Title:

Management of adults with primary frozen shoulder in secondary care (UK FROST): a multicentre, pragmatic, parallel group, three-arm, superiority, randomised clinical trial

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Summary

Background: Manipulation under anaesthesia (MUA) or arthroscopic capsular release (ACR), are costly and invasive treatments for frozen shoulders but their effectiveness remains uncertain. We compared these two surgical interventions with early structured physiotherapy plus steroid injection (ESP).

Methods: A pragmatic, non-blinded, parallel group, three-arm trial in 35 hospitals across the United Kingdom. Participants were adults with unilateral frozen shoulder, characterised by restriction of passive external rotation in the affected shoulder to less than 50% of the opposite shoulder. Participants were randomly assigned to MUA:ACR:ESP in the ratio of 2:2:1. The primary outcome was the Oxford Shoulder Score (OSS) at 12 months post-randomisation, analysed by intention-to-treat. We sought a target difference of five OSS points between ESP and MUA or ACR, or four points between MUA and ACR. The trial registration is ISRCTN48804508.

Findings: Between April 2015 and December 2017, we randomly assigned 503 participants to treatment groups (99 to ESP; 201 to MUA; 203 to ACR). Follow-up was completed in January 2019. At 12 months, OSS data were available for 93 participants assigned to ESP (mean estimate 37·2); 189 to MUA (38·3); and 191 to ACR (40·3). Mean group differences at 12 months were 2·01 points between participants randomised to ACR and MUA (95% confidence interval (CI) 0·10 to 3·91), 3·06 points between ACR and ESP (95% CI 0·71 to 5·41), and 1·05 points between MUA and ESP (95% CI -1·28 to 3·39). Eight serious adverse events were reported with ACR and two with MUA. At a £20,000 per Quality-Adjusted Life Year willingness-to-pay threshold, MUA had the highest probability of being cost-effective (0·8632) then ESP (0·1366) and ACR (0·0002).

Interpretation:
All of the mean differences on the assessment of shoulder pain and function (OSS) at the primary endpoint of 12 months were less than the target differences. Therefore, none of the three interventions were clinically superior. ACR carried higher risks. MUA was the cost-effective option.

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Keywords: Frozen shoulder; Adhesive capsulitis; Physiotherapy; Intra-articular injection; Manipulation under anaesthesia; Arthroscopic capsular release; Randomised controlled trial

Research in Context:

Evidence Before this study:

Frozen shoulder is a common and painful condition where movements in the shoulder become restricted. Whilst it is often a self-limiting condition, there may be slow and incomplete resolution during which people may struggle with basic daily activities, work and have disturbed sleep from the pain. Generally, conservative treatments are provided in a primary care setting in the UK. More invasive, surgical treatments, such as MUA or arthroscopic capsular release (ACR), are used in hospital.

In 2012, we published a NIHR HTA programme funded systematic review of 28 randomised controlled trials (RCT), one quasi-experimental study, and two case series. Nineteen databases and sources including CINAHL, Science Citation Index, BIOSIS Previews and DARE were searched up to March 2010 and EMBASE and MEDLINE up to January 2011, without any language restrictions. The review concluded that there was limited evidence on the clinical and cost-effectiveness of different treatment options in the management of a primary frozen shoulder, including intensive or invasive interventions. The need for high quality primary research was recommended.

The findings of our national survey of 303 health care professionals in the UK (conducted in 2010) determined that Physiotherapy, MUA and ACR were the more frequently used interventions in a secondary care setting that needed comparing within an RCT. Only 6% of respondents at the time suggested Hydrodilatation as a comparator for an RCT. Early Structured Physiotherapy (ESP) was a multi-component secondary care physiotherapy intervention including steroid injection that we developed using recommendations from national guidelines and a Delphi study of shoulder specialist physiotherapists. We then

conducted a randomised, pragmatic, non-blinded, parallel, three-arm, superiority trial called UK FROST to determine the clinical (pain and function) and cost-effectiveness of ESP compared with MUA; ESP compared with ACR; and MUA compared with ACR.

Added value of this study:

To our knowledge, UK FROST is the largest randomised trial including 503 participants that compared ESP, MUA and ACR. Surgical interventions (MUA or ACR) did not have better clinically important outcomes for shoulder pain and function compared with ESP at 12 months. ACR carried higher risks. ESP was a low-cost option which could be accessed quicker but was not clinically superior. The health economic comparison found MUA to be the most cost-effective intervention within the UK healthcare setting. Our embedded qualitative study identified early medical help and quicker access to NHS care pathways was important to patients.

A focused update of the 2012 systematic review using searches until December 2018 assembled the current evidence of RCTs for the effectiveness of interventions evaluated in UK FROST. Hydrodilatation was included because of evidence of its increasing popularity in spite of a paucity of evidence. Nine trials (including UK FROST) were included with the number of participants in other trials ranging from 26 to 136. The quality of the included trials was variable and considerable heterogeneity of the interventions made it difficult to combine studies or draw conclusions. Only two trials were pooled in a meta-analysis, UK FROST and another trial, which compared long term functioning between ACR and physiotherapy plus steroid injection. The pooled effect favoured ACR (SMD 0.32, 95% CI 0.08, 0.56), but was smaller in magnitude than the clinical threshold of the standard effect size used in UK FROST. Evidence of Hydrodilatation's effectiveness from four trials was inconclusive.

Implications of all the available evidence:

UK FROST provides robust evidence confirming that none of the three trial treatments were superior on patient-reported outcomes for shoulder pain and function at 12 months. There could be, however, a potentially marginal clinically important benefit in the wider population in favour of ACR compared with ESP. Our specifically designed ESP pathway with

a steroid injection was accessed quicker than the other treatment options and is lower in cost; therefore, its potential for implementation into clinical practice to the same standards as in the trial should be carefully considered. Importantly MUA was the most cost-effective option. This was because the modest additional cost for an MUA to maximise patients' health-related quality of life would be considered good value for money to the UK NHS at the NICE threshold of willingness-to-pay. MUA is an existing pathway in the NHS and requires limited use of theatre time compared with ACR. ACR also carries higher risks and costs compared with MUA and ESP but fewer participants allocated to this group required further treatment for their frozen shoulder. The evidence suggests ACR should be used more selectively, when less costly and less invasive interventions fail. These treatment options should be discussed between patients and clinicians in shared decision-making. Further evaluation is recommended to address the increasing popularity of Hydrodilatation owing to the paucity of high quality evidence.

