Clinical and cost effectiveness of progressive exercise compared to best practice advice, with or without corticosteroid injection, for the treatment of rotator cuff disorders: a 2x2 factorial randomised controlled trial

Short Title: The GRASP Trial - "Getting it Right: Addressing Shoulder Pain"

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ISRCTN16539266 **EudraCT Number:** 2016-002991-28 **IRAS ID:** 199243 **UTN:** U1111-1185-3750

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Conflict of interest declaration
There are no conflicts of interest to declare.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigator team, host organisation, and members of the Research Ethics Committee, unless authorised.

ABBREVIATIONS

BESS	British Elbow and Shoulder Society
DSMC	Data Safety Monitoring Committee
GCP	Good Clinical Practice
GP	General Practitioner
GRASP	Getting it Right: Addressing Shoulder Pain
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
MHRA	Medicines and Health care products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
nIMP	Non-Investigational Medicinal Product
NIHR	National Institute for Health Research
OCTRU	Oxford Clinical Trials Research Unit
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SPADI	Shoulder Pain and Disability Index
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIDieR	Template for Intervention Description and Replication
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCRC	United Kingdom Clinical Research Collaboration

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1. TRIAL SUMMARY

World Health Organization Registration Data Set

Title	Clinical and cost effectiveness of progressive exercise compared to best practice advice, with or without corticosteroid injection, for the treatment of rotator cuff disorders: a 2x2 factorial randomised controlled trial
Trial register and number	EudraCT Number: 2016-002991-28 ISRCTN16539266
Date of registration	14/07/2016
Sources of monetary or material support	National Institute of Health Research Health Technology Assessment Programme (Project reference: 15/26/06)
Sponsor	University of Oxford
Central contact	GRASP Trial Manager University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, Windmill Road, Oxford, UK, OX3 7LD.Tel: 01865 737432; Email: GRASP@ndorms.ox.ac.uk
Brief title (acronym)	GRASP - Getting it Right: Addressing Shoulder Pain
Countries of recruitment	UK
Focus of study	To assess the clinical and cost effectiveness of individually tailored, progressive exercise compared with best practice advice, with or without corticosteroid injection, in patients with a rotator cuff disorder.
Interventions **i) Progressive exercise** **ii) Best practice advice** **iii) Progressive exercise and corticosteroid injection** **iv) Best practice advice and corticosteroid injection**	 Participants receive up to six sessions with a physiotherapist over 16 weeks. These sessions have a strong behavioural component to encourage adherence to exercises to be performed at home. Participants receive a single face-to-face session with a physiotherapist, lasting up to 60 minutes. The best practice advice session has substantially greater reliance on self-management. As progressive exercise, except that the sessions are preceded with a subacromial corticosteroid injection. Where clinically indicated, a second injection may be administered at 6 weeks. As best practice advice, but this session is preceded by a subacromial corticosteroid injection. Where clinically indicated, a second injection may be administered at 6 weeks.
Key eligibility criteria	Men and women ≥18 years with a new episode of shoulder pain attributable to a rotator cuff disorder (tendonitis, impingement

	syndrome, tendinopathy or tears) who are not currently receiving physiotherapy or being considered for surgery.
Study design	Study type: Interventional trial (CTIMP) Allocation: Randomised Intervention model: Factorial Primary purpose: Treatment Phase: Phase 3 Blinding: Investigator blind
Target sample size	704
Duration of follow up	12 months
Planned trial period	44 months
Primary outcomes	Outcome: Pain and function (Shoulder Pain And Disability Index) Timeframe: 12 months
Secondary outcomes	Outcome: Pain (Shoulder Pain and Disability Index, 5-item subscale) Timeframe: 0, 8 weeks, 6 months, 12 months Outcome: Function (Shoulder Pain and Disability Index, 8-item subscale) Timeframe: 0, 8 weeks, 6 months, 12 months Outcome: Health-related quality of life (EQ-5D-5L) Timeframe: 0, 8 weeks, 6 months, 12 months Outcome: Psychological factors (Fear Avoidance Belief Questionnaire) Timeframe: 0, 8 weeks, 6 months, 12 months Outcome: Sleep disturbance (Insomnia Severity Index) Timeframe: 0, 8 weeks, 6 months, 12 months Outcome: Return to desired activities (Patient-reported) Timeframe: 8 weeks, 6 months, 12 months Outcome: Global impression of change (Likert scale) Timeframe: 8 weeks, 6 months, 12 months Outcome: Patient-reported adherence to exercise Timeframe: 8 weeks, 6 months, 12 months Outcome: Use of medication (Patient-reported) Timeframe: 8 weeks, 6 months, 12 months Outcome: Work disability (Days off sick) Timeframe: 8 weeks, 6 months, 12 months Outcome: Use of healthcare resources Timeframe: 8 weeks, 6 months, 12 months

	Outcome: Out-of-pocket expenses (Patient-reported) Timeframe: 8 weeks, 6 months, 12 months

2. LAY SUMMARY

GRASP - Getting it Right: Addressing Shoulder Pain

Shoulder pain is very common, with around 1% of adults in the UK consulting their GP about a new shoulder problem each year. Most new cases of shoulder pain is caused by problems with muscles and tendons in the shoulder, called the rotator cuff. The rotator cuff can be damaged through irritation and inflammation, trapping of the tendons and/or muscle tears. The main symptom is pain, both when still and when moving the shoulder. Shoulder pain can seriously affect a person's ability to work, sleep soundly and perform daily tasks. Common treatments include advice, rest, painkillers, anti-inflammatories, physiotherapy and steroid injections. We don't yet know how to optimise physiotherapy for shoulder pain, even though it is often used. We don't know which physiotherapy techniques work best for shoulder pain, how exactly they should be delivered, and whether patients do better if they get a steroid injection before starting an exercise programme.

The GRASP trial will test whether people with a rotator cuff problem do better after a progressive exercise programme supervised over 16 weeks by a physiotherapist or after one best-practice advice session with a physiotherapist. The trial will also test whether getting a corticosteroid injection in the shoulder joint before starting either regime helps to relieve pain, enabling comfortable exercise and improving function. Each of these treatment programmes is already commonly used by NHS physiotherapists to treat shoulder pain. The GRASP trial is recruiting men and women with a new episode of shoulder pain due to a rotator cuff problem and who are not currently receiving physiotherapy or being considered for surgery.

We aim to recruit 704 people from one of at least eight NHS-based musculoskeletal centres in the UK for this trial. They will be randomised to one of four treatment groups: 1) progressive exercise (up to six sessions); 2) best practice advice (one session); 3) progressive exercise and a shoulder corticosteroid injection; or 4) best practice advice and a shoulder corticosteroid injection. The exercise programme will include techniques to help people to do their exercises regularly, as there is strong evidence that how a person thinks affects how well they get into the habit of doing exercises. The trial participants will be asked about their level of shoulder pain and their ability to perform basic daily tasks over a year. The GRASP trial will assess which of these routine interventions, or combination of interventions, are most clinically and cost effective for patients and the NHS.

3. INTRODUCTION

3.1. BACKGROUND AND RATIONALE

3.1.1. Problem and diagnosis

Shoulder pain is very common. Annually, around 1% of adults over 45 in primary care present with a new episode of shoulder pain (1), accounting for 2.4% of all GP consultations in the UK (2). The most common attribution is the rotator cuff, which results in around 70% of cases (1). The cuff is a group of four small muscles and their tendons/attachments. The cuff actively moves and stabilises the shoulder joint, enabling a wide range of efficient movement at the shoulder. Disorders of the rotator cuff are associated with substantial disability (e.g., unable to dress independently) and pain. Rotator cuff disorders can persist for long periods. Up to half of those who present for treatment, particularly older people, continue to have pain and/or functional disturbance for up to two years (3).

The majority of shoulder pain is managed in primary care or at primary care interface musculoskeletal services by physiotherapists and GPs. Musculoskeletal services treat people with a range of musculoskeletal conditions. Primary care interface services are designed to incorporate early referral and rapid assessment by specialist practitioners. They aim to promote more community-based management options for patients rather than traditional hospital-based care and provide a more efficient, cost-effective and sustainable model for dealing with high-volume conditions. Treatments for rotator cuff disorders aim to improve pain and function. Standard primary care options include rest, advice, analgesia, non-steroidal anti-inflammatory drugs, physiotherapy and corticosteroid injections (4, 5). However, usual care can be highly variable and there are no recommended National Institute for Health and Care Excellence (NICE) clinical guidelines.

A diagnostic algorithm (1) has been developed as part of the NICE-accredited standards developed by the British Elbow and Shoulder Society (BESS) and other professional bodies (e.g., the Royal College of Surgeons and the Chartered Society of Physiotherapy and British Orthopaedic Association) to confirm when a diagnosis of rotator cuff disorder is highly likely, based on a patient's history and simple shoulder tests (4). The tests recommended have been selected with primary care application in mind (6), although they do require a reasonable degree of clinical skill. Imaging is not recommended in primary care due to the poor fit between structural change and symptomatic

presentation (7). We will use the BESS algorithm (Appendix 1) to define the entry criteria for the trial, thus ensuring that the trial is consistent with national guidance.

3.1.2. Justification for undertaking this research

Problems associated with rotator cuff disorders can seriously affect patient health and wellbeing. The prevalence of shoulder complaints in the UK is estimated at around 14% (8), increasing with age (2) and highest in those aged 60 and above. Shoulder problems are a significant cause of morbidity and disability in the general population and have a significant socioeconomic burden, as they affect an individual's capacity to work and ability to perform daily tasks and social activities. They have a significant impact on primary care services; the average spend per patient in the NHS with a musculoskeletal condition is £461.13 per head per year (9), with wide geographical variability. The estimated cost to the UK economy is £7.4 billion per year.

The NHS currently invests vast amounts of money on unproven therapies and corticosteroid injections. A corticosteroid injection typically costs £147-£332, depending on the mode of delivery, the cheapest of which is by a physiotherapist without ultrasound. In comparison, a set of six physiotherapy sessions costs around £321 and an assessment and advice session costs £53 (10). It is important for the NHS to develop cost-effective, pragmatic methods for dealing with high-volume conditions. Rotator cuff disorders are self-limiting if they are managed effectively in primary care, as patients can regain function and pain is reduced. However, the consequences of poor initial management are an increased likelihood of recurrent or persistent problems in older age and the need for surgical intervention (4).

We propose a large well-powered randomised controlled trial, using a factorial design, to co-test two interventions commonly used in the management of rotator cuff disorders in primary care: progressive exercise delivered by a physiotherapist and corticosteroid injection. We will use a best-practice advice session and no injection as the comparators. The interventions tested will use the current patient pathway for those with a rotator cuff disorder. We want to assess which of these interventions, or combination of interventions, are most clinically and cost effective for the NHS. The primary outcome for the trial will be shoulder function assessed using the well-validated Shoulder Pain and Disability Index (SPADI) (11, 12), a tool that was developed to measure current shoulder pain and disability in an outpatient setting.

