Follow up begins
- Months **14** Submit protocol, including the intervention for publication
- Month 18 DMEC review of interim data
- Month **27** End of Recruitment. Qualitative study of pt experience starts.
- Month **37** End of follow-up. Dissemination of qualitative study
- Month **38** Closure of all databases
- Month **42** Submission of draft report and draft papers

Table 2 Project timetable														
Year	Year 1				Year 2				Year 3				Year 4	
Quarter	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Set-up **12** sites, Piloting,														
Recruitment (n=480)														
Follow up assessments														
Qualitative study of patient experience and write-up														
Health Economics analysis and write up														
Main study analysis and write up														

Expertise

This proposal is lead by the WMSCTU with an expert team of national collaborators. Warwick Medical School Clinical Trials Unit (WMSCTU) was launched officially in September 2005, building on a solid base of pre-existing trials activity in the University of Warwick and the considerable expertise of new international professorial appointments. WMSCTU is central to the research strategy of the Medical School and the University. This is evidenced in substantial institutional investment in posts and infrastructure. The Unit has received over £7.2 million in highly competitive NHS HTA awards, and anticipates the award of approximately £6 million of funding currently under review.

Our area of expertise is Phase III pragmatic trials. We also undertake other activities (trials methodology, systematic reviewing, qualitative and translational research) to support future developments, and in response to NHS needs (e.g. NICE). Our programmes are emergency/critical care; injuries; musculo-skeletal and cancer. We have clinical experts in the Unit including ICU anaesthetists, musculo-skeletal/trauma (SL, MU, **MW**); injury prevention (SL). We also work in close collaboration with key external collaborators on joint programmes of work to which we make very substantial contributions (complex intervention development, study design, recruitment, study management, statistical analysis, randomisation and/or programming). We are members of the West Midlands Stroke Local Research Network, Central England Primary Care Local Research Network, Thames Valley Diabetes Local Research Network, National Physiotherapy Research Network and West Midlands South Comprehensive Local Research Network. We support clinical trials in a number of local NHS Trusts, by information sharing and joint development of policies and procedures.

A solid programme of methodological work underpins our trial activity. We have a strong team of statisticians and trial methodologists who, as well as being involved with running trials on a day-to-day basis, develop new methods. We have a strong interest in the design and interpretation of complex interventions for chronic disorders. As well as our practical experience of running such trials on topics as diverse as back pain, whiplash, diabetes and ankle sprain, we have developed an excellent understanding of the potential pitfalls inherent in trials of this nature through systematic reviews of cluster-randomised trials (SE) and clinical service innovations for heart failure (MU). This is an experienced team comprising experts in: exercise prescription for frail older people (SL), research in RA hands (JA, AB, AO'B) design and analysis of cluster trials (SL, MU), complex interventions (SL, **MW**, JA, MU), assessment and modification of behaviours (CB), health economics (JL, MU), medical statistics (CMC, SL) and qualitative research (**EW**, JA). We have clinical expertise in rheumatology (AR), general practice (MU), physiotherapy (SL, **MW**, AB), occupational therapy (JA) and health psychology (CB). In addition to our co-investigators we have

Consultant Rheumatology collaborators at each recruitment hub Dr Edwards (Southampton), Dr Marguerie (Warwick), and Dr Celiah (Wrightington). Dr Adams has developed a strong network of rheumatology recruitment sites, utilised in her recently completed PhD in RA hand assessment. The responsibilities of the team are summarised below.

Individual	Responsibility
Lamb (SL)	Chief Investigator Assuming overall responsibility for the delivery of the project
Williams(MW)	To assume day to day responsibility for the delivery and supervision of the project To provide clinical expertise To supervise the recruitment and intervention development team
Underwood (MU)	Clinical lead for medicine; social science and economic evaluation. Supervise qualitative study.
McConkey (CM)	To lead the statistical evaluation
Lord(JL)	To lead the economics evaluation Supervise the economics research fellow
Bridle (CB)	To lead the development and evaluation of the behavioural components of the study
Rahman (AR)	To provide Rheumatological expertise
Dr C Marguerie (Midlands), Dr C Edwards (South), Dr A Celiah (Wrightington) collaborators.	To provide Rheumatological lead at the **three** hubs
Adams (JA)	To coordinate recruitment and conduct of study at the **eight** sites of the **Southern** hub
Ann Birch (AB), collaborator.	To coordinate the Wrightington hub recruitment and intervention
Anne O'Brien (AO'B), collaborator.	To contribute to refinement of the intervention

