The Adhesive Capsulitis Corticosteroid and Dilation (ACCorD) randomized controlled trial

a feasibility study in primary care

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Aims

Is it feasible to conduct a definitive multicentre trial in community settings of corticosteroid injections (CSI) and hydrodilation (HD) compared to CSI for patients with frozen shoulder? An adequately powered definitive randomized controlled trial (RCT) delivered in primary care will inform clinicians and the public whether hydrodilation is a clinically and cost-effective intervention. In this study, prior to a full RCT, we propose a feasibility trial to evaluate recruitment and retention by patient and clinician willingness of randomization; rates of withdrawal, crossover and attrition; and feasibility of outcome data collection from routine primary and secondary care data.

Methods

In the UK, the National Institute for Health and Care Excellence (NICE) advises that prompt early management of frozen shoulder is initiated in primary care settings with analgesia, physiotherapy, and joint injections; most people can be managed without an operation. Currently, there is variation in the type of joint injection: 1) CSI, thought to reduce the inflammation of the capsule reducing pain; and 2) HD, where a small volume of fluid is injected into the shoulder joint along with the steroid, aiming to stretch the capsule of the shoulder to improve pain, but also allowing greater movement. The creation of musculoskeletal hubs nationwide provides infrastructure for the early and effective management of frozen shoulder. This potentially reduces costs to individuals and the wider NHS perhaps negating the need for a secondary care referral.

Results

We will conduct a multicentre RCT comparing CSI and HD in combination with CSI alone. Patients aged 18 years and over with a clinical diagnosis of frozen shoulder will be randomized and blinded to receive either CSI and HD in combination, or CSI alone. Feasibility outcomes include the rate of randomization as a proportion of eligible patients and the ability to use routinely collected data for outcome evaluation. This study has involved patients and the public in the trial design, dissemination methods, and how to include groups who are underserved by research.

Conclusion

We will disseminate findings among musculoskeletal clinicians via the British Orthopaedic Association, the Chartered Society of Physiotherapy, the Royal College of Radiologists, and the Royal College of General Practitioners. To ensure wide reach we will communicate findings through our established network of charities and organizations, in addition to preparing dissemination findings in Bangla and Urdu (commonly spoken languages in northeast London). If a full trial is shown to be feasible, we will seek additional National

Institute for Health and Care Research funding for a definitive RCT. This definitive study will inform NICE guidelines for the management of frozen shoulder.

Take home message

- A Cochrane Review found that insufficient evidence exists to determine whether hydrodilatation (HD) is superior to alternative non-operative treatments in terms of movement, function or pain. These authors recommended further trials for effectiveness of corticosteroid (CSI) injection and corticosteroid injection with hydrodilation (CSI/HD). These conclusions are similar to other reviews.
- We describe our methods for conducting a feasibility randomised controlled trial in primary care evaluating two treatments: CSI alone versus CSI/HD for frozen shoulder.
- If feasible we will conduct a definitive trial.
- This is significant because we will be able to demonstrate if frozen shoulder can be effectively managed in primary care/community settings and potentially reducing the burden on secondary care.

Introduction

Shoulder pain accounts for 3% of all visits to a GP, with frozen shoulder being the most common cause of pain. Prevalence of frozen shoulder is estimated to be 10% of working age adults, having a significant impact on function and the ability to work. The National Institute for Health and Care Excellence (NICE) advocates early treatment of frozen shoulder; however, there is significant variation in treatment offered with many people referred to secondary care. The steady rise in orthopaedic outpatient referrals and the impact of COVID-19 has led to a 20% increase in waiting times for an appointment. The creation of musculoskeletal (MSK) hubs nationwide provides infrastructure for the early and effective management of frozen shoulder in the community. This potentially reduces costs to individuals and the wider NHS, perhaps negating the need for a secondary care referral.

Shoulder problems are a common cause of MSK pain, with 3% of all adults presenting with new symptoms to their GP annually; frozen shoulder is the most common cause of these symptoms.[1-3] The problem involves inflammation, scarring, and contracture of the shoulder capsule, leading to significant pain and disability. The UK prevalence of frozen shoulder is estimated to be between 8% and 10% of working age adults,[4] and the annual incidence is between 2% and 5%.[5]

Individuals presenting with frozen shoulder are typically aged between 50 to 60 years,[6] and often have comorbidities, such as diabetes, thyroid disease, and Dupuytren's contracture. The most common of these is diabetes, associated with a lifetime risk of frozen shoulder of 10% to 20%.[7] The condition often spontaneously resolves over 18 to 24 months, although many people can have residual pain, stiffness, and reduced function lasting several years.[8,9] A minority of patients report ongoing symptoms at four years, with 6% reporting severe symptoms and loss of function.[9,10]

In Scandinavia, the mean healthcare cost per patient presenting with shoulder pain is €326, and the costs associated with sick leave are €4,139 per patient. These costs increased by a third if a referral to secondary care was made.[11] In the UK, NICE advises that prompt early management of frozen shoulder is initiated in primary care settings with analgesia, physiotherapy, and joint injections;[12] most people can be managed without an operation.[13]

Currently, there is variation in the type of joint injection: 1) Surgical treatment is reserved for the minority of people in whom nonoperative procedures have failed to reduce pain or late presentation where the disease process has become established;[14] and 2) it involves manually manipulating and tearing, or surgically dividing, the shoulder capsule under anaesthesia.