3.1.3. Choice of comparators

Exercise intervention

There is promising evidence from small, short-term trials that physiotherapist-prescribed exercise is effective. However, there is a lack of evidence about its long-term effectiveness and cost effectiveness (13-15), despite the widespread provision of physiotherapy for these conditions. There is also uncertainty about which types of exercise and delivery mechanisms are associated with the best outcomes (13, 14, 16-18). This evidence is limited by problems in study design and choice of comparators (14). There are also competing ideologies around which exercise programmes should be considered and which we are equipped to address, to ensure a worthwhile trial. Resistance training to improve muscular strength, whether supervised or home-based, has been identified as a core component of exercise for rotator cuff disorders, although there is no evidence that any specific programme is superior (19, 20). Manipulation of the exercise volume and intensity will be achieved by varying the frequency, load, number of sets, repetitions and rest intervals (21). A trial of strength training found that duration, specificity of exercises, progression criteria and individualisation (i.e. adjusting the programme to suit each participant) were also important (22). We will not consider other forms of physiotherapy, such as electrotherapy, acupuncture, soft tissue mobilisation, manipulation or stratified care, because of lack of evidence of their efficacy (23, 24).

Little attention has been paid to the need for behavioural frameworks to enhance adherence and tackle pain beliefs and behaviour (25). Non-adherence to physiotherapy treatment is estimated to be up to 70% (26). In a large trial of exercise for lower back pain that did not include a behavioural component to increase exercise adherence, only around half of the participants attended the minimum number of treatment sessions (27). Risk factors for low adherence include low levels of physical activity, low self-efficacy, depression, anxiety, poor social support and greater perceived barriers to exercise (25). Some of these risk factors are modifiable, in the context of a physiotherapy intervention. We have previous expertise in this area (28) and will include a strong behavioural component as part of the trial progressive exercise intervention.

Corticosteroid injection

There is good systematic review evidence that, in comparison with placebo, corticosteroid injections have a short-term benefit in the shoulder, as in other areas of the body. However, there are some concerns about their longer-term benefits (29-31). The combination of injection and physiotherapy has intuitive appeal, with some evidence of an additive, but not interactive, effect in the short term (3-4 months) (31-34). We believe that the longer-term benefits of injections require more study and

will include them as part of our study design. We will use a no-injection comparison as finding an inert robust placebo is challenging and, given the existing evidence (29-31), we believe that it is unethical and undesirable to progress a placebo arm in a large phase III trial. In our study based in NHS musculoskeletal services, extended-scope physiotherapists will typically deliver the injections. This is increasingly common practice in the NHS, where therapists undertake additional training to deliver injections, working within a local Patient Group Directive or equivalent (www.nice.org.uk/guidance/mpg2). Physiotherapists are considered highly effective in injection therapy due to their thorough understanding of anatomy and musculoskeletal symptoms. Although the use of ultrasound to guide injections in primary care has become increasingly common, emerging evidence from the SUPPORT trial and others have demonstrated that it is no more effective than standard injection practice (3, 35). Ultrasound guidance also substantially increases the cost and reduces the practicality of injection therapy. Therefore, injection will be performed without the use of ultrasound.

3.2. OBJECTIVES

The aim of the GRASP (Getting it Right: Addressing Shoulder Pain) trial is to assess the clinical and cost effectiveness of individually tailored, progressive exercise compared with best practice advice, with or without corticosteroid injection, in patients with a new episode of a rotator cuff disorder at 8 weeks, 6 months and 12 months after randomisation. The primary objective is to assess whether:

- An individually tailored progressive exercise programme, including behavioural change strategies, led by a physiotherapist provides greater improvement in shoulder pain and function at 12 months post-randomisation versus a best practice advice session with a physiotherapist supported by high quality materials; and whether a subacromial corticosteroid injection provides greater improvement in shoulder pain and function at 12 months post-randomisation than no injection.

The secondary objectives of GRASP are to investigate if there are any differences at 8 weeks, 6 and 12 months in randomised participants in: shoulder pain; shoulder function; health related quality of life; psychological factors; sleep disturbance; return to desired activities including work, social life and sport activities; patient global impression of change; adherence to exercises use of medication (prescribed and over-the-counter); time of work; health resource use (consultation with primary and secondary care) and additional out-of-pocket expenses.

A parallel within-trial health economic analysis will also be conducted at each time points.

3.3. TRIAL DESIGN

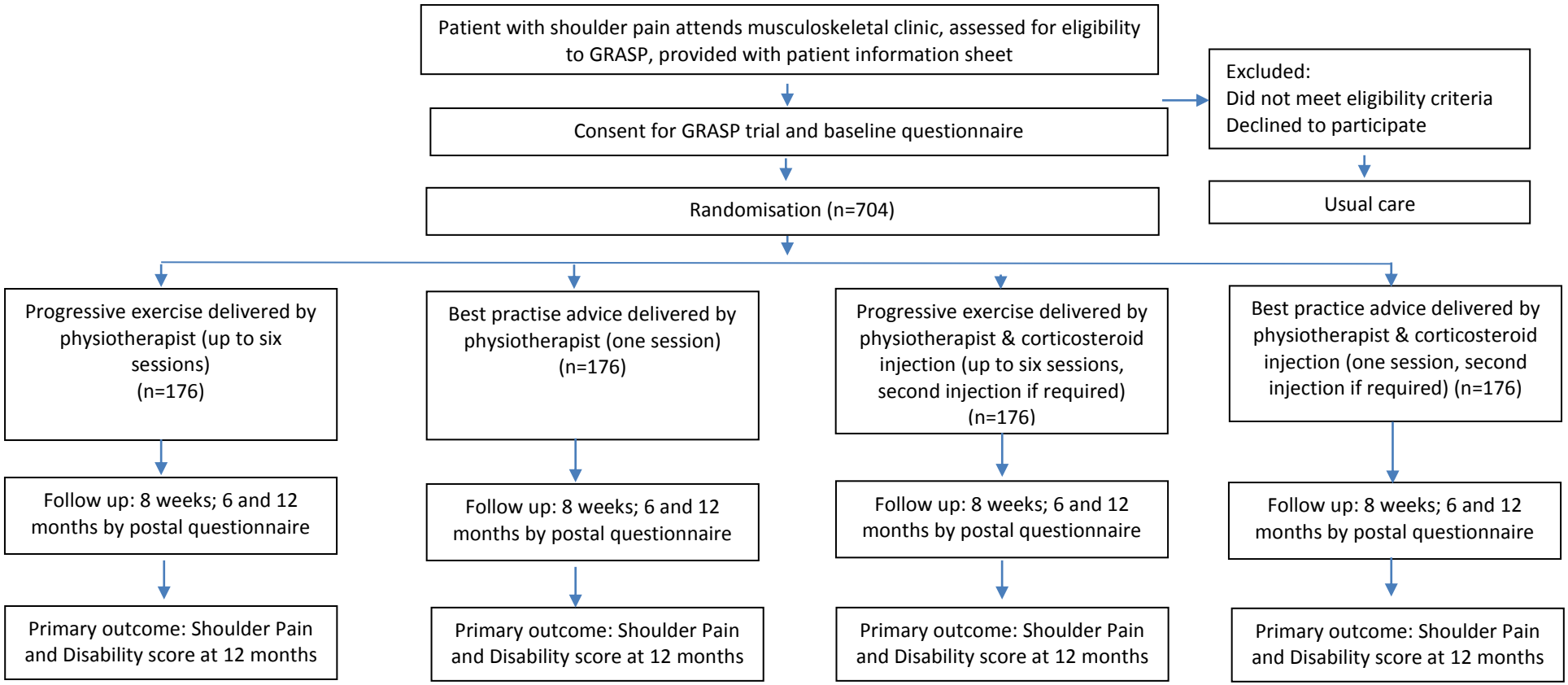
A 2x2 factorial randomised controlled trial (Figure 1) design will be used to test the four physiotherapy-led interventions: 1) a progressive exercise programme, including behavioural change strategies to enhance adherence (up to six sessions); 2) a best practice advice session with a physiotherapist supported by high quality materials (one session); 3) a progressive exercise programme, including behavioural change strategies to enhance adherence (up to six sessions), preceded by a subacromial corticosteroid injection; and 4) a best practice advice session with a physiotherapist supported by high quality materials (one session), preceded by a subacromial corticosteroid injection.

The factorial design (Table 1) will allow two primary comparisons, based on the assumption that there is no interaction: 1) progressive exercise programme versus best practice advice session and 2) subacromial corticosteroid injection versus no injection.

Table 1: GRASP trial 2x2 factorial design

	No corticosteroid injection	**Corticosteroid injection**	**No. participants**
Progressive exercise	176	176	352
Best practice advice	176	176	352
No. participants	352	352	704

Figure 1: Study flow diagram for GRASP[1] trial



[1] GRASP – Getting it Right: Addressing Shoulder Pain

3.3.1. Internal pilot

The internal pilot trial will mirror the procedures and logistics undertaken in the main definitive trial. Data from the internal pilot trial will contribute to the final analysis, assuming there are no substantive changes in the trial design or delivery of the trial interventions. The internal pilot will be conducted across at least three primary-care based musculoskeletal services and their related physiotherapy services. The internal pilot will randomise a minimum of 42 participants across the three sites over 4 months at a target recruitment rate of at least four to five participants per site per month. The purpose of the internal pilot is to test and refine the recruitment process and explore treatment acceptability. The decision to progress to the main trial will be made in collaboration with the trial steering committee (TSC) and National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme based on pre-defined progression criteria, which are reaching the target recruitment rate (42 participants) within the specified time frame (four months). The internal pilot will also identify how well the sites are able to accommodate the delivery of the interventions within their existing workloads. If the decision to progress to main trial is not made, participants will receive all of their allocated intervention and data collection will proceed as per the protocol and all patients will be followed-up to 12 months

3.3.2. Main randomised controlled trial

The main trial will be conducted across at least eight primary care musculoskeletal services and their related physiotherapy services in the UK. The launch of the additional five sites will be in quick succession following the decision to progress from the internal pilot. Recruitment will be closely monitored against the recruitment target of at least four to five participants per month per site over the remaining 20 months of the trial. Data from the internal pilot trial will inform any revisions about the number of sites and the timeline for the main trial.

