Study Title: SPiRIT (Shoulder Pain: Randomised trial of Injectable Treatments) A randomised feasibility study of Autologous Protein Solution (APS) vs Corticosteroids for treating subacromial shoulder pain.

Internal Reference Number / Short title: SPiRIT (Shoulder Pain: Randomised trial of Injectable Treatments)

Ethics Ref: 21/EE/0211

IRAS Project ID: 294982

Date and Version No: V3.0 27Jan2023

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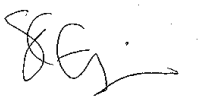
Funder:	National Institute for Health and Care Research – Research for Patient Benefit (NIHR201473)
Chief Investigator Signature:	

Statistician Signature: 

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, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY CONTACTS

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2. LAY SUMMARY

Shoulder pain is very common, and accounts for thousands of appointments in general practice and hospitals each year in the UK. The most common reason for this pain is inflammation to the tissues just below the outside of the shoulder. Over the years, many different treatments have been tried to treat this pain. The most common treatments that we use currently are steroid injections combined with physiotherapy, or keyhole surgery. Recently, there have been questions about whether using steroid injections is actually safe in the long term. There are concerns that they may affect tendons (the tissue that connect muscles to bones) or contribute to the development of arthritis. At the same time, some research suggests that operations may also not be as effective for shoulder pain as previously thought. As such, healthcare workers have to look for other safe and effective treatment options for this painful condition. Laboratory studies have shown that painful shoulders often go together with poor tendon health and inflammation. This has led to recent improvements in injection treatments. These new injections aim to help tendons repair themselves and so reduce inflammation and pain. These are termed 'biologic' injections. Whilst the theory behind these injections is good, and they have been found to be safe, no one has conducted a study to see if the treatments are more or less effective than steroid injections. The aim of our study is to see if it is feasible to compare one of these biologic-injection treatments against steroid injections. The injection we aim to test involves us taking a sample of the person's blood. We would then take out some of the most useful parts of the blood and inject it back into the shoulder to aid healing. The patient will then receive physiotherapy as normal, regardless of what injection they have. Before we can conduct a full large study, we need to do this smaller study to see how quickly we can recruit patients and whether the patients and doctors are happy with how the study works. In this study we will recruit 50 patients. We will ask patients to join the study who have already been referred to us for shoulder pain and are about to start normal treatment for this. If they decide to take part the only change in their treatment will be the difference in the type of injection they receive. If this feasibility study is successful, we will then go on to conduct a larger study to see whether the new type of injection is better than steroids for shoulder pain. If this turns out to be the case then our study could help large numbers of patients in the NHS with this painful condition.

3. SYNOPSIS

Study Title	SPiRIT (Shoulder Pain: Randomised trial of Injectable Treatments) A randomised feasibility study of Autologous Protein Solution (APS) vs Corticosteroids for treating subacromial shoulder pain.		
Internal ref. no. / short title	SPiRIT (Shoulder Pain: Randomised trial of Injectable Treatments		
Study registration	ISRCTN: 12536844		
Sponsor	University of Oxford Joint Research Office, 1st floor, Boundary Brook House Churchill Drive, Headington, OX3 7GB; Email: RGEA.Sponsor@admin.ox.ac.uk		
Funder	National Institute for Health Research (NIHR) – Research for Patient Benefit (RfPB)		
Study Design	A feasibility study of a single-blinded, parallel group Randomised Controlled Trial		
Study Participants	Adults, over 18 years of age who have been triaged by a MSK-triage service with symptoms suggestive of subacromial pain syndrome and would be offered CorticoSteroid Injections (CSI) as part of their standard care		
Sample Size	50		
Planned Study Period	Total length of the project: 22 months 01/08/2021- 30/06/2023 Duration of individual participant's involvement: 6 months		
Planned Recruitment period	September 2021 - April 2022 (7 Months)		
	Objectives	***Outcome Measures***	***Timepoint(s)***
Primary	To determine the feasibility of recruiting study participants into a trial comparing Autologous Protein Solution (APS) vs Corticosteroids for subacromial shoulder pain	The conversion rate of eligible to randomised participants and total number of participants recruited	End of recruitment period
Secondary	To estimate an appropriate sample size for a future definitive trial	Levels of retention at follow-up dates Data compliance at follow-up	End of follow-up period
	Ensure it is possible to collect appropriate outcome measures	Completion rates of PROMIS upper limb physical function, PROMIS pain interference questionnaire, Oxford Shoulder	PROMIS, OSS, EQ-5D: baseline, 3 and 6 months post-randomisation

	to allow a comprehensive efficacy assessment in a fully powered future trial	Score (OSS), Pain visual analogue score (VAS), EQ-5D-5L score and Complications	VAS: baseline, weekly up to 8 weeks, 3 and 6 months post-randomisation Complications/: up to 6 months post randomisation
	Ensure it is possible to collect data to furnish a robust cost-effectiveness assessment in a fully powered future study	Completion rates of Work Productivity Impairment Questionnaire (WPAI) and patient and hospital reported resource use including referral rates for shoulder surgery	WPAI: baseline, 3 and 6 months post-randomisation Resource use: 6 months post-randomisation
Intervention(s)	Autologous Protein Solution (APS) injection into the subacromial space		
Comparator	CorticoSteroid Injections (CSI)		

4. ABBREVIATIONS

AEs	Adverse events
APS	Autologous Protein Solution
BESS	British Elbow and Shoulder Society
BOA	British Orthopaedic Association
CAT	Computer Adaptive Test
CGI	Clinical Global Impression
CI	Chief Investigator
CRF	Case Report Form
CSI	CorticoSteroid Injections
CTRG	Clinical Trials & Research Governance, University of Oxford
DMP	Data Management Plan
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to Treat
MSK	Musculoskeletal
NDORMS	Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OCTRU	Oxford Clinical Trials Research Unit
OSS	Oxford Shoulder Score
PI	Principal Investigator
PPI	Patient & Public Involvement
PROMIS	Patient-Reported Outcomes Measurement Information System
PRP	Platelet-rich Plasma
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RfPB	Research for Patient Benefit
SAEs	Serious Adverse Events

SAP	Statistical Analysis Plan
SA	Sub Acromion
SFQ	Site Feasibility Questionnaire
SOP	Standard Operating Procedure
SPiRIT/ SPIRIT	Shoulder Pain: Randomised trial of Injectable Treatments
TMG	Trial Management Group
TNF	Tumour Necrosis Factor
VAS	Visual Analog Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WPAI	Work Productivity and Activity Impairment

5. BACKGROUND AND RATIONALE

Shoulder pain accounts for 1–2% of all adult consultations with a GP [1]. Of this shoulder pain, around 70% is subsequently attributed to pain arising from the tendons which move and stabilise the shoulder, the rotator cuff. Most commonly these problems are due to inflammation and degeneration of the tendons [2]. Shoulder pain does not always have a favourable outcome with current treatments. Only 59% of patients treated in primary care show a complete recovery within 6 months [3]. Symptoms may be disabling in terms of the patient`s ability to carry out daily activities at home and at the workplace, resulting in time off work. This poses a substantial burden to the individual and society [4-6]. In the United States, the annual financial burden of shoulder pain management has been estimated to be $3 billion [2]. A mechanical explanation for shoulder pain has previously been favoured, whereby contact occurs between the rotator cuff tendons and the overlying bone. This 'rubbing' process was felt to result in inflammation of the rotator cuff tendons and nearby structures including a fluid-filled sac called the subacromial bursa.