Current evidence

A Cochrane Review found that insufficient evidence exists to determine whether hydrodilation (HD) is superior to alternative nonoperative treatments in terms of movement, function, or pain.[15] The authors recommended that further high-quality trials are required to evaluate the effectiveness of HD with saline and corticosteroid injections (CSI) compared with CSI alone.[15] These conclusions are similar to other reviews and a NICE technology assessment,[16–19] which included clinical effectiveness and economic studies.

Despite recommendations for initial assessment and treatment to be based within community settings, a recent trial tested hospital-based therapies.[20] This trial reinforced our understanding that surgical treatments are no more effective than physiotherapy or physiotherapy and CSI injection into the shoulder, and provided no data about alternative nonoperative care pathways which could be delivered in community settings. The study did not evaluate the effectiveness of HD.

Rationale

MSK hubs are multidisciplinary groups of healthcare providers, based in a community setting, with expertize in bone and joint conditions. They routinely provide standardized care for MSK conditions in centralized hubs within Clinical Commissioning Groups (CCG) so that patients can be rapidly assessed and treated by expert teams. This, in turn, reduces the demand on secondary care.

Annual NHS outpatient elective orthopaedic appointments have almost doubled to 120 million since 2005/2006. The steady rise in referrals has led to a 20% increase in waiting times, with 418,000 patients waiting longer than the 18 weeks standard for an appointment in September 2017.[21] These data precede the staggering rise in waiting lists associated with the COVID-19 pandemic.

The diagnosis of frozen shoulder is largely clinical. However, the most effective current treatment is uncertain, which is reflected in the wide variation in clinical practice.[14] Most people with this common condition are identified and could be managed in community settings, with only refractory cases requiring onward referral to secondary care services. Setting up this study in MSK hubs can streamline services for

patients and potentially be a cost saving for the NHS through decreased wait times, improved and faster care, and quicker return to function for individuals living with a frozen shoulder.

Risks and benefits

The risks are pain and soreness at the injection site, infection at injection site, and that the injection may not work to relieve symptoms. The benefits are improvement in shoulder pain, improvement in upper limb movement, and improved function of upper limb.

Treatment justification

CSI and HD are both commonly used standard interventions for frozen shoulder. A survey of the British Elbow and Shoulder Society (BESS) reported members' first-line treatment of frozen shoulder is nonoperative; approximately one half of the responders routinely use HD,[14] and the remainder CSI alone. Furthermore, patients and clinicians have prioritized research into the treatment of frozen shoulder in a recent James Lind Alliance Priority Setting Partnership.[22] Patients reported that they value prompt diagnosis, clear treatment pathways, and written, as well as verbal, explanations of their care.

Infection at injection site

There is a small risk of infection at the injection site.

Mitigation

- Standardized aseptic technique will be used for all injections.
- Participants will be provided with education and informational materials about the signs and symptoms of infection and to monitor their inject site for these signs.
- If participants identify signs of infection, they will be advised to contact their GP.

Pain at injection site

There is a small risk of pain at the injection site.

Mitigation

- Education to patients to take pain medication as they normally would the day of the injection if needed.
- If they experience pain at injection site, to take pain medication as recommendation.

Injection given will not reduce symptoms

There is a small chance that either intervention will not relieve the individual's symptoms such as pain, stiffness, or reduced shoulder range of motion (ROM).

Mitigation

- Education to patients on the outcomes of the interventions, what to expect, and how long it may be till symptoms are relieved.

Study objectives

Definitive trial objective

In people with frozen shoulder managed in community settings, what is the clinical and cost-effectiveness of CSI with HD compared with CSI alone at six months after randomization?

Feasability objectives

1. To assess patients' acceptance of participating in a trial of CSI and HD compared to CSI alone in primary care.
2. Taken together to determine the rates of withdrawal, crossover, and attrition to properly determine the sample size needed to ensure sufficient precision in the planned primary outcome analysis at six months follow-up in a definitive trial.
3. To validate efficient approaches for data collection using routinely collected primary and secondary care data with more traditional case report forms to increase the efficiency of data collection in a larger definitive trial.
4. To observe intercurrent events to facilitate the definition of the estimand for the main trial.

Feasibility endpoints

1. The rate of eligible participants presenting to the MSK hubs per month.
2. The proportion of eligible participants that clinicians are willing to recruit.
3. The proportion of eligible participants that are randomized.
4. Adherence to the study protocol and attrition at six months follow-up.
5. Data completeness using traditional clinical reporting forms and routine data sources.

Other endpoints/assessments (secondary outcomes)

These are the proposed outcome measures for use in a full trial; feasibility of collection will be assessed during the feasibility trial: Upper limb function will be assessed using the Oxford Shoulder Score (OSS);[23] quality of life will be assessed using the EuroQol five-dimension five-level questionnaire (EQ-5D-5L);[24] upper limb ROM; and healthcare and other resource use.

Study population

Inclusion and criteria

The inclusion criteria was adults with frozen shoulder, defined as being aged 18 years and older, having loss of passive external rotation of at least 50% compared with the contralateral side, presence of symptoms for at least four weeks, and plain radiographs demonstrating the absence of glenohumeral osteoarthritis or other pathology.