The Warwick Clinical Trials Unit has randomised over 6,000 participants since its launch in 2003, working in a range of areas but specialising in the evaluation of complex interventions. It has successfully completed a range of trials for Cancer Research UK, NCCHTA, ARC and other funders, on time and on budget. With a multi-disciplinary environment comprising trial managers, data clerks, programming, randomisation, statistics and trial methodologists, it is fully compliant with MRC-GCP; DH clinical trial unit accreditation is expected in late 2006. The senior staff at WMSCTU have considerable experience of supervising and supporting the development of junior research staff. The unit has a philosophy of ensuring that junior research staffs have the appropriate in-service training both to support the delivery of individual projects and to assist the research staff's career progression at the end of the study.

Service Users

By the nature of this study, user involvement is essential. As detailed in our method, we will convene user group meetings in each locality during the pilot study, we will organise separate focus groups to explore expectations of treatment and to exercise generally. We already have a commitment from a panel of users/experts including representatives from relevant charities (National Rheumatoid Arthritis Society and INVOLVE) to meet annually during the study to advise on its conduct. We will have clinician and lay representation on the Trial Steering Committee.

Justification of support

Research costs: The study requires a full-time experienced research co-ordinator, to manage the day-to-day running of the trial. The post has been remunerated at a level that reflects the responsibilities of a senior position. In order to reduce costs we have sought funding to employ only the research co-ordinator (1.0 FTE), clinical fellow (1.0 FTE) and PI (**MW** 0.1 FTE) for the full duration of the grant at 42 months. The majority of involvement in the trial is costed for 36 months with the recruitment therapist / nurse being 0.33FTE for 15 months and the four research therapists at 0.33 for 27 months. We are asking for a 0.33 FTE Data manager / secretary to support the co-ordinator, in duties such as arranging meetings and office duties, but we will use this money flexibly across the study period. The clinical fellow will be based at Warwick University (lead fellow) and will co-ordinate the activities of the recruitment and treatment therapists at remote sites. At each hub a co-investigator will assume academic responsibility (JA – **Southern** hub, AR - London hub, AB - Wrightington hub and **MW** - Warwick hub).

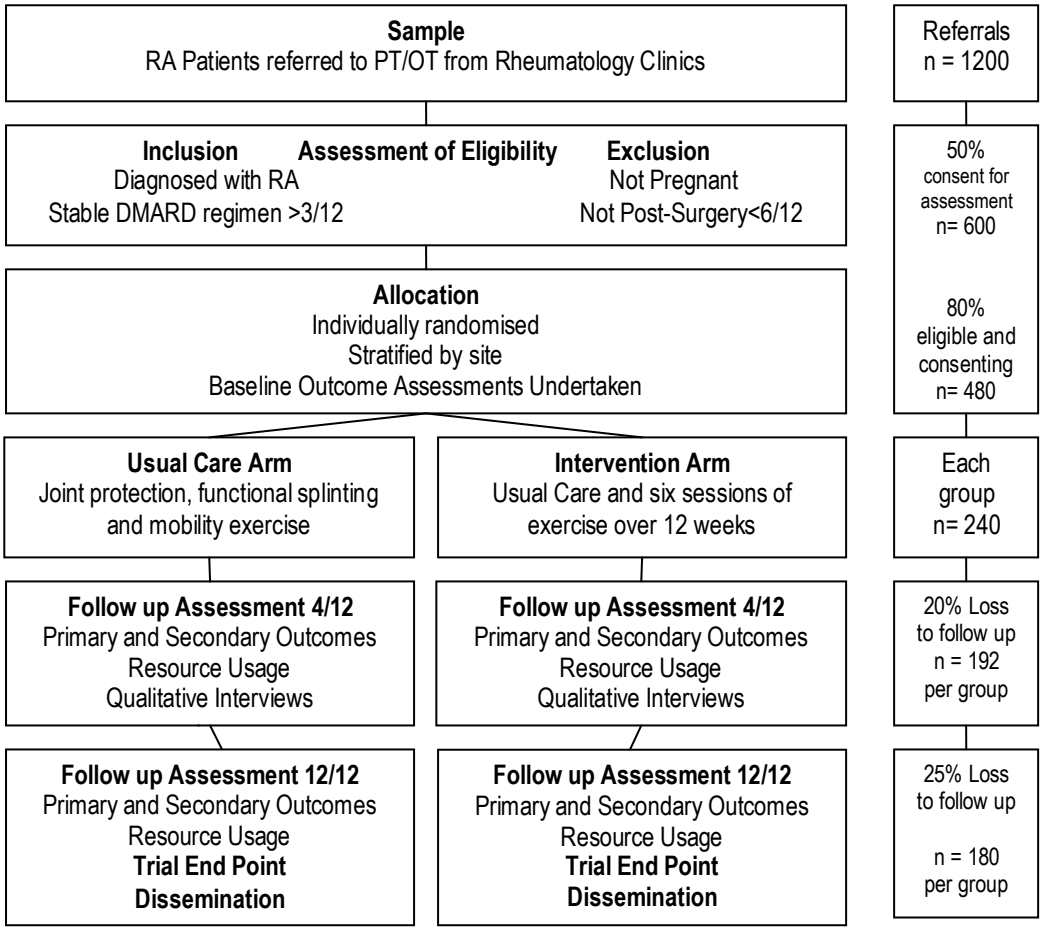
There are also costs for quality control checks, and to cover the eventuality that a small number of participants will be telephoned during follow up. We have requested a 20% senior statistician for each of the three years of the study to be used flexibly across the grant. We have requested a junior health economist at 0.33FTE for 36 months, supported by Professor Bryan at 0.05FTE. The health economics team will be involved in the refinement of data collection tools prior to the start of the study, conduct of the pilot study, and take responsibility for the costing study, cost analyses and economic modelling as well as contributing to the final report.