Treatments have historically been directed at reducing this inflammation and rubbing process, either by injections of corticosteroids (to address the inflammation) or surgical intervention to remove some of the bone, which was felt to be rubbing on the tendon.

Evidence for the efficacy of both surgical and non-surgical treatments of shoulder pain is limited. A recent publication by the British Elbow and Shoulder Society (BESS) and the British Orthopaedic Association (BOA) recommends shared decision-making in the management of subacromial pain. It recommends that the clinician considers the severity of symptoms in deciding the most appropriate treatment (injections, physiotherapy or surgery). It also highlights the lack of evidence for a number of interventions used to treat subacromial shoulder pain [7]. Consequently, the BESS/BOA guidelines recommend research into the clinical and cost-effectiveness of injectable treatments for subacromial shoulder pain.

Given the large numbers of patients who present to general practice with subacromial shoulder pain, any developments in the treatment of this chronically painful condition should improve the care of thousands of patients each year in the UK.

Currently, Corticosteroid injections (CSI) remain the mainstay of initial treatment in the majority of cases of shoulder pain presenting to both general practice and secondary care. The efficacy of CSI has been tested in a number of trials and subsequently through systematic review. These have reported differing conclusions, but the consensus view is that any benefits seen are most likely to be short-term and there remains a significant number of patients who go on to have surgical intervention despite CSI.

In addition to the lack of strong evidence towards the efficacy of CSI, there have also been theoretical and lab based deleterious effects of corticosteroids on tendon biology reported. CSI might impair the potential for intrinsic tendon repair mechanisms and it may increase the risk of subsequent tendon tearing. Any iatrogenic damage from CSI is therefore potentially responsible for the future development of rotator cuff tears, arthritis and disability [8]. In light of these potential harmful effects, health researchers have been considering two broad alternative approaches; 1) optimising physical therapy to avoid the need for CSI, or 2) alternative pharmacological or bioactive therapies to replace CSI.

Contemporary understanding of the biology of shoulder tendons gives potential targets for new pharmaceutical or biological treatments. Previous pre-clinical work highlights an opportunity to explore

the efficacy of targeted therapy that addresses the catabolic pro-inflammatory/anti-inflammatory cytokine and anabolic growth factor imbalance in sub-acromial pathologies. This offers hope to patients, as it may provide pain relief and promote tendon health.

An example of such a strategy is the use of injectable platelet-rich plasma (PRP). PRP is a popular cell-free therapy that is used worldwide to treat tendinopathy. PRP, is a concentrate of platelet-rich plasma protein derived from whole blood, centrifuged to remove red blood cells. Basic science studies have consistently shown the beneficial effects of PRP on tendons including increased tendon cell proliferation, increased expression of anabolic genes and proteins, and reduced tendon inflammation [9-11]. Unfortunately, these in-vivo findings have not translated to reliable clinical application when subject to clinical trials [12]. Consequently, there is a recognition that robust evidence must be produced before blood derived therapies are further introduced into clinical practice [13]. An alternative to PRP is the injection of an Autologous Protein Solution (APS). APS is prepared using a single-use device that produces a cell concentrate from autologous blood.

Conceptually, APS and PRP are very similar as they both aim to isolate anti-inflammatory cytokines and anabolic growth factors from a patient's own blood, allowing this to be reintroduced at the site of pain. Both PRP and APS aim to address intrinsic degeneration of the tendon as a source of inflammation and pain or reduce inflammation through modulating the effects of the pro-inflammatory proteins IL-1 & TNFa. [7,14]. They aim to effectively treat the underlying cause of the shoulder pain, optimising the tendons' inherent ability to repair through both anti-inflammatory and pro-resolution cellular mechanisms.

Unlike PRP systems, the APS production process preferentially concentrates anti-inflammatory cytokine production by white blood cells, including IL-1 receptor antagonist and TNF receptor inhibitor [15]. The use of APS is expanding both in the UK and worldwide. Clinicians have open access to the technology, which has been subject to a number of preclinical trials, animal models, and human studies. In preclinical studies, APS has been shown to reduce pro-inflammatory cytokines, which are known to be upregulated in painful musculoskeletal conditions. When incubated with macrophages stimulated with IL-1ß, APS decreased the effect of IL-1ß and limited the expression of the pro-inflammatory cytokines IL-8 and TNF-α [16]. Randomised placebo trials in animals have shown that compared to a single intra-articular injection of saline, a single injection of APS statistically reduced evidence of cartilage degradation [17], and lameness evaluation in horses [18]. Feasibility studies investigating APS in humans, in the context of knee arthritis have been conducted. Endpoints included scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), clinical global impression (CGI), and patient global impression scales, as well as safety, and cytokine analysis. Efficacy outcomes reported a 72% reduction in WOMAC pain at 6 months (n=10) [19]. The outcomes suggested that APS was effective, with significant improvements in pain, stiffness, and function. The treatment also demonstrated a favourable safety profile and was well tolerated.

In a further study in patients with arthritis, 46 patients were randomised into receiving a single ultrasound-guided injection of APS, or a single saline injection. Patient-reported outcomes and adverse events at 2 weeks, 1, 3, 6, and 12 months post-injection were collected. The patients and evaluators were blinded to the treatment allocation, and the outcome was evaluated through visual analogue scale (VAS) and WOMAC scores. The average improvement from baseline to 12 months in WOMAC pain score was 65% in Group 1 and 41% in Group 2 ($p = 0.02$). Additionally, average VAS pain improvement was 49% in Group 1 and 13% in Group 2 ($p = 0.06$). Average WOMAC function improvement from baseline to 12

months was 57% in Group 1 and 44% in Group 2 (p = 0.24) [20]. No similar work currently exists to assess the efficacy of APS in treating shoulder pain. In this work we will seek to explore the clinical and cost-effectiveness of APS compared to corticosteroids in the treatment of subacromial shoulder pain.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To determine the feasibility of recruiting study participants into a trial comparing Autologous Protein Solution (APS) vs Corticosteroids for subacromial shoulder pain	The conversion rate of eligible to randomised participants and total number of participants recruited;	End of recruitment period
Secondary Objectives To estimate an appropriate sample size for a future definitive trial	• Levels of retention at follow-up dates • Data compliance at follow-up	End of follow-up period
Ensure it is possible to collect appropriate outcome measures to allow a comprehensive efficacy assessment in a fully powered future trial	• PROMIS upper limb physical function • PROMIS pain interference questionnaire • Oxford Shoulder Score (OSS) • Pain visual analogue score (VAS) • EQ-5D-5L score • Complications	PROMIS, OSS, EQ-5D: at baseline, 3 and 6 months post-randomisation VAS: baseline, weekly up to 8 weeks, 3 and 6 months post-randomisation Complications: up to 6 months post-randomisation
Ensure it is possible to collect data to furnish a robust cost-effectiveness assessment in a fully powered study	Completion rates of Work Productivity Impairment Questionnaire (WPAI) and patient and hospital reported resource use including referral rates for shoulder surgery	WPAI: at baseline, 3 and 6 months Resource use: up to 6 months post-randomisation

6.1. Proposed Outcome Measures

Proposed primary outcome measure for this feasibility study:

Screening Log

Numbers of screened ineligible patients will be noted to ensure recruitment for the main trial is feasible within this patient population. Numbers of screened eligible participants declining versus converted to randomised participants will be noted to ensure that the conversion rate of eligible to randomised participants is accurately estimated.