Patients were excluded if they had recurrent ipsilateral frozen shoulder, presentation following breast cancer or local radiotherapy, known rotator cuff tear as demonstrated on ultrasound, and long-term systemic corticosteroid use, or previous ipsilateral shoulder CSI within 12 months.

Study design

The study is to be designed as a participant-masked, parallel group, multicentre, randomized feasibility study. Three MSK hubs will be recruited from northeast London, UK, and one from Cambridgeshire, UK. Participants will be randomly allocated on a 1:1 ratio to CSI and HD versus CSI alone, stratified by recruiting centre. Allocation will be at the time of the injection and follow-up will be continued for six months. The delivery of the treatment pathways will be piloted within the four MSK hubs.

Participant flow into and through the trial will be recorded, as well as data completeness for the measures of clinical effectiveness and resource use using various means of data collection.

Data collection methods

Baseline data, follow-up, complications, and review of records during and at end of the trial will be directly entered onto the database by the local research team and/or participants.

The initial assessment, study intervention, and first follow-up appointment at six weeks will be face-to-face (and via telephone if mutually convenient). The subsequent assessment at 12 weeks and final assessment at 26 weeks will be performed remotely. We will collect routine GP and hospital data through a linkage with national databases. (Table I)

The patient will be encouraged to complete outcome measures and a self-assessment of ROM immediately prior to the visit with the help of information sheets on how this is performed.

Although outcome data will principally be collected remotely; however, this first appointment (six weeks) will be used to assess the feasibility and accuracy of self-assessment of ROM. Participants will be given the option to receive notifications by SMS or email to access a link to an online interface (REDCap) to complete the patient-reported outcome measures (OSS, EQ-5D-5L) and resource use.

Some participants may prefer not to or be unable to use a fully online system; they will be given the option to complete the questionnaires over the phone or by post. Participants will be invited to send a picture, via email, of their upper limb in forward elevation and external rotation for the research team to estimate their ROM and compare this with the patients' own assessment of this. They will be randomly allocated to conduct the self-assessment just prior or just after the in-person visit.

Study procedures

Recruitment and screening

Participants will be identified from MSK hubs by clinicians, physiotherapists, and first contact practitioners. Patients aged over 18 years, who present with shoulder pain with a duration of at least four weeks, will be evaluated by the treating clinician to confirm possible eligibility. The clinical team will notify the research team of any potentially eligible patients.

Non-identifiable patient details will then be used for screening by the research team. Pre-enrolment eligibility checks, such as age and diagnosis, will be carried out by the research team in collaboration with information from the clinician to ensure that participants are not enrolled in error. Inclusion of the participants in the study will be recorded in the clinical notes by the research associate; a letter of recruitment will be sent to the participant's GP.

Consent

A member of the research team who is appropriately good clinical practice-trained and delegated will provide the individual with a participant information sheet via email or post. Individuals will then be invited to have an informed consent discussion (telephone/remote) with a trained member of the research team to discuss the study and answer any questions they may have.

Individuals will then be given as much time as possible to decide if they would like to take part. Individuals will be encouraged to speak to their friends and family about the study. It will be clearly stated in the participant information sheet that the individual is free to leave the study at any time without giving a reason, and that their medical care will not change.

Recruitment

Prior to any study procedures taking place, individuals will provide written informed consent either in person or remotely through REDCap on the latest approved version of the informed consent sheet. It is a secure data management system and will be used to collect, store, and manage the data of this study.

A copy of the signed informed consent will be emailed or posted to the participant at their preference and downloaded by the research team to be placed into the patient's medical notes.

Randomization

Randomization will only occur when the research team confirms eligibility, and the participant has provided written, informed consent. Participants will be randomized in a 1:1:1:1 ratio, stratified by recruiting centre, to one of the following:

- CSI and HD and patient to self-measure ROM self-measured before six weeks (± three days) visit.
- CSI and HD and patient to self-measure ROM self-measured after six weeks (± three days) visit.
- CSI alone and patient to self-measure ROM self-measured before six weeks (± three days) visit.
- CSI alone and patient to self-measure ROM self-measured after six weeks (± three days) visit.

The allocation will be determined just prior to the time of the injection, using a web-based, distant randomization service administered by the pragmatic clinical trials unit (PCTU) at Queen Mary University of London, UK. Allocation lists using random permuted blocks of sizes four and eight will be prepared by the trial statistician, with the final lists being uploaded to the randomization system by an independent statistician.

The clinician providing the injection will contact a member of the research team once the participant has arrived for their appointment. The research team member, who is appropriately and sufficiently trained and delegated to complete randomization, will randomize the patient and communicate the allocation to the treating clinician.

Blinding

Participants will be blinded to the allocated treatment. It is not possible to blind the practitioners giving the injection; however, the outcome assessor at the six weeks face-to-face follow-up assessment will be blinded. The trial management group and the trial steering committee will not see results broken down by treatment arm during the trial. No formal testing of the blinding will be performed.