Introduction

Frozen shoulder, also known as adhesive capsulitis, is a painful condition that most commonly affects people in the sixth decade of life.[1 2] The capsule of the shoulder joint becomes inflamed, then scarred and contracted causing pain, stiffness and loss of function.[3] People with frozen shoulder may struggle with basic daily activities and have sleep disturbance due to shoulder pain.[4] The cumulative incidence of frozen shoulder is estimated at 2·4 per 1000 population per year,[1] affecting 8·2% of men and 10·1% of women of working age.[2] The exact cause remains unknown, which is why it is often labelled 'idiopathic' or 'primary' frozen shoulder. Recognised associations include diabetes mellitus, cardiovascular disease, trauma, stroke, neuro-surgery and thyroid disease. Association with diabetes mellitus is considered to make it more resistant to treatment.[5]

Diagnosis of frozen shoulder is based on clinical features of insidious onset deep seated pain in the shoulder and upper arm with increasing stiffness and clinical findings of limited active and passive external rotation in the absence of crepitus.[6] X-rays are not routinely required,[7] but may be performed to exclude shoulder arthritis or posterior dislocation that could present with similar clinical signs.

Frozen shoulder can spontaneously resolve, but recovery may be slow or incomplete. Around 40% of patients report persistent symptoms even after four years from onset.[8] Primarily, the severity of pain and disability arising from restriction of movement drives patients to seek treatment.[4] A range of treatment options with increasing degrees of invasiveness are available, but there is uncertainty about when these should be offered, and their clinical or cost-effectiveness.[9] A survey of specialist health professionals that we conducted in the United Kingdom (UK) identified three interventions as being most commonly used: Physiotherapy; Manipulation Under Anaesthesia (MUA); and Arthroscopic Capsular Release (ACR).[10] The UK national physiotherapy guidelines for frozen shoulder, based on a systematic review, recommends exercise and manual therapy either in isolation; or to supplement intra-articular injection of glucocorticoid (steroid), MUA or ACR.[11] We further developed and standardised the non-surgical care pathway for this trial to include intra-articular steroid injection followed by structured physiotherapy using the best available evidence and consensus from expert shoulder physiotherapists. We called this 'Early' Structured Physiotherapy (ESP) as it is more quickly accessible within secondary care than the surgical interventions.[12] It is not known whether ESP, or either of the surgical interventions (MUA or ACR) followed by physiotherapy is more effective.[13] Systematic reviews have identified large gaps in evidence and a need for high quality primary research.[13 14] With the intention of facilitating quicker recovery, MUA and ACR are increasingly used in spite of lack of good evidence.[13 15]

We designed the UK Frozen Shoulder Trial (UK FROST) to assess the effectiveness and cost-effectiveness of three care pathways to treat adults with a frozen shoulder: two commonly used surgical interventions within the UK National Health Service (NHS) hospitals (MUA and ACR); and our specifically designed non-surgical ESP pathway.

Methods

Study design

Our detailed study protocol has been published.[16] We conducted a multicentre, randomised, pragmatic, superiority trial comparing three parallel groups (ESP versus MUA

versus ACR) for patients referred to secondary care for treatment of primary frozen shoulder. The trial recruited from 35 hospital sites in the UK; 90 surgeons and 285 physiotherapists, who were experienced in using these treatments, delivered the trial interventions. Two additional hospitals screened patients but did not recruit to the trial.

Ethics approval was obtained on 18 November 2014 from the National Research Ethics Service (NRES Committee North East – Newcastle & North Tyneside 2; Research Ethics Committee Reference 14/NE/1176). Local site-specific NHS research and development approvals were obtained from each participating site. The study was adopted to the UK Clinical Research Network portfolio (17719).

Participants

Patients referred to participating NHS hospitals were eligible if they were 18 years or older and presented with a clinical diagnosis of unilateral frozen shoulder characterised by restriction of passive external rotation (50% or more) in the affected shoulder[17] for which there is evidence of good inter-rater agreement.[18] Plain radiographs (antero-posterior and axillary view) of the affected shoulder were obtained to exclude other pathology. Detailed exclusion criteria are in the protocol, which included bilateral concurrent frozen shoulders; secondary causes (other than diabetes); and if any of the trial treatments were contraindicated. Patients with diabetes were included, as this is significantly associated with impaired shoulder mobility in this patient population.[19] Informed consent was obtained from all trial participants by suitably qualified local study personnel at each participating site.

Randomisation and masking

Surgeons or physiotherapists confirmed eligibility. Following collection of baseline data for eligible and consenting patients, the research nurse accessed a secure remote randomisation service via telephone or internet provided by a registered clinical trials unit at the University of York. Individual participants were randomly assigned with unequal allocation (2:2:1) to ACR, MUA, or ESP to allow for different sought effect sizes between groups. Allocation was based on a computer generated randomisation algorithm that used random block sizes of 10 and 15 and stratified by presence of diabetes. Registering

participants before remote computer-generated randomisation with randomly varying block sizes ensured concealment.

Blinding of participants and clinicians to treatment allocation was not possible or desirable in this pragmatic trial. Therefore, participants and clinicians were informed about treatment allocation immediately after randomisation. All three groups comprised a programme of physiotherapy.