Proposed Secondary outcomes measures:

Levels of participant retention and data compliance will be measured by loss to follow up, missing data and withdrawal at the end of the trial. The following secondary outcome measures are being collected in this feasibility study in order to determine their viability in the definitive trial. The PROMIS will become the primary outcome during the full trial:

PROMIS Physical Function (upper extremity) and PROMIS Pain Interference
Pain VAS
Oxford Shoulder Score
EQ-5D-5L
Work Productivity Impairment Questionnaire (WPAI)
Complications
Health Resource Use

7. STUDY DESIGN

SPIRIT is a feasibility study of a single-blinded, parallel group randomised controlled trial. Participants will be followed up clinically as per NHS standard of care. They will also be followed-up via questionnaires by the central trial team for a period of 6 months post-treatment.

8. PARTICIPANT IDENTIFICATION

8.1 Study Participants

Adults, over 18 years of age referred to musculoskeletal triage service with clinical symptoms suggestive of subacromial pain syndrome are potentially eligible to take part.

8.2 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female, aged 18 years or above.
- Clinician believes patient may benefit from Corticosteroid treatment

8.3 Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Participants with a history of significant shoulder trauma (Fracture or Dislocation in last 5 years)
- Previous shoulder surgery on the affected shoulder
- Contraindications to APS therapy or CSI
- A pre-existing neuro-degenerative and/or vascular condition that affects the function of the shoulder.
- Received CSI/APS injection in 2 months prior to randomisation
- The participant is unable to follow trial procedures
- Patient does not have access to email/ smartphone directly or indirectly

9. PROTOCOL PROCEDURES

9.1. Recruitment

We will recruit fifty participants from established NHS Musculoskeletal (MSK)-triage centres in England. We intend to recruit from at least two recruitment centres.

Figure 1 shows the standard patient pathway, as part of usual care for management of shoulder pain, MSK-triage clinicians will initially prescribe structured physiotherapy to all patients. In addition to structured physiotherapy, patients will be offered an injection into the subacromial space at a separate appointment, as per current clinical practice. Completion of physiotherapy treatment for the patient will not impact on patient's eligibility for SPIRIT trial as, depending on access to physiotherapy, this could start either before or after the injection has taken place.

Participants will be screened and identified as per Section 9.2

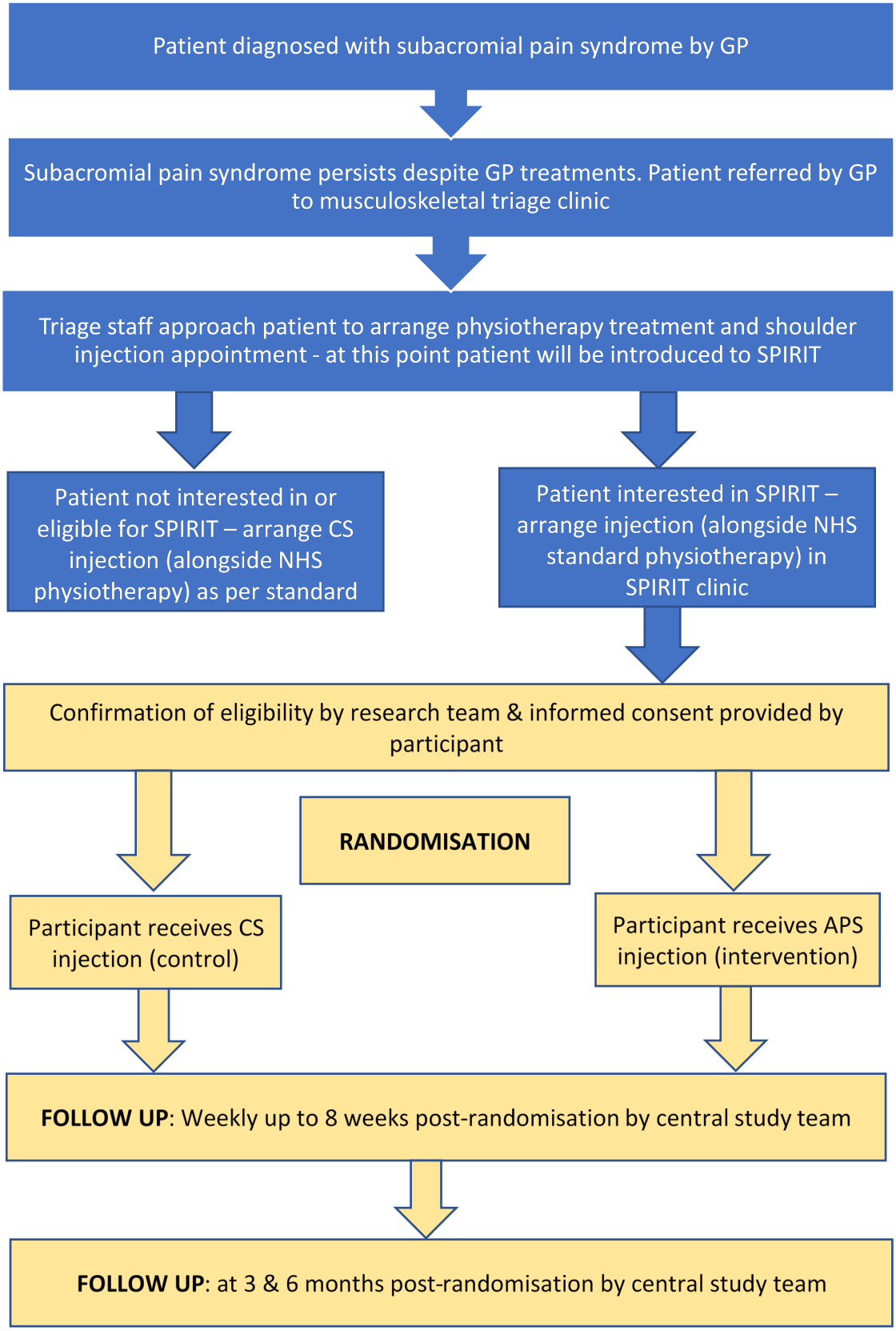


Figure 1: Patient pathway for subacromial shoulder pain (yellow indicates study-specific steps)

9.2. Screening and Eligibility Assessment

Patients who have been identified as requiring treatment for their shoulder pain will be screened for eligibility against the inclusion and exclusion criteria. The trial eligibility screening will be undertaken as an extension of the initial paper triage screening by the musculoskeletal service or local research teams.

Screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for exclusion. In addition, the number of eligible and recruited patients, and the number of patients who decline consent or withdraw will be recorded.

9.3. Initial Approach

As per standard practice, once the patient has been referred to the triage service by their GP a member of the triage team will contact the patient via phone to arrange a date, time and location of their treatment appointment. During this interaction the eligible patients will initially be asked by the intermediate care team if they would be interested in learning more about the SPIRIT trial which they may be suitable for.

