ACCorD

Statistical and Health Economics Analysis Plan (SHEAP)

Version: 1.0
Date: 16/02/2024

Person(s) contributing to the analysis plan	
Name(s) and position(s)	Xavier Griffin (Co-Chief Investigator) Borislava Mihaylova (Professor of Health Economics) Thomas Hamborg (Senior Statistician) Yuk Lam Wong (Trial statistician)
Authorisation	
Position	**Chief or principal investigator**
Name	Xavier Griffin
Signature	Xavier Griffin Digitally signed by Xavier Griffin
Date	Date: 2024.02.19 08:36:59 Z
Position	**Senior health economist**
Name	Borislava Mihaylova
Signature	Borislava Mihaylova Digitally signed by Borislava Mihaylova
Date	Date: 2024.02.16 16:08:21 Z
Position	**Senior trial statistician**
Name	Thomas Hamborg
Signature	Thomas Hamborg Digitally signed by Thomas Hamborg
Date	Date: 2024.02.16 16:02:25 Z
Position	**Independent statistician**
Name	Chris Newby

Tick once reviewed	✓
Date	09/FEB/2024

1. Administrative Information

1.1 Trial registration number:

IRAS number 314582

REC Reference 22/LO/0718

This SHEAP is based on protocol version 3.0 (date 18/Nov/2022)

1.2 SHEAP revision history

Protocol version	Updated SHEAP version no.	Section number changed	List of changes from previous version/protocol	Author of change	Date
V3.0	NA	NA	NA	Yuk Lam Wong	May 11th 2023
V3.0	V0.2	All	All sections	Yuk Lam Wong Thomas Hamborg Borislava Mihaylova	Dec 20th 2023
V3.0	V0.3	1. Administrative Information 3. Outcome measures 5. Analysis methods 6. Other analyses, data summaries, and graphs 8. Appendices	1. Administrative Information - added table of abbreviations 3. Outcome measures - confirmed and expanded definitions of outcomes 5. Analysis methods - specified analysis methods according and adapting to updated definitions of outcomes in section 3 - added model specification in 5.3.1 for	Yuk Lam Wong Thomas Hamborg Borislava Mihaylova Xavier Livio Christopher Newby	Jan 17th 2024

			when full trial is not deemed feasible 6. Other analyses, data summaries, and graphs - added description on estimand framework, safety analyses, graphs, withdrawal and deviation summaries 8. Appendices - added dummy tables		
V3.0 & Substantial Amendment 0s01	V0.4	2. Background and trial design 5. Analysis methods 6. Other analyses, data summaries, and graphs 8. Appendices	2. Background and trial design - updated trial setting according to substantial amendment 001 5. Analysis methods - updated convergence strategies - updated sensitivity analyses on missing items in OSS 6. Other analyses, data summaries, and graphs - inserted description on OSS AUC analyses - updated estimand framework, intercurrent event definitions, and intercurrent event suitable strategies - expanded withdrawal and deviation analyses - added description on sample size calculation for definitive trial 8. Appendices	Yuk Lam Wong Thomas Hamborg	Feb 5th 2024

			- added table for participant experience questionnaire - separated OSS simple summary measures (table 13) from mixed model parameter estimates (table 14) - included MI analyses simple summary measures for OSS (table 13) - added rows for mixed model parameter estimates respectively for EQ-5D-3L and ROM in table 14		
V3.0 & Substantial Amendment 001	V0.5	3. Outcome Measures 5. Analysis Methods 7. References	3. Outcome measures - added new outcome measures for data completeness in section 3.1 - outcome timeframe updated in section 3.2 5. Analysis Methods - added descriptions for new outcomes in 3.1 in section 5.2 7. References - a complete list of references added	Yuk Lam Wong Thomas Hamborg Borislava Mihaylova Xavier Livio	Feb 9th 2024
V3.0 & Substantial Amendment 001	V1.0	All	Accepted all tracked changes		Feb 16th 2024

*If the SHEAP has been published, indicate which version.

1.3 Members of the writing committee

The SHEAP writing committee comprises Yuk Lam Wong (YLW) and Thomas Hamborg (TH). YLW was primarily responsible for writing v1.0 of the Statistical Analysis Plan and TH for overseeing it. Borislava

Mihaylova (BM) added sections on health economic analysis. Xavier Griffin (blinded co-Chief Investigator) and Chris Newby (independent statistician) reviewed the SHEAP and provided feedback prior to sign off.

1.4 Timing of SHEAP revisions in relation to unblinding of data/results

Version 1.0 SHEAP was written before any contributors to the SHEAP had access to any trial data or to any trial results.

1.5 Timing of statistical analysis

The statistical and health economical analysis is conducted once the SHEAP has been signed off and the last participant has completed the last follow-up case report form.

1.6 Analysis software

All analyses and data presentations described in this document will be performed using Stata version 17.0 or higher unless otherwise specified.

1.7 Remit of SHEAP

This SHEAP covers the quantitative analysis of the ACCorD feasibility study. The analysis plan does not provide details on the process evaluation or other qualitative analyses.

1.8 Abbreviations

SHEAP	Statistical and Health Economics Analysis Plan
MSK	Musculoskeletal
CCG	Clinical Commissioning Group
CSI	Corticosteroid Injection
CSI & HD	Corticosteroid injection with hydrodilatation
OSS	Oxford Shoulder Score
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level Instrument
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Instrument
ROM	Range of motion
SD	Standard Deviation
IQR	Interquartile Range
AE	Adverse Event
SAE	Serious Adverse Event
IE	Intercurrent Event
CCA	Complete case analysis
SI	Single imputation
MI	Multiple imputation
CI	Confidence interval
AUC	Area under the curve

2. Background and trial design

Study objectives	To determine the feasibility of an adequately powered definitive trial we will assess: • The rate of eligible participants presenting to the MSK hubs. • The proportion of eligible participants that clinicians are willing to recruit. • The proportion of eligible participants that are randomised. • Adherence to the study protocol and retention at 6 months. • Data completeness using traditional clinical reporting forms and routine data sources. • Data concordance between traditional clinical reporting forms and routine data sources • Estimand for a definitive trial
Study design	Primary research – Multi-centre, individually-randomised controlled feasibility interventional trial
Setting	A total of four Musculoskeletal (MSK) Hubs: Three located within Tower Hamlets, Newham and Waltham Forest (TNW) collaborative of Clinical Commissioning Group (CCG). One in Norfolk (East Coast Community Care C.I.C and James Paget Hospitals NHS Foundation Trust).
Participants	Inclusion Criteria: • Adults with frozen shoulder • Aged 18 years and older • Loss of passive external rotation of at least 50% compared with the contralateral side • Plain radiographs demonstrating the absence of glenohumeral osteoarthritis or other pathology Exclusion Criteria: • Recurrent ipsilateral frozen shoulder • Presentation following breast cancer or local radiotherapy • Known Rotator cuff tear • Long term systemic corticosteroid use or previous ipsilateral shoulder injection within 12 months
Interventions	*Usual care group* Corticosteroid injection (CSI): 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. 3ml of 1% lignocaine, 3ml 0.25% bupivacaine and 80mg depomedrone will be infiltrated into the joint. *Intervention Group* Corticosteroid injection with hydrodilatation (CSI & HD): 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. 10ml of 1% lignocaine, 5ml 0.25% bupivacaine 80mg depomedrone and between 5 and 20ml of sterile normal saline will be injected into the glenohumeral joint under ultrasound guidance visualising 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 20ml of fluid will be used to confirm a hydrodilatation has taken place.
Feasibility outcomes	• The rate of eligible participants presenting to the MSK hubs per month. • The proportion of eligible participants that clinicians are willing to recruit. • The proportion of eligible participants that are randomised. • Participant adherence to study protocol • Retention at 6 months follow-up • Data completeness • Concordance of primary care and hospital care data collected with case report forms against routinely collected linked data

