Anti-TNF (adalimumab) injection for the treatment of adults with frozen shoulder during the pain-predominant phase: a multi-centre, randomised, double blind, parallel group, feasibility study

Short Title: The Anti-Freaze-F Study- "Anti-TNF for Treatment of Frozen Shoulder – a Feasibility Study"

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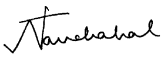
Chief Investigator Signature:	

Conflict of interest declaration
Professor Sir Marc Feldman and Professor Jagdeep Nanchahal are co-founders and hold equity in 180 Life Sciences, the company funding the purchase of adalimumab, the investigational medicinal product to be used in this trial.

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 and Regulatory Authorities unless authorised to do so.

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This study will be coordinated by the UKCRC registered Oxford Clinical Trials Research Unit (OCTRU) at the University of Oxford.

ABBREVIATIONS

Anti-Freaze	Anti-TNF for Treatment of Frozen Shoulder
BESS	British Elbow and Shoulder Society
DSMC	Data Safety Monitoring Committee
GCP	Good Clinical Practice
GP	General Practitioner
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
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	Anti-TNF (adalimumab) injection for the treatment of shoulder pain in adults with frozen shoulder: a feasibility study
Trial register and number	EUDRA-CT: 2021-003509-23
Date of registration	21 June 2021
Secondary Trial ID Number/s	REC Reference: 21/NE/0214
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Brief title (acronym)	Anti-Freaze-F - Anti-TNF for Treatment of Frozen Shoulder – a Feasibility Study
Countries of recruitment	England
Health condition	Frozen Shoulder (adhesive capsulitis)
Focus of study	To assess the feasibility of conducting a large randomised controlled trial to assess whether an intra-articular injection of adalimumab can reduce pain and improve function in people with pain predominant early stage frozen shoulder.
Interventions **i) Anti-TNF injection** **ii) Placebo injection** **Physiotherapy advice leaflet**	 Intra-articular injection of anti-TNF (adalimumab 160mg; 3.2ml), under guided ultrasound. A second injection of 80mg in 1.6ml will be administered 2-3 weeks after the first injection Placebo injection (saline [0.9% sodium chloride] 3.2ml), under guided ultrasound. A second injection of 1.6ml saline will be administered 2-3 weeks after the first injection All participants will receive a physiotherapy advice leaflet about the management of frozen shoulder.
Key eligibility criteria	Men and women ≥18 years with a new episode of shoulder pain attributable to early stage frozen shoulder who have not received injection or physiotherapy for shoulder pain in the last 3 months, nor being considered for surgery.
Study design	Study type: A feasibility study Allocation: Randomised 1:1 Intervention model: Parallel Primary purpose: Treatment Phase: Pilot Blinding: Participant and outcome assessor blind
Target sample size	84 (1:1 randomisation)
Duration of follow up	3 months
Planned trial period	24 months
Primary objectives	The main objectives of the feasibility study are to assess the: • Ability to screen and identify potential participants with pain-predominant early stage frozen shoulder (i.e. within approximately 3 to 9 months of onset of symptoms).

	• Willingness of eligible participants to consent and be randomised to intervention. • Practicalities of delivering the intervention, including time to first injection (within 2 weeks of randomisation) and number of participants receiving second injection. • Standard deviation of the Shoulder Pain and Disability Index (SPADI) score and attrition rate at 3 months from baseline in order to estimate the sample size for a definitive trial.
Secondary objectives	To assess the follow up rates and viability of patient reported outcome measures and range of shoulder motion at 3 months follow up for a definitive trial: Patient reported: • Pain and function (Shoulder Pain And Disability Index) • Pain (Shoulder Pain And Disability Index, 5-item subscale) • Function (Shoulder Pain And Disability Index, 8-item subscale) • Psychological factors (Fear Avoidance Belief Questionnaire) • Pain Self Efficacy Questionnaire • Sleep disturbance (Insomnia Severity Index) • Return to desired activities (Patient-reported) • Global impression of change (Likert scale) • Participant Range of Movement Questionnaire • Healthcare resource use • Adverse events graded 3 or above (clinician assessed) related to intra-articular injection of adalimumab in the shoulder Clinician assessed: • Shoulder range of movement Embedded qualitative sub-study (optional participation): • To explore the patients' experiences of being recruited to a randomised trial of anti-TNF injection for frozen shoulder. • To understand what helps or hinders participant recruitment to the trial intervention.
Data Sharing statement	Summary results data will be available on the trial registration database within 12 months of the end of the trial. Requests for data (anonymised trial participant level data) will only be provided at the end of the trial to external researchers who provide a methodologically sound proposal to the trial team (and who will be required to sign a data sharing access agreement with the Sponsor) and in accordance with the NIHR guidance. After the end of the study a anonymised study dataset will be created and stored for as long as it is useful, and may be shared with other researcher upon request (as defined above). Participant consent for this is included in the informed consent form for the study.

2. LAY SUMMARY

Anti-Freaze-F - Anti-TNF for Treatment of Frozen Shoulder – a Feasibility Study

Frozen shoulder is a common condition affecting approximately 9% of people aged 25-64 years. During the early phase the pain is usually unbearable and the later restriction in movement is severely limiting. It occurs when the flexible tissue (capsule) that surrounds the shoulder joint becomes inflamed, thickened and tight. It's not fully understood why this happens but it is more common in people with diabetes or Dupuytren's disease, which causes the fingers to curl into the palm. It can also occur following shoulder injury or surgery. The pain can be very severe and lasts 3-9 months, followed by a 4-12 month period of increasing stiffness, after which the condition usually improves. Frozen shoulder often affects a person's ability to sleep, carry out everyday activities, and work. Current treatments include rest, painkillers, anti-inflammatories, physiotherapy and steroid injections. If stiffness persists, surgery is sometimes recommended. However, there is no evidence that any of these treatments lead to significant benefit in the long term, with many being ineffective. Steroid injections only help in the short term.

The aim of this study is to find out if it is possible to run a larger trial to test whether an injection of adalimumab can reduce pain and prevent the disease from getting worse, if given during the early painful phase of frozen shoulder. We need to conduct this smaller study first to be sure it's possible to identify and treat people with early stage frozen shoulder within the current NHS system, before we conduct a much larger trial to find out if this treatment works.

In this study we will include 84 adults with painful early stage frozen shoulder who have not yet received treatment. People will be randomised to receive either an injection of the drug adalimumab or a dummy injection of saline (placebo) directly into the shoulder joint, both guided by ultrasound. All participants will also receive standardized advice on how to manage their shoulder pain. We will assess participants before treatment and three months later. Adalimumab has been used very successfully to treat other inflammatory diseases such as rheumatoid arthritis. This drug has been chosen as the biological processes underlying frozen shoulder are similar to those in Dupuytren's disease, where we found it helps to stop the cells causing the disease.

The views of patients with frozen shoulder are important to us and have been incorporated into this study. We have worked with a group of patients who have experienced frozen shoulder. All were supportive of our study aims and design. They provided useful feedback that has been incorporated into the study. A patient representative is part of the team for this application. Patient representatives will also be part of the committee that oversees the study.

3. INTRODUCTION

3.1. BACKGROUND AND RATIONALE

3.1.1. Problem being addressed

Frozen shoulder (adhesive capsulitis) is an extremely painful and debilitating condition and affected individuals struggle with activities of daily living and significant sleep disturbance as a result of pain (1). The condition is very common, affecting about 9% of people in the UK aged 25-64 years (2), and 20% develop the same problem in the other shoulder (3). Frozen shoulder may develop as a primary condition or secondarily following surgery or trauma. Up to 30% of patients with diabetes develop frozen shoulder and the symptoms are more persistent and recalcitrant in this group (1).

The classic description of the development of frozen shoulder is of three overlapping phases (4, 5). The initial pain predominant inflammatory phase is characterised by constant pain and difficulty sleeping, and lasts between 3 and 9 months. This progresses to a stiffness predominant fibrotic stage with progressive restriction of motion, particularly external rotation and elevation of the shoulder, and impairment of function, and lasts between 4 and 12 months. The pain changes from being constant to being manifest at the end of range of motion and of reduced intensity. There is a gradual improvement in range of motion and stiffness over a 12-48 month period, although end of range pain may persist.
The average duration of the condition is 30 months (range 1 to 3.5 years) (6). Full resolution of symptoms does not always occur, but persistent symptoms are usually mild. At the mean follow-up of 52 months, 59% have a near normal shoulder, 35% have mild/moderate symptoms, and 6% have severe symptoms (3).

3.1.2. Why is this research important?

Problems associated with frozen shoulder can have a major impact on patient health. They are a significant cause of morbidity and disability with substantial socioeconomic burden, affecting an individual's capacity to work and perform daily activities. The NHS currently invests vast amounts of money on unproven therapies and steroid injections (7, 8). Shoulder problems have a major impact on primary care services, accounting for 2.4% of all GP consultations in the UK (9). The average spend per patient in the NHS for a musculoskeletal condition is £461.13 per person each year, costing the UK economy £7.4 billion per year (10).