3.3.3. Cost effectiveness analysis

An economic evaluation is integrated within the trial design. The economic evaluation will be conducted from the recommended NHS and personal social services (PSS) perspective (36). Data will be collected on health and social service resources used in the treatment of each participant during the period between randomisation and 12 months post-randomisation using self-reported patient (37) questionnaires at 8 weeks, 6 months and 12 months post-randomisation. The cost of delivering each intervention, including development and training of providers, delivering the progressive exercise and advice sessions, the corticosteroid injections, and any follow-up/management defined

in the trial treatment protocols, will be estimated. Permission will be requested from the study participants during the initial consent process for long-term follow-up (up to five years) beyond the timeframe of the outcomes assessed in the GRASP trial using routine data (hospital episode statistics (HES) records).

4. METHODS - PARTICIPANTS, INTERVENTIONS AND OUTCOMES

4.1. STUDY SETTING

Participants will be recruited from NHS primary-care-based musculoskeletal services. Musculoskeletal services treat people with a range of musculoskeletal conditions. They provide a screening, assessment and treatment service and are usually run by specialist practitioners including extended-scope physiotherapists, GPs with a specialist interest in musculoskeletal conditions, clinical nurse specialists and, in some instances, rheumatologists and orthopaedic consultants. Patients referred to the service are assessed by a practitioner most appropriate to deal with their condition. For shoulder pain this is often extended scope physiotherapists who will then provide appropriate treatment which could include advice on how to manage the problem, delivery of a steroid injection to relieve pain or referral for physiotherapy. In some instances it may involve referral to diagnostic x-ray, ultrasound, MRI, or secondary care.

4.2. ELIGIBILITY CRITERIA

The target population is men and women aged 18 and older who consult within the NHS with a new, but not necessarily first, episode of shoulder pain attributable to a rotator cuff disorder, who are predominantly seeking treatment for one shoulder. Consecutive patients referred to a musculoskeletal service will be assessed for eligibility by the responsible NHS practitioner; The diagnostic algorithm (Appendix 1) developed by the British Elbow and Shoulder Society (BESS) and other professional bodies (e.g., the Royal College of Surgeons and the Chartered Society of Physiotherapy and British Orthopaedic Association) and part of the NICE-accredited standards (1) will be used to confirm when a diagnosis of rotator cuff disorder is highly likely, based on a patient's history and simple shoulder tests (4). The participants will not undergo diagnostic imaging such as MRI or ultrasound as a requirement of the trial, as this is generally not recommended in primary care.

4.2.1. Inclusion criteria

We will include:

1) Men and women aged 18 years and above;

2) With a new episode of shoulder pain (i.e., within the last 6 months) attributable to a rotator cuff disorder (e.g., cuff tendonitis, impingement syndrome, tendinopathy or rotator cuff tear) using the diagnostic criteria set out in the BESS guidelines (4) (Appendix 1);

3) Who are not currently receiving physiotherapy;

4) Who are not being considered for surgery;

5) Able to understand spoken and written English.

4.2.2. Exclusion criteria

We will exclude:

1) Participants with a history of significant shoulder trauma (e.g., dislocation, fracture or full thickness tear requiring surgery);

2) Those with a neurological disease affecting the shoulder;

3) Those with other shoulder disorders (e.g., inflammatory arthritis, frozen shoulder, glenohumeral joint instability) or with red flags consistent with the criteria set out in the BESS guidelines (4);

4) Those who have received corticosteroid injection or physiotherapy for shoulder pain in the last 6 months; and

5) Those with contra-indications to corticosteroid injection.

4.3. INTERVENTIONS

4.3.1. Subacromial corticosteroid injection

The subacromial corticosteroid injection will be given as per its marketing authorisation and in accordance with its normal indication and therapeutic dosage. The corticosteroid will typically be given together with local anaesthetic in one injection at the same time, or separately, depending on local treatment protocols at sites.

The corticosteroid injected will either be:

- methylprednisolone acetate (up to 40mg) or
- triamcinolone acetonide (up to 40mg),

depending on local treatment protocols for subacromial injection at each site. These are the two routinely injected corticosteroids for shoulder pain; there is no clear evidence that either corticosteroid is more effective than another (31).

The local anaesthetic will either be:

- 1% lidocaine (up to 5 ml) or
- 0.5% bupivacaine hydrochloride (up to 10 ml),

depending on local treatment protocols. We will only select sites that are consistent within these prescribing boundaries. The choice and dose of corticosteroid and local anaesthetic (including volume) will be recorded for each participant in the trial data collection forms.

This trial has a Clinical Trial Authorisation approval that specifies the active ingredient of the corticosteroid injection either methylprednisolone acetate or triamcinolone acetonide and not a specific brand or formulation. Within this trial, lidocaine and bupivacaine hydrochloride are Non-Investigational Medicinal Products (NIMPs).

The corticosteroid and NIMP will be used from normal pharmacy stock at sites and will not be labelled specifically for clinical trial use. The injection/s will be delivered in the musculoskeletal services in a separate appointment before the progressive exercise or best practice advice intervention, predominately by extended-scope physiotherapists working within a local Patient Group Directive or equivalent (www.nice.org.uk/guidance/mpg2). This delivery method reflects an increasingly common practice in the NHS and ensures that the injections are delivered in the most cost-effective manner possible. The subacromial corticosteroid injection and NIMP will be stored and administered in accordance with local standard operating procedures (SOPs) for injection therapy at the individual study sites. Local SOPs for injection therapy will be reviewed by the GRASP study team prior to a study site being approved to take part in the trial.

Participants will be advised to take care and avoid heavy lifting for 24-48 hours post-injection. Appointments will be coordinated so that participants typically receive their injection within 10 days of randomisation and start their exercise sessions within 14 to 28 days of randomisation, as per local appointment availability.

Very occasionally a second injection can be given after 6 weeks (but within 16 weeks of the patient being randomised), but will only be administered to those patients who receive good initial benefit

from their first injection and who request further pain relief to facilitate their exercises. Any participants that receive a second injection will have the dose, drug and date of administration recorded in their trial data collection form.

4.3.2. Progressive exercise sessions

All of the physiotherapists delivering study interventions, progressive exercise sessions and best practice advice will have access to a comprehensive intervention manual and will be required to have undertaken trial-specific training, either face-to-face delivered at recruiting sites by a GRASP trial research physiotherapist and/or via a training video (DVD or online using a personalised login). The trial research physiotherapists will be experienced musculoskeletal practitioners, under the supervision of one of the expert physiotherapists on the applicant team. The training will include comprehensive guidance on the theory and practical delivery of the trial interventions.

The participants randomised to the progressive exercise programme will receive up to six sessions with a physiotherapist over 16 weeks. These sessions will have a strong behavioural component to encourage adherence to the exercises. A similar rationale has been used to good effect in other trials (22, 38). This number of sessions, spread over this time, allows progression of the intensity of exercise and sufficient time for a physiological response in the neuromuscular system to significantly improve function. It also allows time to instigate longer-term health behaviour change. Appointments will be coordinated so that participants typically start their first exercise session within 14 to 28 days of randomisation, as per local appointment availability. The initial session will last up to 60 minutes for assessment and starting the exercise programme, followed by up to five follow-up sessions of 20 to 30 minutes each. The physiotherapists will record the number of prescribed treatment sessions attended by each participant. The intervention has been designed to ensure that sufficient dose is delivered and to maximise compliance. Importantly, the intervention can be delivered within the current NHS commissioning paradigm (39). The progressive exercise programme consists of three phases:

Phase 1 **-** *Assessment and advice:* Participants will be given education, reassurance and advice on pain management and activity modification. They will also be given shoulder exercises to practice at home until their next session.

Phase 2 - Progressive structured resistance training: Resistance exercises will be added that are highly structured and aim to improve the shoulder's functional capacity. The exercises will be

rehearsed in the physiotherapy department and then practised at home. The progression of the volume and load of the resistance training will be based on existing guidelines (21) and will take into account each individual's capabilities and preferences. The modified Borg scale of perceived exertion will be used to regulate the intensity of the resistance exercise (40). The load will initially be set at a moderate level to permit progression, enhance motivation and adherence, and reduce the possibility of symptom flare-up. The exercises will target the patient's movement difficulties; these may include shoulder internal rotation, external rotation and abduction performed in increasingly elevated shoulder positions during the programme, and weight bearing through the upper limb. This regime is consistent with expert consensus (41). Progression will be achieved by increasing the resistance/and or the number of repetitions. Hand weights or resistance bands will be used to add resistance. Participants will be advised that some pain during the exercises is acceptable, provided the participant is happy and the symptoms resolve on rest (42). Patient preference for how each core exercise is performed (where, when and position) will be agreed with the physiotherapist. The participants and therapists will negotiate an effective dose of exercise, progressively giving the participant overall control (Figure 2).

Therapist's role Initial session or session two	**Therapist's and patient's roles** Subsequent sessions	**Patient's role** As sessions progress
• Assesses • Gives advice on pain management and self-care of shoulder • Teaches exercises and gives advice on progression and regression • Provides resistance band (if required) • Introduces exercise planner and diary • Facilitates goal setting, planning where and when to do exercises, contingency plans, explores barriers.	• Re-assess • Review goals, adherence to exercises and give advice • Discuss successes and challenges • Negotiation of progression and regression of exercises • Facilitate independent problem-solving to promote self-confidence.	• Exercising independently regularly with confidence • Competent in progression and regression of exercise • Independent problem-solving in overcoming challenges and barriers to exercise • Requires less feedback to manage exercises as programme progresses.

Figure 2: Framework for progression of the exercise intervention, based on Williams et al.(43)

Phase 3 - Patient-specific functional restoration: The final stage of training involves modifying the core resistance training exercises towards the specific strengthening movements required to achieve the functional goals of the individual.

Behavioural change strategies to encourage adherence

Established behavioural change strategies (44) will be used to maximise adherence to the exercise intervention. Implementation intentions and action planning techniques (45) have been found to be effective in improving physical activity levels. These intentions will form part of a behavioural exercise plan and exercise diary, which patients have reported to be helpful in promoting adherence (43). The physiotherapists delivering the intervention will be trained in questioning techniques, based on cognitive behavioural models (46), to elicit and address unhelpful beliefs about shoulder pain or exercise that may impede adherence (47). Although diaries are of questionable reliability for measuring adherence due to real-time compliance and recall bias (48), they do promote adherence (49). The treating physiotherapists will be trained to prescribe a programme of exercise that the participants are confident with. Patients will be asked to rate their confidence on a visual analogue scale (44) as part of the treatment sessions.

