Generating an evidence base to guide clinical practice in the management of Frozen Shoulder

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Abstract

This thesis describes how my clinical and research leadership supported a collaborative research endeavour resulting in the generation of good quality evidence to guide clinical practice in the management of Frozen Shoulder (also known as Adhesive Capsulitis). Frozen shoulder is a disabling condition that makes the shoulder very painful, tight, and stiff. People with the condition may struggle with basic daily activities and have sleep disturbance. The estimated cumulative incidence of Frozen Shoulder is 2.4 per 1000 population per year, affecting around 8% of men and 10% of women of working age. There was considerable variation in treatment provision, and despite lack of good quality evidence invasive surgical treatment was being increasingly used.

The original body of work covered by the papers included in this thesis has generated new knowledge and made significant contributions to our understanding of Frozen Shoulder and its response to treatment. The methods used in the five included papers span research priority setting, identifying uncertainties, conduct of the largest randomised clinical trial to date of commonly used secondary care treatments for Frozen Shoulder (The UK FROzen Shoulder Trial or UKFROST), Delphi consensus development in standardising physiotherapy pathways for Frozen Shoulder, and a systematic review contextualising the results of UKFROST to guide clinical practice.

There was a clear need to standardise care pathways for Frozen Shoulder. The surgical treatments were not superior to the structured physiotherapy pathway that was developed and used in UKFROST. If that structured physiotherapy is provided routinely as the initial treatment, more invasive surgery can be avoided. The body of work presented in this thesis has informed national guidelines for clinical practice. It is hoped that it will help improve and standardise the care provided to individuals who develop a Frozen Shoulder and help guide future primary research on the topic.

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Published core thesis papers

Acknowledgements

I thank my thesis advisor Professor David Torgerson; and all the collaborators, patients and the public, and co-authors who have worked with me on the research. I particularly thank Dr Stephen Brealey and Dr Lucksy Kottam, who worked tirelessly with me to see the UK Frozen Shoulder Trial (UKFROST) to a successful completion. Finally, I would like to thank the NIHR for funding and supporting the conduct of UKFROST.

Author's declaration

The five papers that form the core of this thesis are listed below along with the full citations. The integrative chapter that binds these papers into the thesis is solely my own work. I declare that this thesis is a presentation of original work, and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

Paper 1. ***Rangan A,*** *Upadhaya S, Regan S, Toye F, Rees JL.* Research priorities for shoulder surgery: results of the 2015 James Lind Alliance patient and clinician priority setting partnership. **BMJ Open**. 2016 Apr 11;6(4):e010412.
doi: https://doi.org/10.1136/bmjopen-2015-010412
Paper 2. ***Rangan A,*** *Hanchard N, McDaid C:* What is the most effective treatment for Frozen Shoulder? **BMJ** 2016 Aug 23;354:i4162.
doi: https://doi.org/10.1136/bmj.i4162
Paper 3. *Hanchard NCA, Goodchild L, Brealey SD, Lamb SE,* ***Rangan A.*** Physiotherapy for primary frozen shoulder in secondary care: Developing and implementing stand-alone and post operative protocols for UK FROST and inferences for wider practice. **Physiotherapy.** 2020 Jun;107:150-160.
doi: https://doi.org/10.1016/j.physio.2019.07.004

Paper 4. ***Rangan A****, Brealey SD, Keding A, Corbacho B, Northgraves M, Kottam L, Goodchild L, Srikesavan C, Rex S, Charalambous CP, Hanchard N, Armstrong A, Brooksbank A, Carr A, Cooper C, Dias JJ, Donnelly I, Hewitt C, Lamb SE, McDaid C, Richardson G, Rodgers S, Sharp E, Spencer S, Torgerson D, Toye F; UK FROST Study Group*. Management of adults with primary frozen shoulder in secondary care (UK FROST): a multicentre, pragmatic, three-arm, superiority randomised clinical trial. **Lancet.** 2020 Oct 3;396(10256):977-989.
doi: https://doi.org/10.1016/s0140-6736(20)31965-6
Paper 5. *Rex SS, Kottam L, McDaid C, Brealey S, Dias J, Hewitt CE, Keding A, Lamb SE, Wright K,* ***Rangan A.*** Effectiveness of interventions for the management of primary frozen shoulder : a systematic review of randomized trials. **Bone Jt Open**. 2021 Sep;2(9):773-784. doi: https://doi.org/10.1302/2633-1462.29.bjo-2021-0060.r1