Interventions

The interventions have been developed in line with established practice and our patient and public involvement (PPI) team. All participants will undergo a multidisciplinary shoulder assessment and receive a physiotherapy rehabilitation programme encompassing education, manual therapy and a home exercise programme as per routine care. The physiotherapy plan of care will be individualized to the participant and their level of functioning.

Table 1

Study intervention	Baseline (visit 1)	Intervention (visit 2)	6 weeks (visit 3)	12 Weeks (visit 4; remote)	26 weeks (visit 5; remote)
Timeframe	**-0 to ± 1 week**	**±3 to ± 5 days**	**± 1 week**	**±1 week**	**±1 week**
Eligibility assessment	X				
Consent	X				
Radiograph of shoulder		X			
Randomization		X			
Trial treatment delivery (CSI vs CSI + HD)		X			
OSS	X		X	X	X
Range of motion	X		X	X	X
EQ-5D-5L	X		X	X	X
Resource use	X		X	X	X
Participant experience questionnaire					X

CSI, corticosteroid injection; EQ-5D-5L, EuroQol five-dimension five-level questionnaire; HD, hydrodilation; OSS, Oxford Shoulder Score.

Participants will undergo radiological evaluation of the shoulder (anteroposterior and lateral radiographs) and ultrasound of the rotator cuff. If the radiographs reveal significant bone or joint pathology, or ultrasound reveals a full thickness or more than 50% partial thickness cuff tear, abnormal no injection will be undertaken.

The CSI or CSI and HD will be conducted by an appropriately trained sonographer or musculoskeletal radiologist under ultrasound guidance within the MSK hub pathway:

Corticosteroid injection

With the patient in a lateral decubitus position and via a posterior approach, using an aseptic technique a needle will be inserted into the glenohumeral joint under ultrasound guidance. Overall, 3 ml of 1% lignocaine, 3 ml 0.25% bupivacaine, and 80 mg depomedrone will be infiltrated into the joint.

Corticosteroid injection with hydrodilatation

With the patient in a lateral decubitus position and via a posterior approach, using an aseptic technique a needle will be inserted into the glenohumeral joint under ultrasound guidance. A total of 10 ml of 1% lignocaine, 5 ml 0.25% bupivacaine, 80 mg depomedrone, and between 5 ml and 20 ml of sterile normal saline will be injected into the glenohumeral joint under ultrasound guidance visualizing the posterior capsule. The volume of fluid will be used to create capsular distention. Once capsular collapse/decompression occurs, injection of saline ceases. Injection of saline also ceases if the procedure is poorly tolerated. The total volume of injection is recorded. A minimum total of 20 ml of fluid will be used to confirm a hydrodilatation has taken place.

Following the randomized interventions, participants will continue on existing local care pathways that are established for frozen shoulder, which is routinely a course of rehabilitation supervised by a physiotherapist or a self-directed rehabilitation programme. The structure of rehabilitation will be as per local procedures and individualized to the participant's presentation and level of function. Details of the rehabilitation or any additional interventions will be collected using the case reporting forms (CRFs).

In line with the pathway for management of MSK conditions in community care, there is persisting pain or limitation in function, participants will be discussed within the hub multidisciplinary team for consideration of onward referral to secondary care.

Data collection and follow-up procedures

Participants will complete outcome measures at four time points during the study – baseline and at six, 12, and 26 weeks following randomization.

Baseline, intervention, and six-week follow-up visits will be performed face-to-face to allow for accurate assessment of shoulder ROM. Significant treatment effect is anticipated by six weeks and the patients experience of their intervention can be assessed. The additional benefit of a Face-to-face appointment will be to allow for education on desired information required for outcome measures and assessment of ROM using the ROM graphic. Subsequent follow-up at 12 and 26 weeks will be performed remotely by the participants.

Participants will be asked to provide their contact details and preferred method for follow-up – SMS or email. Participants who decline these means of communication will be offered telephone or remote follow-up. Participants who choose SMS and email follow-up will either receive a SMS or email with a secure link to complete the outcome measures online via REDCap at each follow-up time point. Participants who choose telephone or remote follow-up will be contacted by a member of the research team. The ROM will be self-assessed by the participant at the 12- and 26-week follow-up appointments with the help of a ROM assessment graphic, and they will be invited to submit standardized photographs of their ROM to the trial team.

Participants will be sent a SMS or email to let them know they will be receiving a link to complete the outcome measures in the following five days. Participants will then receive a link to complete the outcome measures. Participants

that do not complete the outcome measures will be sent a follow-up reminder SMS or email requesting them to complete the outcome measures. If this does not elicit a response, a member of the research team will telephone the participant to request completion over the phone.

Outcomes

Feasibility

1. The rate of eligible participants presenting to MSK hubs per month.
2. The proportion of eligible participants that clinicians are willing to recruit.
3. The proportion of eligible participants that are randomized.
4. Adherence to the study protocol and attrition at six months.
5. Data completeness using clinical reporting forms and routine data sources.

Effectiveness

We will pilot our data collection systems for the following outcomes that we intend to access in a future definitive trial. The primary end point is at six months, reflecting the time point at which patients have told us they would hope to have experienced alleviation of their symptoms.