Interventions

Participants underwent standardised physiotherapy programmes in all three arms of the trial. ESP and post-procedural (following MUA and ACR) physiotherapy programmes were standardised using evidence from a systematic review,[13] UK guidelines, previous surveys of UK Physiotherapists and Delphi consensus methodology.[20] The full, standard course of ESP and post-procedural physiotherapy was 12 sessions over up to 12 weeks. If the physiotherapist and participant were satisfied with their progress, not all 12 sessions were necessary; but otherwise, participants were encouraged to attend the full, standard course. In the ESP intervention, the intra-articular steroid (glucocorticoid) injection before starting physiotherapy was administered with or without imaging guidance depending on usual practice of the hospital site, as current evidence did not support superiority of either approach.[21] Full details about the ESP and post-procedural physiotherapy programmes are detailed elsewhere.[12 16]

MUA and ACR were performed as day case surgical procedures. With MUA, the surgeon manipulated the affected shoulder in a controlled fashion to stretch and tear the tight capsule when the participant was under general anaesthesia; and that was supplemented by an intra-articular steroid injection. If the MUA was judged to be incomplete, the surgeon did not cross-over intra-operatively to do ACR in order to allow assessment of outcome of the MUA. ACR was performed under general anaesthesia by a surgeon to surgically divide the contracted anterior capsule in the rotator interval; and was supplemented with MUA to complete and confirm optimal capsular release. Additional procedures like posterior capsular release were permitted at the discretion of the operating surgeon and were recorded. Both MUA and ACR were followed by post-procedural physiotherapy. All

participants were provided with instructions on a graduated home exercise programme progressing from gentle pendular exercises to firm stretching exercises according to stage of frozen shoulder, as is accepted good practice.[11 20]

All interventions were delivered by participating surgeons who were familiar with the surgical procedures and by qualified physiotherapists (i.e. not students or assistants). There was no minimum number of surgical procedures that the surgeon had to have performed and no grades of surgeon were excluded. No additional training was required for either programme of physiotherapy.

Outcomes

The primary outcome was the Oxford Shoulder Score (OSS), a 12-item patient-reported outcome measure of shoulder pain and function with five response categories and an overall scale ranging from 0 (worst) to 48 (best).[22] The primary end-point was 12 months after randomisation.

Secondary patient-reported outcome measures were QuickDASH (Disabilities of the Arm, Shoulder and Hand)[23] as a further region-specific measure of response to treatment;[24] health related-quality of life using the EQ-5D-5L (5 Level version);[25] NRS (Numeric Rating Scale) for pain;[26] and perceived extent of recovery measured by a single VAS (Visual Analogue Scale) ranging from 0 to 100 (0 – no need / 100 - definite need to seek further treatment). The VAS about treatment recovery was purposefully designed for the study with input from patients and clinicians. All outcome measures were collected at baseline, three, six and 12 months after randomisation. In addition, OSS was collected at start of treatment and six months post treatment. Any complications and adverse events were recorded. Following completion of the allocated intervention, any further treatments for the frozen shoulder were recorded.

A full description of the sample size calculation and statistical analysis plan is in the published protocol.[16] The sample size was based on the primary outcome measure (OSS) at 12 months after randomisation and was calculated using a minimum clinically important difference of five points when comparing ESP with either surgical treatment; or a difference

of four points when comparing the two surgical treatments. The larger difference when comparing ESP with a surgical treatment was required to justify the greater costs and potential risks associated with surgery.[22] To observe the above differences with 90% power and 5% two-sided significance, adjusting for a conservative estimate (r=0·4) of the correlation between OSS over 12 months and allowing for 20% loss to follow up, a total sample size of 500 patients was required (MUA:200, ACR:200, ESP:100). No adjustment was made for multiple comparisons, owing to the a priori specified sequence of treatment comparisons (MUA vs ESP, ACR vs ESP, MUA vs ACR; results were interpreted as if from three independent trials, with inference for one comparison not dependent on the outcome of another).[27]

Statistical analysis

The analysis of primary and secondary outcomes followed intention–to-treat (ITT) principles (comparisons according to the randomised group, irrespective of compliance, without imputation for minimal missing data). A linear mixed model incorporating all time points and using an unstructured covariance pattern was used. The model adjusted for age (in years), gender (male / female), diabetes status (diabetic / non-diabetic), and OSS at baseline as fixed effects and recruitment site (35 sites) as a random effect. A single model was used for the analysis, and treatment group differences at each time point were presented as three separate two-way comparisons (i.e. MUA vs ESP; ACR vs ESP; and ACR vs MUA). The OSS at 12 months, QuickDASH, pain NRS, and extent of recovery VAS were analysed in a similar manner.

To address the impact of delays in receiving the allocated treatment, a separate secondary intention to treat linear mixed model incorporated time as a continuous variable, including data from all available time points for each participant (additionally including pre-treatment and 6 months post-treatment OSS scores) and adjusting for the same covariates as the primary analysis model. Treatment effect estimates were extracted at three, six and 12 months post-randomisation.

Complier Average Causal Effect (CACE) analysis investigated the effect of adherence with ESP on the OSS at 12 months using instrumental variable regression. Additional sensitivity

analyses included additional adjustment for predictors of missing data, exclusion of response data received beyond six weeks of each intended follow-up and adjustment for observed baseline differences in employment status. Subgroup analyses explored whether the treatment response was influenced by presence of diabetes, prior physiotherapy treatment and participant treatment preference at baseline by including treatment by sub-group interactions in the model. Adverse events and complications were listed by allocated group and compared by chi-squared test.

All statistical testing was done at the two-sided 5% significance level and estimates given with 95% Confidence Intervals (CIs) using Stata 15. The statistical analysis plan was approved by an independent data monitoring committee and the trial steering committee. The trial is registered with the International Standard Randomised Controlled Trial Register, ID: ISRCTN48804508.

Health economic analysis

Economic analyses were conducted in accordance with the National Institute for Health and Care Excellence (NICE) reference case standards.[28] The base-case analysis was conducted on an ITT basis with multiple imputation for missing data, which was assumed missing at random. The analysis was conducted from an NHS and Personal Social Services perspective and included the cost of the initial intervention, hospital stays and outpatient appointments after initial intervention and visits to primary and community health care professionals over one year. Costs were calculated using National UK unit costs and expressed in British Pound Sterling (GBP) at the 2018 price. Outcomes were measured in terms of quality-adjusted life year (QALYs) over one year. We used a mapping function to derive utilities,[29 30] and the Area Under the Curve method to estimate QALYs.

Differences in mean costs and mean QALYs at 12 months were used to derive the incremental cost-effectiveness ratios (ICERs), which represents the greater benefit per GBP spent. This was estimated by comparing mean differences in expected costs and QALYs between treatment groups. The mean estimates and their 95% CI were generated by means of seemingly unrelated regression (SUR). Decisions about whether a treatment is efficient or not (i.e. value for money) are determined as to whether the cost per QALY gained (i.e. ICER)

is below some threshold value. The threshold represents the opportunity cost of delivering an intervention (i.e. the health forgone from providing this intervention). At present, NICE threshold ranges between £20,000 and £30,000 per QALY. According to the current established decision rules, if the estimated cost per QALY is below the £20,000 threshold, the intervention would be considered cost-effective in terms of QALYs gained.