The aetiology of frozen shoulder is poorly understood and consequently there is no consensus on the optimal treatment. The majority of patients with early stage frozen shoulder are managed in primary

care or at primary care interface musculoskeletal services by physiotherapists and GPs. During the pain predominant phase, standard treatment consists of rest, advice, analgesics, physiotherapy and corticosteroid injections to address the symptoms. A corticosteroid injection typically costs £147-£332, depending on the mode of delivery. A set of six physiotherapy sessions costs around £321 and an assessment and advice session costs £53 (11). Evidence of their effectiveness remains poor, usual care can be highly variable, and there are currently no recommended National Institute for Health and Care Excellence (NICE) approved clinical guidelines (4). Patients with persistent stiffness may be referred to secondary care for capsular release by manipulation under anaesthesia, hydrodilatation or arthroscopic capsular release (4). From NHS Reference Costs (11) the average cost for MUA manipulation under anaesthesia is £424, and with rehabilitation and surgical review this increases to £1446. The cost of arthroscopic capsular release is £1182 and with similar follow-up is £2204.

Due to the lack of evidence, a NIHR funded trial (UK FroST ISRCTN48804508) compared physiotherapy plus corticosteroid injection, manipulation under anaesthesia with a steroid injection, and arthroscopic capsular release supplemented with a steroid injection in patients with unilateral frozen shoulder characterised by ≥50% restriction in external rotation of the shoulder (12). None of the treatments were found to be clinically superior and the mean differences in the assessment of shoulder pain and function were less than the target difference for all three treatments. This trial recruited patients from secondary care and so it is very unlikely that it will include many people with early stage frozen shoulder in the initial pain-predominant inflammatory phase. Anti-Freaze-F is specifically targeting people with early stage pain-predominant frozen shoulder. If successful, this research could provide evidence for a new treatment for a very common debilitating condition, avoiding the need for surgery and prolonged physiotherapy, thereby reducing NHS costs.

Our study is specifically designed to address an unmet medical need for a common disabling condition. It will address shortcomings of previous research by targeting the diseased tissue directly at the early pain- predominant inflammatory stage to prevent the progression to fibrosis and the need for more invasive treatments and prolonged recovery. Our aim is to assess the feasibility of conducting a large randomised controlled trial to assess whether an intra-articular injection of adalimumab (a drug targeting the inflammatory mediator tumour necrosis factor [TNF]) can reduce pain and prevent the disease from getting worse if given during the early pain- predominant phase (i.e. within approximately 3 to 9 months of onset of symptoms). Our proposed research is the first stage in the development of a new treatment for frozen shoulder that is based on the pathology of the disease and delivered during the early inflammatory stage. If successful, this research could provide evidence for a new treatment

for a very common debilitating condition and thereby reduce NHS costs.

3.1.3 Review of existing evidence

There is limited efficacy for the treatment currently offered to patients with frozen shoulder. Two Cochrane reviews have concluded that whilst oral steroid or local steroid injections lead to short term benefit in pain and range of motion, the effects are not maintained beyond 6 weeks (8, 12, 13). A more recent systematic review (based on data from 5 RCTs) also found some short-term benefit of corticosteroid injection compared to placebo but this pain relief was not sustained in the long term (14). Other Cochrane reviews concluded that there is no evidence that physiotherapy or ultrasound therapy are beneficial (15), and that manual therapy with exercise is less effective than corticosteroid injection in the short term (16). These findings are supported by an HTA report which found that, of all treatment options available, the only short-term benefit (based on data from 2 RCTs) was from steroid injection in addition to home exercise in patients with symptoms of less than 6 months (17). In addition, manipulation under anaesthesia was found to be no better than home exercise programme (17), and the use of arthrographic joint distention with glucocorticoid and saline was no better than sham procedure (18). None of the treatment modalities assessed in the UK FROST trial (manipulation under anaesthesia, arthroscopic capsular release or early structured physiotherapy, all supplemented with steroid injection) achieved the target improvement in the score of shoulder pain and function (19).

3.1.3. Choice of comparators

Anti-TNF (adalimumab) injection

Whilst the pathogenesis of frozen shoulder remains largely unknown, a recent systematic review confirmed the presence of fibrosis and the role of inflammation (6). The affected tissues are infiltrated by immune cells, including macrophages, mast cells, T cells, and there are elevated levels of pro-inflammatory cytokines, including TNF, IL-6 and IL-1ß (20, 21), with myofibroblasts contributing to matrix deposition and fibrosis (22). More than 50% of patients with frozen shoulder also have Dupuytren's disease (23) and the underlying pathology of frozen shoulder is similar to Dupuytren's disease (22, 24) where we have shown that the myofibroblast phenotype is critically dependent on the local production of low levels of the pro-inflammatory cytokine TNF (25). In a dose-ranging proof of concept phase 2a clinical trial (RIDD trial) we found that local injection of 40mg of adalimumab in 0.4ml directly into Dupuytren's nodules resulted in downregulation of the myofibroblast phenotype (26). The only previous study to examine the effects of anti-TNF in frozen shoulder administered 40mg of adalimumab subcutaneously systemically in 8 patients or intra-articular steroid (40mg prednisolone)

in 10 patients every 2 weeks on up to 3 occasions (27). The authors found no improvement in the adalimumab group although there was improvement in the steroid cohort. However, the patients were not selected from those at the early pain-predominant inflammatory phase of disease. Importantly, the anti-TNF was administered systemically and, based on analysis of tissue obtained from patients participating in our trial of adalimumab for Dupuytren's disease (26), we believe that a trial of intralesional administration is more likely to target the involved tissues since cytokines like TNF are primarily local mediators, leading to local inflammation.

The palmar nodules in patients with Dupuytren's disease are readily identifiable clinically. However, the only means of accurately delivering adalimumab to the involved areas in patients with frozen shoulder is by ultrasound guidance. Furthermore, due to the larger area involved, we will use 160mg of adalimumab in 3.2ml. It is possible that some patients may fail to gain significant improvement in symptoms following administration of 160mg of adalimumab. The half-life of adalimumab is 2 weeks and up to 160mg can be administered as a loading dose in patients with inflammatory disorders such as Crohn's disease (https://bnf.nice.org.uk/drug/adalimumab.html#indicationsAndDoses . Patients will receive a second injection of adalimumab (80mg in 1.6ml) at 2-3 weeks after the initial injection.

We are not aware of any other trials for frozen shoulder investigating the efficacy of using a drug targeting a defined inflammatory cytokine. The anti-TNF drugs have a very strong safety profile, having been used in over 10 million people, adalimumab in over 5 million, and more than 25,000 patients have been recruited to trials of adalimumab, which is approved for 9 different disorders. In these, only 0.2% of patients with chronic inflammatory disorders discontinued long-term use of the drug, which is administered every 2 weeks, due to adverse effects. Anti-TNF drugs not routinely administered as an intra-articular injection, although there are a few reports of outcomes in patients with inflammatory or osteoarthritis (28-31). We are not aware of any trials where intra-articular injection of adalimumab has been used in people with frozen shoulder. Adalimumab is not currently licenced for use as an intra-articular injection for pain-predominant early-stage frozen shoulder and therefore will be used off license for the purposes of this trial. Therefore, as part of this feasibility trial we will also assess the safety of anti-TNF injection when given as an intra-articular injection, by recording any clinician reported grade 3 or above adverse events.

Administration of adalimumab should not pose any risks in relation to COVID-19 vaccinations or to patients who may have contracted COVID-19. None of the approved vaccines involve live viruses. Adalimumab was being trialled in UK care home residents for the treatment of COVID-19, although this trial has been closed because of the lack of eligible participants due to the success of the

vaccination programme. Adalimumab is also being trialled by the US military for this indication.

Placebo injection

Given that the available evidence suggests that at best steroid injection only leads to short-term pain relief (14), we will use a placebo injection of saline (0.9% sodium chloride) as the comparator. We believe that the use of a placebo injection is ethical in the context of this trial given that lack of existing treatment options specifically targeting people with early stage frozen shoulder in the initial pain-predominant inflammatory phase (17). Unlike steroid (triamcinolone), which is a white suspension, saline has the same appearance and viscosity as adalimumab which means we will be able to blind participants as to their treatment allocation. This is especially important given the subjective nature of some of the outcomes we plan to assess in the trial which are patient-reported, including one of our primary objectives, which will be utilised as outcomes in the definitive trial.

3.2. AIM AND OBJECTIVES

Our overall aim is to assess the feasibility of conducting a large randomised controlled trial to assess whether an intra-articular injection of adalimumab can reduce pain and improve function in people with early stage frozen shoulder.

Primary objectives

The main objectives of this feasibility study are to assess the:

- Ability to screen and identify potential participants with pain-predominant early stage frozen shoulder (i.e. within approximately 3 to 9 months of onset of symptoms).
- Willingness of eligible participants to consent and be randomised to intervention.
- Practicalities of delivering the intervention, including time to first injection (ideally within 2 weeks of randomisation) and number of participants receiving a second injection.
- Standard deviation of the Shoulder Pain and Disability Index (SPADI) score and attrition rate at 3 months from baseline in order to inform an estimation of the sample size for a definitive trial.

To be certain that we inject participants while they are still in the early pain-predominant inflammatory stage, which can be within as little as 3 months of onset of symptoms.,. Our experience of the NIHR HTA funded GRASP trial (ISRCTN16539266) (32) for people with shoulder pain due to a rotator cuff disorder suggests that this will be challenging within the current NHS treatment pathways; hence the need to conduct a study to assess feasibility prior to a definitive trial.

Secondary outcomes

To assess the follow up rates and viability of patient reported outcome measures and range of shoulder motion at the 3 month follow up stage for a definitive randomised controlled trial to assess the effectiveness of local injection of adalimumab. Three-month follow up has been chosen to reflect the primary outcome of the future definitive trial, which is improvement in shoulder pain and function, reflecting the need to treat participants while in the early pain-predominant inflammatory stage.