If the patient indicates they are interested and agree, their contact details will be passed to the SPIRIT clinical team (if this is different to the intermediate care team). A record of the patient agreeing to being contacted further about the study will be kept in the patient's medical notes. The patient will then be contacted by the SPIRIT clinic team via phone and if they confirm they are interested in participating in the trial they will be booked into a specific SPIRIT intervention clinic. A participant information sheet (PIS) will then be sent via email or post by the SPIRIT clinic team, together with contact details of the Oxford University trial team, in case the patient wishes to ask specific questions in response to the PIS. Patients may also visit the trial website, which outlines the trial processes and procedures. All outgoing communication with the participant will be marked as confidential. It will be clearly stated what the patient can expect if they decide to take part and what will happen if they decide not to take part. The patient will be made aware that if they decide to take part, they are free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

Whether a patient agrees to participate or not they will receive NHS routine clinical care as normal.

9.4. Informed Consent

The informed consent process will commence when the usual-care clinician confirms the patient should be treated with a therapeutic injection, meets the eligibility criteria for the SPIRIT trial and the patient is willing to take part.

At the SPIRIT intervention appointment a trial clinician (who may be a member of the usual-care clinical team, or a research clinician) will have an informed consent discussion with the patient and if happy to proceed the patient will provide written electronic consent using a trial tablet, computer or other electronic device.

Prior to any study related procedures or data being collected, participants will complete the latest approved version of the consent form and provide their contact details in order for an electronic copy of the form to be sent to them immediately and securely. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the PI. Once completed, an

electronic version of the signed consent form will be automatically emailed to the participant via the REDCap database system. If the participant does not have access to email, then a paper copy of their consent form will be printed and provided by the local research team. The local research team will download copies to place in the participant's medical notes and investigator site file.

9.5 Baseline Assessments

Baseline demographic data, patient function and pain data using the PROMIS physical function, PROMIS Pain interference, Oxford Shoulder Score, VAS and Work Productivity Impairment questionnaires will be collected after the participant has provided consent. Participants will also be asked to complete the EQ-5D-5L health-related quality-of-life questionnaire (6) to indicate their typical health status. All case report forms (CRFs) including screening, consent, randomisation and baseline assessment will be completed online on the REDCap database.

Demographic data collected at baseline will include:

- Participant handedness
- Smoking Status
- Diabetic Status
- Previous treatment information
- Duration of symptoms

PROMIS Physical Function (upper extremity) and PROMIS Pain Interference

Patient Reported Outcome Measurement Information System (PROMIS) questionnaires are patient reported outcome measures which are administered electronically. They represent a form of Computer Adaptive Test (CAT). CATs have been validated in a variety of chronic health conditions. Multiple instruments have been designed including the United States (US) National Institute of Health, PROMIS. PROMIS instruments cover a variety of domains and are scored from 0 to 100 with 50 points representing the mean score for the US general population and higher scores indicate better function. This study will utilise the Physical Function (upper extremity) which focusses on function and disability and the pain-interference PROMIS questionnaires which investigates pain intensity and impact.

Oxford Shoulder Score

The Oxford Shoulder Score (OSS) is a 12-item patient-reported patient reported outcome specifically designed and developed for assessing outcomes of shoulder surgery e.g., for assessing the impact on patients' quality of life of degenerative conditions such as arthritis and rotator cuff problems.

Pain VAS

To assess pain recovery in the immediate post-randomisation period (weekly up to week 8), a visual analogue scale (VAS) on a scale of 0-100, where 0 is no pain at all and 100 is the worst pain imaginable, will be used (1). This will be administered through SMS/text message or email.

Work Productivity Impairment Questionnaire (WPAI)

The Work Productivity and Activity Impairment (WPAI) questionnaire is a self-administered instrument used to assess the impact of disease on productivity. The WPAI measures work productivity loss due to general health or a specified health problem (5).

EQ-5D-5L

The EuroQol 5 Dimensions (EQ-5D-5L) is a validated, generalised and standardised instrument comprising a VAS measuring self-rated health and a health status instrument, consisting of a five-level response (no problems, some problems, moderate problems, severe problems and unable) for five domains related to daily activities; (i) mobility, (ii) self-care, (iii) usual activities, (iv) pain and discomfort and (v) anxiety and depression. Responses to the health status classification system are converted into an overall score using a published utility algorithm for the UK population. A respondent's EQ-VAS gives self-rated health on a scale where the endpoints are labelled 'best imaginable health state' (100) and 'worst imaginable health state' (0).(4) We will follow the most up-to-date position statement from NICE when processing the data. Utility scores for the UK population will be used to derive 6 months quality-adjusted life years (QALYs) using the area under the curve method.

9.6 Randomisation

Once informed consent has been given, the participant will be randomised by the local research team. Allocations will be implemented immediately after randomisation.

The randomisation will be on a 1:1 basis to either a Corticosteroid injection or an Autologous Protein Solution injection to go alongside structured physiotherapy, using a validated computer randomisation program managed through a secure (encrypted) web-based service by the Oxford Clinical Trials Research Unit (OCTRU), using the method of minimisation. The Randomisation sequence, prepared by the trial statistician, will be stratified by centre, duration of symptoms (≤/> 6 months) and baseline PROMIS pain interference scores.

On randomisation of a participant the central trial office, main site contact and local study team will be notified. This will take place via an automated email as part of the randomisation process.

Full details of the randomisation will be stored in the Randomisation and Blinding Plan in the confidential statistical section of the Trial Master File.

9.7 Blinding

To avoid bias in the delivery of the intervention and completion of patient reported outcomes, the patients are to be kept blind about the treatment that is allocated. This blinding will be achieved by collecting the blood sample required for APS (55 ml, approximately the volume of an egg cup) from both groups of patients. In the intervention group, this blood will be used for the preparation of the APS; in the control group, this blood will be sham-prepared as APS, but discarded. This approach was discussed with the Oxford Trauma PPI (patient and public involvement) group and they collectively agreed that this was an acceptable approach to avoid any placebo-effect. Researchers and the clinical team are not blinded to the intervention received.

Blood collection and preparation of the injections (both APS and CSI) will be performed by an appropriately trained clinician who may be the usual-care clinician or study-team clinician depending on

training. The injectable solution (CSI or APS) will be prepared in an opaque syringe to ensure blinding of the participants.

9.8 Description of study intervention, comparator and study procedures (clinical)

As part of usual care for management of shoulder pain, MSK-triage clinicians will initially prescribe structured physiotherapy to all patients. In addition to structured physiotherapy, patients will be offered an injection into the subacromial space at a separate appointment, as per current clinical practice. Completion of physiotherapy treatment for the patient will not impact on the patient's eligibility for SPIRIT as, depending on access to physiotherapy, this could start either before or after the injection has taken place.

Patients will be randomised to either receive an APS injection or a CSI injection. Injections will be given by a trained member of the study team. Based on site capability this will be administered under ultrasound guidance where possible. Administration under ultrasound guidance would be preferrable, but participants would not be excluded if this is not possible.

9.8.1 Description of study intervention

Structured Physiotherapy ("shoulder pain advisory group") plus injection of APS into the subacromial space. After the consent and randomisation processes, a 55 ml (approximately an egg cup) sample of blood will be obtained and taken to the sample preparation area. The blood will be used for the preparation of the APS injection. The solution will be created as per the manufacturer's guidelines. It is a two-step process taking 15-20 minutes – firstly the blood is separated by centrifuging it, after which it is concentrated in specialised tubes. The total volume of the resultant APS is approximately 5mls. This solution will be delivered in an identical manner to the control treatment but provided in a 'blinding syringe' (non-transparent sides).