In order to compute the probability of each intervention being cost-effective, the SUR was conducted within a bootstrapping approach on five imputed data sets to generate 10,0000 replicates of incremental costs and benefits. The probability that each intervention is cost-effective is reported at the cost-effectiveness threshold applied by NICE of £20,000 to £30,000/QALY, and a further recommended threshold of £13,000/QALY.[31 32]

Role of the funding source

The funders monitored the trial progress but had no role in study design, data collection, data analysis, data interpretation, or writing or approving or the decision to submit the publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 2015 and December 2017, we randomly assigned 503 patients (out of 914 screened patients with a frozen shoulder) to receive the following treatments: 201 to MUA, 203 to ACR and 99 to ESP (Figure 1). Baseline characteristics as randomised and as analysed in the three groups have been presented (Table 1).

Within the allocated treatment groups, 82% of participants (n=164) completed MUA, 80% completed ACR (n=162) and 81% completed ESP (n=80). There were also 82% of participants (n=164) who had a steroid injection in the MUA group, 22% in the ACR group (n=45) and 80% in the ESP group (n=79). Further details about the delivery, type and dose of the steroid are provided in the Supplementary Material. Sixteen participants (3%) crossed over to a different trial treatment, and 17 (3%) received an alternative treatment. Overall, 64 participants (13%) did not receive any treatment. Waiting times to the start of each

randomised treatment varied considerably. Participants waited a median of 14 days (IQR 7 to 22) for ESP, median of 56·5 days (IQR 34·5 to 88·5) for MUA, and a median of 71·5 days (IQR 42 to 116) for ACR (Supplementary material). Following completion of their randomised treatment, a number of participants received further treatment (Table 2). The highest number of further treatments were received by participants in the ESP arm (15%, n=15); fewer by MUA participants (7%, n=14) and the fewest further treatments by ACR participants (4%, n=8).

At the primary end point at 12 months, many participants improved to nearly full shoulder functioning (median overall OSS of 43 out of 48 points). Participants randomised to ACR had on average statistically significantly higher (better) OSS scores than MUA (40·3 versus 38·3 points, difference: 2·01, 95% CI 0.10 to 3·91) and ESP (40·3 versus 37·2 points, difference: 3·06 points, 95% CI 0·71 to 5·41). MUA had higher mean OSS than ESP (38·3 versus 37·2 points, difference: 1.05, 95% CI -1.28 to 3.39) (raw means in Figure 2). Mean estimates were short of the minimal clinically important effect size of four to five OSS points (Table 3). For the short-term follow-up at three months post-randomisation, ACR had lower (worse) outcomes compared with the other two interventions. Differences of clinically important magnitude as defined above were included in the 95% CIs for the benefit of MUA and ESP compared with ACR at three months and ACR compared with ESP at 12 months.

Compared with the primary analysis, group differences in the model adjusted for waiting times tended to be of smaller magnitude, with the exception of the difference between ACR and ESP at 12 months (3.26 points in favour of ACR, 95% CI 1·18 to 5·35) (Supplementary material). From the CACE analysis, outcomes for participants who adhered to ESP treatment remained lower than for participants in other treatment arms (-1·84 OSS points, 95% CI -4·41 to 0.74), although the difference was not statistically significant. Predictors of missingness were age and OSS outcomes prior to being missing. These are already incorporated in the primary analysis. Sensitivity analyses regarding the timing of questionnaire return and adjustment for employment status did not show marked differences from the primary results. There were no significant sub-group interactions.

Of the secondary outcomes, QuickDASH and shoulder pain followed a similar pattern to the OSS with significantly poorer outcomes for ACR participants at three months but better outcomes at 12 months post-randomisation compared with MUA or ESP. There were no clear group differences in extent of recovery based on the treatment-seeking VAS.

In total, there were ten serious adverse events (SAEs), reported for nine participants, of whom eight were in the ACR group (4%) and two in the MUA group (1%). There was one participant in the ACR group who had an SAE from non-trial physiotherapy (Table 4). Numbers were insufficient for formal analysis. There were 33 non-serious adverse events, reported for 31 participants with comparable rates in the three arms (n=14 / 7% of MUA patients, n=12 / 6% of ACR patients and n=5 / 5% of ESP patients). There was no evidence for statistical differences in the proportion of non-serious adverse events (p=0·19).

The base-case economic analysis, with multiple imputation, showed that MUA was £276 (95% CI £65·67 to £487·35) more expensive per participant than ESP. ACR was substantially more costly than ESP [on average £1,733.78 more per participant (95% CI 1,529·48 to 1,938·06)] and MUA [£1,457·26 more per participant (95% CI 1,282·73 to 1,631·79)]. Overall, ACR had worse QALYs compared with MUA (mean difference -0·0293; 95% CI -0·0616 to 0·0030) and MUA had better QALYs compared with ESP (mean difference 0·0396; 95% CI -·0008 to 0·0800). MUA was the intervention most likely to be cost-effective at a £20,000 per QALY threshold (MUA 86% > ESP 14% > ACR 0%) (Supplementary material).

Discussion

UK FROST is the largest randomised clinical trial to date that evaluated common surgical interventions and a specifically designed Physiotherapy pathway with a steroid injection (ESP) for the treatment of adults with a frozen shoulder in the UK NHS. Patient-reported shoulder pain and function improved significantly from baseline with all three trial treatments. At the primary endpoint of 12 months, the magnitude of difference of ACR over MUA and ESP was statistically significant but unlikely to be clinically important. This finding was consistent for all patient reported clinical outcomes. ACR was associated with higher risks. MUA was the most cost-effective option. A detailed economic evaluation of relative

cost-effectiveness of the three treatment options will be published separately, but key results have been included as they are integral to interpreting the main clinical effectiveness findings.