Patient reporting outcomes will comprise Pain and function (Shoulder Pain And Disability Index (SPADI)); Pain (Shoulder Pain and Disability Index, 5-item subscale); Function (Shoulder Pain and Disability Index, 8-item subscale); Psychological factors (Fear Avoidance Belief Questionnaire); Pain Self Efficacy Questionnaire; Sleep disturbance (Insomnia Severity Index); Return to desired activities; Global impression of change (Likert scale); Health resource use.

Adalimumab is not currently licenced for use as an intra-articular injection for people with pain-predominant early-stage frozen shoulder and will be used off license for the purposes of this trial. Therefore, as part of this feasibility trial we will also assess the safety of anti-TNF injection and record Adverse Events assessed by a clinician to be grade 3 or above as a result of the IMP injection.

Clinician assessed outcome:

- Shoulder range of movement.

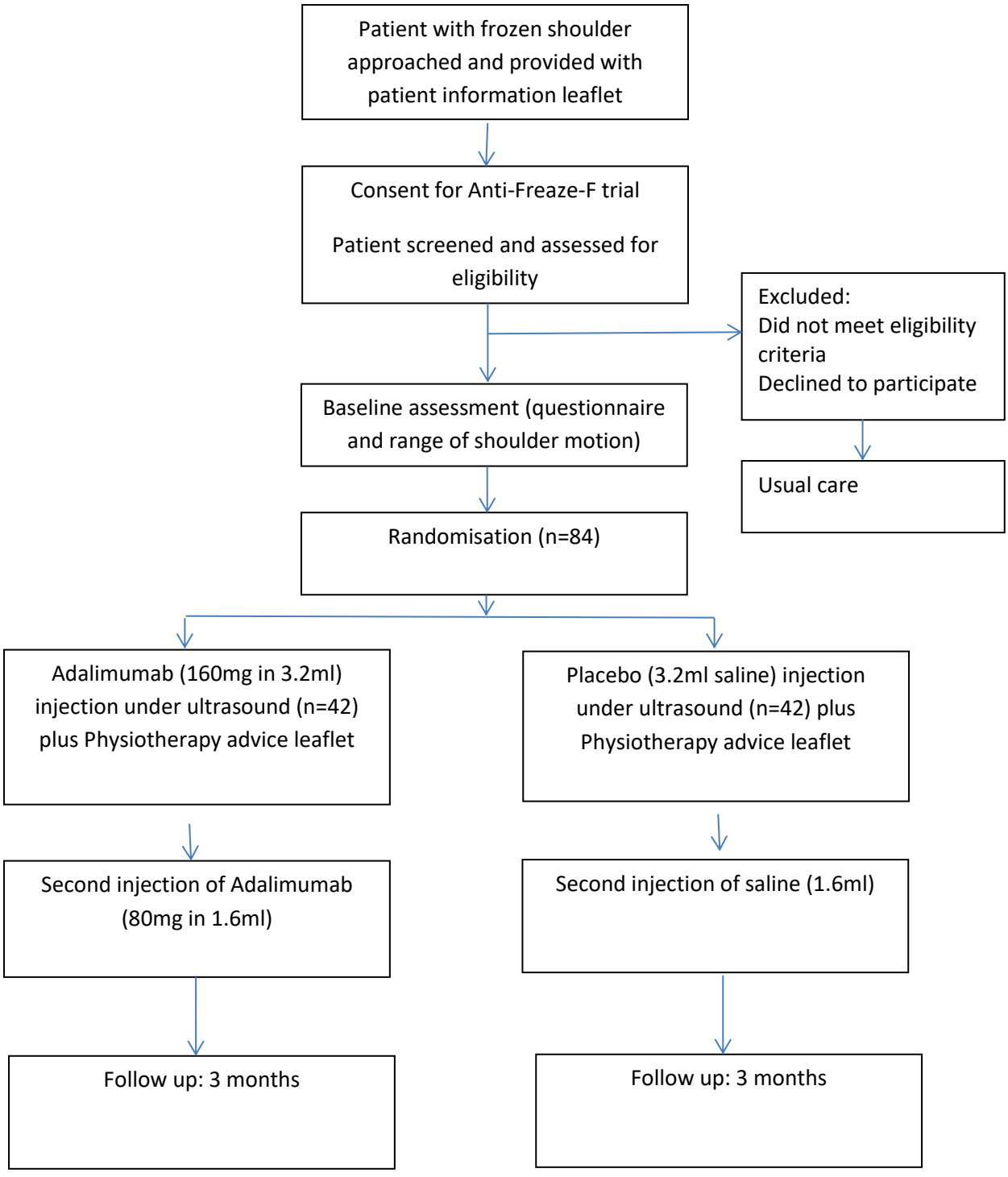
Embedded qualitative sub-study (optional participation):

- To explore the patients' experiences of being recruited to a randomised trial of anti-TNF injection for frozen shoulder.
- To understand what helps or hinders participant recruitment to the trial intervention.

3.3. DESIGN

Multi-centre, randomised, double blind, parallel group, feasibility study, with an embedded qualitative sub-study. Participants will be allocated to receive either: 1) intra-articular injection of anti-TNF (adalimumab 160mg) or 2) placebo injection (saline), both under ultrasound guidance. A second injection of the allocated treatment (adalimumab 80mg) or equivalent volume of placebo will be administered at 2-3 weeks. All participants will receive a physiotherapy advice leaflet providing education and advice about frozen shoulder and pain management.

Figure 1: Study flow diagram



4. METHODS - PARTICIPANTS, INTERVENTIONS AND OUTCOMES

4.1. STUDY SETTING

Participants will be recruited from at least five NHS primary-care-based musculoskeletal services and their related physiotherapy services, with treatment delivered within these services or the local secondary care site dependant on the local service provision. Participants may also be recruited from directly from NHS secondary-care-based musculoskeletal services, dependant on local service provision at sites. 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, rheumatologists and orthopaedic surgeons, dependent on local service provision at site.

4.2. ELIGIBILITY CRITERIA

Adults aged 18 years and above with a new episode of shoulder pain attributable to pain-predominant stage of frozen shoulder (i.e. within approximately 3 to 9 months of onset of symptoms) diagnosed using British Elbow and Shoulder Society (BESS) guidelines and part of the NICE-accredited standards (33), who are not being considered for surgery and able to understand spoken and written English will be assessed for eligibility. Imaging, including plain radiographs, may be used to confirm a diagnosis of frozen shoulder and rule out other pathology such as glenohumeral arthritis (34) as per standard NHS care (i.e. not as part of trial procedures).

Following a diagnosis of frozen shoulder, eligibility for Anti-Freaze-F will be assessed.

4.2.1. Inclusion criteria

We will include:

- Men and women aged 18 years and above.
- With a new episode of shoulder pain attributable to pain-predominant stage of frozen shoulder (i.e. within approximately 3 to 9 months of onset of symptoms) diagnosed using criteria set out in the BESS guidelines (35) (Appendix 1);
- Who are not being considered for surgery;
- Able to understand spoken and written English;
- Willing and able to give informed consent for trial participation and comply with all study requirements and time line;

- Willing to allow his or her General Practitioner be notified of participation in the trial.
- If female, and of child-bearing potential, willing to use effective contraception throughout the treatment period and for 5 months after the last injection. See section 7.3 and 7.3.1 for definitions.

4.2.2. Exclusion criteria

We will exclude:

- Those with frozen shoulder secondary to significant shoulder trauma (e.g., dislocation, fracture or full thickness tear requiring surgery) or other causes (e.g. recent breast cancer surgery or radiotherapy);
- Those with a neurological disease affecting the shoulder;
- Those with bilateral early stage frozen shoulder;
- Those with other shoulder disorders (e.g., inflammatory arthritis, rotator cuff disorders, glenohumeral joint instability) or with red flags consistent with the criteria set out in the BESS guidelines (35);
- Those who have received corticosteroid injection for shoulder pain in the last 12 weeks to either shoulder;
- Those currently taking any anti-TNF drug;
- Those being treated with coumarin anticoagulants, such as warfarin;
- Those who have participated in another research study involving an investigational medicinal product in the past 12 weeks;
- Those with significant renal or hepatic impairment;
- Those with contra-indications to anti-TNF injection:
    - Known allergy to any anti-TNF agent or any of the excipients;
    - Known Active tuberculosis (TB) or history of TB or at risk of developing TB e.g. through the use of immunosuppressants (see below (3))
    - Known Active infection (chronic or localised) or known history of recurring infections or condition which may predispose patients to infection, including the use of concomitant immunosuppressive medications;
    - Known Moderate to severe heart failure (NYHA class III/IV);
    - Those known to have HIV, Hepatitis B or C;
    - Those at risk of Hepatitis B infection;

- Those diagnosed with Multiple Sclerosis (MS) or other central or peripheral nervous system demyelinating disorders;
- Those who have ever been diagnosed with cancer, except basal cell carcinoma (BCC);
- Those requiring live vaccination within 5 months of the last trial injection or within the 4 weeks prior to randomisation;
- Those taking biologic DMARDS;
- Females who are currently breastfeeding.

- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.