Contribution to the papers

I have led or co-led, and substantially contributed to the work covered by all the listed papers. Papers 3-5 are publications from a large-scale UK-wide multicentre clinical trial funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme where I was the lead applicant and Chief Investigator. I contributed substantially to the study design, led the grant application, and had overall responsibility for the conduct and reporting of the trial.

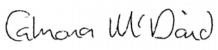
1) **Rangan A**, Upadhaya S, Regan S, Toye F, Rees JL. Research priorities for shoulder surgery: results of the 2015 James Lind Alliance patient and clinician priority setting partnership. **BMJ Open**. 2016 Apr 11;6(4):e010412.

Contribution of the candidate: I was an academic clinician member of the James Lind Alliance (JLA) Priority Setting Partnership (PSP) Steering Group, and made substantial contributions to study design, data collection, analysis, interpretation, writing, editing, and approving the final version as first author.

Amar Rangan | Jonathan Rees

2) **Rangan A**, Hanchard N, McDaid C: What is the most effective treatment for Frozen Shoulder? **BMJ** 2016 Aug 23;354:i4162

Contribution of the candidate: I formulated the idea of the article, contributed to review and interpretation of the literature search, preparation of the first draft and subsequent revisions of the manuscript and approval of the final version as the lead and corresponding author.



Amar Rangan | Catriona McDaid

3) Hanchard NCA, Goodchild L, Brealey SD, Lamb SE, **Rangan A.** Physiotherapy for primary frozen shoulder in secondary care: Developing and implementing stand-alone and post operative protocols for UK FROST and inferences for wider practice. **Physiotherapy.** 2020 Jun;107:150-160.

Contribution of the candidate: I was involved in the conceptualisation of the research question, contributed significantly to the study design and conduct, led the distribution of the Delphi questionnaires to the BESS clinician network, contributed to data extraction, analysis and interpretation, and preparation of the manuscript including subsequent revisions, and approval of the final version as last, senior and corresponding author.

Amar Rangan | Stephen Brealey

4) **Rangan A**, Brealey SD, Keding A, Corbacho B, Northgraves M, Kottam L, Goodchild L, Srikesavan C, Rex S, Charalambous CP, Hanchard N, Armstrong A, Brooksbank A, Carr A, Cooper C, Dias JJ, Donnelly I, Hewitt C, Lamb SE, McDaid C, Richardson G, Rodgers S, Sharp E, Spencer S, Torgerson D, Toye F; UK FROST Study Group. Management of adults with primary frozen shoulder in secondary care (UK FROST): a multicentre, pragmatic, three-arm, superiority randomised clinical trial. **Lancet.** 2020 Oct 3;396(10256):977-989.

Contribution of the candidate: I was the overall trial lead and Chief Investigator, involved in the conceptualisation of the research question by contributing to the vignette that led to the NIHR commissioned call. I led the grant application to NIHR, including significant contribution to the study design, and was responsible for the overall conduct of the clinical trial including regulatory and ethics approvals; clinician engagement and site recruitment; review of adverse events; regular reporting to funder, sponsor, and ethics committee; convening of regular Trial Management Group meetings and independent trial oversight committees. I was involved in the development and approval of the statistical and health economic evaluation plans, review of data analyses, and securing agreement on the reporting format. As first and corresponding author I led the preparation of the manuscript including subsequent revisions and approving the final version.

Amar Rangan

Stephen Brealey

5) Hanchard NCA, Goodchild L, Brealey SD, Lamb SE, **Rangan A.** Physiotherapy for primary frozen shoulder in secondary care: Developing and implementing stand-alone and post operative protocols for UK FROST and inferences for wider practice. **Physiotherapy.** 2020 Jun;107:150-160.