The differences in patient reported outcomes between the treatment groups seen at three months were influenced by longer waiting times (13% of MUA participants and 23% of ACR participants commenced treatment after the three-month follow-up) for the surgical interventions. The planned analysis of our primary outcome, the Oxford Shoulder Score (OSS), adjusted for variable waiting times between the three interventions using additional data collected on the day of treatment and six months post-treatment. In this analysis, the difference in benefit of ACR over ESP at 12 months included a confidence interval that marginally overlapped with the minimal clinically important difference of five points. Therefore, clinically meaningful group differences may potentially exist between ACR and ESP in the wider population. There were no meaningful differences observed in the OSS between the two surgical interventions of MUA and ACR at any time-point. Although diabetic patients had poorer outcomes compared with non-diabetic patients at all timepoints, there was no evidence of an effect of participants' diabetes status, receipt of previous physiotherapy, baseline treatment preferences or length of frozen shoulder symptoms at baseline on the primary outcome.

Serious complications were rare, although the ACR group was relatively less safe. Only two participants allocated to MUA had a serious complication. One of the participants in the ACR group diagnosed with a deep vein thrombosis actually received non-trial physiotherapy. There was, therefore, only a marginal difference in the safety profile between MUA and ESP for which in the latter group there were half the participants. Whilst no participants allocated to ESP had a serious complication, these participants were more likely to need further treatment. Participants in the ACR group received fewest further treatments.

It is notable that the difference in OSS scores and the difference in health-related quality of life are in the same direction, with only a small difference in OSS scores and QALYs observed across groups. A possible trend of ACR group improving over time, which might continue with longer term follow up, could be explained by the timing of the delivery of the

interventions which has been examined and does not alter the interpretation of the findings of the primary analysis. We are confident that important costs, including costs of complications, have been captured during the trial follow-up. The strengths of this study were the pragmatic design, recruiting from 35 hospitals (including 90 surgeons and 285 physiotherapists) across a range of rural and urban areas with minimal exclusions. This makes the results generalisable and applicable to clinical practice in the UK. There were low levels of attrition within and between groups in the completion of the extensively validated patient-reported primary outcome, which measures pain and impact of any stiffness on shoulder function.[22] There was also limited cross-over. The statistical model used meant only six per cent of trial participants were not included in the primary analyses and consequently ensured we at least achieved the planned 90% statistical power. The results were robust to the sensitivity and sub-group analyses. Diagnosis of frozen shoulder can be challenging and there is no reference standard for comparison.[6] As visual estimation of external rotation has fair to good reliability,[13] restrictions (typically with pain) in both passive and active external rotation have been used as diagnostic criteria in clinical studies.[7] This helped to ensure correct diagnosis in our study population. We also focused on delivering good standards of care, with surgeons using techniques with which they were familiar, and most operations being conducted by consultant surgeons. Physiotherapy was delivered by qualified physiotherapists. Crucially, we standardised the physiotherapy pathway in all arms of the trial to reduce variations in care between participants and trial arms. All participants were provided with written advice detailing the home exercises they needed to perform.[20]

The main limitation of the study was that participants who had ACR or MUA had to wait longer to receive their treatment. Our additional analysis incorporating different waiting times confirmed this did not influence the main trial results. For participants who started treatment, it was reassuring that the OSS was stable between baseline and start of treatment, but it is possible that only participants with a more resistant frozen shoulder had surgery. This analysis is also limited, as it reflects treatment effects at pragmatic follow-up times accounting for the different outcome trajectories, rather than observing what would have happened if all three trial treatments were delivered at similar times. Given the nature of the trial treatments, the blinding of participants and clinicians to treatment allocation

was not possible or desirable in this pragmatic trial. The lack of any sub-group effect of participant baseline treatment preferences on the OSS may in part mitigate concerns from a lack of blinding. A further potential threat to study validity was non-compliance with the treatments. However, the trial findings were consistent when analysed both as randomised (ITT) and with CACE analysis. Finally, only 6% of UK practitioners were using Hydrodilatation when we surveyed practice to inform the design of UK FROST and consequently this was not identified as a priority intervention for evaluation.[10] Its popularity has increased since then and whilst there are recent small trials that have compared Hydrodilatation with MUA, ACR and intra-articular steroid injections,[33 34] the evidence of Hydrodilatation's effectiveness is inconclusive.

In conclusion, all three treatments in our study led to significant improvements in patient-reported shoulder pain and function. None of the treatments were clearly superior. ACR resulted in the least number of further treatments but carried higher risks and costs. The ESP pathway with steroid injection could be accessed quickly in the NHS, but more patients who had ESP needed further treatment. MUA was the most cost-effective option but with a longer waiting time to access than ESP. These findings should help clinicians discuss treatment options with patients during shared decision making and encourage surgeons to use ACR more selectively when less costly and less invasive interventions fail.

Contributors

AR was the Chief Investigator and lead applicant. SB, MN, LK, CC, ID, SR, LG and ES all contributed to trial conduct and data collection. AK and CH provided the statistical expertise. BC and GR provided the health economic expertise. CS and FT led on the qualitative aspects of the study. SR, LK, SB and CMcD undertook the focussed systematic review. AR, SB, DT, NH, SL, SS provided expert trial methodological input. AR, CPC, AA, AB, AC and JD provided expertise as orthopaedic surgeons. NH, LG and SL provided expertise as physiotherapists. SS provided expertise on patient-reported outcome measures. AR, SB, AK and BC led on writing the manuscript. All authors read, commented on and approved the final manuscript.

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Data sharing agreement

All data requests should be submitted to the corresponding author for consideration as agreed in our publication plan. Access to anonymised data may be granted following review with the Trial Management Group and agreement of the Chief Investigator (Prof Amar Rangan and corresponding author). Related documents including the Statistical Analyses Plan will be available on request.