The APS injection kit is manufactured on behalf of Zimmer Biomet, a medical device manufacturer, it has the trade name of nSTRIDE. nSTRIDE is fully licenced for use in the UK, and the processing machines have the appropriate CE markings.

9.8.2 Description of comparator

Structured Physiotherapy plus injection of CSI [23-25] into the subacromial space.

After the consent and randomisation process, a 55 ml (approximately an egg cup) sample of blood will be obtained and taken to the sample preparation area. This blood will be discarded in the sample preparation area whilst a sham-centrifuge process is performed in order to maintain participant blinding. Participants will then receive the CS injection, which contains Depo-medrone (40mg) mixed with 3mls of 0.5% bupivacaine local anaesthetic, administered using standard aseptic techniques, but provided in a 'blinding syringe' (non-transparent sides).

9.8.3 Post-injection follow-up

For both treatments, immediately after the injection the participant will receive standard advice and can immediately resume normal daily activities. After 6-8 weeks if no significant medium-term benefit, as defined by usual clinical assessment, is reported, the patient will be referred to secondary care to discuss alternative treatment options as per standard care pathways.

Participants will be asked to desist from receiving other forms of pharmacological treatment in the form of painkillers for the first 6-8 weeks during the trial or follow-up periods. Following this time patients will not be asked to continue desisting from other treatments. Compliance and use of these other treatments will be recorded on a case report form at each follow-up time-point.

To ensure that the participant's clinical team know what treatment they have already received as part of the study when they revert back to their standard care, the participant's medical notes will state their involvement in the SPIRIT trial and that the site research team should be contacted prior to further treatment commencing to establish which intervention the participant originally received.

9.9 Sample Handling

If a participant is randomised to the APS intervention, a blood sample will be taken, processed by centrifuge spinning and then injected into the participant as soon as possible. If a participant is randomised to the CSI intervention, a blood sample will also be obtained and will be taken out of the participant's sight and discarded in order to ensure participant blinding from the intervention. No samples will be stored or transferred off site and any unused blood will be disposed of in accordance with the human tissue authority's code of practice.

9.10 Early phase follow up (up to 8 weeks)

Participants will receive a weekly text/email/phone call (according to participant preference) up to week 8 post-randomisation with a link to a visual analogue scale (VAS) asking them to indicate their level of pain in the previous 24 hours and a weekly compliance CRF asking if they have taken any painkillers for their injury, which if not completed will be followed up by phone by the central trial team 24 hours later.

9.11 Late phase follow up (3 and 6 months)

At 3 and 6 months post-randomisation, participants will be contacted by the central study office via automated SMS or email from the REDCap database and invited to complete the PROMIS, OSS, EQ-5D-5L, VAS, WPAI, health resource use and complications questionnaires. If participants do not complete the triggered URL link they will be contacted by phone by the central trial team 7 days later.

Health Resource Use

Resource use will be monitored to answer the feasibility questions related to the economic evaluation perspectives.

Resource use following discharge, including National Health Service (NHS) and Personal Social Services costs will be recorded via a short questionnaire which will be administered at 6 months post-randomisation. Patient self-reported information on service use has been shown to be accurate in terms of the intensity of use of different services.

Complications

Complication data will be collected from patients at 3 and 6 months post-randomisation. Complications will be patient reported via their 3 and 6 month questionnaires and verified by research nurses at site. At

6 months post-randomisation the site staff will be asked to complete a medical notes review to ensure all expected complications are recorded.

9.12 Early Discontinuation/Withdrawal of Participants

During the course of the trial a participant may choose to withdraw early from the study at any time, without giving reasons, and without prejudicing their clinical care.

Participants will not have the option to withdraw the data collected up until the point of withdrawal, as the data will be required for the intention-to-treat analysis and safety analysis. The options for withdrawal will be explained clearly in the Participant Information Sheet (PIS). The type of withdrawal and reason for withdrawal, if the participant is willing to provide one, will be recorded in the withdrawal Case Report Form (CRF).

If the participant is withdrawn due to a serious adverse event, the Investigator will arrange for telephone calls until the event has resolved or stabilised.

Withdrawal may be complete or partial. Complete withdrawal would mean that the participant would not receive any further communications from the study team. Partial withdrawal would mean that the participant would no longer receive any outcome questionnaires. Site staff will however be asked to complete a medical notes review at 6 months post randomisation to enquire whether the participant has been referred to see a shoulder surgeon, were on the waiting list for shoulder surgery or had undergone shoulder surgery.

9.13 Definition of End of Study

The end of the study is defined as the last follow up time-point of the last participant and once all queries have been resolves.

10. SAFETY REPORTING

Safety reporting for each participant will begin from the point of consent and will end when the participant has reached their final follow up time point, at 6 months post-randomisation. This is a low risk, pragmatic trial where both of the trial interventions are licensed in the UK and are in common use. In light of this, we do not anticipate many serious adverse events (SAEs) associated with either treatment.

10.1 Definition of Serious Adverse Events

A serious adverse event 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
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: 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.

10.2 Reporting Procedures for Serious Adverse Events

If an SAE arises in the period between consent and the final follow-up visit, that is deemed related to the trial interventions, the site will complete an SAE form and record the description, date of onset, end date, severity and assessment of relatedness to trial intervention.

For the purpose of safety recording for this trial, only unforeseeable SAEs potentially related to the intervention will be reported immediately to the central trial team. When the local research team becomes aware of an SAE in a trial participant, the PI will review the SAE locally and make a decision about the causality (i.e. likelihood of the event to be related/attributed to the intervention). Further details on the grades of causality are available in the *SAE Reporting Guidelines* document in the Investigator Site File. Following the assessment of causality the PI will assess any related events for expectedness. For any SAEs assessed as unexpected and potentially related, the details of the event will be entered on an SAE reporting form on the database, and the local research team will notify the central trial team via email or telephone within 24 hours of the PI becoming aware of the event. Once received, causality and expectedness will be confirmed by the Chief Investigator (CI) or delegate (Nominated Person). In the event that consensus is not reached between the PI and Nominated Person about assessment of causality and expectedness, this will be escalated to the CI for further discussion. However, if no consensus decision is reached about expectedness after further discussion within one working day, and the SAE is judged to be unexpected by any one of either the PI, Nominated Person or CI, the event will be classified as an unexpected event.

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

Adverse events (AEs) that are unrelated to the injury, intervention or treatment will not be reported.

10.3 Reporting Procedures for Foreseeable Serious Adverse Events and Adverse Events Not Defined as Serious

Foreseeable SAEs and adverse events not defined as serious that are related to the interventions will be recorded by participants or site staff but will not need to be reported immediately. These events will be recorded on patient-reported questionnaires or by the site investigators in the 'Complications' CRF if they become aware of such an event.

Foreseeable adverse events to be recorded as complications include:

- Septic arthritis
- Dizziness
- Nervousness
- Facial flushing
- Insomnia
- Flare-up of pain intensity at the injection site
- Injection site skin pigmentation change (skin gets lighter or darker around the injection site)
- Subcutaneous fat atrophy
- (For diabetic patients only) Increased episodes of hypo / hyper glycaemia - low or high blood sugars

11. STATISTICS AND ANALYSIS

11.1 Statistical Analysis Plan (SAP)

The statistical aspects of the study are detailed here. Interim analyses of the efficacy outcomes are not planned. It is anticipated that all analysis will be undertaken using Stata (Stata Statistical Software: Release 16 or later, StataCorp LLC) or other well validated statistical packages. A trial statistician embedded within OCTRU will contribute to all the statistical aspects of the study.