4.3. INTERVENTIONS

4.3.1. Adalimumab/Placebo Injection

Eligible participants will be allocated to receive either an intra-articular injection of adalimumab (160mg in 3.2ml for the first injection, 80mg in 1.6ml for second injection) or placebo (normal saline [0.9% NaCl] 3.2ml for the first injection and 1.6ml for the second injection). The dose of 160mg followed by 80mg two weeks later was selected as this is the approved loading dose in patients with inflammatory bowel disease. The shoulder joint capsule is vascular and we anticipate that absorption into the blood stream will follow similar kinetics as when the adalimumab is administered subcutaneously. The injection will be given into the anterior shoulder joint space in the rotator cuff interval where there is maximal inflammation of the capsule and synovium, under guided ultrasound. The injection treatment is to be given within ideally 2 weeks after randomisation by an appropriately qualified practitioner, with experience of treating frozen shoulder by ultrasound guided injection who is appropriately delegated to do so. The practitioner will be either a GP with a specialist interest in musculoskeletal conditions, rheumatologist, extended scope physiotherapist, orthopaedic surgeon, sonographer or radiologist, dependant on the local service provision at site. The practitioner will need to confirm that the participant is still in the pain predominant phase before administering the first injection. If the practitioner deems that the participant is no longer in the pain predominant phase, the participant will not receive the injection and the reason will be recorded on the trial specific injection treatment log; the participant will still be included in the 3-month follow up assessment.

If a participant has symptoms of COVID-19, tests positive for COVID-19 or is self-isolating due to government guidelines and is unable to attend for either injection, the visit will be delayed until they

receive confirmation of a negative test result or have recovered as long as they remain in the pain predominant stage. If a participant is no longer considered to be in the pain predominant stage and is unable to have the injections this will be recorded on the injection CRF and will be recorded as a withdrawn from treatment but they will continue to be followed up at 3 months.

The only means of accurately delivering the drug to the involved areas in patients with frozen shoulder is by ultrasound guidance. The skin at the site of injection of adalimumab/placebo will be infiltrated with the local anaesthetics to reduce the pain of the injection in accordance with local practice for an injection into the shoulder joint. Following administration of the local anaesthetic, there will be minimal discomfort associated with the intra-articular injection. Once adalimumab has been drawn up, it tends to lose it potency and this precludes preparation of the syringes before the patient presents for treatment. For this trial, no more than 30 minutes will elapse from when the injection is drawn up to when the injection is given.

The adalimumab/placebo will typically be delivered using a syringe fitted with typically a 21 gauge needle or greater. All participants irrespective of whether they are still in the pain predominant phase, will receive a second injection (adalimumab/placebo) administered 2-3 weeks after the first injection, unless the participant declines the second injection. The reason will be recorded on the trial specific injection treatment log and the participant will still be included in the 3-month follow up assessment. Participants will be advised to continue with their physiotherapy and resume normal activities immediately after the injection. Participants will be provided with a written information leaflet advising them that there will be no restriction on their activities after the injection and what to do if they experience any side effects. Each patient will receive a maximum of two injections, either adalimumab or placebo. Injection details, including time from randomisation to injection delivery, will be recorded on a trial specific injection treatment log. A second injection will not be administered if any related grade 3 or above Adverse Event as per the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 occur following the first injection, or if the patient tests positive for TB or hepatitis B surface antigen.

4.3.1.1 IMP Description

Adalimumab is a human monoclonal antibody with Marketing Authorisation but will be used off-label for this trial.

Normal saline (0.9% NaCl) will be used as the placebo.

4.3.1.2 Supply and Storage of IMPs

Participating sites are to procure adalimumab (Idacio from Fresenius Kabi) (40mg / 0.8 ml vials) and normal saline (0.9% NaCl). The adalimumab must be stored in a refrigerator (2°C – 8°C) and must not be frozen. The vial should be kept in the outer carton in order to protect from light, it may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. Sites need to ensure that they procure the adalimumab from Fresenius Kabi in vials rather than a pre-filled syringe or pen. The needles fitted to the pre-filled syringes is too short for shoulder joint injection. Fresnius Kabi is the only company that supplies the adalimumab in vials. Use of this product will avoid the necessity to transfer the IMP from the pre-filled syringe to another syringe before injection. The cost of IMP purchase for the trial will be reimbursed by the Sponsor. Funding for purchase of the adalimumab and placebo will be provided by 180 Life Sciences. The IMP will be dispensed upon receipt of a trial-specific prescription. Where the IMP is collected from pharmacy/handled by staff who are blinded to treatment the IMP packaging will be obscured, in a sealed opaque plastic bag. Specific instructions that will cover the importance of keeping the IMP blinded will be provided at the Site Initiation Visit as it is not always possible for unblinded staff to collect the IMP from pharmacy. Trial-specific dispensing logs are required to be maintained. Trial-specific accountability for bulk receipt and returns/destruction will be required. There will be no provision of the IMP after the trial period.

4.3.1.3 Preparation and labelling of IMPs

A trial-specific annex 13 compliant label will be applied to the IMP prior to dispensing under the Regulation 37 exemption. Preparation of the IMP needs to occur in a clinic room/area separate from the participant to ensure the participant remains blinded to their treatment allocation immediately prior to injection.

Adalimumab:
The adalimumab, 160mg in 3.2ml or 80mg in 1.6ml, will be drawn up from the vials.

Normal saline:
3.2ml or 1.6 ml of saline (0.9% NaCl) will be drawn up.

Both the IMP and placebo have a similar viscosity and appearance so that the two treatments, adalimumab or saline, will be indistinguishable. The same type of syringe and needle will be used for injection of both adalimumab and saline thus maintaining the blinding of the participant and staff not involved in preparation or administering the IMP.

4.3.3. Physiotherapy advice leaflet

All participants will receive a physiotherapy advice leaflet providing education and advice about frozen shoulder and pain management, which is especially important during the early pain-predominant stage of frozen shoulder (4). Physiotherapy during the early pain-predominate stage of frozen shoulder is primarily directed at pain relief (e.g. heat, cold and other pain relieving modalities) as forcing the joint to move can make it more painful and is best not pursued. Participants will be advised to take over-the-counter analgesia (e.g. paracetamol with or without codeine, oral or topical nonsteroidal anti-inflammatory drug) as required, in accordance with the BESS guidelines (35). In addition, all of the participants will be provided with advice on modifying activities that exacerbate symptoms and on sleeping positions, drawing on materials used in the GRASP trial (32) and UK FROST trial (12). In addition, the advice leaflet will include a simple set of self-guided physiotherapy exercises, which participants can use once the early pain-predominant stage reduces and to increase shoulder joint mobilisation. Exercises will include passive mobilisation of the shoulder and capsular stretching, drawing on materials used in the UK FroST trial where appropriate (12). Joint mobilisation combined with stretching exercises has been found to be more effective than stretching exercises alone (36, 37). 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.

4.3.4. Concomitant care

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 (e.g. through GP referral) to do so. Additional treatments (including consultation with primary and secondary care, additional physiotherapy, injection use, or alternative therapies) will be recorded as a treatment outcome as part of the 3 month follow up questionnaire.

4.3.5 Contraindicated medications

Concomitant administration of biologic DMARDS is contraindicated during the treatment period and until 4 months after the last injection. The use of live vaccines must also be avoided until 12 weeks after the last injection.

4.3.6 Post-trial treatment

Participants will transfer to normal care at the end of the trial. There will be no provision of the IMP beyond the trial period.

4.3.7 Compliance with treatment

Adherence to treatment will be defined as receiving an injection within 2 weeks of randomisation. The number of participants receiving a second injection will also be recorded.

4.4. OUTCOMES

4.4.1. Feasibility objectives

The main aim of this feasibility study is to determine whether a future definitive trial would be feasible and to determine the sample size for the definitive trial to assess the effectiveness of adalimumab. We will focus on the main areas of uncertainty relating to the acceptability to be randomised to intra-articular injection of the anti-TNF (adalimumab) and the ability to identify and recruit and treat participants who have pain-predominant early stage frozen shoulder within the current NHS patient pathway for musculoskeletal conditions. In addition, we will collect outcome measures at 3 months, including SPADI and range of shoulder motion.

We have confidence from screening data from the GRASP trial (32) (where frozen shoulder is an exclusion criteria) that there are sufficient potential participants to investigate the feasibility criteria. To determine the feasibility of a definitive randomised controlled trial, the success criteria will be:

- Ability to screen and identify potential participants with pain-predominant stage frozen shoulder.
- Willingness of eligible participants to consent and be randomised to intervention.
- Practicalities of delivering the intervention, including time to first injection and number of participants receiving a second injection.

Data to assess our feasibility objectives will be collected at each site via a trial specific screening log; reasons for ineligibility and / or participants declining to participate in the trial will be recorded where available. The screening log will not contain any patient identifiers and will use screening numbers. Injection details, including time from randomisation to injection delivery, will be monitored based on the information recorded on the trial specific injection treatment logs.

4.4.2. Outcomes

Outcomes (Table 2) will be collected at baseline and at 3-months to assess the feasibility of collecting these in a future definitive trial and to obtain the variability estimates required for estimation of the sample size of the definitive trial. Patient reported outcomes will include shoulder pain and function measured using the SPADI scale (primary outcome for definitive trial) (38, 39); sub-domains of pain (SPADI 5-item pain subscale), function (SPADI 8-item disability subscale) (38, 39); shoulder range of motion (Participant Shoulder Movement Questionnaire); psychological factors (Fear Avoidance Belief Questionnaire) (40); pain self-efficacy questionnaire (41); sleep disturbance (Insomnia Severity Index) (42); patient global impression of change (43); return to desired activities; additional health resource use for index shoulder (e.g. consultation with primary and secondary care, additional physiotherapy, injection use, or alternative therapies).

The choice of outcome measures is based on OMERACT 2016 core outcome set for shoulder disorders (44) and a systematic review of core outcomes used in studies of frozen shoulder (45).