Declaration of interests

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Table 1: Baseline characteristics

	As Randomised N=503			As Analysed N=473		
Characteristic	**MUA**	**ACR**	**ESP**	**MUA**	**ACR**	**ESP**
Gender, n (%)						
Male	72 (36%)	77 (38%)	35 (35%)	68 (36%)	74 (39%)	31 (33%)
Female	129 (64%)	126 (62%)	64 (65%)	121 (64%)	117 (61%)	62 (67%)
Age (years)						
N	201	203	99	189	191	93
Mean (SD)	54·5 (7.7)	53·9 (7.7)	54·5 (7·8)	54·4 (7·3)	54·4 (7·6)	54·8 (7·8)
Median (IQR)	54 (54, 60)	54 (54, 59)	53 (53, 60)	54 (54, 60)	55 (55, 59)	53 (53, 60)
Diabetic, n (%)						
No	141 (70%)	143 (70%)	69 (70%)	131 (69%)	135 (71%)	66 (71%)
Type I	12 (6%)	12 (6%)	5 (5%)	12 (6%)	11 (6%)	5 (5%)
Type II	48 (24%)	48 (24%)	25 (25%)	46 (24%)	45 (24%)	22 (24%)
Affected shoulder, n (%)						
Left	127 (63%)	121 (60%)	56 (57%)	119 (63%)	114 (60%)	54 (58%)
Right	73 (36%)	80 (39%)	43 (43%)	69 (37%)	75 (39%)	39 (42%)
Missing	1 (1%)	2 (1%)	0 (0%)	1 (1%)	2 (1%)	0 (0%)
Dominant arm affected, n (%)						
Yes	81 (40%)	82 (40%)	39 (39%)	77 (41%)	76 (40%)	36 (39%)
No	115 (57%)	120 (59%)	59 (60%)	107 (57%)	114 (60%)	56 (60%)
Ambidextrous	0 (0%)	1 (<0.5%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Missing	5 (2%)	0 (0%)	1 (1%)	5 (3%)	0 (0%)	1 (1%)
Duration of symptoms (months)						
N	196	201	98	185	190	92
Mean (SD)	10·5 (8·6)	11·3 (10·0)	10.8 (8·8)	10·7 (8·7)	11·3 (10·1)	11·0 (9·0)
Median [IQR]	8 [6, 12]	9 [6, 12]	8 [6, 12]	8 [6, 12]	9 [6, 12]	8 [6, 12]
min, max	2, 60	0, 96	2, 72	2, 60	2, 96	2, 72
Duration of symptoms (grouped), n (%)						
< 9 months	103 (51%)	95 (47%)	51 (52%)	96 (51%)	90 (47%)	48 (52%)
≥ 9 months	93 (46%)	106 (52%)	47 (47%)	89 (47%)	100 (52%)	44 (47%)
Missing	5 (2%)	2 (1%)	1 (1%)	4 (2%)	1 (1%)	1 (1%)
X-rays, n (%)						
Anteroposterior view	200 (100%)	201 (99%)	99 (100%)	188 (99%)	190 (99%)	93 (100%)
Axillary view	174 (87%)	179 (88%)	86 (87%)	163 (86%)	169 (88%)	80 (86%)
Modified Axillary	29 (14%)	24 (12%)	14 (14%)	27 (14%)	24 (13%)	14 (15%)
Employment status summary, n (%)						
In paid work	129 (64%)	118 (58%)	53 (54%)	124 (66%)	111 (58%)	50 (54%)
Not in paid work	69 (34%)	82 (40%)	46 (46%)	62 (33%)	78 (41%)	43 (46%)
Missing	3 (1%)	3 (1%)	0 (0%)	3 (2%)	2 (1%)	0 (0%)
Type of employment, n (%)						
Unskilled manual	17 (8%)	15 (7%)	8 (8%)	16 (8%)	13 (7%)	7 (8%)
Skilled manual	21 (10%)	18 (9%)	18 (18%)	19 (10%)	16 (8%)	17 (18%)
Unskilled non-manual	19 (9%)	17 (8%)	4 (4%)	19 (10%)	17 (9%)	4 (4%)
Skilled non-manual	41 (20%)	37 (18%)	13 (13%)	40 (21%)	37 (19%)	12 (13%)
Professional	13 (6%)	19 (9%)	10 (10%)	13 (7%)	18 (9%)	10 (11%)
Other	20 (10%)	17 (8%)	10 (10%)	18 (10%)	15 (8%)	10 (11%)

	As Randomised N=503			As Analysed N=473		
Characteristic	**MUA**	**ACR**	**ESP**	**MUA**	**ACR**	**ESP**
Currently taking steroids for affected shoulder, n (%)						
Yes	2 (1%)	7 (3%)	0 (0%)	2 (1%)	7 (4%)	0 (0%)
No	196 (98%)	195 (96%)	99 (100%)	184 (97%)	183 (96%)	93 (100%)
Missing	3 (1%)	1 (<0.5%)	0 (0%)	3 (2%)	1 (1%)	0 (0%)
Had steroid injection for affected shoulder, n (%)						
Yes	97 (48%)	117 (58%)	55 (56%)	93 (49%)	112 (59%)	53 (57%)
No	102 (51%)	86 (42%)	44 (44%)	94 (50%)	79 (41%)	40 (43%)
Missing	2 (1%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)
Previous physio-therapy for affected shoulder, n (%)						
Yes	125 (62%)	124 (61%)	59 (60%)	117 (62%)	117 (61%)	58 (62%)
No	76 (38%)	77 (38%)	39 (39%)	72 (38%)	73 (38%)	35 (38%)
Missing	0 (0%)	2 (1%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Number of weeks had shoulder problem (median, [IQR])	32 [24-52]	35 [24-52]	32 [24-48]	34 [24-52]	35.5[24-52]	32 [24-48]
Similar shoulder problem on the opposite side, n (%)						
Yes	62 (31%)	53 (26%)	13 (13%)	59 (31%)	51 (27%)	12 (13%)
No	132 (66%)	146 (72%)	85 (86%)	124 (66%)	136 (71%)	80 (86%)
Missing	7 (3%)	4 (2%)	1 (1%)	6 (3%)	4 (2%)	1 (1%)
OSS (0-48)[a]						
N	201	203	99	189	191	93
Mean (SD)	20·4 (8.9)	19·2 (7·7)	20·3 (8·0)	20·6 (8·9)	19·2 (7·5)	20·3 (8·1)
Median	20	19	20	20	19	20
IQR	14, 27	13, 25	15, 26	14, 27	14, 25	15, 26
QuickDASH (0-100)						
N	192	197	96	181	187	90
Mean (SD)	57·0 (21·0)	61·7 (18·5)	59·4 (19·7)	56·8 (21·1)	61·3 (18·5)	59·1 (20·0)
Median	59	64	60	59	64	59·5
IQR	42, 75	52, 75	46, 73	43, 73	50, 73	46, 73
Pain NRS (0-10)						
N	199	201	99	187	190	93
Mean (SD)	6·8 (2·2)	7·0 (1·9)	6·9 (2·4)	6·7 (2·3)	7·0 (1·9)	6·8 (2·4)
Median	7	7	7	7	7	7
IQR	5, 8	6, 8	5, 8	5, 8	6, 8	5, 8
Symptom severity (0-100)						
N	198	201	99	186	189	93
Mean (SD)	83·8 (21·8)	86·2 (20·1)	89·2 (15·4)	83·9 (22·1)	86·0 (20·4)	89·0 (15·5)
Median	90	95	100	90	95	100
IQR	75, 100	80, 100	80, 100	80, 100	80, 100	80, 100