Expenses for travel and subsistence include travel to training days, steering group meetings, DMEC committees and travel between the clinical sites and have been estimated at either 2nd class rail rates, or at mileage rate of 35p per mile. We have sought travel costs for patients to attend three outcome assessments at an estimated taxi fare of £10 return. Phone and stationery are costed at cheapest rates. We will require 3 laptop computers with specialist software, 3 laser printers and office software. A fee of £4,500 has been included for the WMSCTU telephone randomisation service. We have included monies for advertising, associated with recruitment, mail shots to promote recruitment, staff training (such as attendance on a clinical trials course) and conference attendance. Assessment equipment costs include 10 MIE hand assessment units that cannot be leased but are relatively inexpensive at £1500 each. Dexterity and sensation testing equipment at each site amounts to £1500 in total.

Service support costs: The cost of research therapist (Screening, recruitment, assessment) time and the minimal equipment costs have already been accounted for in the research costs, with the NHS R&D costs for excess treatment cost being estimated by the lead centre (University of Coventry and Warwickshire Hospitals).

Flow Diagram

Figure 1: Flow of participants through the study



References

1. Symmons D, Turner G, Webb R, Asten P, Barrett E, Lunt M, Scott D, Silman A: **The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century.[see comment]**. *Rheumatology* 2002, **41**(7):793-800.
2. Young A, Dixey J, Cox N, Davies P, Devlin J, Emery P, Gallivan S, Gough A, James D, Prouse P *et al*: **How does functional disability in early rheumatoid arthritis (RA) affect patients and their lives? Results of 5 years of follow-up in 732 patients from the Early RA Study (ERAS)**. *Rheumatology* 2000, **39**(6):603-611.
3. American College of Rheumatology Subcommittee on Rheumatoid Arthritis G: **Guidelines for the management of rheumatoid arthritis: 2002 Update.**. *Arthritis & Rheumatism* 2002, **46**(2):328-346.
4. Adams J: **The purpose of outcome measurement in rheumatology**. *British Journal of Occupational Therapy 2002 Apr; 65(4):172-4*.
5. Kennedy N, Sayers K, Cassidy C, Ward S, Bresnihan B, Fitzgerald O, Stokes E: **The effect of a period of rehabilitation in a rheumatic diseases unit**. *British Journal of Therapy & Rehabilitation 2001 Jan; 8(1):29-36).*
6. Hammond A: **Rehabilitation in Rheumatoid Arthritis: A Critical Review**. *Musculoskeletal Care* 2004, **2**(3):16.
7. Henderson SE, McMillan IR: **Pain and function: occupational therapists' use of orthotics in rheumatoid arthritis**. *British Journal of Occupational Therapy 2002 Apr; 65(4):165-71*
8. Hammond A: **Joint protection education: what are we doing?** *British Journal of Occupational Therapy 1997 Sep; 60(9)::401-6*.