At the 3-month follow up, a blinded outcome assessor will collect an objective measure of shoulder function and performance:

- Participants will undergo measurement of range of motion of the shoulder, including active flexion, extension, abduction internal and external rotation, limitation of which has been shown to be pathognomonic of frozen shoulder in the absence of glenohumeral arthritis (46).

Table 2: Summary of patient outcomes assessed

Outcome	Measurement
Pain and function	Shoulder Pain and Disability Index (SPADI) (38, 39) 13-item total scale
Pain	Shoulder Pain and Disability Index (SPADI) (38, 39) 5-item subscale
Function	Shoulder Pain and Disability Index (SPADI) (38, 39) 8-item subscale
Shoulder range of motion	Participant Shoulder Movement Questionnaire
Psychological factors	Fear Avoidance Belief Questionnaire – physical activity 5-item subscale (40) Pain Self-efficacy questionnaire (short form) (41)
Sleep disturbance	Insomnia Severity Index (42)
Global impression of treatment	Patient-rated Likert scale (43)
Return to desired activities	Patient-reported return to desired activities, including work, social life and sport activities
Health resource use	Patient-reported

Adverse Events	Any Grade 3 or above AEs that have occurred from Consent up until the 3 month Follow up.

See section 7.2. SAFETY REPORTING for safety data collection

4.5. PARTICIPANT TIMELINE

TIMEPOINT (post randomisation unless stated otherwise)	Screening	0-2 weeks	4-5 weeks	3 month follow up
ENROLLMENT:				
Screening log	✓			
Informed consent	✓			
Eligibility confirmed	✓			
Randomisation	✓			
INTERVENTIONS:				
1st Anti-TNF/placebo injection		✓		
Physiotherapy advice leaflet provision	✓			
2nd Anti-TNF/placebo injection			✓[1]	
ASSESSMENTS:				
Serological testing e.g. TB ELISpot, Hepatitis B surface antigen		✓		
Pregnancy testing (if needed)	✓			
Baseline questionnaire	✓			
ROM Assessment	✓			✓
Follow-up questionnaire				✓
Follow-up clinic visit				✓
Qualitative interview (optional)				✓* within 4 weeks of intervention delivery
AE Reporting (grade 3 or above)	✓	✓	✓	✓

1. The second injection must be 2-3 weeks after the 1st injection.

4.6. RECRUITMENT

4.6.1. Recruitment of sites

The feasibility study will be conducted across at least five primary care-based musculoskeletal services and their related physiotherapy services, and as appropriate to local service provision/facilities their local secondary care site in the UK. Participants may also be recruited from directly from NHS secondary-care-based musculoskeletal services, dependant on local service provision at sites. We will utilise our existing network of collaborators from the GRASP trial which recruited from 20 sites in England (32). 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. Participants may also be recruited directly from NHS secondary-care-based musculoskeletal services, dependant on local service provision at sites.

4.6.2. Recruitment of participants

Participants will be recruited from the musculoskeletal services if referred by their GP, physiotherapy service, or self-referred for investigation/treatment of a new episode of shoulder pain. GPs and primary-care-based physiotherapy services within the local area surrounding each study site will be informed about the trial. Posters advertising the Anti-Freaze-F trial will be displayed in local GP surgeries, physiotherapy departments and musculoskeletal clinics to raise awareness of the trial with patients and clinicians. The trial will also have a presence on social media to further raise awareness of the trial amongst the public and professionals as well as being used to provide an update on trial progress. The trial will have a dedicated website hosted by Oxford Clinical Trials Research Unit. We will also contact patient organisations such as the Dupuytren's Society and Diabetes UK which represent patient groups with a high prevalence of frozen shoulder. These methods of recruitment have proved very useful in our trial of anti-TNF injections for people with early stage Dupuytren's disease (47). Participants will be able to claim for reasonable reimbursement for travel to and from their study appointments using the University of Oxford expense form which will be provided in the investigator Site File.

4.6.3. Screening and eligibility assessment

Potential participants will attend their musculoskeletal service clinic appointment in accordance with standard NHS procedures at each site. The treating practitioner will undertake a clinical assessment according to their usual practice. If a patient fulfils the criteria for pain-predominant stage of frozen shoulder, the option to participate in the trial will be discussed and they will be assessed by an appropriately qualified practitioner (i.e. a member of the participant's direct care team) to determine whether they meet the Anti-Freaze-F trial eligibility criteria based on their medical history and where available medical records (as described in Section 4.2) (i.e. no trial specific tests would be undertaken until informed consent is given). Patients will be provided with a copy of the participant information sheet, and asked if they wish to participate in the trial. Patients who meet the eligibility criteria and who would like to participate in the trial will be approached for informed consent and only then will the trial-specific screening tests be undertaken.

4.6.4. Informed consent

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. This second research appointment may be either face-to-face or virtual depending on local facilities at each site. 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. We will record anonymised information on the age, ethnicity and sex of those who decline to participate so that we can assess the generalisability of those recruited. 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.

A clinical member of the site staff for example A Research Nurse or Clinician Responsible for the patient or another member of the research team who has been trained in Good Clinical Practice (GCP), authorised to do so by the Principal Investigator, will obtain informed consent. A medically qualified doctor will be available during or following the consent process in case of queries relating to their medical care. The process for seeking, confirming and documenting informed consent will be either

paper based (written consent) or digital (eConsent) depending on local facilities at each site. Where consent is taken in person at site, for written 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 in the Investigator Site File. For consent that is taken digitally within REDCap (handwritten signature using a finger or a stylus or biometric eSignatures), a copy of the participants consent form will be emailed to the participant to an email address provided by them. The eConsent form will be downloaded from SIMS (an Oxford Clinical Trials Research Unit programme that transfers data securely from REDCap so that sites are able to download completed CRFs and consent forms) by the site research team and retained in the Investigator Site File. Electronic tablets will be provided to each site to log onto the REDCap Data Management system to enter the data directly into the trial database.

Where consent is taken remotely, as part of a virtual consultation, eConsent will be used with participants asked to provide a handwritten signature using a finger or a stylus or biometric eSignature on their tablet, mobile phone or other electronic device.

5. METHODS - ASSIGNMENT OF INTERVENTIONS

5.1. ALLOCATION

Consented participants will be randomised to intervention groups (1:1) using a validated web-based centralised randomisation service provided by the Oxford Clinical Trials Research Unit . This will either be undertaken directly by the research team 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. If the telephone option is used, site staff will need access to the Screening and Randomisation CRF to provide screening and eligibility details to the Trial Office member of staff so that they can enter these details into the randomisation system and provide site staff with a Trial ID. Randomisation will be computer-generated and stratified by centre, using a variable block size to ensure the participants from each study site have an equal chance of receiving either intervention. Participants will only be randomised following eligibility assessment and after informed consent has been obtained.

5.2. BLINDING

Study participants will be blinded to their treatment allocation. The clinician delivering the treatment injection will not be blinded to the treatment allocation as they will be required to prepare and administer the IMP. They will not be involved with any further trial-specific assessment of the participant. They will be educated on the importance of maintaining the blind of both study participants and the rest of the site staff. All other site staff, except pharmacy staff, will be blinded. The clinician assessed outcomes at the 3 month follow-up clinic visit will be undertaken by a blinded member of the clinical team at site. The trial statistician, Trial Office staff member undertaking checks of dispensed medication, and data entry personnel will not be blinded to the treatment allocation. The remaining members of the trial management team, including the staff conducting the qualitative interviews will be blinded to treatment allocation until after the data analysis is complete.

5.3 TRIAL-SPECIFIC SCREENING TESTS

Participants will undergo serological testing (e.g. TB ELISpot) to check for latent TB, as detailed in the adalimumab SmPC. Participants will also undergo serological testing for hepatitis B surface antigen as detailed in the adalimumab SmPC. Approximately 10ml of blood will be taken from each participant for these tests. These tests are to be carried out locally therefore the samples will be processed within 72 hours at the local site lab and any remaining should be destroyed in compliance with HTA and local procedures.

These tests will be performed at the time the patient attends for their first injection appointment. The risks of reactivation of TB are well-documented only in patients who receive anti-TNF therapy on a regular basis e.g. every 2 weeks for adalimumab, in the long term. Discussions with Prof Chris Conlon, former head of the Oxford TB service, indicated that the risk of TB reactivation following a single injection are low and any participant for whom the serology test result shows them to be TB positive will be referred for a chest X-ray and to the local TB service and will not receive any further trial treatment; they will still be included in the 3 month follow up assessment as specified in the protocol. Similarly, the risk of reactivation of latent hepatitis B after a single injection of adalimumab is very low and any participant that test positive for hepatitis B surface antigen will be referred to their local infectious disease service. They will be recorded as withdrawn from treatment but will continue to be followed up at the 3 month time point.

Participants who do not meet the eligibility criteria or who do not wish to participate will receive the standard NHS treatment. We will record anonymised information on the age and sex of those who

decline to participate so that we can assess the generalisability of those screened. The reasons for declining will be asked and any answers given will be recorded.

5.4 CODE BREAK

Based on the well-known safety profile of the IMP, it is not anticipated that there will be any suspected unexpected serious adverse reactions. In the event that the participant has a serious adverse reaction within 3 months of the last injection and there is a need to unblind for emergency purposes the PI at site will have 24/7 access to the randomisation database (RRAMP) and can access the treatment allocation for that one participant without delay. The CTU will be notified immediately that an unblinding has occurred.