Shoulder function

Shoulder function is measured using the OSS at baseline, and at six, 12, and 26 weeks. The OSS is a validated patient self-reported instrument developed with patients, including those with frozen shoulder.[23] It has been used in randomized trials of patients with frozen shoulder and in long-term follow-up studies.[20] The OSS is a 12-item measure with five response categories and a range of scores from 0 (worst) to 48 (best). The minimal clinical important difference between groups is estimated to be approximately four points, representing a moderate change in pain or function. It has been tested against alternative functional scores and generic health related quality of life instruments.[25] The face validity of the instrument has been assessed by our patient representative group who support this measure.

Range of motion

Participants will be provided with written instructions and images of how to complete the motion of forward flexion and external rotation. The individual will move their limb into the desired location for measurement and take a photograph. The photograph will be emailed to the research team which will estimate their ROM. This method will allow for collection of data where follow-ups are conducted remotely and telephone if required. The methods of participants self-reporting ROM on a chart is currently employed for data collection within the PROFHER-2 trial (HTA 16/73/03).[26] This will be validated against their OSS score and, where patients are reviewed in the MSK hub, as part of the routine care with clinician measures of ROM.

Active range of forward flexion and external rotation will be recorded at baseline, and at six, 12, and 26 weeks following randomization. We will explore the feasibility of using patient self-reported charts to self-measure their ROM, as well as using photographs of the participant completing the specific joint ROM which will be estimated by members of the research team.

Health-related quality of life

Health-related quality of life will be measured using the EQ-5D-5L, which consists of a five-dimension health status classification system and a separate visual analogue scale. This patient-reported outcome measure (PROM) has been validated and used for a variety of MSK conditions, including frozen shoulder.[20] Data will be collected at baseline (retrospective recall prior to symptom onset and on-the-day measure prior to treatment), and at six, 12, and 26 weeks.

Complications

All complications related to the index condition and its treatment will be recorded. Complications will be classified as related systemic complications, related local complications, and unrelated to the trial protocol. The number and type of related serious adverse events and reactions up to six months will be recorded.

Resource use

Health resource data will be collected at baseline, and at six, 12, and 26 weeks using GP records, hospital records, and self-administered participant questionnaires. Data will also be collected on social care costs and out of pocket costs. This will include days lost from work, private expenses (including private healthcare), and other day-to-day activities, such as help with personal care.

Participant experience questionnaire

At the visit at four and six months post-injection, participants will complete a questionnaire exploring their experience and perspective of the study and study documents. Examples of what questions would encompass are participant information sheets, consent process and forms, data collection procedures, and outcome measures. There will be an opportunity for free text comments of what worked well and what could be done differently. This information will be used to inform the next phase of the trial if the results of this study are deemed feasible, this will ensure the trial is robust and participant centred.

Data sources

Case reporting forms

Bespoke electronic CRFs will be created to augment completion of each of the study outcomes that are being collected from the routinely collected data sources. The CRFs and data will be stored electronically on REDCap. The PROMs will be collected per patient request. Participants can be sent a link via SMS or email to complete the outcome measures via electronic CRFs which originate from and stored within REDCap.

Alternatively, participants have the option to have a telephone or remote visit with a member of the research team to complete the outcome measures, and telephone interpreters can be used as needed. The member of the research team will input the data directly into REDCap.

Photographs to assess ROM

One week prior to their 12- and 26-week follow-up visits, participants will email a photograph of their upper limb in

specific positions allowing the research team to evaluate their available active ROM. Participants will be provided with written instructions and images of how to position the limb to assess the ROM.

Electronic health GP records

All GP practices within the Tower Hamlets, Newham, Waltham Forest (TNW) CCG publish their entire patient-level electronic healthcare record into the Discovery Data Service. Episodes of care are encoded using SNOMED for each contact between a patient and the GP practice.

For data in the Cambridgeshire CCG, we will extract anonymized data using local Business Intelligence Unit services. Episodes of care are encoded using Systematized Nomenclature of Medicine (SNOMED) for each contact between a patient and the MSK hub.

Electronic health hospital records

A single dataset aggregated from multiple health record flows, principally the Cerner Millennium electronic health record across all hospitals within the Barts Health NHS Trust. Much of the secondary care provided to patients within TNW CCG group is delivered within Barts Health NHS Trust and therefore we expect to capture the great majority of secondary care episodes for the participants. Inpatient and outpatient activity is encoded throughout using OPCS 4[27] and ICD 10.[28] One of the principal flows out the dataset creates the Health Resource Groups (HRGs) & Commissioning Dataset (CDS) required for hospital reimbursement for all activity within the Trust. The advantage of the CDS is that the dictionary and requirement for curation of this dataset is mandated centrally from NHS England and therefore this data source can be generalised for use in a future definitive study. Similar to Barts, Cambridge University Hospitals NHS Trust will provide the majority of secondary care services for the majority of participants recruited in Cambridgeshire.

Participant withdrawal

Participants are free to withdraw at any point in the study without giving a reason, which will be clear in the participant information sheet. Withdrawing from the study will not impact on their healthcare or treatment in any way.

If participants have already had data collected on them during the study period, that data will be kept according to data management processes outlined below. If individuals are willing to share their reason for withdrawal this will be recorded on the withdrawal CRF.