3. Outcome measures

3.1 Feasibility outcomes

The feasibility outcomes measured are:

Recruitment

- The average rate of eligible participants presenting to MSK hubs per month:
    - No. of eligible participants presenting to MSK hubs during recruitment period/ length of recruitment period (in months)
- Proportion of eligible participants clinicians willing to recruit (see appendix 2 for more detail):
    - No. of eligible participants clinicians willing to recruit/ no. of eligible participants presented to MSK hubs
- Proportion of eligible participants that are randomised:
    - No. of eligible participants randomised/ no. of eligible participants presented to clinicians.

Adherences

- Participant adherence to study protocol:
    - No. of participants receiving injections / no. of randomised participants

Retention

- General retention:
    - No. of participants who provided any follow-up data / no. of randomised participants for study visits listed in section 3.2, overall and by treatment groups
- Oxford Shoulder Score (OSS) questionnaire retention:
    - No. of participants who answered any OSS items / no. of randomised participants for study visits listed in section 3.2, overall and by treatment groups

Data completeness

- Proportion of missingness in each outcome at each time point (as specified in section 3.2), overall and by reasons of missingness (where available):
    - No. of participants who provided complete outcome (usable in analysis without imputation)/ no. of randomised participants
- Proportion of randomised participants who returned resource use questionnaire, by study visits, overall and by reason of missingness (where available):
    - No. of randomised participants who returned resource use questionnaire/ no. of randomised participants for study visits listed in section 3.2 where such a questionnaire is due
- Proportion of randomised participants who were successfully linked to administrative primary care records
    - No. of randomised participants successfully linked to administrative primary care records/ no. of randomised participants
- Proportion of randomised participants who were successfully linked to administrative hospital care records
    - No. of randomised participants successfully linked to administrative hospital care records/ no. of randomised participants

Concordance of health care data collected with case report forms against routinely collected linked data

- Proportion of discrepancy in demographic variables (age, gender, ethnicity, smoking history, and alcohol history) between routinely collected linked data and data collected with case report forms
    - No. of participants with inconsistent answers/ no. of randomised participants with available linked data, by demographic variables of interest
- Proportion of participants with reported resource use
    - No. of participants with reported resource use / no. of randomised participants with returned or linked data for resource use categories listed in section 3.2, by study visit
- Rate of resource use per participant
    - No. of resource use items (consultations, medications)/ no. of randomised participants with returned or linked data for resource use categories listed in section 3.2, by study visit

3.2 Clinical and health economics endpoints

These are the proposed outcome measures for use in a full trial; feasibility of collection will also be assessed (see 3.1 and 5.2.1).

These outcomes will be collected according to the following schedule.

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*	*+/- 3 weeks*	*- 3/ +7 weeks*	*-7 weeks to end of follow-up*
Demographic information for concordance analyses: - Age - Gender - Ethnicity - Smoking history - Alcohol history	x				
Oxford Shoulder Score (OSS)	x		x	x	x
Range of Motion (ROM)	x		x	x	x
EQ-5D-5L	x		x	x	x
Resource Use Questionnaire	x		x	x	x
Participant Experience Questionnaire					x
Resource Use categories in concordance analyses: - Shoulder surgery - Consultation with orthopaedics, radiology or other hospital specialist	x		x	x	x

- NHS hospital physiotherapy or occupational therapy - Consultation with GP - Consultation with nurse in primary/community care - NHS community physiotherapy, occupational therapy - Prescribed medication Additional shoulder injection (outside study)					

Upper limb function – Oxford Shoulder Score

Upper limb function will be assessed using the Oxford Shoulder Score (OSS). The OSS is a validated patient self-reported instrument developed with patients, including those with frozen shoulder[1]; it has been used in randomised trials of patients with frozen shoulder and in long-term follow-up studies.[2]

The OSS is a 12-item measure, where each item is scored from 0 (worst/most severe) to 4 (best/fewest symptoms). The 12 items are then summed to give a total score between 0 and 48, where a lower score indicates a higher degree of disability.[1,3] OSS is the proposed primary outcome for the definitive trial.

Health-related quality of Life

Health-related quality of life will be assessed using the EuroQol 5 dimensions instrument (EQ-5D-5L)[4]; a valid measure of health-related quality-of-life, consisting of a five-dimension health status classification system (where the lowest level of severity is coded 1 and the highest 5) and a separate visual analogue scale ranging from 0 to 100, with 100 indicating "the best health you can imagine" and 0 indicating "the worst health you can imagine." VAS score shows the patient's perceived overall health and requires no further derivation.

Overall QoL utility scores will be derived for all contributing study participants' quality of life assessments using the UK National Institute for Health and Care Excellence (NICE) decision support unit EQ-5D scoring algorithm[5]. The estimation algorithm will directly map from individual-specific, EQ-5D-5L, health states to individual-specific, EQ-5D-3L, utility scores, using age and gender as necessary covariates[5]. The Stata command eq5dmap will be used to derive the utility scores. Estimated, individual-specific, EQ-5D-3L utility scores will be used as the outcome during statistical analysis. The overall score of the EQ-5D-3L index ranges from -0.594 to 1.000 (i.e., higher scores correspond to a better quality of life).

Upper limb range of motion: forward flexion

Active range of forward flexion is measured between 0-180 degrees, where higher degrees indicate higher mobility of the joint.

The participant will use self-reported charts to self-measure their active range of forward flexion. Research team will also be asked to estimate the participant's specific range of motion using photographs provided by the participant.

Written instructions and images of how to complete the motion of forward flexion will be provided to the participant. 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 method of participants self-reporting ROM on a chart is currently employed for data collection within the PROFHER-2 Trial (HTA 16/73/03). 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.