4.3.3. Best practice advice session

The participants randomised to the best practice advice session will receive a single face-to-face session with a physiotherapist, lasting up to 60 minutes. Appointments will be coordinated so that participants typically start their exercise session within 14 to 28 days of randomisation, as per local appointment availability. The best practice advice session will have substantially greater reliance on self-management. After a comprehensive shoulder assessment, the participants will be given education, reassurance and self-management exercise advice, including advice on pain management and activity modification. They will also be given a simple set of self-guided exercises that can be progressed and regressed depending on their capability. We will draw on the SELF trial intervention (developed by Littlewood (42)) as a basis for the approach to self-managed exercise. This simplified approach to exercise therapy and focus on self-management has been found to be as effective as standard physiotherapist treatment (42). Strategies to encourage adherence to exercise will be less extensive than in the progressive exercise intervention as they need to be feasible to deliver within a single session. Simple regular shoulder exercises will be progressed by adding load by use of resistive exercise band or hand weights. The exercises will be designed using similar concepts to the progressive exercise intervention, but will not be supervised or underpinned by the additional

reassurance of follow-up physiotherapy appointments and the more comprehensive behavioural aspects of the intervention.

There is strong evidence that patients do not always retain information that they are provided with face to face. The best practice advice session will be supported by high-quality patient self-management information, drawing on materials used in the UKUFF trial (50), and exercise video available through the web (using a personalised login) or a DVD. As low health literacy levels are a major consideration when developing materials, plain English and patient representative involvement will be used to optimise material accessibility. Using different media aims to make the information accessible and more appealing to a wide range of individuals (51) and has been used successfully in other trials of painful musculoskeletal disorders.

A best practice advice session has been selected as the comparator because it is consistent with current clinical practice guidelines (4, 5). This intervention also minimises the use of some physiotherapy treatments that, whilst commonly used, have evidence of no or minimal effect. In addition, many people find a single advice session and DVD more beneficial as they do not have to come back to the hospital, take time off work or make carer arrangements, for example. This intervention may best serve commissioners, patients and clinicians in the long term.

4.3.4. Concomitant care

All of the trial participants will be advised to take over-the-counter analgesia (paracetamol with or without codeine, or an oral nonsteroidal anti-inflammatory drug) as required, in accordance with the BESS guidelines (4). In addition, all of the participants will be provided with advice on modifying activities that exacerbate symptoms and on sleeping positions. Participants may seek other forms of treatment during the follow-up period of the trial, but will be informed that they should use usual routes (predominantly NHS referral) to do so. Additional treatments, including contact with their GP or other health professional, changes in medication, use of physical treatment and alternative therapies, will be recorded as a treatment outcome through patient questionnaires at 8 weeks, 6 months and 12 months post-randomisation.

4.4. OUTCOMES

4.4.1. Primary outcome

The primary outcome is shoulder pain and function at 12 months measured using the well-validated Shoulder Pain and Disability Index (SPADI) (11, 12), which was developed to measure current shoulder pain and disability in an outpatient setting. A systematic review of outcome measurement sets for shoulder pain trials showed that SPADI is the most commonly used measure to assess pain and disability (52). It has good psychometric properties, is used widely in the field and can be completed using a postal questionnaire.

4.4.2. Secondary outcomes

Secondary outcomes (Table 2) will include: sub-domains of the SPADI which are pain measured using the SPADI 5-item pain subscale (11, 12) and function measured using the SPADI 8-item disability subscale (11, 12); health-related quality of life measured using the 5-level version of the well-validated EQ-5D-5L score (53); psychological factors measured using the Fear Avoidance Belief Questionnaire (physical activity 5-item subscale)(54) and Pain Self-efficacy questionnaire (short form) (55); sleep disturbance measured using the Insomnia Severity Index (56); patient global impression of change (57); return to desired activities, including work, social life and sport activities; patient adherence to exercise; any serious adverse events (SAEs); health resource use (consultation with primary and secondary care, prescribed and over-the-counter medication use, additional physiotherapy or injection use, and hospital admission); additional out-of-pocket expenses; and work absence (number of sickness days).

Table 2: Summary of outcomes assessed

Outcome	Measurement
Primary	
Pain and function	Shoulder Pain and Disability Index (SPADI) (11, 12) 13-item total scale
Secondary	
Pain	Shoulder Pain and Disability Index (SPADI) (11, 12) 5-item subscale
Function	Shoulder Pain and Disability Index (SPADI) (11, 12) 8-item subscale
Health-related quality life	EQ-5D-5L score (53)
Psychological factors	Fear Avoidance Belief Questionnaire – physical activity 5-item subscale (54) Pain Self-efficacy questionnaire (short form) (55)
Sleep disturbance	Insomnia Severity Index (56)

Global impression of treatment	Patient-rated Likert scale (57)
Return to desired activities	Patient-reported return to desired activities, including work, social life and sport activities
Exercise adherence	Patient-reported adherence to exercise
Medication usage	Patient-reported prescribed and over-the-counter medications, additional steroid injection
Work disability	Sick leave (days)
Healthcare use	NHS outpatient and community services (e.g., GP, additional physical therapy) NHS in patient and day case (e.g., radiography or MRI) Private health care services
Out-of-pocket expenses	Patient-related out-of-pocket expenses recording form

4.5. PARTICIPANT TIMELINE

TIMEPOINT	Pre-randomisation	Baseline	0-3 months	8-week follow up	6-month follow up	12-month follow up	Extended follow-up via HES
ENROLLMENT:							
Screening log	✓						
Eligibility confirmed	✓						
Informed consent	✓						
Randomisation		✓					
INTERVENTIONS:							
Steroid injection (if randomised to)		✓					
Progressive exercise intervention (if randomised to)			✓				
Best practice advice intervention (if randomised to)			✓				
ASSESSMENTS:							
Baseline questionnaire	✓						
Follow-up questionnaire				✓	✓	✓	

TIMEPOINT	Pre-randomisation	Baseline	0-3 months	8-week follow up	6-month follow up	12-month follow up	Extended follow-up via HES
Follow-up reminders				✓	✓	✓	
HES follow-up							✓

4.6. RECRUITMENT

4.6.1. Recruitment of sites

The trial will be conducted across at least eight primary-care based musculoskeletal services and their related physiotherapy services in the UK. Sites will be chosen so they reflect a range of settings (urban and rural) and are able to deliver the trial interventions. The local principal investigator will be responsible for the conduct of the research at their site. The principal investigator will identify the staff responsible for the conduct of the trial and ensure that the trial roles and responsibilities are assigned in writing using the trial delegation log. They will also help with local queries and study promotion. All potential sites will be screened with a site feasibility questionnaire to ensure they have sufficient potential participants and the clinical expertise and capacity to provide the treatments and manage the patients.

4.6.2. Recruitment of participants

Participants will be recruited from the musculoskeletal services if referred by their GP or physiotherapy service for investigation/treatment of a new episode of shoulder pain. People who self-refer directly to the musculoskeletal service will also be assessed for eligibility as the typical route of referral can vary across services. GPs and primary-care-based physiotherapy services within the local area surrounding each study site will be informed about the trial and encouraged to refer potentially eligible participants. Posters advertising the GRASP trial will be displayed in the musculoskeletal clinics to raise awareness of the trial with patients and clinicians.

4.6.3. Screening and eligibility assessment

Potential participants will attend their musculoskeletal service clinic appointment in accordance with standard NHS procedures. The treating practitioner within the musculoskeletal services will undertake a clinical assessment according to their usual practice. If a patient fulfils the criteria for a rotator cuff disorder, they will be assessed to see whether they meet the GRASP trial eligibility

criteria (as described in Section 4.2). Patients will be provided with a copy of the participant information sheet and asked if they wish to be considered for the trial. Patients who meet the eligibility criteria and would like to participate in the trial will be approached for informed consent. Participants who do not meet the eligibility criteria or who do not wish to participate will receive the standard NHS treatment. We will record anonymous information on the age and sex of those who decline to participate so that we can assess the generalisability of those recruited. The reasons for declining will be asked and any answers given will be recorded.

4.6.4. Informed consent

After the participants have been assessed for eligibility, informed consent for participation in the trial will be sought. As part of the process of obtaining informed consent, the exact nature of the study will be explained, what it will involve for the participant including expectations that the participant will be willing and able to attend sessions to receive the study intervention, and any risks involved in taking part. The potential participant will have the opportunity to discuss issues and ask questions. The process of obtaining informed consent may take place during the initial musculoskeletal clinic appointment, or may require a second research appointment. All participants will be informed that they can decline to participate and can withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. Participants may request a follow-up phone call if they require more time to consider the study or wish to speak to their GP or other independent parties before deciding whether they will participate in the study.

If the potential participant is deemed eligible and is happy to proceed, then the process of consent will continue. A researcher facilitator who has been trained in Good Clinical Practice (GCP), authorised to do so by the chief investigator (authority will be designated to the research lead for the project), will obtained informed consent. The consent form will be signed and dated by the participant and the researcher; a copy of the signed consent form will be given to the participant. The original consent form will be retained at the study site and a copy will be returned to the trial office.

5. METHODS - ASSIGNMENT OF INTERVENTIONS

5.1. ALLOCATION

Consented participants will be randomised to intervention groups (1:1:1:1) using the centralised computer randomisation service RRAMP (https://rramp.octru.ox.ac.uk) provided by the Oxford Clinical Trials Research Unit (OCTRU). This will either be undertaken directly by the research facilitator at the site or by contacting the trial office over the phone, which will access the system on their behalf, depending on the facilities available at the study sites. Randomisation will be computer-generated and stratified by centre, age and gender, using a variable block size to ensure the participants from each study site have an equal chance of receiving each intervention. Participants will only be randomised following eligibility assessment and after informed consent has been obtained.

5.2. BLINDING

Physiotherapists delivering the intervention and study participants will be informed of their treatment at the initial appointment and so will not be blinded to the treatment allocation. The trial statistician and data entry personnel will also not be blinded to the treatment allocation. The remaining members of the trial management team will be blinded to treatment allocation until after the data analysis is complete.

5.3. SAMPLE SIZE

The target sample size for the trial is 704 randomised participants (176 in each treatment arm). This sample size is based on 90% power and 1% two-sided statistical significance to detect a minimally clinically important difference (MCID) of 8 points on the SPADI total scale (11), assuming a baseline standard deviation of 24.3 (chosen as representative of the patient population (58)). This difference is the equivalent of a standardised effect size of 0.33, which requires a sample size of 550 participants (Power Analysis and Sample Size (PASS) 13, www.ncss.com). Allowing for a potential loss to follow-up at 12 months of 20% inflates the sample size to 688. We have further inflated the sample size to take into account the potential for a small clustering by physiotherapist effect in the

progressive exercise group. We use an ICC of 0.001, based on our experience with individually tailored physiotherapy interventions (59), and expect each physiotherapist to treat approximately 20 participants in the progressive exercise group. This leads to an inflation of f = 1+(m-1)*ICC = 1+(20-1)*0.001 = 1.019 and increases the sample size to a total of 704 participants (176 per arm).