End of study definition

The trial will be ended upon completion of the last follow-up of the last participant. All participants will be followed up to collect data on their status at six months post-randomization; this will be their last contact. If it has not been possible to collect this data eight weeks after the six-month follow-up time point, the participant will be classed as a non-responder. This will be the final episode of the trial. Following this, participants will be treated as per normal standard of care.

The sponsor and main Research Ethics Committee (REC) will be notified in writing within 15 days if the trial has been concluded or terminated early.

Sample size considerations

There is no agreed procedure for estimating appropriate sample sizes in feasibility studies. Agreed recommendations in the literature suggest recruiting 50 to 70 participants.[29,30] Correspondingly, we have selected a convenience sample of 66 participants to determine our feasibility objectives. The 95% confidence interval (CI) for a rate estimated to answer a feasibility objective would be at most ± 12.2% wide with a sample size of 66.

We expect ten people per month to be diagnosed with frozen shoulder in each MSK hub. If 25% of these are ineligible and half of the remaining consent to participate in the study, we expect to be able to recruit two to four participants per month per site and therefore the convenience sample of 66 participants within six months. If these rates were confirmed, we would be able to recruit the required definitive trial sample (anticipated number including attrition = 448) within approximately 14 months from eight hubs, based upon a recruitment rate of four per centre per month and an attrition estimate of 15%.

Statistical analysis

The feasibility objectives are to assess the study parameters of recruitment, crossover, and attrition rates. Each of these will be analyzed using descriptive statistics (point estimates and variances) and associated CIs. A more accurate sample size calculation for the definitive trial based on estimates obtained in this study will be reported to inform the decision on whether the subsequent randomized controlled trial (RCT) is feasible.

PROMs will be collected with the aim of assessing their suitability and completeness to inform the planned definitive RCT. Should the study demonstrate that it is feasible to conduct a full trial, these outcomes will only be presented descriptively by group, and no inferential analyses are planned to explore between group differences.

Agreement between self-measured and clinician-measured ROM at six weeks will be assessed using Bland and Altman's method of estimating 95% limits of agreement and creating Bland Altman plots.[31]

A completely specified estimand for the primary definite trial objective will be defined following assessment of the feasibility study data. Observed intercurrent events will be taken into consideration and potential further intercurrent events not observed will be discussed within the team.

If a trial is not deemed feasible, the primary analysis will investigate differences in OSS between the treatment arms on an intention to treat basis. An exploratory area under the curve analysis of OSS at baseline, and at six, 12, and 26 weeks will also be conducted. Differences will be assessed using mixed model repeated measures analysis adjusted for centre and other relevant covariates as specified in the statistical analysis plan. Estimates of the treatment effect will be presented with 95% CIs; however, it will be clearly stated in any presentation of these estimates that the study was not sufficiently powered for this assessment. An equivalent analysis would be performed for the other outcome measure collected. The number and distribution of complications will be reported descriptively. No formal hypothesis testing of between group differences will be undertaken since the sample will be small and unlikely to be informative for these rare outcomes.

A statistical analysis plan will be written prior to data analysis taking place, and any member of the writing team having access to unblinded data.

Health economic analysis

This feasibility study will provide preparatory work for a subsequent economic analysis to be conducted alongside the definitive RCT. Item completeness for quality-of-life and resource use measures will be reported. The feasibility of acquiring primary and hospital care data directly from the healthcare providers will be piloted, and the estimates of resource use compared with bespoke participant questionnaires. These bespoke questionnaires will also be used to collect further participant data to explore the contribution of time-off-work, personal care and out-of-pocket expenses (including private care) to overall costs.

Resource use will be costed using nationally representative unit costs from NHS reference costs for hospital services,[32] unit costs for health and social care for primary care and community services,[33] and national wage information.

Ethics

Appropriate approvals will be sought by the sponsor, Health Research Agency, and NHS Research Ethics Service. The Medicines and Healthcare products Regulatory Agency (MHRA) confirm that this proposed study is not a clinical trial of an investigational medicinal product, as defined by the EU Directive 2001/20/EC, and no submission to the clinical trials unit at the MHRA is required.

Annual safety reporting

The trial manager will coordinate the delivery of an annual progress report to the REC and sponsor on behalf on the chief investigator (CI) using the HRA template on the anniversary of the REC favourable opinion. The annual safety report will include information around adverse events or reactions, serious adverse reaction or event and suspected serious adverse events (SAEs).

Mitigation plans

Data collection using images

Participants will be invited to provide photographs of their joint ROM.

Mitigation plan

A trial specific instruction will be provided, explaining that participants should wear clothes for the photograph. Participants will be given an opportunity to decline providing images.

Recruitment

Another potential issue is the recruitment participants from underserved populations, for example, those from South Asian communities in the UK; however, this is a priority for the NIHR.[34] This is of particular relevance in this trial; diabetes is more prevalent in the South Asian community, and the incidence of frozen shoulder increases with this chronic illness.

Mitigation plan

Our proposed recruiting sites serve a diverse range of communities and we have worked with our PPI representatives to make this trial as accessible as possible.

Recruitment will be led by clinicians in the MSK hub rather than research associates, this will aid in building trust. Further training on recruitment of patients (in addition to completion of Good Clinical Practice) will be provided and facilitated by DIMASCIO, ARESTI, KASSAM and SEEHRA. The study team recognises that a number of participants may not speak English as their primary language. The study team have incorporated feedback from our PPI group to mitigate any issues this may cause with a focus on actively involving this group.