Upper limb range of motion: external rotation

Active range of external rotation is measured between 0-90 degrees, where higher degrees indicate higher mobility of the joint.

The ROM is collected and estimated using the same methods described above for forward flexion.

4. Sample size and randomisation

4.1 Sample size calculation

There is no agreed procedure for estimating appropriate sample sizes in feasibility studies. Guidelines suggest recruiting 50-70 participants.[6,7] Correspondingly, we have selected a convenience sample of 66 participants to determine our ACCORD Protocol version 3.0, 18 November 2022 Page 23 of 32 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 n=66.

We expect 10 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 2-4 participants per month per site and therefore the convenience sample of 66 participants within 6 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 8 Hubs, based upon a recruitment rate of 4 per centre per month and an attrition estimate of 15%.

4.2 Randomisation procedure

Randomisation will only occur when the research team confirms eligibility, and the participant has provided written, informed consent.

Participants will be randomised in a 1:1:1:1 ratio, stratified by recruiting centre, to one of the following:

- CSI&HD and patient to self-measure ROM self-measured before 6 week (+/- 3 days) visit
- CSI&HD and patient to self-measure ROM self-measured after 6 week (+/- 3 days) visit
- CSI alone and patient to self-measure ROM self-measured before 6 week (+/- 3 days) visit
- CSI alone and patient to self-measure ROM self-measured after 6 week (+/- 3 days) visit

The allocation will be determined just prior to the time of the injection, using a web-based, distant randomisation service administered by the Pragmatic Clinical Trials Unit, QMUL. Allocation lists using random permuted blocks of sizes 4 and 8 will be prepared by the trial statistician with the final lists being uploaded to the randomisation 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 randomisation will randomise the patient and communicate the allocation to the treating clinician.

4.3 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 6 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.

5. Analysis methods

5.1 Baseline characteristics

Baseline characteristics will be summarised for each treatment group, using mean (SD) and median (IQR) for continuous variables and n (%) for categorical variables.

The baseline variables are:

- Oxford Shoulder Score (OSS)
- Quality of life will be assessed using the Euroquol (EQ-5D-5L)
- Upper limb range of motion (ROM) – forward flexion
- Upper limb range of motion (ROM) – external rotation
- Demographic questions:
    - Age
    - Gender
    - Ethnicity
- Baseline characteristics:
    - Medical history
    - Duration of shoulder pain
    - Smoking and alcohol history

5.2 Analysis of feasibility outcomes

Feasibility outcomes will be summarised using mean (SD) and median (IQR) for continuous variables and n (%) for categorical variables.

5.2.1 Analysis of study logistics parameters

Feasibility Outcomes	**Analysis**	
Recruitment	The average rate of eligible participants presenting to MSK hubs per month	No. of eligible participants presenting to MSK hubs during recruitment period/ length of recruitment period (in months)
	Proportion of eligible participants clinicians are willing to recruit	No. of eligible participants clinicians are willing to recruit/ no. of eligible participants presented to MSK hubs
	Proportion of eligible participants randomised	No. of eligible participants randomised/ no. of eligible participants presented to clinicians
Adherence	Participant adherence to study protocol	No. of participants receiving injections / no. of randomised participants
Retention	General retention	No. of participants who provided any follow-up data / no. of randomised participants for study visits listed in section 3.2, overall and by treatment groups
	OSS questionnaire retention	No. of participants who answered any OSS items / no. of randomised participants for study visits listed in section 3.2, overall and by treatment groups

Data completeness	Proportion of missingness in each outcome at each time point (as specified in section 3.2), overall and by reasons of missingness (where available):	No. of participants who provided complete outcome (usable in analysis without imputation)/ no. of randomised participants
	Proportion of randomised participants who returned resource use questionnaire, by study visits, overall and by reason of missingness (where available):	No. of randomised participants who returned resource use questionnaire/ no. of randomised participants for study visits listed in section 3.2 where such a questionnaire is due
	Proportion of randomised participants who were successfully linked to administrative primary care records	No. of randomised participants successfully linked to administrative primary care records/ no. of randomised participants
	Proportion of randomised participants who were successfully linked to administrative hospital care records	No. of randomised participants successfully linked to administrative hospital care records/ no. of randomised participants
Data concordance	Proportion of discrepancy in demographic variables (age, gender, ethnicity, smoking, and alcohol history)	No. of participants with inconsistent answers/ no. of randomised participants with available linked data, by demographic variables of interest
	Proportion with reported resource use	No. with reported resource use /no. of randomised participants with returned or linked data for resource use categories listed in section 3.2, by study visit
	Rate of reported resource use	No. of reported resource use items (consultations, medications)/ no. of randomised participants with returned or linked data for resource use categories listed in section 3.2, by study visit

5.2.2 Analysis of feasibility of self-measuring ROM

Agreement between self-measured and clinician-measured ROM at 6 weeks (flexion and external rotation respectively) will be assessed using the Bland and Altman's method.

Differences between the two methods of measurements will be plotted against their means. An overall mean difference (or bias) will be marked on the graph.[8] Regression-based estimates of 95% limits of agreement will be plotted on the graph using STATA command blandaltman.

5.3 Analysis of clinical and health economics outcomes

Descriptive statistics will be used to summarise all clinical and health economics outcome measures at each time point in each group.

As this is a feasibility study and the sample size is small, there will be no significance testing, except for circumstances described in 5.3.1, where the definitive trial is deemed infeasible.

Complete case analyses are assumed unless otherwise specified.

For Oxford Shoulder Score (OSS):

- Mean (SD) and median (IQR) will be presented for each group at each time point
- Sensitivity analyses will be conducted on mean (SD) and median (IQR) by presenting and comparing statistics derived using different methods of imputation on individual missing items (see 5.6 for more details)
- Percentage of missing will be presented for each group at each time point

For range of motion (ROM) – forward flexion:

- Mean (SD) and median (IQR) will be presented for each group at each time point
- Percentage of missing will be presented for each group at each time point

For range of motion (ROM) – external rotation:

- Mean (SD) and median (IQR) will be presented for each group at each time point
- Percentage of missing will be presented for each group at each time point

For each domain of health-related quality of life (EQ-5D-5L):

- Proportion of participants at each level
- Percentage of missing will be presented for each group at each time point

For health-related quality of life (EQ-5D-5L) summary index:

- Mean (SD) and median (IQR) will be presented for each group at each time point
- If the score for a domain is missing, then the overall index would be treated as missing
- Percentage of missing will be presented for each group at each time point

For health-related quality of life (EQ-5D-5L) VAS score:

- Mean (SD) and median (IQR) will be presented for each group at each time point
- Percentage of missing will be presented for each group at each time point

For cost of resources used (2023£): healthcare costs, personal care costs, time-off-work costs, out-of-pocket costs

- Mean (SD) and median (IQR) will be presented for each group at each time point

- Percentage of missing will be presented for each group at each time point

5.3.1 Analysis of OSS if full trial is not feasible

If a trial is not deemed feasible the primary analysis will investigate mean differences in OSS between the treatment arms at each follow-up time point on an intention to treat basis.