This sample size assumes that there is no interaction effect and is powered for the two main effect comparisons: 1) progressive exercise versus best practice advice and 2) corticosteroid injection versus no injection when no interaction is present. However, the number of participants will also provide 80% power and 5% two-sided significance to detect an interaction standardised effect size of 0.35, if an interaction effect does exist. The interaction effect will be tested before the main effect comparisons are undertaken. It should be noted that a nonsignificant interaction effect does not preclude a smaller interaction that this study is not powered to detect. We have chosen 90% power and 1% two-sided significance to provide more convincing evidence of any treatment effects discovered. No further adjustment to the sample size has been made due to multiple testing. It is anticipated that the Data Monitoring and Ethics Committee (DMEC) will review the sample size assumptions after approximately 50% of the participants have been recruited.

6. METHODS - DATA COLLECTION, MANAGEMENT AND ANALYSIS

6.1. DATA COLLECTION METHODS

6.1.1. Baseline data collection

After the participants have been assessed for eligibility and informed consent has been obtained, participants will be asked to complete a baseline assessment questionnaire that will record simple demographic information and baseline measurements for the primary and secondary outcomes, shown in Table 3. The participants will complete the baseline questionnaire before learning the outcome of the randomisation.

Table 3: Time points at which the outcomes will be assessed

Outcome	Measurement	Time point
Demographic	Age, Sex, Height, Weight, Ethnicity, Marital status, Smoking, Date of rotator cuff diagnosis, Duration of symptoms, Hand dominance, Affected shoulder, Current work status, Level of education, Place of	0

Outcome	Measurement	Time point
	residence, Household income, State benefits	
Primary		
Pain and function	Shoulder Pain and Disability Index (SPADI) (11, 12) 13-item total scale	0, 8 wk, 6 mth, 12 mth
Secondary		
Pain	Shoulder Pain and Disability Index (SPADI) (11, 12) 5-item subscale	0, 8 wk, 6 mth, 12 mth
Function	Shoulder Pain and Disability Index (SPADI) (11, 12) 8-item subscale	0, 8 wk, 6 mth, 12 mth
Health-related quality life	EQ-5D-5L score (53)	0, 8 wk, 6 mth, 12 mth
Psychological factors	Fear Avoidance Belief Questionnaire physical activity 5-item subscale (54) Pain Self-efficacy questionnaire (short form) (55)	0, 8 wk, 6 mth, 12 mth
Sleep disturbance	Insomnia Severity Index (56)	0, 8 wk, 6 mth, 12 mth
Global impression of treatment	Patient-rated Likert scale (57)	8 wk, 6 mth, 12 mth
Return to desired activities	Patient-reported return to desired activities, including work, social life and sport activities	8 wk, 6 mth, 12 mth
Exercise adherence	Patient-reported adherence to exercise	8 wks, 6mth, 12 mth
Medication usage	Prescribed and over-the-counter medications, additional steroid injection	8 wk, 6 mth, 12 mth
Work disability	Sick leave (days)	8 wk, 6mth, 12mth
Healthcare use	NHS outpatient and community services (e.g., GP, additional physical therapy) NHS inpatient and day case (e.g., radiography, MRI) Private health care services	8 wk, 6 mth, 12 mth
Out-of-pocket expenses	Patient-related out-of-pocket expenses recording form	8 wk, 6 mth, 12 mth

6.1.2. Follow-up data collection

Measurements for the primary and secondary outcomes are all patient-reported and will be collected using either postal or web-based questionnaires at 8 weeks, 6 months and 12 months after randomisation. Detail of the outcomes to be assessed, how they will be measured and at which time points are shown in Table 3. The participants will be asked to complete the questionnaire and return it to the GRASP study team in a prepaid envelope or online as appropriate. In addition, participants may be randomised to receive either a standard text message or a personalised text message (which will include their name) prior to receiving the 6 month follow up questionnaire – if they choose to take part in the PROMPTS sub-study (described in Appendix 2). For those who do not respond to the

initial questionnaire at least one postal reminder will be sent; a web-based version of the questionnaire, telephone and email follow-up will be used to contact those who do not respond to the postal questionnaire. Telephone and email follow-up will also be used to collect a core set of questionnaire items if these have not been fully completed on the returned questionnaire. In order to maximise response rates for the 12 month follow up a small monetary incentive (in the form of a gift voucher) will be sent to all participants along with their 12 month follow up questionnaire as a thank you for the time and effort involved.

Participants in the progressive exercise group will also be asked to keep exercise diaries documenting the time spent on their home based physiotherapy, these will be reviewed by the treating physiotherapist at the end of the intervention.

Permission will be requested from the study participants for long-term follow-up (up to five years), using routine data (HES data) beyond the timeframe of the outcomes assessed in the trial.

6.1.3. Discontinuation / withdrawal of participants

Participants will be informed that they have the right to withdraw from the GRASP trial at any time without having to provide a reason and with no impact on their future health care. A participant may wish to discontinue their trial treatment and/or withdraw from the data collection process. If a participant wishes to discontinue their trial treatment, the study team will contact the participant and ask if they are still willing to participate in the collection of follow-up data. Participants that continue to participate in follow-up will not be considered a withdrawal. If a participant wishes to withdraw from the data collection process, the study team will ask the participant if they may use the data collected to the point of withdrawal. In addition to participant self-withdrawal, an investigator may decide to withdraw a participant from GRASP if considered necessary for any reason including ineligibility either arising during the study or retrospectively, having been overlooked at screening. The reason for withdrawal (if given) will be recorded on the study withdrawal case report form. Withdrawn participants will not be replaced as we have allowed for possible withdrawals and loss to follow-up in the estimated sample size.

6.1.4. Definition of end of trial

The end of the trial is defined as when all data have been received and all queries resolved.

6.2. DATA MANAGEMENT

All data will be processed according to the Data Protection Act 1998 and all documents will be stored safely in confidential conditions. A data management and sharing plan will be produced for the trial and will include reference to confidentiality, access and security arrangements. All trial-specific documents, except for the signed consent form and follow-up contact details, will refer to the participant with a unique study participant number/code and not by name. Participant identifiable data will be stored separately from study data and in accordance with OCTRU SOPs. All trial data will be stored securely in offices only accessible by swipe card by the central coordinating team staff in Oxford and authorised personnel.

Data will be collected from participants and treating physiotherapist via questionnaires and case report forms that will be returned to the central trial office in Oxford via post using a pre-addressed freepost envelope or email as appropriate. Copies of consent forms will be collected during site visits and returned to the trial office. Sites will send copies to the trials office via secure NHS email, or via recorded delivery. Participant data will be stored and transported in accordance with the Data Protection Act 1998 and SOPs. Upon completion of the trial, and with appropriate participant consent, fully anonymised research data may be shared with other organisations at the behest of the funder.

6.3. STATISTICAL METHODS

The primary statistical analysis will be carried out on the basis of intention-to-treat, with all randomised participants included and analysed according to their allocated treatment group, irrespective of which treatment they actually received or their compliance with the proposed interventions. A separate statistical analysis plan (SAP) with full details of all statistical analyses planned for the data of this study will be drafted early in the trial and finalised prior to any primary outcome analysis. The SAP will be reviewed and will receive input from the Trial Steering Committee (TSC) and the Data Monitoring and Ethics Committee (DMEC). The independent DMEC will meet early in the trial to agree the terms of reference and to review confidential interim analyses of accumulating data. Any changes or deviations from the original SAP will be described and justified in the protocol, final report and/or publications, as appropriate. It is anticipated that all statistical analysis will be undertaken using Stata (StataCorp LP, www.stata.com) or other well-validated statistical packages.

6.3.1. Outcomes analyses

The primary outcome measure is shoulder pain and function measured using the SPADI (11, 12) patient-reported outcome scale (total) at 12 months post-randomisation. The scale is based on 13 questions, all scored on a 0-10 numerical rating scale on which 10 is the worst score, with a 5-item pain subscale and an 8-item disability subscale. The subscale items and total are summed and converted to a 0-100 scale, where a higher value denotes more pain and/or disability. The SPADI scale will also be collected at baseline, 8 weeks and 6 months. There will be two main effect comparisons for this 2x2 factorial trial: 1) progressive exercise versus best practice advice and 2) subacromial corticosteroid injection versus no injection. The analysis will be conducted as intention-to-treat and all randomised patients will be used in both comparisons.

The analysis will be undertaken using longitudinal methods in a multivariable analysis with adjustment for the baseline SPADI score, stratification factors, important prognostic factors, clustering by physiotherapists and taking into account the multiple time-points. Statistical significance will be set at the 1% level and corresponding 99% confidence intervals will be reported for the primary outcome. For all other outcomes, 5% significance and 95% confidence intervals will be reported. The data distribution will be formally assessed and if evidence for departure from normality is found, nonparametric techniques will be used with no adjustment (for example the Mann-Whitney test or the Kruskal-Wallis test).

Secondary outcomes will include the individual components (pain and disability) of the SPADI scale (11, 12), health-related quality of life measured using the 5-level version of the well-validated EQ-5D-5L score (53), psychological factors measured using the Fear Avoidance Belief Questionnaire (physical activity 5-item subscale)(54) and Pain Self-efficacy questionnaire (short form) (55), sleep disturbance measured using the Insomnia Severity Index (56), patient global impression of change (57), return to desired activities, including work, social life and sport activities, and patient adherence to exercise intervention. The secondary outcomes will be analysed using the same methodology as for the primary outcome.

6.3.2. Missing data

A linear mixed longitudinal model will be used to analyse all available data for the primary outcome. This method can take account of missing observations either due to missed visits or to a participant leaving the study prematurely, and can also be used when the participants are not all assessed at

exactly the same time-point, as the exact time for each observation is used in the analysis. Missing data will be reported and summarised by treatment arm. The distribution of missing data will be explored to assess the assumption of data being missing at random. Multiple-imputation will be used, if appropriate. Full details will be provided in the SAP.

6.3.3. Additional analyses

An interaction between the two main effects is not expected, but the trial is powered to identify a moderate standardised interaction effect. The presence of an interaction between the two interventions will be formally investigated before testing their effects on the primary outcome. If an interaction is detected, the comparisons will be presented within each intervention arm, i) progressive exercise versus best practice advice and ii) progressive exercise plus corticosteroid injection versus best practice advice plus corticosteroid injection to test the effect of the effect of the physiotherapy program; and iii) progressive exercise versus progressive exercise plus corticosteroid injection and iv) best practice advice versus best practice advice plus corticosteroid injection to test the effect of the corticosteroid injection.

Pre-specified subgroup analyses will explore possible treatment effect modification of clinically important factors, through the use of treatment by factor interactions, and will be interpreted cautiously. We will confirm the final subgroups in the SAP, but these are likely to include the duration or severity of the presenting symptoms and the presence or absence of widespread pain.