11.2 Description of the Statistical Methods

The feasibility outcomes of total number of participants recruited the conversion rate of eligible to randomised participants, levels of retention at follow-up dates will be shown in the form of a CONSORT diagram, clearly showing the flow of participants through the screening process and trial.

Data availability for the patient reported questionnaires, i.e. pain VAS, PROMIS Physical Function (upper extremity), PROMIS Pain Interference, Oxford Shoulder Score, EQ-5D-5L, Work Productivity Impairment questionnaire and health resource use will be reported overall and by treatment arm at each relevant time point. Information on number of evaluable questionnaires, and percentage out of all randomised participants will be provided.

Compliance with the intervention will be described, and the number of participants who did not receive their randomised interventions will be presented, with reasons for non-adherence where available.

Numbers of withdrawals and loss to follow-up, together with timing, will be described, together with reasons, where available.

Descriptive statistics will be presented for all patient reported outcomes at baseline and follow-up Complications and adverse events/ serious adverse events reported during the trial follow-up will also summarised. Data will be presented by treatment arm and overall. Mean and standard deviation (or median and interquartile range if non-normally distributed) for continuous variables and the number and percentage of participants in each group for binary or categorical variables will be presented.

Differences in outcomes between treatment arms at the follow-up time points will be presented as mean differences with corresponding 90% confidence intervals for continuous data, and risk differences and odds ratios with 90% confidence intervals for binary data, where appropriate. If sufficient outcome data are available, differences will be adjusted for duration of symptoms (<=/> 6 months) and baseline scores for continuous variables, where applicable, and derived from multilevel mixed-effects linear or logistic regression models. If insufficient data are available, unadjusted differences will be presented.

Summaries by treatment arm will be based on the intention to treat (ITT) population, as defined below (section 11.4).

The sample size for a future definitive trial will be established based on the PROMIS pain interference score and the standard deviation observed around it in this study.

11.3 Sample Size Determination

Fifty participants will be recruited to this feasibility study. This sample size will be sufficient to estimate the rate of recruitment (i.e., participants randomised out of those screened) and retention.

Fifty participants should provide a robust estimate of the standard deviation around the PROMIS upper limb physical function to be used in the sample size calculation for a definitive trial. For a small-standardised difference (0.1-0.3) and 80% power, 40 participants would be a sufficient sample size to provide a feasibility study arm to the trial, from which descriptive statistics can be derived [21]; 50 participants will allow for up to 20% loss to follow-up. In order to recruit 50 participants in the 7-month recruitment period, we would need to recruit a mean of 6.25 participants per month. In each proposed recruiting site, an average of 12-14 eligible patients are seen per month, allowing for a good chance of success in conduct of a feasibility trial.

11.4 Analysis populations

The ITT population will include all participants with available data for at least one of the follow-up time-points up to and including 6 months follow-up in the randomised groups to which they were allocated regardless of the treatment they actually received.

11.5 Decision points

No interim analyses are planned for this study, and a single final analysis will take place once all participants have completed their follow-up and sufficient time has been allowed for data cleaning.

11.6 Stopping rules

N/A The trial does not include formal stopping rules before the end of recruitment and follow-up

11.7 The Level of Statistical Significance

No statistical tests will be presented in the main study report. The reporting of this study focusses on descriptive statistics only.

11.8 Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data will be minimised by careful data management. Missing data will be described with reasons given where available; the number and percentage of individuals in the missing category will be presented by treatment group, as part of the feasibility outcomes of this study. All data collected on data collection forms will be used, since only essential data items will be collected. No data will be considered spurious in the analysis since all data will be checked and cleaned before analysis.

11.9 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Sufficient detail on the planned summaries is included in this study protocol, and no separate statistical analysis plan will be written. Deviations from the planned analyses outlined in this document will be described and justified in the final report.

11.10 Health Economics Analysis

Data on health resource use, additional out-of-pocket expenses, and work absence will also be collected via the WPAI questionnaire as part of the feasibility randomised trial to inform data collection in a future definitive RCT but a full health economic evaluation will not be conducted. The completeness and return of this data will be reviewed at the end of the study. This health economics data will be collected by participant questionnaires alongside the other outcome measures.

12. DATA MANAGEMENT

The data management aspects of the study are summarised here with full details described in the Data Management Plan (DMP).

At enrolment, participants will be asked to indicate their preference for the delivery and completion of follow-up questionnaires during the first 8 weeks and 3 and 6 months post-randomisation. Data collected in electronic format will be done by direct entry onto the trial database (REDCap), including the collection of documentary evidence of consent. All data entered will be encrypted in transit between the participants/recruitment centre and server. All electronic patient-identifiable information will be held on a server located in an access-controlled server room at the University of Oxford. The data will be entered into a Good Clinical Practice (GCP) compliant data collection system and stored in a database on the secure server, accessible only to the research team based on their role within the study. The database and server are backed up to a secure location on a regular basis.

Identifiable data will be limited to contact details including patient details e.g. name, NHS number, date of birth, sex, and telephone number/ email address and will be accessed separately from the outcome data obtained from/about the participants and managed within the rules of the clinical database system. In all other data, participants will be identified by a trial ID only. Contact details will be retained for 6 months after the last data collection in case of any queries arising from the data provided by participants. Study data will be retained for a minimum of three years after publication of the trial; the anonymised research data will be stored separately from the consent forms.

12.1 Source Data

Source documents are where data is first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, patient-reported outcome measures that are submitted directly to the trial management team and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study specific documents, other than the signed consent, the participant will be referred to by their study ID, not by name.

12.2 Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations. Site staff will have access to the centrally collected patient-reported outcome data for participants that they recruit at their site on REDCap, to ensure that they can download a complete dataset for their patients at the end of the trial.

12.3 Data Recording and Record Keeping

The CRFs will be designed by the trial manager in conjunction with the trial management team and statisticians.

Whenever possible, data will be collected in electronic format with direct entry onto the trial database, including the collection of documentary evidence of consent. Electronic data collection has the major advantage of building "data logic" and "edit checks" into forms, minimising missing data, data input errors and ensuring the completeness of consent forms.

Trial data will be collected and managed using REDCap electronic data capture tools hosted at OCTRU, University of Oxford. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Wherever possible, trial data will be entered directly into the trial database by site staff or participants. Data on paper forms or captured during phone calls to participants will be entered into the trial database by suitably trained central office staff. Full details will be recorded in the DMP. The participants will be identified by a unique trial specific number in any data extract. Identifiable data will only be accessible by members of the study team with a demonstrated need (managed via access controls within the application) and only used to communicate with the participant (e.g., sending follow-up reminders for online form completion or telephone follow-up).

13. QUALITY ASSURANCE PROCEDURES

This study will be coordinated by the by the UKCRC registered Oxford Clinical Trials Research Unit (OCTRU) at the University of Oxford. A rigorous programme of quality control will be implemented to ensure

compliance to the current approved protocol, GCP, relevant regulations and OCTRU Standard Operating Procedures (SOPs). Quality assurance checks will be undertaken by the trial management team to ensure integrity of randomisation, study entry procedures and data collection. Inspections of the Trial Master File will be carried out by the OCTRU Quality Assurance team (at least once in the lifetime of the study, more if deemed necessary). Furthermore, the processes of consent taking, randomisation, registration, provision of information and provision of treatment will be monitored centrally.