The analysis will use a mixed-effects repeated measures model with restricted maximum likelihood estimation. Patient level random effects will not be specified. Instead, an unstructured covariance matrix for the residual errors will be used to model correlation within repeated measures.[9] Observations from different participants are assumed independent. Satterthwaite approximation for degrees of freedom will be used to avoid upward bias of type I error due to the relatively small sample size.[10-11] Gender, age, site and baseline OSS will be adjusted for in the model as fixed effects. An interaction effect between post-randomisation time point (as a categorical variable) and baseline OSS will be fitted. An interaction effect between the randomised treatment group and post-randomisation time point will also be fitted to allow for a saturated model for the mean at each time point for each treatment group.[9] Missing baseline OSS scores will be imputed using mean imputation.

ROM and EQ-5D will be analysed using the same mixed-effects model as specified for OSS or an equivalent model appropriate for the outcome type.

Strategy for analysis of clinical outcomes if full trial is not feasible and if the above model fails to converge:

1. Remove interaction effects between visits and baseline OSS
2. Remove fixed effect gender
3. Remove fixed effect age
4. Remove fixed effect Site
5. Remove main fixed effect baseline OSS
6. Forgo mixed-effects repeated measures model and adopt simple between group t-tests at each time point

5.4 Interim analyses

There'll be no interim analysis for the study.

5.5 Subgroup analyses

There'll be no subgroup analysis for the study.

5.6 Sensitivity analyses

Different approaches for individual item missingness in OSS will be compared. Single imputation where missing items for a participant's OSS are substituted by the mean of their provided OSS items will be conducted. Furthermore, multiple imputation will be applied to individual items missing in the 12-item OSS questionnaire, assuming missing at random.

This will be done at each time point respectively for sets of results where there are no more than 2 items missing[2], as well as sets of results where there is at least 1 item completed.

Summary statistics derived will be presented together with summary statistics derived under complete case analyses for comparison (see table 13).

5.7 Information for CONSORT flow diagram

Flow of patients through study will be summarised in a CONSORT diagram, see Appendix 1.

6. Other analyses, data summaries, and graphs

6.1 Exploratory OSS analysis – Area Under Curve Summary Statistics

Inconclusive evidence suggested resolution of frozen shoulder symptoms within 12-24 months regardless of intervention for most patients. However, quicker resolution is preferable. The trajectory of OSS scores over time between treatment groups will therefore be explored using graphical summaries. Difference between groups over the whole follow-up period (rather than at single, fixed time points) will be assessed using area under the curve (AUC) summary statistics based on a linear combination of parameter estimates from the repeated measures mixed model formulated in 5.3.1 (see ref for details on parameter combination). Group specific estimates of AUC are calculated to inform the sample size calculation of the full trial should AUC be chosen as the primary outcome. [12]

6.2 Estimand framework

Inference on the proposed primary outcome for the full trial (OSS score) is complicated by the potential occurrence of inter-current events. Here we describe components of the estimand, inter-current events (IEs) identified *a priori* and strategies which theoretically could be used to handle them[13].

Additional IEs observed will be added in the statistical analysis report. Strategies and implications for handling different IEs will be discussed with the clinical team at the analysis stage and a strategy for each IE will be selected based on suitability and viability.

The primary outcome estimand framework including its relevant sensitivity analysis strategies will be fully specified in the report. Sample size calculation suitable for the primary outcome estimand framework will also be specified in report. Frequencies of IEs (pre-specified + observed) will be tabulated by treatment arms.

Aspect	Definition
Target population:	Participants who fulfil the following inclusion criteria: • Adults with frozen shoulder • Aged 18 years and older • Loss of passive external rotation of at least 50% compared with the contralateral side • Plain radiographs demonstrating the absence of glenohumeral osteoarthritis or other pathology And who do not meet the following exclusion criteria: • Recurrent ipsilateral frozen shoulder • Presentation following breast cancer or local radiotherapy • Known Rotator cuff tear • Long term systemic corticosteroid use or previous ipsilateral shoulder injection within 12 months
Variable/endpoint:	Oxford Shoulder Score (OSS)
Treatment conditions:	*Usual care group* Corticosteroid injection (CSI): 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. 3ml of 1% lignocaine, 3ml 0.25% bupivacaine and 80mg depomedrone will be infiltrated into the joint.

	Intervention Group Corticosteroid injection with hydrodilatation (CSI & HD): 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. 10ml of 1% lignocaine, 5ml 0.25% bupivacaine 80mg depomedrone and between 5 and 20ml of sterile normal saline will be injected into the glenohumeral joint under ultrasound guidance visualising 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 20ml of fluid will be used to confirm a hydrodilatation has taken place.
Population level summary measure	Mean difference in change from baseline between groups
Intercurrent events	**Suitable Strategies**
Unforeseen un-associated shoulder/ arm injury	While on treatment, hypothetical, treatment policy, principal stratum
Unrelated Serious Illness	While on treatment, hypothetical, treatment policy, principal stratum
Death	While alive, composite, principal stratum
Receiving surgery for injury	Treatment policy, while on treatment, composite, hypothetical, principal stratum
Receiving less than 20ml of fluid (CSI+HD arm only)	Treatment policy, hypothetical, principal stratum
Use of any non-study treatment in the follow-up period	Treatment policy, hypothetical, principal stratum
Receiving wrong dose of intervention	Treatment policy, hypothetical, principal stratum
Receiving the wrong intervention	Hypothetical, principal stratum

6.3 Safety analyses

SAE: We will report the total number of serious adverse events (SAEs) related to the ACCorD intervention overall and in each treatment group. We will also report the number of patients with at least one SAE by treatment group at injection visit (visit 2) and at each time point post injection (visit 3, visit 4, and visit 5).

AE: We will report the number of unexpected and expected AEs (complications) in each treatment group. We will also report the number of patients with at least one AE by treatment group at injection visit (visit 2) and at each time point post injection (visit 3, visit 4, and visit 5).

6.4 Graphs

We will create a plot tracking the changes in treatment effect (mean OSS difference) and its 95% CIs throughout study.

We will create a Bland-Altman, regression-based, difference-vs-mean plot assessing the agreement between self-measured and clinician-measured ROM.