6.3.4. Economic evaluation

A within-trial economic evaluation will be conducted in parallel with the assessment of the clinical effectiveness of the four intervention groups. The factorial design of the study will also allow the economic evaluation of the two primary comparisons: 1) progressive exercise versus best practice advice and 2) corticosteroid injection versus no corticosteroid injection, both for the treatment of rotator cuff disorder. Data on the use of primary, community and social healthcare services will be collected at 8 weeks, 6 months and 12 months post-randomisation by postal or web-based self-reported patient questionnaires. HES data will also be collected for long-term routine data capture beyond the outcomes assessed in the trial (up to 5 years). Rotator cuff disorders are associated with a significant socioeconomic burden, as they affect an individual's capacity to work. The patient questionnaires will therefore also record employment status, indirect costs borne by the participants

and their carers as a result of attending hospital visits, and direct non-medical costs (including travel expenses) attributable to their disorder. These costs will be reported separately from health and social care costs. Unit cost data will be obtained from national databases such as the British National Formulary and PSSRU Costs of Health and Social Care (60).

Health-related quality of life will be estimated using the EQ-5D-5L (61). The trial participants will be asked to complete the EQ-5D-5L at baseline and 8 weeks, 6 months and 12 months post-randomisation. The responses to the EQ-5D will be converted into multi-attribute utility scores using an approved "cross-walk" to the three-level instrument and its established utility algorithm for the UK (62, 63), or the new UK-approved five-level utility tariff, if published. The economic evaluation will be conducted from a UK NHS and Personal Social Services perspective (PSS) (36) and will compare the costs and outcomes at 12-month follow-up using the trial data. The outputs of the economic evaluation will be presented in terms of expected incremental cost effectiveness ratios. Cost effectiveness acceptability curves will be generated via nonparametric bootstrapping and displayed graphically, alongside cost-effectiveness planes and expected net benefit statistics. Probabilistic sensitivity analyses will be performed to explore the implications of parameter uncertainty on the incremental cost-effectiveness ratios. Subgroup analysis using predefined subgroups will investigate potential treatment moderators such as age, sex and other baseline characteristics for which cost effectiveness is predicted to be different.

The at-the-margins approach (without interactions) may treat the factorial trial as though it were two overlapping two-arm randomised trials and may effectively ignore the factorial design as it assumes that factors have purely additive effect. If there is no interaction, ignoring interactions is statistically efficient, answering two questions with the same sample size required for one. However this form of analysis gives biased or misleading results if there is any interaction. Regression analysis provides a convenient way to evaluate interactions and main effects. Including covariates within regression facilitates adjustment for baseline imbalance, which may be particularly important for factorial trials. For the purpose of the economic evaluation, we will investigate the possible interactions with quality-adjusted life-years and costs. The distribution of costs and benefits and correlation between costs and effects will also be considered. If factors are thought to have a multiplicative effect, a general linear model may be appropriate in transformed data.

7. MONITORING METHODS

7.1. DATA MONITORING

7.1.1. Data Monitoring and Ethics Committee

A Data Monitoring and Ethics Committee (DMEC) will be appointed to safeguard the interests of the trial participants to assess the safety and efficacy of the interventions during the trial, and to monitor the overall conduct of the trial, protecting its validity and credibility. The DMEC will be independent of the trial investigators and sponsor and will adopt a DAMOCLES charter that defines its terms of reference and operation in relation to oversight of the trial. It will meet at least every 12 months over the duration of the trial. The DMEC will not be asked to perform any formal interim analyses of effectiveness. It will, however, review accruing data and summaries of that data presented by the treatment group and will assess the screening algorithm against the eligibility criteria. It will also consider emerging evidence from other related trials or research and review any related SAEs that have been reported. The DMEC may advise the chair of the Trial Steering Committee at any time if, in its view, the trial should be stopped for ethical reasons, including concerns about participant safety or clear evidence of the effectiveness of one of the treatments. The DMEC will comprise an independent medically qualified clinician, specialist physiotherapist, statistician, and health service researcher.

7.1.2. Interim analysis

There are no plans for carrying out any formal interim analysis of the main outcomes of the trial. We considered using an early stopping rule, but rejected this idea as the treatment period is extensive and there is no strong link demonstrated between early response and later outcomes.

7.2. SAFETY REPORTING

7.2.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product that is related to any dose administered to that participant. The phrase “response to an investigational medicinal product” means that a causal relationship between a trial medication and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

	All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	An SAE is any untoward medical occurrence that: • results in death, • is life-threatening, • requires inpatient hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability/incapacity, or • consists of a congenital anomaly or birth defect. Other "important medical events" may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting investigator, is believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) for that product.

Pregnant women will not be excluded from the trial. The corticosteroid injection is safe to administer to pregnant women under its current licence. The corticosteroid is administered as a one-off injection or occasionally as a second injection. We will therefore not collect information on whether participants become pregnant during the trial.

7.2.2. Procedures for recording adverse events

Foreseeable adverse events occurring as a result of the trial intervention(s) will not be recorded as part of the trial. Corticosteroid injection is part of the standard treatment pathway for patients with shoulder pain and has a good safety profile (31). Participants will be provided with information on the potential adverse events resulting from exercise and corticosteroid injection (if applicable) as

part of their treatment, including what they should do if they experience an adverse event, as would happen as part of standard NHS procedures.

7.2.3. Reporting procedure for serious adverse event

SAEs are likely to be very rare and are highly unlikely to occur as a result of either the exercise or corticosteroid injection therapy delivered in this trial.

However if an SAE arises from the participants enrolment in the trial to their final visit for their allocated intervention, the site must complete a SAE form and record the description, date of onset, end date, severity and assessment of relatedness to trial medication (if applicable). All SAEs must be reported on the GRASP SAE reporting form and be faxed or scanned and emailed to the GRASP office within 24 hours of the site becoming aware of the SAE. The SAE form will be reviewed by the chief investigator, who together with the trial management team in the OCTRU office will make an independent assessment of causality and will perform an assessment of expectedness. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and faxed or scanned and emailed to GRASP office.

The SAE form is likely to be completed by the treating physiotherapist, who in the case of corticosteroid injection is qualified to provide the extended scope intervention working within a local Patient Group Directive or equivalent (www.nice.org.uk/guidance/mpg2) and will make an assessment of causality at the site which will be confirmed by an appropriately qualified medical doctor, listed on the trial delegation log.

The trial protocol states only the active ingredient and not a specific drug brand that should be used in the trial. As required there can only be one source to be used as the Reference Safety Information for the drugs, therefore the summaries of product characteristics for methylprednisolone (when produced as the product Depo-Medrone) and triamcinolone acetonide (when produced as the product Kenalog) will be employed for the trial.

7.2.4. Reporting procedure for Suspected Unexpected Serious Adverse Events

Any SAEs that fulfil the definition of a SUSAR will be reported to the Competent Authority of the Medicines and Health care products Regulatory Agency (MHRA) (if the SUSAR is the related to the IMP), Research Ethics Committee (REC) and sponsor within 7 calendar days of the trial management team in the OCTRU office becoming aware of the event that resulted in death or was life threatening, or 15 calendar days for any other event. In the unlikely event of a SUSAR due to the NIMP only, this will be reported via the Yellow Card scheme to the MHRA and not under the above SUSAR reporting mechanism.

7.3. QUALITY ASSURANCE PROCEDURES

This research will be coordinated by the Critical Care, Trauma, Rehabilitation (CCTR) Trials Group, which falls under the Oxford Clinical Trials Research Unit (OCTRU) and CCTR personnel work according to OCTRU SOPs. The OCTRU SOPs and related quality assurance and control procedures will be used by CCTR to ensure that the study procedures are assessed and carried out as defined in this protocol. The study may be monitored or audited in accordance with the current approved protocol, GCP, relevant regulations and SOPs. A monitoring plan, including risk assessment, will be developed according to OCTRU SOPs. The monitoring activities will be based on the outcome of the risk assessment and may involve central monitoring or site monitoring visits.

A rigorous quality control programme will be conducted to ensure intervention fidelity. Quality assurance checks will be made by the trial team, who will observe treatment sessions for practitioners. Site visits will be conducted periodically to observe the recruitment, consent and randomisation procedures, data collection, injection therapy, exercise and best practice advice sessions. A minimum of 2 visits per site, per year, will be conducted over the duration of the trial. Permission will be sought from the trial participants to observe treatment sessions. Data will be collected on intervention delivery and number of treatment sessions attended, including details about the core and adaptable components, to facilitate monitoring and reporting. Case report forms will be used to monitor intervention fidelity. Responsibility for intervention quality control will be shared with the local site coordinating physiotherapist. The sites will regularly receive feedback from quality control visits to help maintain and improve fidelity. Any issues identified will be addressed by engaging the site staff in more training and by increasing the intensity of monitoring by the central trial team. If issues persist, they will be escalated to the trial oversight committees.

7.4. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of “serious breaches” to the MHRA within 7 days of the sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected, the sponsor (University of Oxford) will be contacted within 1 working day. In collaboration with the chief investigator, the serious breach will be reviewed by the sponsor and, if appropriate, the sponsor will report it to the REC, MHRA and the NHS host organisation within 7 calendar days.

8. APPROVAL AND DISSEMINATION

8.1. APPROVALS

The trial protocol and all related documentation (e.g., informed consent forms, participant information leaflets, patient questionnaires and any proposed advertising material) has been approved by the Berkshire B Research Ethics Committee (REC). The trial has been given the identification number REC Ref: 16/SC/0508 and the Integrated Research Application System (IRAS) ID 199243. The trial has also been approved by the UK Competent Authority, the Medicines and Healthcare Regulatory Agency (MHRA), as it has been classified as a clinical trial of an investigational medicinal product (CTIMP). The trial has the EuDRACT number 2016-002991-28. The trial will be conducted in accordance with the principles of the Declaration of Helsinki and the Medical Research Council’s GCP guidelines.

8.2. PROTOCOL AMENDMENTS

Modifications to the protocol that may affect the conduct of the study, the potential benefit to the patient or patient safety, including significant changes in the study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects, will require a formal amendment to the protocol. Substantive amendments will be agreed by the trial management group (TMG) and Sponsor office (University of Oxford) and submitted for REC approval prior to implementation. Similarly, where appropriate, any substantive amendments will also be submitted to the MHRA for approval. All substantive amendments will be transparently described in resulting

trial reports. Non-substantive amendments to the protocol will be agreed by the TMG. The REC will be notified of any non-substantive amendments.