Additionally, the study may be monitored, or audited by sponsor or host sites in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1 Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2 Study monitoring

Regular central monitoring will be performed according to the study specific Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the study specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical study is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The CI and the Trial manager will develop data management and monitoring plans.

13.3 Trial Oversight

The trial will be conducted in accordance with the principles of GCP and guidelines, the Declaration of Helsinki, OCTRU SOPs, relevant UK legislation and this Protocol. All participating PIs will be required to have GCP training to conduct the trial.

13.4 Study Committees

The day-to-day management of the trial will be the responsibility of the Trial Manager, supported by a Senior Trial Manager. This will be overseen by the Trial Management Group (TMG), who will meet monthly to assess progress. A PPI representative will be an integral member of the TMG. It will also be the responsibility of the Trial Manager to undertake training of the research staff at each of the trial centres. The trial statistician and the information specialist will be closely involved in setting up data capture systems, design of databases and clinical reporting forms. As this a low-risk, small feasibility study no Trial Steering or Data and Safety Monitoring Committee will be convened. The TMG will maintain robust oversight of trial conduct and safety issues.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g., consent process or administration of study intervention) or from Good

Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

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

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3 Approvals

Following Sponsor approval, the protocol, ICF, PIS and other study materials will be submitted to an appropriate Research Ethics Committee (REC), and Health Regulatory Authority (HRA) for written approval.

The CI will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4 Other Ethical Considerations

All participants will have a 55ml blood sample taken from them regardless of which intervention they are randomised to so that they remain blinded to the intervention they receive. Participants randomised to the CSI for which their blood is not required for preparation of the injection will have their samples discarded straight away. Participants will be made aware of this possibility during the consent discussion and will only proceed if they are happy to do so. The value of keeping participants blinded to their intervention will significantly outweigh the inconvenience caused by taking a blood sample of this size which carries no other risks than those minimal risks associated with taking blood samples. This consideration has been proposed to PPI lay representatives who have raised no concerns. There may be minor bruising, local tenderness or pre-syncopal symptoms associated with venepuncture. Drawing

blood may cause slight pain and occasionally bruising at the site where the needle enters. Rarely, people feel light-headed or even faint. All samples will only ever be taken by staff who are full trained to do so.

16.5 Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6 Transparency in Research

Prior to recruitment of the first participant, the trial will have been registered on a publicly accessible database; [ISRCTN xxxxxxxxxxx].

The trial team undertakes to keep trial data up to date and to make the results publicly available.

16.7 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a trial ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. The authorisation functionality within the data collection system will be utilised to ensure that identifiable data can only be accessed by appropriate members of the trial team. All documents will be stored securely and only be accessible to study staff and authorised personnel. The study will comply with the UK General Data Protection Regulation and the Data Protection Act (2018) which requires data to be de-identified as soon as it is practical to do so.

16.8 Expenses and Benefits

Participants will not undergo any hospital visits in addition to normal care, therefore no expenses will be payable.

17. FINANCE AND INSURANCE

17.1 Funding

This study is funded by the National Institute for Health Research for Patient Benefit (NIHR 201473).

17.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

A final study report will be prepared for the funder by the trial management team upon completion of the trial. The Investigators will be involved in reviewing drafts of manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. No patient identifiable information will be contained in any form of dissemination of study results.

Dissemination will be via traditional and novel methods:

- Conference: Traditional conference dissemination will focus on presentations to include the key professional stakeholders (orthopaedic surgeons, physiotherapists, occupational therapists and trainees in orthopaedic surgery).
- Publications: Key outputs will be published in high-impact journals with publicity sought in other professional journals. We will ensure that plain English summaries are published alongside the full paper, along with links to other digital media on the trial website to explain the trial result in an accessible format. Given the frequency of the condition, this is also likely to be of interest to international press outlets.
- Policy Makers: We will ensure the development of links with key organisations such as NICE and the British Orthopaedic Association to contribute to and capitalise on their networks. Most importantly the outputs will directly contribute to the NICE recommendations on treatment options for shoulder pain at their scheduled update.
- Public Dissemination: To ensure a broad campaign we will target a range of social media outlets (e.g. NDORMS twitter) with an explainer video and infographic. We have used the explainer videos and infographics on a number of recent studies, with excellent PPI feedback.

18.1 DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable

19. ARCHIVING

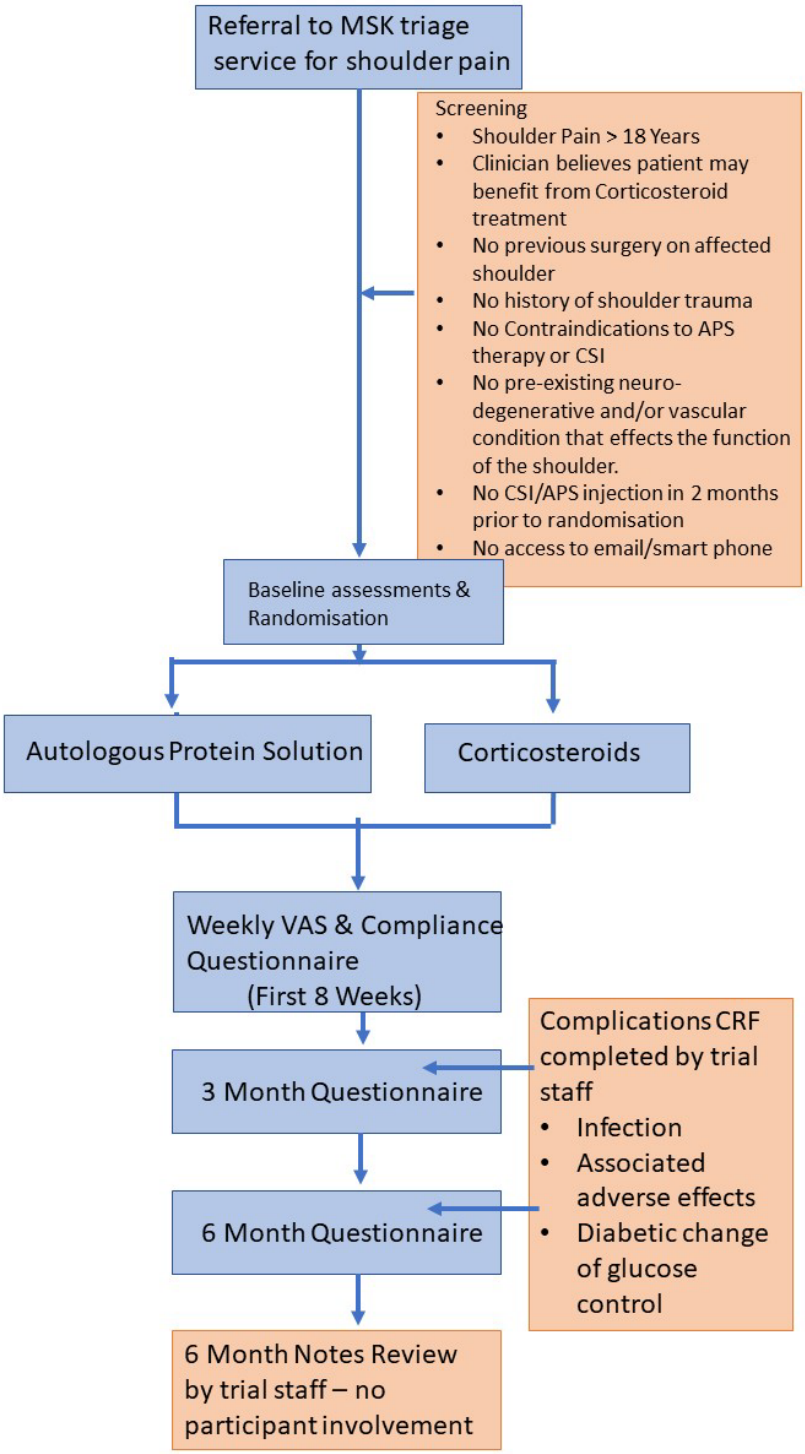
Documents and electronic systems will be archived as per the appropriate SOPs as prepared by OCTRU.