6.5 Withdrawal and deviations

Withdrawal: We will report the total number of withdrawals and the reasons for withdrawal overall and by treatment group at each time point. Reasons for withdrawal are specified in table 19 and categorised as follows:

- Withdrawal by PI
- Adverse event related
- Withdrawal by patient
    - Withdrawal by patient for intervention only
    - Withdrawal by patient for the whole study

Protocol deviation: We will report the total number of deviations and the types of deviations overall and by treatment group and site. The types of deviations are specified in table 21 and categorised as follows:

- Data deviation
- Deviation in consent
- Randomisation deviation
- Intervention deviation
- Follow-up deviation
- Others

6.6 Sample Size Calculation for Full Trial

From the observed paired OSS differences in this feasibility trial we obtain SD estimates, which we will use to calculate the sample size needed for a full trial, given power and significance level. The SD estimates will be used conservatively due to upwards bias of SD estimates from small samples.

Based on the final primary estimand specification (6.2) retention and data availability will be estimated and used for the sample size specification.

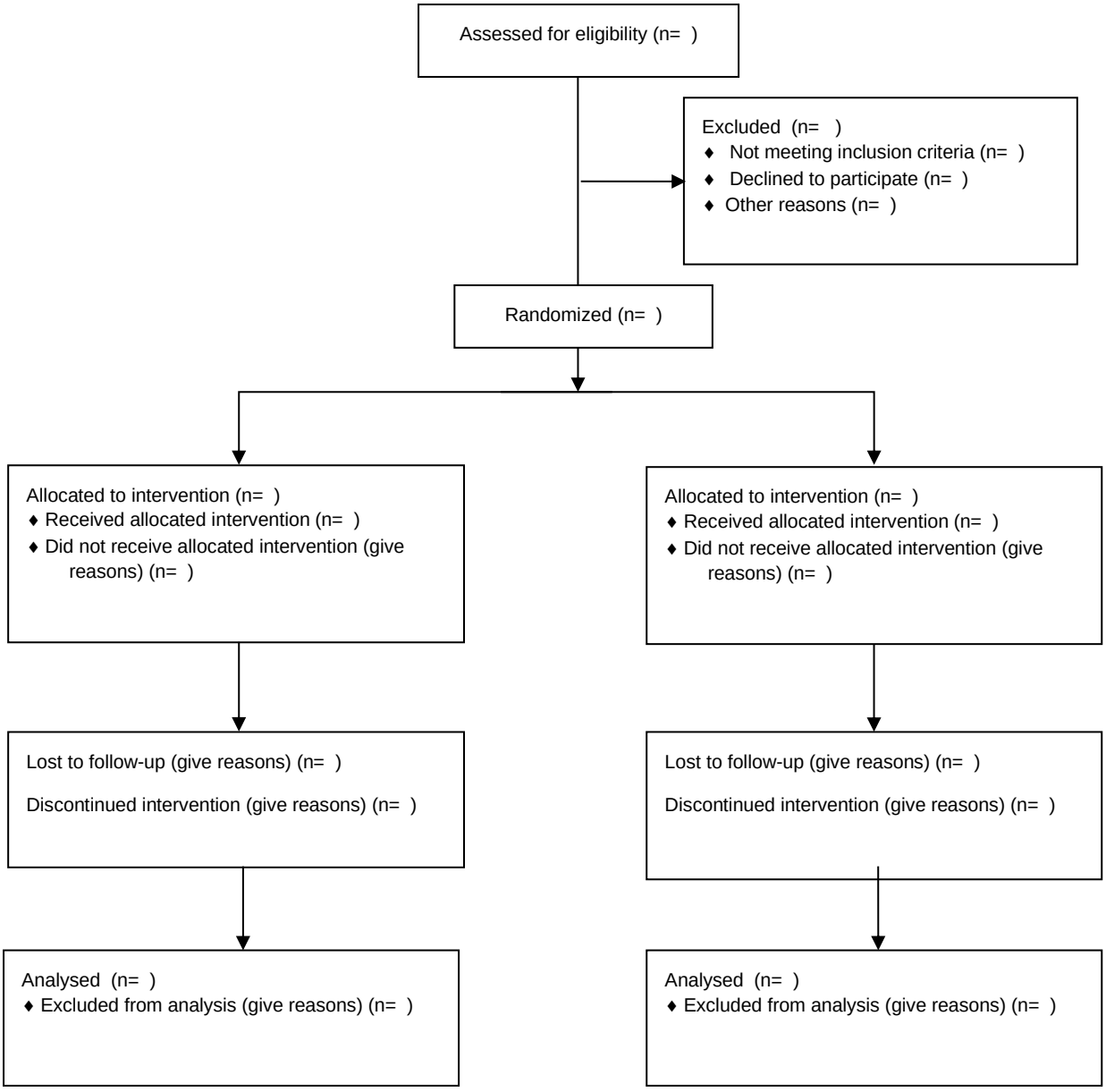
Recruitment rates observed in this feasibility trial would also be used to estimate the length of recruitment period needed for the full trial, given the number of sites and the overall required sample size.

7. References

1. Dawson, J., R. Fitzpatrick, and A. Carr. 'Questionnaire on the Perceptions of Patients about Shoulder Surgery'. The Journal of Bone and Joint Surgery. British Volume 78-B, no. 4 (July 1996): 593–600. https://doi.org/10.1302/0301-620X.78B4.0780593
2. Rangan, Amar, Stephen D Brealey, Ada Keding, Belen Corbacho, Matthew Northgraves, Lucksy Kottam, Lorna Goodchild, et al. "Management of Adults with Primary Frozen Shoulder in Secondary Care (UK FROST): A Multicentre, Pragmatic, Three-Arm, Superiority Randomised Clinical Trial." The Lancet 396, no. 10256 (October 2020): 977–89. https://doi.org/10.1016/S0140-6736(20)31965-6
3. Dawson, Jill, Katherine Rogers, Ray Fitzpatrick, and Andrew Carr. 'The Oxford Shoulder Score Revisited'. Archives of Orthopaedic and Trauma Surgery 129, no. 1 (January 2009): 119–23. https://doi.org/10.1007/s00402-007-0549-7
4. 'EuroQol - a New Facility for the Measurement of Health-Related Quality of Life'. Health Policy 16, no. 3 (December 1990): 199–208. https://doi.org/10.1016/0168-8510(90)90421-9
5. Hernández Alava, Mónica, Steve Pudney, and Allan Wailoo. 'Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study'. PharmacoEconomics 41, no. 2 (February 2023): 199–207. https://doi.org/10.1007/s40273-022-01218-7
6. Teare, M Dawn, Munyaradzi Dimairo, Neil Shephard, Alex Hayman, Amy Whitehead, and Stephen J Walters. 'Sample Size Requirements to Estimate Key Design Parameters from External Pilot Randomised Controlled Trials: A Simulation Study'. Trials 15, no. 1 (December 2014): 264. https://doi.org/10.1186/1745-6215-15-264
7. Sim, Julius, and Martyn Lewis. 'The Size of a Pilot Study for a Clinical Trial Should Be Calculated in Relation to Considerations of Precision and Efficiency'. Journal of Clinical Epidemiology 65, no. 3 (March 2012): 301–8. https://doi.org/10.1016/j.jclinepi.2011.07.011
8. Chatfield, Mark D., Tim J. Cole, Henrica C. W. De Vet, Louise Marquart-Wilson, and Daniel M. Farewell. "Blandaltman: A Command to Create Variants of Bland–Altman Plots." The Stata Journal: Promoting Communications on Statistics and Stata 23, no. 3 (September 2023): 851–74. https://doi.org/10.1177/1536867X231196488
9. Molenberghs, G. "Analyzing Incomplete Longitudinal Clinical Trial Data." Biostatistics 5, no. 3 (July 1, 2004): 445–64. https://doi.org/10.1093/biostatistics/kxh001
10. Giesbrecht, F. G., and J. C. Burns. 'Two-Stage Analysis Based on a Mixed Model: Large-Sample Asymptotic Theory and Small-Sample Simulation Results'. Biometrics 41, no. 2 (June 1985): 477. https://doi.org/10.2307/2530872
11. Siddiqui, Ohidul. "MMRM versus MI in Dealing with Missing Data—A Comparison Based on 25 NDA Data Sets." Journal of Biopharmaceutical Statistics 21, no. 3 (March 28, 2011): 423–36. https://doi.org/10.1080/10543401003777995
12. Bell, Melanie L., Madeleine T. King, and Diane L. Fairclough. "Bias in Area Under the Curve for Longitudinal Clinical Trials With Missing Patient Reported Outcome Data: Summary Measures Versus Summary Statistics." SAGE Open 4, no. 2 (January 1, 2014): 215824401453485. https://doi.org/10.1177/2158244014534858
13. Kahan, Brennan C, Joanna Hindley, Mark Edwards, Suzie Cro, and Tim P Morris. "The Estimands Framework: A Primer on the ICH E9(R1) Addendum." BMJ, January 23, 2024, e076316. https://doi.org/10.1136/bmj-2023-076316