All participants will be provided with a laminated card to present to any treating physicians with outline details of the trial treatment as well as contact details of the site in the event of unblinding.

5.5. SAMPLE SIZE

The main feasibility objective and therefore the basis of the sample size estimate is participant recruitment at least 5 centres with a staggered start. The target sample size is 84 participants, equivalent of 1 to 2 participants per month per site over 12 months, allowing for staggered opening of sites. Seventy is the recommended minimum target sample size when including an estimate of the SD in an external pilot trial (48). The sample size has been increased from 70 to a total of 84 participants in order to increase precision of the estimate of the standard deviation of SPADI at 3 months, the proposed primary outcome for the definitive trial, and to take into account possible attrition (based on an attrition rate of 15%). This attrition rate is a conservative estimate based on attrition rates for the GRASP trial (14% at 6 months) (32) and UK FroST (11% at 3 months) (12) which represent similar populations to those anticipated in Anti-FREAZE. This sample size will enable an estimate of a participation rate of 30% with a precision of +/- 5% based on 280 eligible participants being identified. We have selected a conservative recruitment rate given the uncertainty around the ability to identify, recruit and inject participants with early stage frozen shoulder. We anticipate that we will be able to recruit the required number of participants over a 12 month period. See Section 6.4 for details related to the sample size for the embedded qualitative sub-study.

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 questionnaires will be available in both an online and paper format as, due to their frozen shoulder, participants may find one format much easier to complete than the other.

Table 3: Outcomes and time points of assessment

Outcome	Measurement	Time point
Demographic	Age, Sex, Height, Weight, Ethnicity, Smoking, Date of frozen shoulder diagnosis, Duration of symptoms, Hand dominance, Affected shoulder. Diabetes and type, Dupuytren's Disease	0
Shoulder range of movement	Clinician assessed (goniometry measured) active shoulder flexion, extension, abduction, internal and external rotation. Patient Reported ROM Questionnaire	0, 3 months
Pain and function	Shoulder Pain and Disability Index (SPADI) (38, 39) 13-item total scale	0, 3 months
Pain	Shoulder Pain and Disability Index (SPADI) (38, 39) 5-item subscale	0, 3 months
Function	Shoulder Pain and Disability Index (SPADI) (38, 39) 8-item subscale	0, 3 months
Psychological factors	Fear Avoidance Belief Questionnaire physical activity 5-item subscale (40) Pain Self-efficacy questionnaire (short form) (41)	0, 3 months
Sleep disturbance	Insomnia Severity Index (42)	0, 3 months
Global impression of treatment	Patient-rated Likert scale (43)	3 months
Return to desired activities	Patient-reported return to desired activities, including work, social life and sport activities (49)	0, 3 months
Health resource use	Consultation with primary and secondary care, additional physiotherapy, injection use, or alternative therapies for index shoulder	3 months
Adverse Events	Any Grade 3 or above AEs that have occurred from Consent up until the 3 month Follow up.	3 months

6.1.2. Follow-up data collection

Follow up will be conducted via face to face clinic assessment and patient reported questionnaire at 3 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.

Participants who are unable to attend the face to face appointment will be asked to complete the 3 month follow up questionnaire and return it to the Anti-Freaze-F Trial Office in a prepaid envelope (the ROM participant Questionnaire can only be completed on paper, these will be supplied to the site to send out to participants if needed) or online (web-based version of the questionnaire) as appropriate. The reason why a participant is unable to attend the face to face clinic appointment will be recorded and whether this was due to potential COVID-19 restrictions or due to other reasons. For those who do not respond to the initial 3 month follow up questionnaire a reminder questionnaire will be sent 2 weeks later. Telephone and email follow-up will be used (2 weeks later) to contact those who do not respond to either the initial or reminder questionnaire. For those participants who have requested for digital communication, the ROM will need to be sent to them via the post in paper format. These participants will be send digital reminders if we do not receive the ROM questionnaire back at the trial office. Telephone and email follow-up will also be used to collect a core set of questionnaire items for the Shoulder Pain and Disability Index (SPADI) (primary outcome) if these have not been fully completed on the returned questionnaire.

6.1.3. Discontinuation / withdrawal of participants

Participants will be informed that they have the right to withdraw from the Anti-Freaze-F 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 treatment and/or withdraw from follow-up data collection. If a participant wishes to discontinue their 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 data collection will not be considered a withdrawal in accordance with the principles of the intention to treat (ITT) analysis. If a participant wishes to withdraw from follow-up data collection, data collected up to the point of withdrawal will still be used, as detailed in the PIL. Results from the blood samples taken will still be used. These will have been destroyed by the local laboratory once the samples have been tested for Hepatitis B/TB. If a participant decides to withdraw before they are given the injection but after the blood sample has been taken, the sample will be destroyed within 72 hours in accordance with HTA and local procedures.

In addition to participant self-withdrawal, an investigator may decide to withdraw a participant from Anti-Freaze-F if considered necessary for any reason including ineligibility arising subsequent to their initial enrolment in the trial or for clinical reasons based on safety grounds (i.e. any relate grade 3 or above Adverse Event as per the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (see Section 7.2) or tests positive for TB or hepatitis B surface antigen). Participants will still be included in the 3-month follow up assessment. The reason for withdrawal (if given) will be recorded on the study CRFs.

6.2. DATA MANAGEMENT

All data will be processed according to the UK General Data Protection Regulations (GDPR) and the Data Protection Act 2018. 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.

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 using an electronic tablet provided by the trial, with the questionnaire already opened to complete. Participants and staff should wash their hands or use anti-bacterial gel before handling the tablets to ensure infection control. Data on paper forms or captured during phone calls to participants will be entered into the trial database by suitably trained Trial 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 any additional processing of this will only be for the purposes of communication with the participant (e.g., sending follow-up reminders for online form completion or telephone follow-up).

Data will be collected from participants via eCRFs at screening, baseline and 3 month follow up. Sites will be provided will an electronic tablet to use for data collection and the ROM assessment will be provided in paper format. If the site or participant are not able to complete the CRFs electronically (due to poor internet connection), paper-based CRFs will be available in the Investigator Site File, these will be returned to the central Trial Office in Oxford via post using a pre-addressed stamped envelope, email as appropriate, or via Trial Office staff at site visits. Sites will send copies of consent forms (if completed paper-based) to the Trial Office via secure NHS email, or via recorded delivery. Participant data will be stored and transported in accordance with OCTRU SOPs. Participants who claim reasonable travel expenses will have their financial information held in accordance with the University of Oxford financial policy for 7 Years.

Upon completion of the trial, and with appropriate participant consent, anonymised research data may be shared with other organisations on request to the Chief Investigator and in accordance with the data sharing policies of OCTRU, the Sponsor and funder(s); as detailed in section 8.4 of the protocol (Access to Data). Participant electronic files will be filed in numerical order and stored in a secure and accessible manner on the ANTI-FREAZE F secure eTMF. Trial documentation including data will be archived for a maximum of 5 years. The Investigator Site File and associated documents should be archived in line with local site R&D policies.

6.2.1 Source Data

Source documents are where data are 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, 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 trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

The following data are expected to be recorded directly on the CRFs hence are to be considered source documents:

- All participant completed questionnaires.

6.3. STATISTICAL METHODS

Feasibility outcomes will be reported, including the number of participants approached, those eligible, consenting to randomisation and follow-up, the delivery of intervention (including time to first injection), withdrawal rate, the number receiving a second injection (per group and overall) and data completeness. Baseline characteristics (including possible stratification factors for the definitive trial) will be reported using descriptive statistics, separately per group and overall using the mean and standard deviation (or median and inter-quartile range if non-normally distributed) for continuous variables and the number and percentage of participants in each group for categorical variables. Measures of central location and dispersion of clinical and patient reported outcome measures, including health resource use, at 3 months will be reported and differences between treatments for the intention-to-treat population (i.e. the population of participants as randomised) will be reported with 95% confidence intervals. The standard deviation of the proposed primary outcome for the larger, main trial, SPADI at 3 months, will be used to inform an estimation of the sample size required for the definitive trial. An estimate of treatment effectiveness will be reported together with its 95% confidence interval. This along with change from baseline in range of shoulder motion at 3 months will provide an indication of potential efficacy of the intervention but will not be powered to provide a definitive result, which will only follow the fully powered definitive main trial. Even small increases in range of shoulder motion are important to people with frozen shoulder, where pain and restricted shoulder movement can be very debilitating. As such, we will use a 10-degree improvement in active flexion with any associated improvement in active external rotation of the shoulder to mean a potentially important difference (50). If we observe this difference between groups in our feasibility study with short follow up and a small sample this would indicate potential efficacy, which should then be formally, tested in the full trial. Adverse events and serious adverse events (S/AEs) will be summarised per group and overall in all patients.

6.4. EMBEDDED QUALITATIVE STUDY

Participants will be invited by the research team to receive further information about the qualitative sub-study at the time of consent to the main trial. Those who have agreed to be receive more information will then be contacted by a member of the qualitative research team within 2 weeks to ask if they would like to participate in the sub study. The aims of the qualitative study are to explore the patients' experiences of being recruited to a randomised trial of anti-TNF injection for frozen shoulder, of the treatment received and follow-up schedule, and to understand what helps participant recruitment to the trial intervention.