8.3. CONFIDENTIALITY

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified by a unique participant study number / code on case report forms and any electronic database holding study data. All documents will be stored securely in locked filing cabinets at the Oxford Clinical Trials Research Group offices and will only be accessible to trial staff and authorised personnel. The trial will comply with the Data Protection Act and any personal details (e.g., addresses for posting follow-up questionnaires) held by the central trial team in paper format or in a separate electronic database will be stored separately from any outcome data. All trial data will only be accessed by authorised personnel. The consent form includes consent for these data to be held.

8.4. ACCESS TO DATA

Direct access to research data will be granted to authorised representatives of the Sponsor, regulatory authorities or the host institution for monitoring and/or auditing of the study to ensure compliance with regulations. Summary results data will be included on the EudraCT database (https://eudract.ema.europa.eu/) within 12 months of the end of the trial. General release will be 5 years after the end of the trial, to allow the investigators sufficient time to complete and report additional analyses of the data set.

8.5. DISSEMINATION POLICY

The findings from the trial will inform NHS clinical practice for the management of patients with a rotator cuff disorder. The trial has been prospectively registered, prior to ethics approval, on the International Standard Randomised Controlled Trial Number register and EudraCT register. The trial protocol will be available via the NIHR HTA website and will be published in an open-access peer-reviewed journal in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement (SPIRIT, www.spirit-statement.org/). The trial results will be published as a monograph as part of the NIHR HTA journal series. They will also be published in a high-impact open-access journal, in accordance with the NIHR's policy on open-access research. The trial results will be reported following the Consolidated Standards of Reporting Trials guideline (CONSORT, www.consort-statement.org), in particular the extensions for non-pharmacological

interventions and patient-reported outcomes. We will use the Template for Intervention Description and Replication (TIDieR) statement (64) for reporting the intervention, ensuring that replication is possible. All trial materials, including the physiotherapist training materials and high-quality patient advice materials and DVDs, will be made freely available via the trial website on completion of the trial. The authors will acknowledge that the study was funded by an NIHR HTA Programme and will comply with the NIHR's publication policy (http://www.nihr.ac.uk/policy-and-standards/publishing-research-findings.htm). Prior to formal publication, we will inform the participants of the trial results. The participants will be asked if and how they would like to be informed of the trial results as part of their original consent process.

9. STUDY ADMINISTRATION

9.1. Key contacts

Central contact

GRASP Trial Manager

University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, Windmill Road, Oxford, UK, OX3 7LD.

Tel: 01865 737432; Email: grasp@ndorms.ox.ac.uk.

Sponsor contact

Ms Heather House

Clinical Trials and Research Governance, University of Oxford, Joint Research Office, Churchill Hospital, Old Road, Headington, Oxford, UK, OX3 7LE.

Email: ctrg@admin.ox.ac.uk

9.2. Roles and responsibilities

9.2.1. Protocol contributors

The GRASP trial is a collaboration between NHS clinical sites from across the UK and several academic and NHS institutions with significant experience in clinical trials and management of musculoskeletal conditions. The trial will be supported by the United Kingdom Clinical Research Collaboration (UKCRC) fully registered CTU - OCTRU, the Centre for Statistics in Medicine and the Health Economics Research Centre at the University of Oxford.

9.2.2. Sponsor and funder

This research is funded by the NIHR HTA Programme (Project reference: 15/26/06).

The sponsor is the University of Oxford. The sponsor has a specialist insurance policy in place – Newline Underwriting Management Ltd at Lloyd's of London – that will operate in the event of any participant suffering harm as a result of their involvement in the research.

9.2.3. Projected trial timelines and milestones

Month Year	Project months	Tasks
October 2016 – January 2017	1-4	Regulatory approvals sought and gained, initial site set-up completed
February 2017 – May 2017	5-8	Internal pilot recruitment
June 2017 – January 2019	9-28	Main trial recruitment
February 2018 – January 2020	17-40	12 month follow-up of participants
February 2020 – May 2020	41-44	Analysis and write up of trial

9.2.4. Trial committees

Trial Management Group

A Trial Management Group (TMG) has been established, consisting of the core trial team, chief investigator and co-applicants. The TMG will be responsible for the day-to-day running of the trial and will meet monthly to report on progress and ensure milestones are met. A trial manager will oversee all aspects of the day-to-day trial management. The trial will be managed by a team at the Oxford Clinical Trials Research Unit.

Trial Steering Committee

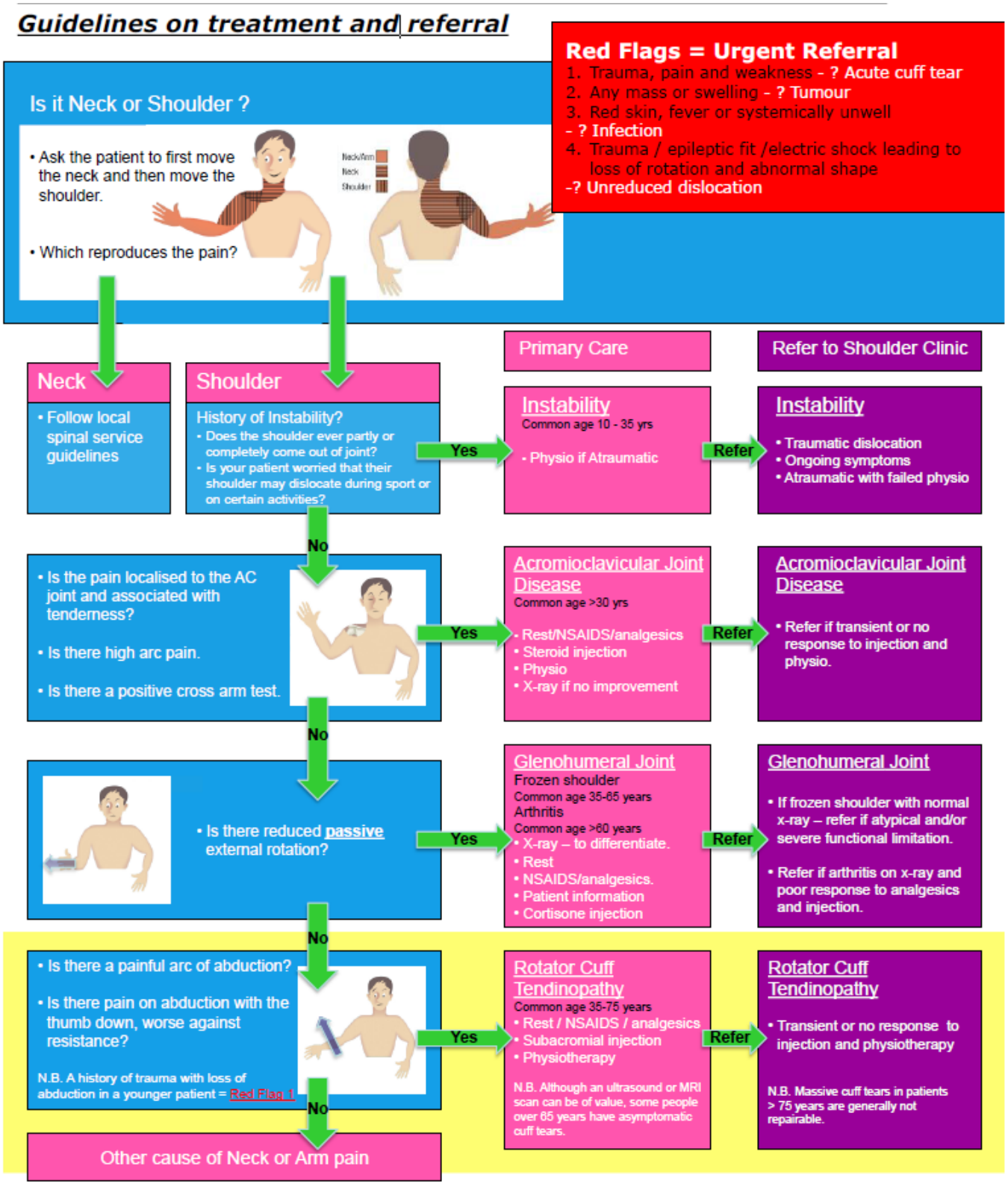
A Trial Steering Committee (TSC) will be appointed and will meet at least annually over the duration of the trial. The TSC will monitor the trial's progress and will provide independent advice. The TSC will comprise independent clinicians, specialist physiotherapists, statisticians, health service researchers and patient representatives.

Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee (DSMC) will be appointed and will meet at least annually over the duration of the trial. The DSMC will monitor the trial's progress and will provide independent advice. It may advise the chair of the TSC at any time if, in its view, the trial should be stopped for ethical reasons, including concerns about participant safety. The DSMC will comprise independent clinicians, specialist physiotherapists, statisticians and health service researchers.

10. APPENDICES

10.1. APPENDIX 1: BRITISH ELBOW AND SHOULDER SOCIETY DIAGNOSTIC ALORITHM



British Elbow and Shoulder Society, diagnosis of shoulder problems in primary care (4)

10.2. APPENDIX 2: GRASP SUB-STUDY

Personalised versus standard text message prompts for increasing trial participant response to postal questionnaires (PROMPTS): protocol for an embedded retention trial

1. BACKGROUND AND RATIONALE

Randomised controlled trials are crucial for evaluating healthcare interventions. In undertaking trials, postal self-completed questionnaires are an inexpensive and widely adopted method for collecting patient reported outcomes, especially from large, geographically dispersed populations [1, 2]. However trialists experience difficulties with maintaining questionnaire response rates from participants, which can introduce bias, reduce the sample size and statistical power and affect the validity, reliability and generalisability of findings [1, 3-6].

Many strategies are used by trialists in an effort to improve response rates; however these are often adopted without being subjected to rigorous evaluation, leading to a relative absence of evidence based interventions [3, 7-9]. There is a need to develop and rigorously evaluate strategies for improving the return of postal questionnaires by embedding them in real-life host trials [10, 11]. Recently, initiatives such as Systematic Techniques for Assisting Recruitment to Trials (START) [12-14], Studies Within A Trial (SWAT) [15, 16] and Trialforge [17] have promoted the development and reporting of embedded recruitment and retention trials, across ongoing multiple host trials.

Short messaging service text messaging ('text messaging') is a simple, cost effective and ubiquitous form of communication. Text messages can be delivered by automated systems, which allow for the content of these messages to be easily and inexpensively varied, so messages can be customised to each recipient. Research on text messages have found them to be effective for instigating behaviour change [18]; reducing nonattendance rates for outpatient clinic appointments [19, 20] and for improving recruitment and response rates in trials [21, 22].