8. Appendices

Appendix 1: Flow-diagram



Appendix 2: Derivation of all outcome measures

1. **Feasibility outcome – recruitment**

   Proportion of eligible participants clinicians willing to recruit:

   - No. of eligible participants clinicians willing to recruit/ no. of eligible participants presented to MSK hubs

   Eligible participants clinicians are willing to recruit may refused to be recruited before randomisation. Therefore, to compute the no. of eligible participants clinicians are willing to recruit, we add the total number of participants clinicians recruited (total number of participants eventually randomised) and the total number of eligible participants who refused to be recruited.

2. **Oxford Shoulder Score (OSS)**

   The OSS is a validated patient self-reported instrument developed with patients, including those with frozen shoulder[1]; it has been used in randomised trials of patients with frozen shoulder and in long-term follow-up studies.[2]

   The OSS is a 12-item measure. Each of the 12 items has 5 potential answers and is scored from 4 (best/fewest symptoms) to 0 (worst/most severe). The total score is the sum of the 12 individual items and therefore ranges from 0 to 48; lower score indicates greater degree of disability.[1,3]

3. **EQ-5D-5L**

   The EQ-5D-5L assesses five dimensions of health (individual health states)[4]: mobility, self-csare, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels of perceived problems, ranging from no problems to extreme problems.

   LEVEL 1: indicating no problem

   LEVEL 2: indicating slight problems

   LEVEL 3: indicating moderate problems

   LEVEL 4: indicating severe problems

   LEVEL 5: indicating unable to/extreme problems

   Overall QoL utility scores will be derived for all contributing study participants' quality of life assessments using the UK National Institute for Health and Care Excellence (NICE) decision support unit EQ-5D scoring algorithm[5]. This estimation algorithm will directly map from individual-specific, EQ-5D-5L, health states to individual-specific, EQ-5D-3L, utility scores, using age and gender as necessary covariates[5] to derive utility scores used as the outcome in analyses. The Stata implementation eq5dmap of this algorithm will be used.

   The overall score of the EQ-5D-3L index ranges from -0.594 to 1.000. A score of -0.594 represents the worst possible health status while a score of 1.000 represents the best possible health status. A score of 0.000 indicates a health status that is considered as bad as being dead (in terms of quality of life). The absolute minimum score of -0.594 indicates that an individual's health status is worse than being dead because an individual of such health status is not only

experiencing significant health problems but is are also experiencing a lower quality of life compared to someone who is deceased. Due to the mapping from 5L to 3L the boundary values cannot be reached and the actual range of possible values is slightly smaller.

The EQ-VAS is a patient-reported measure of perceived overall health. It is a continuous measure that ranges from 0-100, with 100 indicating “the best health imaginable” and 0 indicating “the worst health imaginable.” This score requires no further derivation.

Appendix 3: Dummy tables

Table 1: Baseline demographic and clinical characteristics

	Summary measure	
	Intervention (n=)	**Control (n=)**
Age – mean (SD) median (IQR)		
Gender, n (%)		
Male		
Female		
Prefer to self-describe		
Missing		
Ethnicity, n (%)		
White British		
White Irish		
White Other		
White and Black Caribbean		
White and Black African		
White and Asian		
Other Mixed Background		
Indian		
Bangladeshi		
Pakistani		
Other Asian Background		
Caribbean		
African		
Black Other		
Chinese		
Other		
Prefer Not To Say		
Missing		
Duration of pain – mean (SD) median (IQR)		
Missing		
Smoking history, n (%)		
Yes		
No		
Missing		
Current smoker, n (%)		
Yes		
No		
Missing		
Average number of cigarettes smoked a day, mean (SD) median (IQR)		
Missing		
Former smoker, n (%)		
Yes		
No		
Missing		

Years last smoked, mean (SD) median (IQR)		
Missing		
Does the participant drink, n (%)		
Yes		
No		
Prefer not to say		
Missing		
Units of wine per week, mean (SD) median (IQR)		
Missing		
Units of beer per week, mean (SD) median (IQR)		
Missing		
Units of spirit per week, mean (SD) median (IQR)		
Missing		

Table 2: Feasibility outcome - concordance in baseline variables between CRF-collected and routinely-collected data

	No. of participants with linked data (N=)	**No. of participants with inconsistent linked data (N=)**
Age (%)		
Gender (%)		
Ethnicity (%)		
Duration of pain (%)		
Smoking history (%)		
Current smoker (%)		
Average number of cigarettes smoked a day (%)		
Former smoker (%)		
Years last smoked (%)		
Does the participant drink, n (%)		
Units of wine per week (%)		
Units of beer per week (%)		
Units of spirit per week (%)		