20. REFERENCES

1.Urwin M, Symmons D, Allison T, et al. Estimating the burden of musculoskeletal disorders in the community: the comparativeprevalence of symptoms at different anatomical sites, and the relation to social deprivation.Ann Rheum Dis1998; 557: 649–55.
2.Mitchell C, Adebajo A, Hay E and Carr A. Shoulder pain: diagnosis and management in primary care.BMJ2005; 331: 1124–8.
3.van der Windt DA, Koes BW, Boeke AJ, Deville W, De Jong BA, Bouter LM: Shoulder disorders in general practice: prognostic indicatorsofoutcome.Br J Gen Pract.1996, 46(410):519-523.
4.Pope DP, Silman AJ, Cherry NM, Pritchard C, Macfarlane GJ: Association of occupational physical demands and psychosocial workingenvironment with disabling shoulder pain.Ann Rheum Dis2001, 60(9):852-858.
5.Harkness EF, Macfarlane GJ, Nahit ES, Silman AJ and McBeth J. Mechanical and psychosocial factors predict new onsent shoulderpain:a prospective cohort study of newly employed workers.Occup Env Med2003; 60: 850–7.
6.van der Windt D, Thomas E, Pope DP, etal. Occupational risk factors for shoulder pain: a systematic review.Occup Env Med2000; 57:433–42.
7.Kulkarni R, Gibson J, Brownson P, Thomas M, Rangan A, Carr AJ and Rees JL. Subacromial shoulder pain. BESS/BOA Patient CarePathways.Shoulder & Elbow2015; 7(2): 135-143
8.Evans CH, Kraus VB, Setton LA. Progress in intra-articular therapy.Nat Rev Rheumatol.2014;10(1):11-22.
9.Sardana V, Burzynski J, Hasan K & Zalzal P. Are non-steroidal anti-inflammatory drug injections an alternative to steroid injectionsformusculoskeletal pain?: A systematic review.J Orthop2018,15,812-816.
10.Carr JB & Rodeo SA. The role of biologic agents in the management of common shoulder pathologies: current state and futuredirections.J Shoulder Elbow Surg. 2019, 28(11):2041-2052
11.Lewis JS. Rotator cuff tendinopathy/subacromial impingement syndrome: is it time for a new method of assessment?Br J Sports Med2009; 43: 259–64.
12.Yuan T, Guo SC, Han P, Zhang CQ, and Zeng BF Applications of leukocyte-and platelet-rich plasma (L-PRP) intrauma surgeryCurrentPharmaceutical Biotechnology2012 13(7): 1173–1184
13.Alsousou J, Ali A, Willett K, and Harrison P The role of platelet-rich plasma in tissue regeneration 2013Platelets24(3): 173–182
14.Anitua E, Andía I, Sanchez I et alAutologouspreparations rich in growth factors promote proliferation and induce VEGF and HGFproduction by human tendon cells in cultureJ Orthop Res, 2005 23(2): 281–286
15.Schwitzguebel AJ, Kolo FC, Tirefort J, Kourhani A, Nowak A., Gremeaux V., Saffarini M. & Ladermann A. Efficacy of Platelet-Rich Plasmafor the Treatment of Interstitial Supraspinatus Tears: A Double-Blinded, Randomized Controlled Trial.Am J Sports Med2019,47,1885-1892.
16.Hix J, Klaassen M, Foreman R, Cullen E, Toler K, King W & Woodell-May J. An Autologous Anti-Inflammatory Protein Solution Yielded aFavorable Safety Profile and Significant Pain Relief in an Open-Label Pilot Study of Patients with Osteoarthritis.BioResearch2017,6,151-158.
17.Kon E, Engerbretsen L, Verdonk P, Nehrer S and Filardo G. Clinical outcomes of knee osteroarthritis treated with an autologous proteinsolution injection–A 1-year pilot double-blinded randomised controlled trial.Am J Sports Med2018; 46(1): 171-180
18.Piegorsch, W. Sample sizes for improved binomial confidence intervals.Computational Statistics & Data Analysis, 2004. 46: 309-316
19.Whitehead AL, JuliousSA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trialsample size for the external pilot and main trial for a continuous outcome variable.Stat Methods Med Res.2016 Jun;25(3):1057-73.
20.Cummins CA, Sasso LM and Nicholson D. Impingement syndrome: temporal outcomes of nonoperative treatment.J Shoulder ElbowSurg2009; 18: 172–7.
21.Arroll B, Goodyear-Smith F. Corticosteroid injections for painful shoulder: a meta-analysis.Br J Gen Pract2005;55(512):224-8.
22.Buchbinder R, Green S, Youd JM. Corticosteroid injections for shoulder pain. Cochrane Database of Systematic Reviews2003(1):CD004016.

23.Green S, Buchbinder R, Glazier R, et al. Systematic review of randomised controlled trials of interventions forpainful shoulder: selectioncriteria, outcome assessment, and efficacy.BMJ1998;316(7128):354-60.
24.Dawson J: The Oxford shoulder score revisited.Arch Orthop Trauma Surg. 2009, 129 (1): 119-123. 10.1007/s00402-007-0549-7.
25.Dolan P, Roberts J. Modelling valuations for Eq-5d health states: an alternative model using differences in valuations.Med Care2002;40: 442-446.
26.Fawi HMY, Hossain M & Matthews TJW. The incidence of flare reaction and short-term outcome following steroid injection in theshoulder.Shoulder & elbow2017,9,188-194.
27.Beard DJ, Rees JL, Cook JA, RombachI, Cooper C, Merritt N et al Arthroscopic subacromial decompression for subacromial shoulderpain (CSAW): a multicentre, pragmatic, parallel group, placebo-controlled, three-group, randomised surgical trial.Lancet391; 10118:329-338
28.Paavola M, Malmivaara A, Taimela S, Kanto K, Inkinen J, Kalske J, Sinisaari I., Savolainen V, Ranstam J, Jarvinen TLN &FinnishSubacromial ImpingementArthroscopyControlled Trial (FIMPACT) Investigators.Subacromial decompression versusdiagnostic arthroscopy for shoulder impingement: randomised, placebo surgery controlled clinical trial.BMJ2018,362,k2860.

21. APPENDIX A: STUDY FLOW CHART



22. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
N/A 1st version				
Amendment 04	V3.0	27Jan2023	Hannah Crook Marloes Franssen	Amending the study timeline dates to reflect the 5-month no-cost extension granted by the funder.