Study design and follow-up

Follow-up of participants is challenging and expensive within RCTs.

Mitigation plan

The research team will utilize techniques common in long-term cohort studies to ensure minimum loss to follow-up, such as collection of multiple contact addresses and telephone numbers and email addresses. Furthermore, we are planning to minimize the length of CRFs by collecting most data via routine clinical care reducing burden on participants. Finally, using easy and accessible methods of data collection, such as secure link sent via SMS or email to complete outcome measures online, may contribute to improved data completeness. Using these mechanisms, we would expect less than 15% loss to follow-up on the anticipated primary outcome. The use of data linkage between routinely collected primary care data and CRFs will also reduce attrition.

Public involvement

We have worked with two patient co-applicants in the design of this study. LAVERICK, who has lived experience of frozen shoulder and who can provide a personal patient perspective; and BEGUM, who has worked as an advocate for Bangla-speaking females in their local community when accessing healthcare. Our priorities in joint working are to ensure that the study design is acceptable in addition to the inclusion of underserved populations. Our approach of having two co-applicants each with differing perspectives will aid in addressing our priorities. BEGUM has experience of working with local groups through East London Mosque and PPI representation for National Institute for Health and Care Research doctoral research fellowship award committees. Their input will assist us in our recruitment and dissemination strategy. LAVERICK has helped design the specific protocol for both interventions (standardizing the use of ultrasound guided injection as per gold standard) and confirmed that the outcome measures are appropriate and have face validity. Our local PPI group has also been consulted for a wider perspective on the inclusion of underserved populations and their suggestions incorporated into our proposed study design.

Data handling and record keeping

Data management

The data collected from participants will be entered in de-identified form into the trial database. The trial databases will be built by the PCTU data management team based on CRFs and specifications jointly developed by the research team and the PCTU (data management, statisticians, and trial management teams). REDCap will be used for data collection in the trial. Wherever possible, data will be entered directly

into the database by recruitment centre staff or participants. All data entered will be encrypted in transit between the client and server. All study data will be securely stored and managed from the PCTU safe haven located within ISO 27001-certified BCC data centres. Access to the trial database and data will be restricted only to members of the research team based on their role within the trial. The database and data are backed-up to secure locations on a regular basis based on PCTU and Barts Data Safehaven. Data management will be conducted in line with PCTU standard operating procedures (SOPs).

We expect that direct electronic capture of data will not always be possible, so any paper CRFs collected during the trial will be entered into the database by the local or central research team. The procedure for data entry will be documented in the data management plan.

The CRFs will be designed by the trial management team in collaboration with data management, statisticians, and other research staff. Recruitment centres will enter data directly into an electronic CRF (eCRF) on the trial database. At the follow-up points, participants may complete a paper copy of the CRF. If so, this will be returned to the central research team by post or email and will be entered into the eCRF by relevant members of the research team. A deidentified paper copy will then be scanned and stored in the as per the PCTU's SOPs.

The copies of eCRFs will be kept and stored at each recruitment centre in the site file. The CRFs will be kept for the period as required by trust regulations at each particular recruitment centre. Participant contact details will be entered directly into a secure online database with access provided to team members with a demonstrated need to do so.

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 summarized into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, audio and video recordings, correspondence, and routinely collected hospital administrative records.

CRF entries, such as PROMs that are submitted directly to the site or central research team, 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 unique trial identifier, not by name.

Confidentiality

Information related to participants will be kept confidential and managed in accordance with the UK Data Protection Act, NHS Caldecott Principles, the Research Governance Framework for Health and Social Care, and the conditions of REC approval, or corresponding legislation or approvals for a particular participating country or site. The participants' full name, date of birth, hospital number and NHS number will be collected to allow for follow-up.

The personal data recorded on all documents will be regarded as confidential. All participant-related trial documents are confidential and must be stored securely at each hospital (e.g. written consent forms). Where possible, all documents and stored data will be de-identified using the trial ID as the unique identifier. The principal investigator (PI) must ensure the patient's confidentiality is maintained at all times. The sponsor will ensure that all participating partner organizations will maintain the confidentiality of all participant data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of SAEs. Representatives of the trial management team will require access to participants' notes for quality assurance purposes and source data verification, but participants' confidentiality will be respected at all times. In the case of special problems and/or competent authority queries, it is also necessary to have access to the complete trial records, provided that confidentiality is protected.

Record retention and archiving

Data will be collected in electronic format with direct entry or upload onto the trial database, including the collection of documentary evidence of consent or declaration. All data collected will be de-identified after the collection of the baseline demographic data and all participants given a unique trial identifier at the point of randomization. Identifiable participant data will be held on a separate database and coded with the unique trial identifier to tag identifiable data to the outcome data.

Participants' identifiable data will be securely destroyed as per the applicable PCTU and Barts Health NHS Trust policies current at the time of data destruction.

Once the planned analyses have been completed, the research data will be fully de-identified as per PCTU and Barts Health NHS Trust SOPs. The de-identified data will then be archived for 25 years within the Trust Corporate Records Centre in physical form after which they will be destroyed in accordance with Barts Health NHS Trust SOPs at the time of destruction.