[a] Includes two imputed missing baseline OSS values (1 MUA, 1ACR)

Table 2: Further treatments

	Sub-group: Randomised & Completed Treatment		
	MUA N=164	**ACR N=162**	**ESP N=99**
Further surgical treatment			
ACR	7	0	5
MUA	1	1	3
Further non-surgical treatment			
Steroid injection	3	3	3
Glenohumeral joint injection	2	0	0
Ultrasound guided injection	0	1	1
Other/Further physiotherapy	2	3	6
Rheumatology clinic	0	0	1
Total number of further treatments	**15**	**8**	**19**
Total number of patients having one or more further treatments (% of randomised)	**14 (7%)**	**8 (4%)**	**15 (15%)**

Table 3: Estimated mean outcome differences

	MUA	ACR	ESP	MUA vs ESP		ACR vs ESP		ACR vs MUA	
	Mean Estimate	**Mean Estimate**	**Mean Estimate**	**Mean Difference (95% CI)**	**p-value**	**Mean Difference (95% CI)**	**p-value**	**Mean Difference (95% CI)**	**p-value**
OSS[a]									
3 months	30·2	26·9	31·6	-1·36 (-3·70 to 0·98)	0·25	-4·72 (-7·06 to -2·39)	<0·01	-3·36 (-5·27 to -1·45)	<0·01
6 months	37·1	35·9	34·9	2·15 (-0·12 to 4·42)	0·06	0·98 (-1·31 to 3·26)	0·40	-1·17 (-3·02 to 0·67)	0·21
12 months[b]	38·3	40·3	37·2	1·05 (-1·28 to 3·39)	0·38	3·06 (0·71 to 5·41)	0·01	2·01 (0·10 to 3·91)	0·04
Average	35·2	34·4	34·6	0·61 (-1·31 to 2·53)	0·53	-0·23 (-2·15 to 1·70)	0·82	-0·84 (-2·41 to 0·72)	0·29
OSS Time Adjusted[c]									
3 months	28·2	26·0	29·4	-1·18 (-3·10 to 0·73)	0·23	-3·33 (-5·25 to -1·40)	0·01	-2·14 (-3·71 to -0·57)	0·01
6 months	32·5	31·5	32·7	-0·15 (-1·90 to 1·60)	0·87	-1·13 (-2·88 to 0·62)	0·21	-0·98 (-2·40 to 0·44)	0·18
12 months	41·1	42·5	39·2	1·92 (-0·16 to 4·00)	0·07	3·26 (1·18 to 5·35)	<0·01	1·35 (-0·33 to 3·02)	0·12
EQ-5D-5L[d]									
Baseline	0·46	0·43	0·40	0·05 (-0·01 to 0·12)	0·10	0·03 (-0·04 to 0·09)	0·42	-0·03 (-0·08 to 0·02)	0·28
3 months	0·63	0·57	0·61	0·03 (-0·03 to 0·08)	0·38	-0·04 (-0·10 to 0·02)	0·18	-0·06 (-0·11 to -0·02)	0·01
6 months	0·73	0·68	0·68	0·05 (-0·01 to 0·10)	0·10	-0·004 (-0·06 to 0·05)	0·88	-0·05 (-0·10 to -0·01)	0·02
12 months	0·73	0·74	0·69	0·04 (-0·02 to 0·10)	0·20	0·05 (-0·02 to 0·10)	0·20	0·005 (-0·04 to 0·05)	0·85
QuickDASH[e]									
3 months	38·8	44·4	37·1	1·77 (-3·41 to 6·96)	0·50	7·33 (2·16 to 12·49)	0·01	5·55 (1·32 to 9·78)	0·01
6 months	27·7	27·4	29·2	-3·55 (-8·68 to 1·58)	0·18	-1·82 (-6·94 to 3·31)	0·49	1·73 (-2·39 to 5·86)	0·41
12 months	29·9	18·2	23·4	-0·50 (-5·70 to 4·70)	0·85	-5·20 (-10·42 to 0·02)	0·05	-4·71 (-8·91 to -0·50)	0·03
Pain NRS[f]									
3 months	4·1	4·7	3·7	0·43 (-0·17 to 1·03)	0·16	1·02 (0·42 to 1·61)	<0·01	0·59 (0·10 to 1·07)	0·02
6 months	2·8	2·8	3·0	-0·19 (-0·78 to 0·40)	0·53	-0·14 (-0·74 to 0·45)	0·63	0·05 (-0·43 to 0·52)	0·85
12 months	2·4	1·7	2·5	-0·08 (-0·66 to 0·50)	0·78	-0·81 (-1·39 to -0·23)	0·01	-0·73 (-1·20 to -0·25)	<0·01
Extent of recovery[g h]									
3 months	51·4	54·0	53·9	-2·55 (-11·68 to 6·58)	0·58	0·11 (-9·02 to 9·23)	0·98	2·66 (-4·84 to 10·15)	0·49
6 months	31·9	34·7	38·6	-6·71 (-15·83 to 2·42)	0·15	-3·93 (-13·06 to 5·21)	0·40	2·78 (-4·50 to 10·06)	0·45
12 months	27·3	21·2	26·9	0·46 (-7·79 to 8·70)	0·91	-5·65 (-13·91 to 2·61)	0·18	-6·11 (-12·86 to 0·64)	0·08

[a] linear mixed covariance pattern model adjusted for age, gender, diabetes, OSS at baseline (fixed effects), and site (random effect)

[b] primary endpoint for each treatment comparison

[c] linear mixed random intercept model adjusted for age, gender, diabetes, OSS at baseline (fixed effects), and site (random effect)

[d] Univariate generalised linear model, including group as a fixed effect factor and baseline EQ-5D-5L score as a covariate