9. Hammond A, Klompenhouwer P: **Getting evidence into practice: implementing a behavioural joint protection education programme for people with rheumatoid arthritis**. *British Journal of Occupational Therapy 2005 Jan; 68(1):25-33* .
10. Vliet Vlieland TP: **Rehabilitation of people with rheumatoid arthritis**. *Best Practice & Research in Clinical Rheumatology* 2003, **17**(5):847-861.
11. Stern EB: **Grip strength and finger dexterity across five styles of commercial wrist orthoses... first presented at the 73rd Annual Conference of the American Occupational Therapy Association, Seattle, Washington, June 1993** *American Journal of Occupational Therapy 1996 Jan; 50(1):32-8).*
12. Hammond A, Freeman K: **The long-term outcomes from a randomized controlled trial of an educational-behavioural joint protection programme for people with rheumatoid arthritis**. *Clinical Rehabilitation 2004 Aug; 18(5):520-8).*
13. Haslock DI, Harriman DF, Wright V: **Neuromuscular disorders associated with rheumatoid arthritis**. *Annals of the Rheumatic Diseases* 1970, **29**(2):197.
14. Van den Ende CH, Vliet Vlieland TP, Munneke M, Hazes JM: **Dynamic exercise therapy in rheumatoid arthritis: a systematic review**. *British Journal of Rheumatology* 1998, **37**(6):677-687.
15. Hurley MV, Rees J, Newham DJ: **Quadriceps function, proprioceptive acuity and functional performance in healthy young, middle-aged and elderly subjects**. *Age and Ageing 1998 Jan; 27(1)::55-62).*
16. Stenstrom CH, Minor MA: **Evidence for the benefit of aerobic and strengthening exercise in rheumatoid arthritis**. *Arthritis & Rheumatism* 2003, **49**(3):428-434.
17. de Jong Z, Munneke M, Jansen LM, Ronday K, van Schaardenburg DJ, Brand R, van den Ende CH, Vliet Vlieland TP, Zuijderduin WM, Hazes JM: **Differences between participants and nonparticipants in an exercise trial for adults with rheumatoid arthritis**. *Arthritis & Rheumatism* 2004, **51**(4):593-600.
18. de Jong Z, Munneke M, Zwinderman AH, Kroon HM, Jansen A, Ronday KH, van Schaardenburg D, Dijkmans BA, Van den Ende CH, Breedveld FC *et al*: **Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial**. *Arthritis & Rheumatism* 2003, **48**(9):2415-2424.
19. Munneke M, de Jong Z, Zwinderman AH, Ronday HK, van Schaardenburg D, Dijkmans BA, Kroon HM, Vliet Vlieland TP, Hazes JM: **Effect of a high-intensity weight-bearing exercise program on radiologic damage progression of the large joints in subgroups of patients with rheumatoid arthritis**. *Arthritis & Rheumatism* 2005, **53**(3):410-417.
20. Munneke M, de Jong Z, Zwinderman AH, Vliet Vlieland TP, Hazes JM: **Effect of dynamic strength training on functional capacity in rheumatoid arthritis: comment on the article by Hakkinen et al.**. *Arthritis & Rheumatism* 2002, **46**(1):274-276.