The wording of text messages has also been shown to impact on response rates. In a trial to encourage the payment of delinquent fines, using the name of the recipient in the text message was found to be more effective at inducing response to pay the delinquent fine, than a standardised text message not including the recipient's name, or even a personalised message with the amount of fine to be paid [23]. Additionally, psychological evidence suggests that the use of a person's name increases the likelihood of attracting their attention [24]; that a person will filter out competing stimuli and refocus their attention when their name is mentioned [25]; and that this occurs even when their name appears in printed text [26]. Little research however exists on the use of personalised text messaging for improving trial response rates. A Cochrane systematic review of 38 strategies to improve retention in trials [3] found that while the majority of recruitment

interventions focus on postal return of questionnaires, only three trials involved the use of text messages [27-29], and of these, none examined the impact of personalising text messages on response rates or times.

Our objective is to test the effectiveness of a low-cost personalised text messaging strategy (PROMPTS) to prompt the return of questionnaires, using a randomised controlled trial embedded within the GRASP trial. GRASP (Getting it Right: Addressing Shoulder Pain) is a randomised controlled trial which assesses the clinical and cost effectiveness of individually tailored, progressive exercise compared with best practice advice, with or without corticosteroid injection, in patients with a new episode of a rotator cuff disorder (www.nets.nihr.ac.uk/projects/hta/152606). The study is funded by the National Institute of Health Research

2. OBJECTIVE

The aim of the PROMPTS sub-study is to evaluate the effectiveness of a personalised text message including the recipient's name, versus a standardised text message for prompting response in trial participants to complete and return postal follow-up questionnaires. Time to questionnaire response, the proportion of participants sent a reminder follow up questionnaire and cost of the text message intervention will also be assessed.

3. TRIAL DESIGN

The general methodology of this embedded study within the GRASP trial, of an intervention to improve response rates to postal questionnaires (PROMPTS), will be guided by methodology developed and published by START [12, 13] and will use a randomised controlled trial design. Participants will be randomised (1:1) to receive one of two interventions: 1) a standard text message (control group), or 2) a personalised text message which includes their name (intervention group).

4. METHODS – PARTICIPANTS, INTERVENTIONS AND OUTCOMES

4.1. Participant recruitment

All participants in the PROMPTS sub-study will have consented and be enrolled in the GRASP trial which will act as the host trial. In addition to meeting the inclusion criteria for the GRASP trial, the following inclusion criteria will apply for participants enrolled in the embedded PROMPTS sub-study:

- Participants will have the use of a mobile telephone,

- Participants will be willing to provide this mobile telephone number and consent for contact to be made by the GRASP trial team using this number.

Individual participants will be asked to provide their mobile telephone number and asked to consent to be contacted using this number. Messages will be sent via secure third-party text message gateway software, participants will be asked for consent to share their data with this third party software company to allow the messages to be sent to them. Additionally, participants will be asked how they would like to be addressed using their name in future text-messaging correspondence (e.g. John, Mr J. Smith, Mr John Smith). Participants who do not provide a mobile number or do not consent to receive texts will be excluded.

4.2. Interventions

Participants will be randomised to receive either a standard text message (control group), or a personalised text message which includes their name (intervention group). The text message will be sent to trial participants after they have been posted their trial follow-up questionnaire by the trial team, according to the first postal follow-up specified in the GRASP protocol after implementing the text message trial. The text message will be sent at the same time as they are expected to receive their postal follow-up questionnaire (i.e., normally 2-4 days after the questionnaire is sent, depending on whether first or second class postage is used). The message will be sent in addition to routine trial follow-up procedures, specifically a reminder follow up questionnaire followed by a phone call to those who do not respond to the reminder follow up questionnaire.

Each text message will contain the same core information. Recipients will be reminded about the arrival of the questionnaire, about the importance of their responses and to return the questionnaire as soon as possible. The wording of the proposed SMS messages in the control and intervention groups is outlined in Table 1. For participants in the intervention group, text messages will be customised using their name, according to how they preferred to be addressed. Text messages will be sent via secure third-party text message gateway software. In the event that a message is not delivered, the sender will receive a notification, which will be used to classify the text message as “delivered” or “not delivered”.

Table 1: Messages associated with each arm in PROMPTS

PROMPTS text message condition	Wording in message
Control group	*From the GRASP Trial: We have just sent you a*

	GRASP questionnaire in the post. We would be extremely grateful if when you receive it, you complete it and return it as soon as you can. Thank you
Intervention group	*From the GRASP Trial: [**Mr Smith]** We have just sent you a GRASP questionnaire in the post. We would be extremely grateful if when you receive it, you complete it and return it as soon as you can. Thank you*

4.3. Outcomes

Primary Outcome

The primary outcome measure will be questionnaire response rate, defined as the proportion of GRASP follow up questionnaires returned by participants.

Secondary Outcomes

The secondary outcome measures will be:

- Time to response, defined as the number of days which elapse between the GRASP follow up questionnaire being mailed out to participants and the questionnaire recorded as being returned to the GRASP trial team.
- The proportion of participants sent a reminder follow up questionnaire.
- The cost-effectiveness of the text message intervention.

5. METHODS – ASSIGMENT OF INTERVENTIONS

5.1. Randomisation

Participants will be assigned a unique trial identification (ID) number by the GRASP trial. A computer generated randomisation list will be used to list all participants who provide a mobile telephone number. Half of participants will be randomly allocated (1:1) to the intervention group and half to the control group. Generation of the allocation sequence and assignment of the intervention and control groups will be undertaken independently by a researcher not involved with the delivery of the text messages. To avoid imbalance, block randomisation with equal probabilities of assignment to the intervention and control groups will be used.

5.2. Blinding

GRASP trial participants will be blinded to the nature and objectives of the PROMPTS sub-study. Analyses will be undertaken by a statistician blind to group allocation.

5.3. Sample size

As is usual with an embedded trial within a trial no formal power calculation will be undertaken as the sample size will be constrained by the number of participants included in the GRASP trial receiving follow up questionnaires and consenting to use of their mobile phone number. Based on anticipated recruitment and follow up rates, we anticipate an analysable sample size of approximately 532 participants (266 per text message group). Analysed independently, this sample would give 90% power and 5% significance level to detect differences in return rates of approximately 10% (90% in personalised text messages and 80% in the control group). For a response ratio of 10% with 80% power and 5% significance level the anticipated sample size would be 494 participants (247 per text message arm).

6. STATISTICAL ANALYSIS

All eligible participants will be included in the analysis on an intention-to-treat basis. The analyses will be conducted in Stata (StataCorp). Questionnaire response rates, and whether a reminder follow up questionnaire is sent, will be compared using a chi-square test and reported as risk ratios and 95% confidence intervals. The time to return of the questionnaire will be plotted using a Kaplan-Meier survival curve and the log-rank test will be used to compare the two groups. The cost-effectiveness of the text message intervention will be calculated by dividing the total cost by the number of respondents in the control and intervention groups. Research staff costs will not be calculated as the follow-up of participants will be undertaken during the normal time on the host trial.

7. APPROVAL AND DISSEMINATION

7.1. Ethical approval

Ethical approval will be obtained from the Berkshire B Research Ethics Committee (REC) in the form of a substantive amendment to the GRASP trial (REC Ref: 16/SC/0508; Integrated Research

Application System (IRAS) ID 199243). The GRASP trial has been approved by the UK Competent Authority, the Medicines and Healthcare Regulatory Agency (MHRA) (EuDRACT number 2016-002991-28) and has been registered on the ISRCTN clinical trial register (ISRCTN Number: 16539266); the PROMPTS sub-study will be registered as a sub-study of GRASP on the ISRCTN register. The sub-study will be conducted in accordance with the principles of the Declaration of Helsinki and the Medical Research Council's GCP guidelines.

7.2. Informed consent

Due to the nature and objective of the PROMPTS sub-study participants will not be asked to consent specifically to take part in this sub-study of GRASP. However, we do not consider this to be a major ethical issue as we consider this to be a low-risk sub-study and informing participants that we are looking at questionnaire response rates might impact the impartiality of our results. All participants that consented to be in the GRASP study will be explicitly asked if they consent to being contacted by text and asked for permission for their mobile telephone number to be used; this will also be explained in the participant information sheet. Participants in the PROMPTS sub-study will have text messages sent using a secure UK-based text messaging service and messages will be directed via this third party messaging service. Permission for this is included on the consent form and information about this is also included on the participant information sheet.

7.3. Publication

The findings of the PROMPTS sub-study will be published in a peer reviewed journal and will be reported following the Consolidated Standards of Reporting Trials guideline (CONSORT, www.consort-statement.org). In addition, data from the PROMPTS sub-study will contribute to the Study Within A Trial (SWAT) initiative to improve trial recruitment (www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/) and to the Cochrane review of strategies to improve trial retention (http://onlinelibrary.wiley.com/doi/10.1002/14651858.MR000032.pub2/abstract). It will help to increase the evidence base on the retention of participants to trials. To facilitate this fully anonymised data from the PROMPTS sub-study will be shared, on written request, in order to undertake a meta-analysis of individual patient data in accordance with the 'Good Practice Principles for Sharing Individual Participant Data from Publicly Funded Clinical Trials' [33].

8. EXAMPLES

Text to be included in participant information leaflet (under 'confidentiality' section)

If you agree to us sending a text message your mobile number will be stored on a secure management system at the University of Oxford. Text messages will be sent using a secure UK based text messaging service managed by a third party organisation. The University of Oxford and third party organisation will not use your mobile number for any other purposes, your information will not be shared with anyone else and will be deleted following completion of the study. You would only receive text messages when you have been sent questionnaires to complete.

Wording for the consent form

(Optional) I am willing to receive text message from the GRASP study team.

Information to be included in 'Participant contact form'

Along with the participant's contact details form, the following should be recorded:

How participant prefers to be addressed:

For example, 'Mrs Joan Smith', 'Ms Joan Smith' or 'Miss Joan Smith':

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10.3. APPENDIX 3: AMENDMENT HISTORY

Amendment no.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	Version 2.0	20Mar2017	Sally Hopewell	Clarification of eligibility criteria to include those predominantly seeking treatment for one shoulder (section 4.2.1) Clarification on timelines for injection and physiotherapy referral (section 4.3) Minor clarifications on physiotherapy intervention content, including revision of Figure 2 (section 4.3) Correction to month of recruitment (section 9.2.3) Addition of PROMPTS (personalised versus standard text message reminder) sub-study (Appendix 2)
4	Version 3.0	13Sep2017	Sally Hopewell	Minor clarification regarding methods of data collection and management Minor change of wording regarding injection delivery
12	Version 4.0	25May2018	Sally Hopewell	Addition of monetary incentive at 12 month follow-up time point (section 6.1.2) A web-based version of the questionnaire will be sent to

				patients who do not respond to the initial postal questionnaire and at least one reminder (section 6.1.2)

Protocol amendments will be submitted to the sponsor for approval prior to submission to the REC and MHRA.

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