[e] linear mixed covariance pattern model adjusted for age, gender, diabetes, Quick DASH at baseline (fixed effects), and site (random effect)
[f] linear mixed covariance pattern model adjusted for age, gender, diabetes, Quick DASH at baseline (fixed effects), and site (random effect)
[g] based on 0-100 VAS of perceived need for further treatment
[h] linear mixed covariance pattern model adjusted for age, gender, diabetes, symptom severity at baseline (fixed effects), and site (random effect)

Table 4: Adverse Events by treatment arm as randomised (footnotes denote treatment as received, if different)

	MUA	ACR	ESP
Serious Adverse Events			
Attended A&E for visual disturbance; headache; heaviness and numbness of arm	1a		
Chest Infection		1	
Decreased oxygen saturation		1	
Deep Vein Thrombosis		1b	
Elevated blood sugars (prolonging hospitalisation)		1	
Hypoglycaemic seizure whilst under anaesthetic		1	
Likely anterior dislocation		1c	
Patient noticed facial drooping / weakness after surgery		1	
Septic Joint Arthritis	1		
Stroke (3 months post-treatment)		1	
Total	**2**	**8**	**0**
Non-Serious Adverse Events			
Additional diagnosis requiring further treatment	1		
Adverse reaction to concurrent medication		1	
Allergic reaction to dressing		1	
Chest infection	1		
Episode of inflammation	1		
Infection		1	
Injury to adjacent structures such as nerve, tendon, bone or joint	1	1c	
Ipsilateral face swelling, face flushed and neck and face hot	1		
Long head biceps tendon pain and rupture			1
Neuropathic symptoms	1	2d	
Patient being investigated for neck problems		1	
Persistent pain		1	1
Persistent pain requiring further treatment	1	1	
Persistent stiffness and pain requiring treatment	1		
Pins + needles to hand	1		
Post-procedural worsening of shoulder pain	3	3	1e
Recurrent stiffness requiring further treatment			1e
Supraspinatus tendinopathy			1
Surgical site infection		1f	
Transient hyperglycaemia, steroid flare or joint sepsis following corticosteroid injection	3g		
Total	**15**	**13**	**5**

a Received 'no trial treatment'
b Received 'non-trial physiotherapy'
c Received 'MUA'
d One patient received 'Other' treatment (Subacromial decompression)
e Received 'ACR'
f One patient received 'Other' treatment (ACR without MUA)
g Received 'ESP'

Figure 1: CONSORT flow diagram

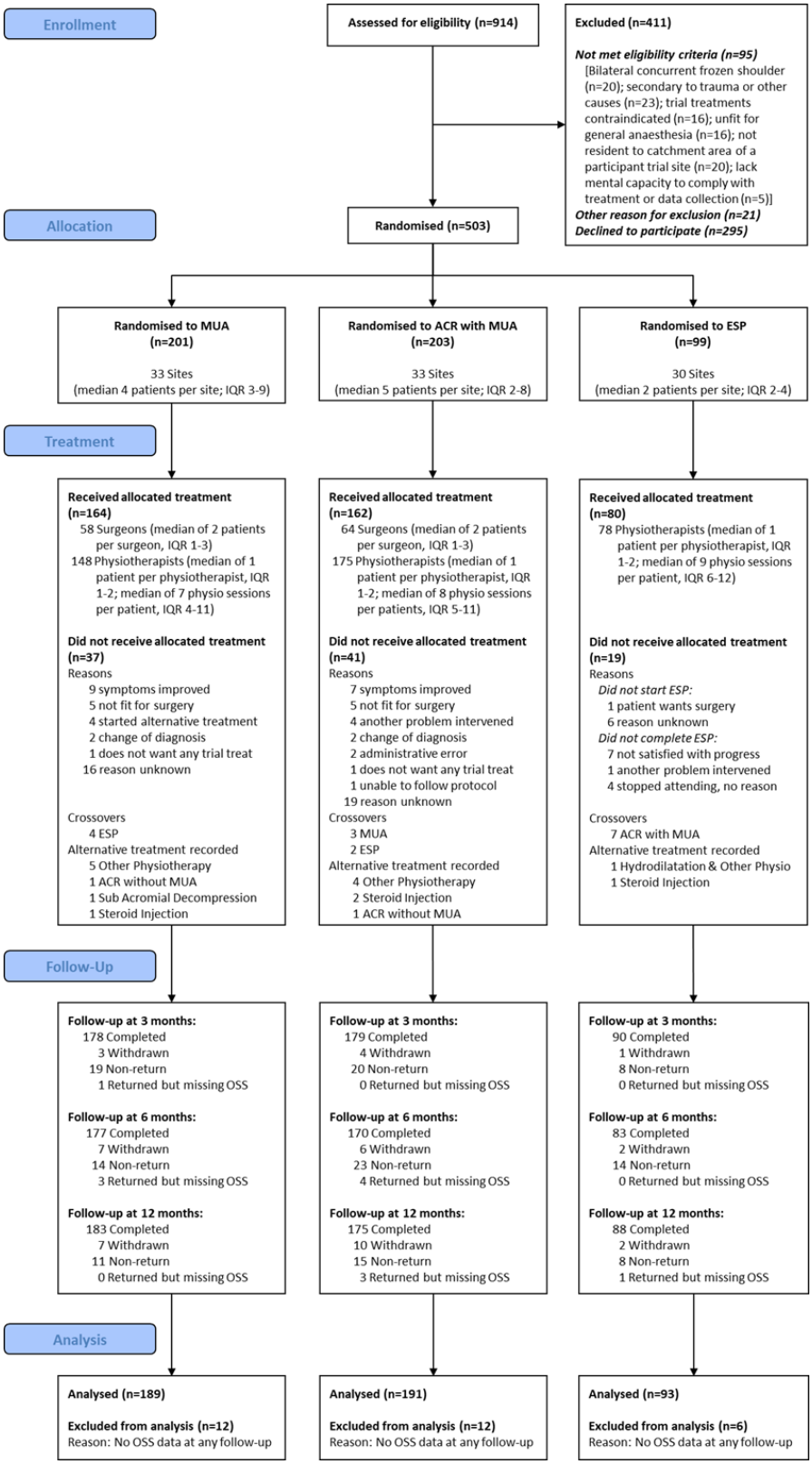

Figure 2: Primary outcome over time (OSS)