Table 3: Feasibility outcomes – recruitment and adherence

Recruitment by MSK Hub	
Tower Hamlets	
No. eligible (N)	
Length of recruitment period (months)	
Rate of eligible patients being presented to hub (N/months)	
No. eligible clinicians willing to recruit (n/N (%))	
No. randomised (n/N(%))	
Newham	
No. eligible (N)	
Length of recruitment period (months)	
Rate of eligible patients being presented to hub (N/months)	
No. eligible clinicians willing to recruit (n/N (%))	
No. randomised (n/N(%))	
Waltham Forest	
No. eligible (N)	
Length of recruitment period (months)	
Rate of eligible patients being presented to hub (N/months)	
No. eligible clinicians willing to recruit (n/N (%))	
No. randomised (n/N(%))	
Cambridge/Norfolk	
No. eligible (N)	
Length of recruitment period (months)	
Rate of eligible patients being presented to hub (N/months)	
No. eligible clinicians willing to recruit (n/N (%))	
No. randomised (n/N(%))	
Overall	
No. eligible (N)	
Length of recruitment period (months)	
Rate of eligible patients being presented to hub (N/months)	
No. eligible clinicians willing to recruit (n/N (%))	
No. randomised (n/N(%))	
Participant adherence	
No. of participants receiving injection (n/ no. randomised (%))	

Table 4: Feasibility outcomes – retention overall and by treatment groups

	Intervention	Control	Overall
General retention			
At 6 Weeks Visit (n/ no. randomised (%))			
At 12 Weeks Visit (n/ no. randomised (%))			
At 26 Weeks Visit (n/ no. randomised (%))			

Table 5: Baseline health economics outcomes – retrospective EQ-5D-5L, EQ-5D-5L at baseline visit

	Intervention (N=)	Control (N=)
Quality of life (EQ-5D-5L) before frozen shoulder		
Mobility, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Self-care, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Usual activities, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Pain/Discomfort, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Anxiety/Depression, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
EQ-5D-5L VAS, mean (SD) median (IQR)		
Missing		
EQ-5D-5L Index, mean (SD) median (IQR)		
Missing		
Quality of life (EQ-5D-5L) at baseline		
Mobility, n (%)		

1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Self-care, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Usual activities, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Pain/Discomfort, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Anxiety/Depression, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
EQ-5D-5L VAS, mean (SD) median (IQR)		
Missing		
EQ-5D-5L Index, mean (SD) median (IQR)		
Missing		

Table 6: Baseline range of motion measurement

	Intervention (N=)	Control (N=)
Range of motion measurement – researcher		
Method of measurement		
Goniometer (n/N %)		
Photograph Estimation (n/N%)		
Missing (n/N%)		
Frozen shoulder		
Right (n/N %)		
Left (n/N %)		
Missing (n/N %)		
Right shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		
External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		
Left shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		
External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		
Range of motion measurement – participant		
Method of measurement		
Goniometer (n/N %)		
Photograph Estimation (n/N%)		
Missing (n/N%)		
Frozen shoulder		
Right (n/N %)		
Left (n/N %)		
Missing (n/N %)		
Right shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		
External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		
Left shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		

External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		

Table 7: Visit 3 health economics outcomes – EQ-5D-5L

	Intervention (N=)	Control (N=)
Quality of life (EQ-5D-5L)		
Mobility, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Self-care, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Usual activities, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Pain/Discomfort, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Anxiety/Depression, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
EQ-5D-5L VAS, mean (SD) median (IQR)		
Missing		
EQ-5D-5L Index, mean (SD) median (IQR)		
Missing		

Table 8: Visit 3 range of motion measurement

	Intervention (N=)	Control (N=)
Range of motion measurement – researcher		
Method of measurement		
Goniometer (n/N %)		
Photograph Estimation (n/N%)		
Missing (n/N%)		
Frozen shoulder		
Right (n/N %)		
Left (n/N %)		
Missing (n/N %)		
Right shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		
External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		
Left shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		
External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		
Range of motion measurement – participant		
Method of measurement		
Goniometer (n/N %)		
Photograph Estimation (n/N%)		
Missing (n/N%)		
Frozen shoulder		
Right (n/N %)		
Left (n/N %)		
Missing (n/N %)		
Right shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		
External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		
Left shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		

External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		

Table 9: Visit 4 health economics outcomes – EQ-5D-5L

	Intervention (N=)	Control (N=)
Quality of life (EQ-5D-5L)		
Mobility, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Self-care, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Usual activities, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Pain/Discomfort, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Anxiety/Depression, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
EQ-5D-5L VAS, mean (SD) median (IQR)		
Missing		
EQ-5D-5L Index, mean (SD) median (IQR)		
Missing		

Table 10: Visit 4 range of motion measurement

	Intervention (N=)	Control (N=)
Range of motion measurement – researcher		
Method of measurement		
Goniometer (n/N %)		
Photograph Estimation (n/N%)		
Missing (n/N%)		
Frozen shoulder		
Right (n/N %)		
Left (n/N %)		
Missing (n/N %)		
Right shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		
External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		
Left shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		
External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		
Range of motion measurement – participant		
Method of measurement		
Goniometer (n/N %)		
Photograph Estimation (n/N%)		
Missing (n/N%)		
Frozen shoulder		
Right (n/N %)		
Left (n/N %)		
Missing (n/N %)		
Right shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		
External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		
Left shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		

External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		

Table 11: Visit 5 health economics outcomes –EQ-5D-5L

	Intervention (N=)	Control (N=)
Quality of life (EQ-5D-5L)		
Mobility, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Self-care, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Usual activities, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Pain/Discomfort, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
Anxiety/Depression, n (%)		
1 no problems		
2 slight problems		
3 moderate problems		
4 severe problems		
5 extreme problems		
Missing		
EQ-5D-5L VAS, mean (SD) median (IQR)		
Missing		
EQ-5D-5L Index, mean (SD) median (IQR)		
Missing		

Table 12: Visit 5 range of motion measurement

	Intervention (N=)	Control (N=)
Range of motion measurement – researcher		
Method of measurement		
Goniometer (n/N %)		
Photograph Estimation (n/N%)		
Missing (n/N%)		
Frozen shoulder		
Right (n/N %)		
Left (n/N %)		
Missing (n/N %)		
Right shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		
External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		
Left shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		
External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		
Range of motion measurement – participant		
Method of measurement		
Goniometer (n/N %)		
Photograph Estimation (n/N%)		
Missing (n/N%)		
Frozen shoulder		
Right (n/N %)		
Left (n/N %)		
Missing (n/N %)		
Right shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		
External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		
Left shoulder ROM		
Flexion, mean (SD) median (IQR)		
Missing (n/N %)		

External Rotation, mean (SD) median (IQR)		
Missing (n/N %)		

Table 13: Descriptive summary statistics for OSS

	Intervention (N=)				Control (N=)			
OSS	Baseline	V3	V4	V5	Baseline	V3	V4	V5
Complete case analysis (CCA) – n/N (%)								
Mean (SD)								
Median (IQR)								
Missing – n/N (%)								
Participants with no more than 2 items missing – n/N (%)								
Mean (SD) – single imputation (SI)								
Mean (SD) – multiple imputation (MI)								
Median (IQR) – SI								
Median (IQR) – MI								
Missing – n/N (%)								
Participants with at least 1 item completed (retention) – n/N (%)								
Mean (SD) – single imputation (SI)								
Mean (SD) – multiple imputation (MI)								
Median (IQR) – SI								
Median (IQR) – MI								
Missing – n/N (%)								

Table 14 Adjusted treatment effects on OSS, EQ-5D-3L summary index, and ROM at post-randomisation time points if full trial is deemed infeasible.