21. Brighton SW, Lubbe JE, van der Merwe CA: **The effect of a long-term exercise programme on the rheumatoid hand**. *British Journal of Rheumatology* 1993, **32**(5):392-395.
22. Buljina AI, Taljanovic MS, Avdic DM, Hunter TB: **Physical and exercise therapy for treatment of the rheumatoid hand**. *Arthritis & Rheumatism* 2001, **45**(4):392-397.
23. O'Brien AV, Jones P, Mullis R, Mulherin D, Dziedzic K: **Conservative hand therapy treatments in rheumatoid arthritis--a randomized controlled trial**. *Rheumatology* 2006, **45**(5):577-583.
24. Rosenstock IM: **Why people use health services**. *Milbank Memorial Fund Quarterly* 1966, **44**(3):Suppl 94-127.
25. Gollwitzer M: **Implementation intentions : strong effects of simple plans.** *The American Psychologist* 1999, **54**(7):493-503.
26. Brealey S, Burton K, Coulton S, Farrin A, Garratt A, Harvey E, Letley L, Martin J, Klaber MJ, Russell I *et al*: **UK Back pain Exercise And Manipulation (UK BEAM) trial--national randomised trial of physical treatments for back pain in primary care: objectives, design and interventions [ISRCTN32683578]**. *BMC Health Services Research* 2003, **3**(1):16.
27. Lamb SE, Lall R, Hansen Z, Withers EJ, Griffiths FE, Szczepura A, Barlow J, Underwood MR, the Back Skills Training Trial T: **Design considerations in a clinical trial of a cognitive behavioural intervention for the management of low back pain in primary care: Back Skills Training Trial**. *BMC Musculoskeletal Disorders* 2007, **8**:14.
28. McCarthy CJ, Mills PM, Pullen R, Roberts C, Silman A, Oldham JA: **Supplementing a home exercise programme with a class-based exercise programme is more effective than home exercise alone in the treatment of knee osteoarthritis**. *Rheumatology* 2004, **43**(7):880-886.
29. Cooke MW, Lamb SE, Marsh J, Dale J: **A survey of current consultant practice of treatment of severe ankle sprains in emergency departments in the United Kingdom.[see comment]**. *Emergency Medicine Journal* 2003, **20**(6):505-507.
30. Cross PL, Ashby D, Harding G, Hennessy EM, Letley L, Parsons S, Spencer AE, Underwood M, Team TS: **TOIB Study. Are topical or oral ibuprofen equally effective for the treatment of chronic knee pain presenting in primary care: a randomised controlled trial with patient preference study. [ISRCTN79353052]**. *BMC Musculoskeletal Disorders* 2005, **6**:55.
31. Hammond A, Freeman K: **Community patient education and exercise for people with fibromyalgia: a parallel group randomized controlled trial**. *Clinical Rehabilitation 2006 Oct; 20(10)::835-46 (41).*
32. Hakkinen A: **Effectiveness and Safety of Strength Training in Rheumatoid Arthritis**. *Current Opinion in Rheumatology* 2004, **16**:5.
33. McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, Silman AJ, Oldham JA: **Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis**. *Health Technology Assessment* 2004, **8**(46):iii-iv.
34. Marcora SM, Lemmey AB, Maddison PJ: **Can progressive resistance training reverse cachexia in patients with rheumatoid arthritis? Results of a pilot study**. *Journal of Rheumatology* 2005, **32**(6):1031-1039.
35. Scott DL, Shipley M, Dawson A, Edwards S, Symmons DP, Woolf AD: **The clinical management of rheumatoid arthritis and osteoarthritis: strategies for improving clinical effectiveness**. *British Journal of Rheumatology* 1998, **37**(5):546-554.
36. Rejeski WJ, Brawley LR, Ettinger W, Morgan T, Thompson C: **Compliance to exercise therapy in older participants with knee osteoarthritis: implications for treating disability**. *Medicine & Science in Sports & Exercise* 1997, **29**(8):977-985.
37. Ettinger WH, Jr., Burns R, Messier SP, Applegate W, Rejeski WJ, Morgan T, Shumaker S, Berry MJ, O'Toole M, Monu J *et al*: **A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness Arthritis and Seniors Trial (FAST).**. *JAMA* 1997, **277**(1):25-31.
38. Sheeran P, Trafimow D, Armitage CJ: **Predicting behaviour from perceived behavioural control: tests of the accuracy assumption of the theory of planned behaviour**. *British Journal of Social Psychology* 2003, **42**(Pt 3):393-410.
39. Sheeran P, Trafimow D, Finlay KA, Norman P: **Evidence that the type of person affects the strength of the perceived behavioural control-intention relationship**. *British Journal of Social Psychology* 2002, **41**(Pt 2):253-270.