Safety reporting

This is a low-risk feasibility trial. All interventions are in common use within the NHS.

Adverse events

An adverse event (AE) is any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE can therefore be any unfavourable or unintended sign, including an abnormal laboratory finding, symptom, or disease temporally associated with study activities.

Notification and reporting of adverse events

If the AE is not defined as serious, the AE will be recorded in the study documents and the participant followed up by the research team. The AE will be documented in the participants' source documents, the complications CRF, and, where appropriate, medical records.

Serious adverse events or reactions

An SAE or reaction is defined as serious if it results in death, is life-threatening, requires hospitalization or prolongation

of existing hospitalization, results in persistent or significant disability or incapacity, consists of a congenital anomaly or birth defect, or is otherwise considered medically significant by the investigator.

Expected SAEs

Both of these treatments are in routine use in the NHS. Some SAEs are therefore anticipated and will be defined as related and expected:

- Pain at injection site.
- Cutaneous infection at injection site.
- Loss of subcutaneous fat at injection site causing at skin dimple.
- Steroid flare (transient significant increase of pain symptoms lasting usually no more than 72 hours).
- Disturbance of menstrual cycle.
- Transient weakness in arm muscles caused by local anaesthetic leaking around nerves and having a temporary numbing effect lasting no more than a couple of hours.
- Significant disturbance in blood sugar level in diabetic patients due to administration of corticosteroid.
- Development of septic arthritis due to the introduction of infection to the shoulder joint following injection.

Notification and reporting of SAEs

SAEs that are considered to be 'related' and 'unexpected' will be reported to the sponsor within 24 hours of learning of the event, and to the REC within 15 days in line with the required timeframe using the SAE CRF.

The treatment code for the participant will be broken when reporting an 'unexpected and related' SAE. The unblinding of individual participants by the CI in the course of a clinical study will only be performed if necessary for the safety of the study participant.

Some SAEs are expected before and during the natural history of frozen shoulder and/or following either of these test treatments. Where these occur after the participant has been enrolled in the study, they do not need to be reported immediately. Expected SAEs should be recorded in the 'complications' CRF. Where possible, data will be collected from the hospital electronic health records to augment the reporting of these adverse events.

Urgent safety measures

The CI will take urgent safety measures if necessary to ensure the safety and protection of the clinical study participant from immediate hazards to their health and safety. The measures will be taken immediately. The approval of the REC prior to implementing urgent safety measures is not required. However, the CI will inform the sponsor and REC (via telephone) of this event immediately.

The CI will inform the REC in writing within three days, in the form of a substantial amendment. The sponsor, Queen Mary University of London, will be sent a copy of the correspondence with regards to this matter.

Annual safety reporting

The CI will send the annual progress report to the REC using the HRA template (the anniversary date is the date on the REC "favourable opinion" letter) and to the sponsor.

Overview of the safety reporting responsibilities

The CI is the medical assessor on behalf on the sponsor and will review all events reported. The CI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

Monitoring and auditing

The sponsor or delegate retains the right to audit any study, study site, or central facility. Any part of the study may be audited by the funders, where applicable.

Quality control procedures will be undertaken during the recruitment and data collection phases of the study to ensure research is conducted, generated, recorded, and reported in compliance with the protocol, GCP and ethics committee. The CI and the trial manager will develop data management and monitoring plans with PCTU quality assurance oversight.

Trial committees

Trial oversight committee

The ACCORD Oversight Committee will act in accordance with the PCTU SOPs. The oversight committee, which includes independent members, provides overall supervision of the trial. Its terms of reference will be drawn up in a charter which will outline its roles and responsibilities. Meetings of the committee will take place at least once a year during the recruitment period.

Trial management

The day-to-day management of the study will be the responsibility of the trial manager. This will be overseen by the Trial Management Group, who will meet monthly to assess progress. It will be the responsibility of the trial manager to undertake training of the research associates at each of the study centres. The trial statistician will be closely involved in setting up data capture systems, design of databases and clinical reporting forms.

Indemnity

The NHS indemnity scheme will apply. It provides cover for the design, management, and conduct of the study.

Dissemination of research findings

We plan a three-strand dissemination strategy: 1) to ensure that patients and the public are informed of the trial results; 2) to engage practitioners and healthcare providers; and 3) to inform national guideline and policy makers. Outputs will include a plain English written summary, podcast, blog and animated video, peer reviewed publications, abstracts at the BOA, the Chartered Society of Physiotherapy, the BESS, and the Royal College of Radiologists. Dissemination of the feasibility outcomes will also be through our established network of local organizations, including Age UK East London, the public advisory group for TNW CCG, and Tower Hamlets public health team.

Social media

Follow L. Di Mascio on X @liviodimascio
Follow T. Hamborg on X @PCTUstats
Follow B. Mihaylova on X @PCTUqmu
Follow J. Kassam on X @BartsBoneJoint

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Data sharing
The datasets generated and analyzed in the current study are not publicly available due to data protection regulations. Access to data is limited to the researchers who have obtained permission for data processing. Further inquiries can be made to the corresponding author.

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Ethical review statement
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