After obtaining signed consent individual telephone interviews will be conducted within 4 weeks of either intervention delivery by a qualitative researcher using a semi-structured interview guide with open-ended questions. All participants will be asked to reaffirm their consent before the start of the interview. We aim to interview a purposive sample of up to 15 participants (or until we reach data saturation, the qualitative researcher will also be blinded) to provide variability for age, gender, ethnicity and geographical representation. Interviews will be audio recorded using a password protected digital recorder and field notes will be taken). Immediately after each interview, the audio files will be saved under unique non-identifiable study IDs on the Anti-Freaze F secure eTMF. The audio files will be transcribed verbatim by an external transcription service approved by the University of Oxford. The audio files and transcripts will be sent and returned using a password protected folder via a suitably secure method. Once returned the transcribing company will not retain any files. The transcripts will be checked against the audio-files and all identifiable information such as names of people or places will be removed. The de-identified transcripts will be stored using the study IDs. The transcripts will be uploaded into QSR NVivo analysis software version 12. As these are considered source data copies of the anonymised typed transcripts and original audio recordings will be kept in a secure place within the University of Oxford for a maximum of 5 years and then destroyed. An inductive thematic analysis will be undertaken to develop categories and themes (51). The study findings will be reported following the Standards for Reporting Qualitative Research (SRQR) guidelines (52).

6.5. PROGRESSION CRITERIA

Progression criteria for the future definitive trial will be judged using a traffic light system whereby 'Green' indicates it is feasible to proceed to a definitive trial with the current procedures, 'Amber' indicates modification to one or more aspect of the study is required before proceeding to the future definitive trial, and 'Red' indicates it is not feasible (53). The decision to progress to a future definitive trial will be made by the Trial Management Group in conjunction with the Trial Steering Committee, based on the criteria in Table 4. It will also be informed by findings from the embedded qualitative study and any potential signal of efficacy due to improvement in range of shoulder motion as a result of anti-TNF injection.

Table 4: Progression criteria

	Green	Amber	Red
Feasibility to recruit: % of potentially eligible patients with frozen shoulder screened across 5	≥33%	≥20% to 32%	<20%

sites in 12 months eligible for recruitment			
Success of consent process: % of eligible participants consented	≥33%	≥20% to 32%	<20%
Intervention delivery: % of participants receive 1st injection as randomised within specified timeframe	≥75%	≥50% to 74%	<50%

7. MONITORING METHODS

7.1. DATA MONITORING

7.1.1. Data Monitoring

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.

7.2. SAFETY REPORTING

7.2.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
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: 1. results in death, 2. is life-threatening,

	3. requires inpatient hospitalisation or prolongation of existing hospitalisation, 4. results in persistent or significant disability/incapacity, or 5. 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.

7.2.2. Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Relationship to intervention	**Attribution (causality)**	**Description**
Unrelated	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

7.2.3 Procedures for recording adverse events

The safety profile of adalimumab is well known, with the most common adverse reactions being mild injection site reactions. The Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (will be used to guide recording Adverse Events including grading of the event. Only clinician assessed AEs, graded 3 and above, occurring during the trial for each participant, from their consent until the 3

month follow up and that are considered related to the IMP will be recorded on the CRF. Participants will be asked by the treating clinician at their 2nd injection visit if they have experienced any AEs as a result of their 1st injection. Similarly, participants will be asked if they have experienced any AEs as a result of their 2nd injection at the 3 month follow up appointment. Based on the information provided by the participant the treating clinician will then make an assessment as to whether it should be recorded as an AE grade 3 or above. The capture of all AEs in the trial CRFs is not deemed necessary due to the period of time for which the IMP has had a marketing authorisation and it's well established safety profile.

The following information will be recorded: adverse event term and grade, date of onset and end date, severity, assessment of relatedness to IMP/injection procedure, other suspect drug or device, action taken and outcome. Follow-up information should be provided as necessary. AEs considered related to the trial medication injection as judged by a medically qualified investigator will be followed either until resolution, or the event is considered stable. It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable. Adverse events occurring as a result of the physiotherapy leaflet issued in the trial will not be recorded as part of the trial. The trial risk assessment identified no safety concerns, as advice and exercises given will be routine exercises that are used in standard care for this population. (16).

7.2.4. Reporting procedure for serious adverse events

SAEs occurring to a participant, from the time of their consent up to 28 days after their last injection of trial treatment, must be reported to the Trial Office. Only SAEs that are related to trial medication (adalimumab/placebo) or the injection of the trial medication are required to be reported to the trial office. The reporting to the trial team of SAEs not related to the IMP/injection is deemed not necessary. Causality (relatedness) must be assessed by a medically qualified doctor.

SAEs must be recorded on the trial specific SAE form electronically via REDCap. The SAE must be reported immediately (within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the SAE) following the Site Study Team becoming aware of the event. Alternatively, a paper SAE form can be completed and must be submitted to the Trial Office via email:

Trial Office contact: aff@kennedy.ox.ac.uk

The Trial Office will review the information on the SAE and raise immediate queries for any key data which is missing. In the event where the reporting site does not provide an assessment of causality the Trial Office will assume that the event is related to the IMP. The SAE form will also be reviewed by a Nominated Person, as per OCTRU SOPs for safety reporting, who will provide an assessment of expectedness in line with the reference safety information for the IMP(s). The SAE form will also be reviewed by the Chief Investigator. In the event where any representative of the Sponsor (CI/Trial team/Nominated Person) disagrees with the assessment of the site PI, a discussion will be encouraged between the two to re-assess the event. If either the PI or the representative of the Sponsor continue to assess the event as related, both assessments will be recorded, and the event will be considered as related. If the event is both related and unexpected this will be reported as a SUSAR by the Trial Office or delegate to the relevant Competent Authorities, UK Ethics, Sponsor and other bodies in which the national and local regulations of participating sites require, as per 7.2.5 below. All related SAEs will be followed till resolved or no further information is expected. SAEs will only be considered closed when signed off by the local PI. For this study, adverse events and serious adverse events are likely to be rare. If they occur, they will be reviewed by the Trial Management Group.

The reference safety information (RSI) will be section 4.8 of the Summary of Product Characteristics (SmPC) for both Adalimumab and placebo. The RSI used will be the current Sponsor and MHRA approved version at the time of the event occurrence. The SmPC to be used as the RSI will be specified in the MHRA applications.

7.2.5. Reporting procedure for Suspected Unexpected Serious Adverse Events

Any SAEs that fulfil the definition of a SUSAR will be reported to the Competent Authority, - the Medicines and Health care products Regulatory Agency (MHRA) (if the SUSAR is related to the IMP/plaecbo), Research Ethics Committee (REC) and sponsor within 7 calendar days of the trial management team in the Trial Office becoming aware of the event if it resulted in death or was life threatening, or 15 calendar days for any other event. Treatment allocation will be unblinded prior to SUSAR reporting.

7.2.6. Development Safety Update Reports

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), and Sponsor.

7.3. Pregnancy

The manufacturer advises women of child-bearing potential to follow adequate contraceptive precautions for 5 months after the last injection. A woman of child bearing potential is defined as a premenopausal female capable of becoming pregnant. The SmPC states that a large number (approx. 1500) of pregnancies exposed to adalimumab in the first trimester does not indicate an increase in the rate of malformation in the newborn, however all females of child bearing potential will be asked if there is a possibility that they could be pregnant as part of the eligibility assessment before being randomised to the study. If there is a possibility they could be pregnant they will be offered a pregnancy test to confirm that they are not pregnant. If they refuse to take a pregnancy test they would be deemed ineligible. If pregnancy does occur in study participants treated with adalimumab – there is a potential for these infants to be at an increased risk of infection as adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Administration of live vaccines (e.g. BCG vaccine) to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

In the occurrence of pregnancy in a trial participant, no further doses of adalimumab are to be given, and the pregnancy must be reported as soon as the trial team are made aware to the Anti Freaze-F Trial team via completion of the Anti-Freaze-F Pregnancy Notification Form which must be emailed to AFF@Kennedy.ox.ac.uk. Alternatively, site can complete the electronic Pregnancy Notification Form via REDCap. The pregnancy must be followed up by the investigator until delivery for congenital abnormality or birth defect, at which point it would fall within the definition of a serious adverse event.

7.3.1 Contraception

The following are considered adequate contraception for the purpose of this trial:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation : oral, intravaginal, transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation : oral, injectable, implantable
- intrauterine device (IUD)

- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner [1]
- sexual abstinence [2]

[1] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[2] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments, in this trial – this is a 120 day period from the last dose of IMP.

7.4. QUALITY ASSURANCE PROCEDURES

This study will be part of the Oxford Clinical Trials Research Unit (OCTRU) trial portfolio, with personnel working according to OCTRU SOPs. The OCTRU SOPs and related quality assurance and control procedures will be used by the trial team 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, principles of GCP, relevant regulations and SOPs.

Quality assurance checks will be carried out by the trial team to ensure that all participants receive the drug treatment to which they are allocated at randomisation. This will be carried out via periodic review of the participating site injection treatment logs by an unblinded member of the trial team. The sites will receive feedback from quality control checks to 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.

7.5. 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 - RGEA – Research Governance, Ethics and Assurance Team) 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) will be approved by the appropriate Health Research Authority Research Ethics Committee (REC). The trial will be given the identification number REC Ref, Integrated Research Application System (IRAS) ID and EudraCT number. The trial will be approved by the UK Competent Authority, the Medicines and Healthcare Regulatory Agency (MHRA), as it is classified as a clinical trial of an investigational medicinal product (CTIMP). The trial will be conducted in compliance with the approved protocol and standard operating procedures (SOPs), the Declaration of Helsinki, the principles of Good Clinical Practice (GCP), the UK Data Protection Act and all other applicable regulatory and governance frameworks including the UK policy framework for health and social care research.