40. Rejeski WJ, Craven T, Ettinger WH, Jr., McFarlane M, Shumaker S: **Self-efficacy and pain in disability with osteoarthritis of the knee**. *Journals of Gerontology Series B-Psychological Sciences & Social Sciences* 1996, **51**(1):P24-29.
41. Hammond A, Lincoln N: **The effect of a joint protection education programme for people with rheumatoid arthritis**. *Clinical Rehabilitation 1999 Oct; 13(5)::392-400*.
42. Orbell S, Sheeran P: **'Inclined abstainers': a problem for predicting health-related behaviour**. *British Journal of Social Psychology* 1998, **37**(Pt 2):151-165.
43. Orbell S, Abraham C: **Behavioural sciences and the real world: report of a community interview scheme for medical students**. *Medical Education* 1993, **27**(3):218-228.
44. Sheeran P, Orbell S: **Using implementation intentions to increase attendance for cervical cancer screening**. *Health Psychology* 2000, **19**(3):283-289.
45. de Jong Z, Munneke M, Zwinderman AH, Kroon HM, Ronday KH, Lems WF, Dijkmans BA, Breedveld FC, Vliet Vlieland TP, Hazes JM *et al*: **Long term high intensity exercise and damage of small joints in rheumatoid arthritis**. *Annals of the Rheumatic Diseases* 2004, **63**(11):1399-1405.
46. Lineker SC, Badley EM, Hawker G, Wilkins A: **Determining sensitivity to change in outcome measures used to evaluate hydrotherapy exercise programs for people with rheumatic diseases**. *Arthritis Care & Research* 2000, **13**(1):62-65.
47. Barton P, Bryan,S., Robinson, S.: **Modelling in the economic evaluation of health care:selectingthe appropriate approach**. *Journal of Health Services & Research Policy* 2004, **9**(2):8.
48. Byford S, Leese,M., Knapp,M.: **Comparison of alternative methods of collection of service use data for the economic evaluation of health care interventions**. *Health Economics* 2007, **16**(5):5.
49. Brazier J, Jones N, Kind P: **Testing the validity of the Euroqol and comparing it with the SF-36 health survey questionnaire.**. *Quality of Life Research* 1993, **2**(3):169-180.
50. Barton P, *et al.*: **The use of modelling to evaluate new drugs for patients with chronic conditions:the case of antibodies against tumour necrosis factor in rheumatoid arthritis**. *Health Technology Assessment* 2004, **8**(11).
51. Massy-Westropp N, Krishnan J, Ahern M. **Comparing the AUSCAN Osteoarthritis Hand Index, Michigan Hand Outcomes Questionnaire, and Sequential Occupational Dexterity Assessment for patients with rheumatoid arthritis.** *J Rheumatol.* Oct 2004;31(10):1996-2001.
52. van der Giesen F, Nelissen R, Arendzen J, de Jong Z, Wolterbeek R, Vliet Vlieland T. **Responsiveness of the Michigan Hand Outcomes Questionnaire--Dutch language version in patients with rheumatoid arthritis.** *Arch Phys Med Rehabil.* Jun 2008;89(6):1121-1126.
53. Chung K, Pillsbury M, Walters M, Hayward R. **Reliability and validity testing of the Michigan Hand Outcomes Questionnaire.** *J Hand Surg [Am].* Jul 1998;23(4):575-587.
54. Parsons S, Carnes D, Pincus T, et al. **Measuring troublesomeness of chronic pain by location.** *BMC Musculoskelet Disord.* 2006;7:34.
55. Adams J, Burridge J, Mullee M, Hammond A, Cooper C. **Correlation between upper limb functional ability and structural hand impairment in an early rheumatoid population.** *Clin Rehabil.* Jun 2004;18(4):405-413.
56. Wolfe F, O'Dell J, Kavanaugh A, Wilske K, Pincus T. **Evaluating severity and status in rheumatoid arthritis.** *J Rheumatol.* Jun 2001;28(6):1453-1462.
57. Ellis B, Bruton A. **A study to compare the reliability of composite finger flexion with goniometry for measurement of range of motion in the hand.** *Clin Rehabil.* Aug 2002;16(5):562-570.
58. LaStayo P, Wheeler D. **Reliability of passive wrist flexion and extension goniometric measurements: a multicenter study.** *Phys Ther.* Feb 1994;74(2):162-174; discussion 174-166.
59. Vitolins MZ, Rand CS, Rapp SR, Ribisl PM, Sevick MA: **Measuring adherence to behavioural and medical interventions**. *Controlled Clinical Trials* 2000, **21**(5 Suppl):188S-194S
60. Haynes RB, Sackett DL, Gibson ES, Taylor DW, Hackett BC, Roberts RS, Johnson AL: **Improvement of medication compliance in uncontrolled hypertension**. *Lancet* 1976, **1**(7972):1265-1268.
61. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, Tyrer P: **Framework for design and evaluation of complex interventions to improve health**. *BMJ* 2000, **321**(7262):694-696.

62. Harding G, Gantley M: **Qualitative methods: beyond the cookbook**. *Family Practice* 1998, **15**(1):76-79.
63. Sibthorpe BM, Glasgow NJ, Wells RW: **Emergent themes in the sustainability of primary health care innovation**. *Medical Journal of Australia* 2005, **183**(10 Suppl):S77-80.