	V3 (N=)	V4 (N=)	V5 (N=)
OSS			
Treatment - n/N (%)			
Control – n/N(%)			
Adjusted difference in mean OSS between treatment groups* - 95% confidence interval (CI)			
p-value			
EQ-5D-3L Summary Index			
Treatment - n/N (%)			
Control – n/N (%)			
Adjusted difference in mean EQ-5D-3L summary index between treatment groups* - 95% confidence interval (CI)			
p-value			
ROM			
Treatment - n/N (%)			
Control – n/N (%)			
Adjusted difference in mean ROM between treatment groups* - 95% confidence interval (CI)			
p-value			

*Direction of difference: treatment group mean – control group mean. Difference is adjusted for fixed effects (site, age, gender, baseline OSS) and interaction effects between baseline measurements and visits.

Table 15: Total number of AEs by treatment groups and overall

	Intervention (N=)	Control (N=)	Overall (N=)
Overall			
Complications/Expected AE			
Pain at injection site			
Cutaneous infection at injection site			
Loss of subcutaneous fat at injection site causing a 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			
Unexpected AE			

Table 16: Number and proportion of patients with at least 1 AE overall and in each treatment group by study visits

	Intervention (N=)	Control (N=)	Overall (N=)
Overall			
Injection visit			
V3			
V4			
V5			

Table 17: Total number of SAEs by treatment groups and overall

	Intervention (N=)	Control (N=)	Overall (N=)
Overall			
Death			
Life-threatening			
Requires in patient hospitalisation or prolongation of hospitalisation			
Results in significant disability or incapacity			
Congenital anomaly or birth defect			
Requires intervention to prevent permanent impairment			
Deemed by the PI to be medically significant			
Other important medical event			

Table 18: Number and proportion of patients with at least 1 SAE overall and in each treatment group by study visits

	Intervention (N=)	Control (N=)	Overall (N=)
Overall			
Injection visit			
V3			
V4			
V5			

Table 19: Reasons for withdrawal overall and by treatment group

	Intervention (N=)	Control (N=)	Overall (N=)
Overall			
Withdrawal by PI			
Adverse event related			
Withdrawal by patient			
Withdrawal by patient for intervention only (data will be collected up to date of withdrawal)			
Withdrawal by patient for whole study			

Table 20: Number and proportion of withdrawals overall and by treatment group at each time point

	Intervention (N=)	Control (N=)	Overall (N=)
Overall			
V1/Baseline			
V2/ Injection Visit			
V3			
V4			
V5			

Table 21: Number and types of deviations overall and by site

	Tower Hamlets	Newham	Waltham Forest	Cambridgeshire and Peterborough	Overall
Overall					
Data deviation					
Deviation in consent					
Randomisation deviation					
Intervention deviation					
Follow-up deviation					
Others					

Table 22: Number and types of deviations overall and by treatment groups

	Intervention	Control	Overall
Overall			
Data deviation			
Deviation in consent			
Randomisation deviation			
Intervention deviation			
Follow-up deviation			
Others			

Table 23: Participant experience questionnaire overall and by treatment groups

	Intervention (N=) – n/N (%)	Control (N=) – n/N (%)	Overall (N=) – n/N (%)
Participation Questionnaire			
The participant information sheet was easy to understand			
Strongly Agree			

Agree			
Neutral			
Disagree			
Strongly Disagree			
Missing			
Education information/booklet about managing frozen shoulder was easy to understand			
Strongly Agree			
Agree			
Neutral			
Disagree			
Strongly Disagree			
Missing			
Education about managing frozen shoulder was helpful in my recovery			
Strongly Agree			
Agree			
Neutral			
Disagree			
Strongly Disagree			
Missing			
The process of speaking with the research team about the study before I joined was helpful			
Strongly Agree			
Agree			
Neutral			
Disagree			
Strongly Disagree			
Missing			
The consent process was easy to understand and complete			
Strongly Agree			
Agree			
Neutral			
Disagree			
Strongly Disagree			
Missing			
I enjoyed participating in the study			
Strongly Agree			
Agree			
Neutral			
Disagree			

Strongly Disagree			
Missing			
I would participate in another research study in the future			
Strongly Agree			
Agree			
Neutral			
Disagree			
Strongly Disagree			
Missing			
Experience on attending study visits			
Visit1 - Baseline			
Face-to-face			
Phone			
Remote			
SMS			
Email			
Missing			
Visit3 - 6-Week Follow-up			
Face-to-face			
Phone			
Remote			
SMS			
Email			
Missing			
Visit4 - 12-Week Follow-up			
Face-to-face			
Phone			
Remote			
SMS			
Email			
Missing			
Visit5 - 6-Month Follow-up			
Face-to-face			
Phone			
Remote			
SMS			
Email			
Missing			
Order of preference for follow-up session (1= most preferable, 4=least preferable)			
Face-to-face			
1			
2			
3			

4			
Phone			
1			
2			
3			
4			
Remote			
1			
2			
3			
4			
SMS/Email			
1			
2			
3			
4			
Missing			
Outcome measures			
The questions on the measure about how you use your shoulder/arm for everyday activities were relevant			
Strongly Agree			
Agree			
Neutral			
Disagree			
Strongly Disagree			
Missing			
The activities asked about on the measure about how you use your shoulder/arm for everyday activities were important to me			
Strongly Agree			
Agree			
Neutral			
Disagree			
Strongly Disagree			
Missing			
The questionnaire about how I use my shoulder/arm for everyday activities was easy to complete			
Strongly Agree			
Agree			
Neutral			
Disagree			
Strongly Disagree			

Missing			
The questions about my quality of life (if I have problems doing things) were relevant			
Strongly Agree			
Agree			
Neutral			
Disagree			
Strongly Disagree			
Missing			
The activities asked about on the measure my quality of life (If you have problems doing things) were important to me			
Strongly Agree			
Agree			
Neutral			
Disagree			
Strongly Disagree			
Missing			
The questionnaire about my quality of life (if you have problems doing things) shoulder for everyday activities was easy to complete			
Strongly Agree			
Agree			
Neutral			
Disagree			
Strongly Disagree			
Missing			