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. Substantial amendments will be agreed by the Trial Management Group (TMG) and Sponsor office (University of Oxford) and submitted for HRA, REC and/or MHRA approval prior to implementation. All substantial amendments will be transparently described in resulting trial reports. Non-substantial amendments to the protocol will be agreed by the TMG and Sponsor office (University of Oxford). The REC will be notified of any non-substantial 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, audio recordings and

transcripts, and any electronic databases holding study data. All paper documents will be stored securely in locked filing cabinets at the Oxford Clinical Trials Research Unit offices and will only be accessible to trial staff and authorised personnel. The trial will comply with OCTRU SOPs and any personal details (e.g., addresses for posting follow-up questionnaires) held by the central trial team in or in an electronic database will be clearly marked as Personal Contact Data so that it will not be included in any extracts used for analysis. All trial data will only be accessed by authorised personnel. The consent form includes consent for these data to be held. If a participant does not wish to receive a summary of the results of the trial (as indicated on the consent form) their contact details will be destroyed when all of their study visits have been completed.

8.4. ACCESS TO DATA

Direct access to source and/or 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 trial registration database within 12 months of the end of the trial. Requests for data (anonymised trial participant level data) will only be provided to external researchers who provide a methodologically sound proposal to the trial team (and who will be required to sign a data sharing access agreement with the Sponsor) and/or in accordance with the NIHR's guidance. 4.6.3 (as defined above). Participant consent for this is included in the informed consent form for the study.

8.5. DISSEMINATION POLICY

The trial will be prospectively registered, prior to ethics approval, on the International Standard Randomised Controlled Trial Number register and a EudraCT number obtained. The trial protocol 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 in an open-access journal, in accordance with funder policy on open-access research. The trial results will be reported following the Consolidated Standards of Reporting Trials guideline (CONSORT, www.consort-statement.org). Shortly after formal publication, we will inform the participants of the trial results in the form of a Trial Newsletter which will be sent to them in the post. The participants will be asked if 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 Trial Office contact

Anti-Freaze-F Trial Manager

Kennedy Institute of Rheumatology, University of Oxford, Roosevelt Drive, Headington, Oxford, OX3 7FY

Email: aff@kennedy.ox.ac.uk

Sponsor contact

Research Governance, Ethics and Assurance Team (RGEA) , University of Oxford, Joint Research Office, 1st floor, Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB

Email: ctrg@admin.ox.ac.uk

9.2. Roles and responsibilities

9.2.1. Protocol contributors

The Anti-Freaze-F study 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 study will be part of the portfolio of the United Kingdom Clinical Research Collaboration (UKCRC) fully registered CTU – Oxford Clinical Trials Research Unit at the University of Oxford.

9.2.2. Sponsor and funder

This research is primarily funded by the National Institute for Health Research – Research for Patient Benefit, with additional funding from 180 Life Sciences via their UK subsidiary Cannbiorex.

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. NHS indemnity operates in respect of the clinical treatment that is provided.

9.2.3. Committees

Trial Management Group

A Trial Management Group (TMG) consisting of the core study team, Chief Investigators and co-applicants will be responsible for the day-to-day running of the study 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.

Combined Trial Oversight Committee

A Combined Trial Oversight Committee consisting of a clinician(s), physiotherapist, trial statistician and participant representative, independent of the TMG and co-applicant team, will be appointed to monitor the trial's progress, provide independent advice and monitor data arising from the trial and recommend whether there are any ethical or safety reasons why the trial should not continue.

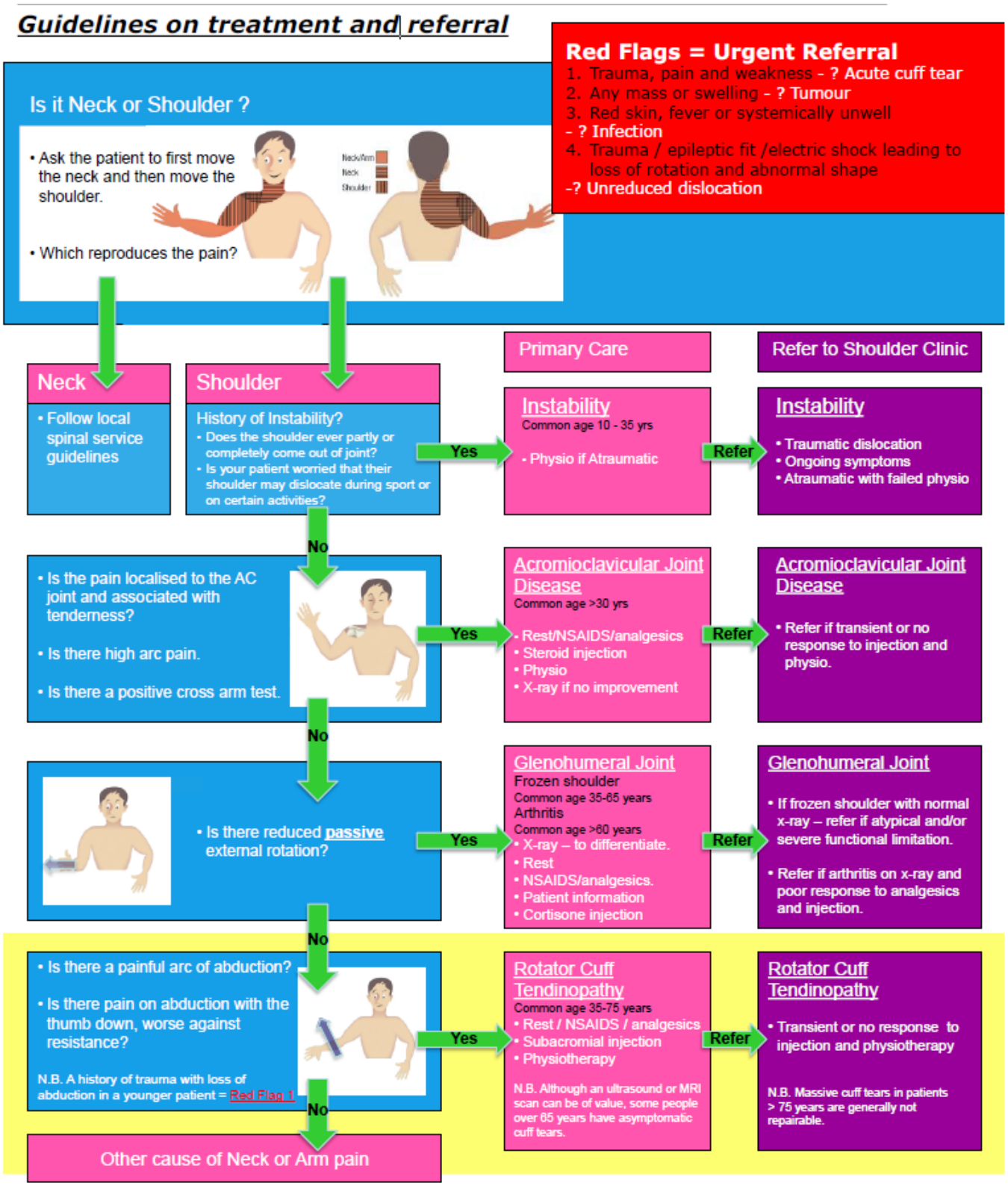
9.2.4. Projected study timelines and milestones

Project months	Tasks
1-5 months	Finalise protocol, regulatory approvals sought and gained, intervention manualisation, initial site set-up
6-17 months	Study recruitment period
9-20 months	3 month follow-up of participants
21-24 months	Analysis and write up of feasibility study

9.2.5 Definition of end of trial

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

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



British Elbow and Shoulder Society, diagnosis of shoulder problems in primary care (35)

10.2. APPENDIX 2: SCHEDULE OF PROCEDURES

Activity	Screening	Visit 1 (injection 1)	Visit 2 (2nd injection)	3 month Follow Up	Qualitative sub-study – optional participation
Diagnosis of pain-predominant frozen shoulder	✓				
Assessment of eligibility for trial	✓				
pregnancy test (if applicable)	✓				
Informed consent	✓				
Blood sample for serological testing for latent TB and Hepatitis B surface antigen		✓			
Completion of questionnaires	✓			✓	
Shoulder range of movement	✓			✓	
Randomisation	✓				
Physiotherapy advice leaflet	✓				
Injection of local anaesthetic		✓	✓		
Injection of adalimumab/placebo under guided ultrasound		✓	✓		
Assessment of AEs (grade 3 or above)	✓	✓	✓	✓	
Qualitative sub-study: telephone interview (optional)					✓✓* within 4 weeks of 1st intervention delivery

10.3: APPENDIX 3: AMENDMENT HISTORY

Amendment no.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
6	V3.0	DDMMMYYYY	Alison Evans	Amended the time frame of inclusion criteria to more accurately reflect the period of pain predominant early stage frozen shoulder of 3 to 9 months. Added the Participant Range of Movement CRF Amended the description of the needle gauge from 18 to 21 Added sentences to reflect the trial presence on social media and its aim of being present on publicly available web-platforms. Added that sites will use SIMS to download completed eConsent Forms for filing. Added that sites can complete an electronic Pregnancy Notification Form via REDCap.

				Added that SAEs should be reported by sites via the electronic form on REDCap and that a paper form is available if necessary and should be emailed to the trial office. **Typographical errors and omissions corrected.**

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

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