Contribution of the candidate: I was involved in the conceptualisation of the research question, contributed significantly to the study design and conduct, led the distribution of the Delphi questionnaires to the BESS clinician network, contributed to data extraction, analysis

and interpretation, and preparation of the manuscript including subsequent revisions, and approval of the final version as last, senior and corresponding author.

Amar Rangan | Stephen Brealey

6) Rex SS, Kottam L, McDaid C, Brealey S, Dias J, Hewitt CE, Keding A, Lamb SE, Wright K, **Rangan A**. Effectiveness of interventions for the management of primary frozen shoulder: a systematic review of randomized trials. **Bone Jt Open**. 2021 Sep;2(9):773-784

Contribution of the candidate: I was involved in the conceptualisation of the research question, funding acquisition, contributed significantly to the study design, search strategy and supervision of conduct of the review, interpretation of extracted data, preparation of the manuscript including subsequent revisions, and approval of the final version as last and senior author.

Amar Rangan | Lucksy Kottam

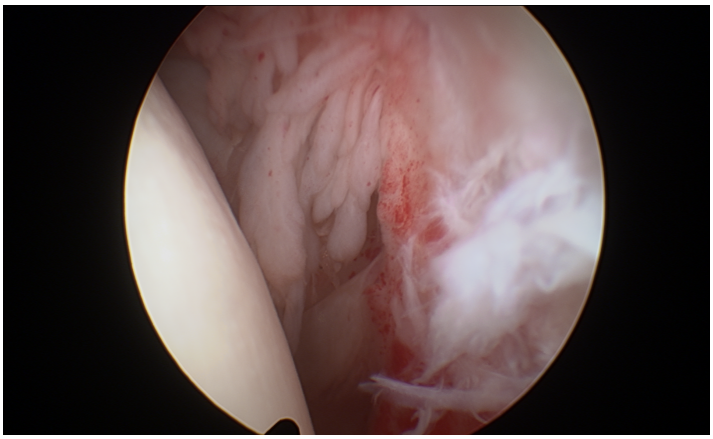
Integrative chapter

This thesis describes key findings from a body of work I led as a clinician and researcher resulting in a collaborative research endeavour that generated important evidence to inform clinical decision making and guide clinical practice in the management of Frozen Shoulder (FS). It is based on five papers that report interrelated aspects that address key treatment uncertainties in the management of FS. This integrative chapter summarises the background, aim and objectives, methods used in the included papers, key findings, and discussion around how the original contribution to knowledge from this body of work should help further the knowledge and inform care pathways in the management of FS. The final remarks and recommendations at the end are based on this original work. Only tables and figures that are essential to present the background and main results are included in the thesis, but more details of the original investigations undertaken are available in the five published papers provided after the appendices.

Background

Frozen shoulder (also known as Adhesive Capsulitis) is a painful and disabling shoulder condition that occurs when the capsule, which is the soft tissue envelope around the ball and socket shoulder joint, becomes inflamed then scarred and contracted. This makes the shoulder very painful, tight, and stiff. It starts with pain, which increases in intensity as stiffness develops.[1] The exact cause of this condition is unknown. Reported associations include diabetes mellitus, cardiovascular disease, trauma, stroke, neurosurgery, and thyroid disease.[1] In the absence of a known association, the condition is labelled as 'idiopathic' or 'primary' frozen shoulder. The pathology of the capsule involves chronic inflammation, and proliferative fibrosis has been reported.[2] [Figure 1] Myofibroblasts contribute to matrix deposition and fibrosis, with the underlying pathology considered as being like Dupuytren's contracture in the hand.[2 3] Whilst both conditions share histological features of fibrosis, there are important differences in their clinical behaviour and natural history. Dupuytren's is generally a painless progressive contracture, whereas Frozen Shoulder (FS) is painful due to complex pathophysiology with underlying capsular inflammation and a natural tendency to resolution. A notable difference has been absence of Matrix Metalloproteinase-14 in FS.[4] The cumulative incidence of frozen shoulder is estimated at 2.4 per 1000 population per year, most commonly affecting individuals in their sixth decade of life, affecting 8.2% of men and 10.1% of women of working age.[5]

Figure 1. Arthroscopic view showing macroscopic appearance of capsular reaction in FS, with inflammation and proliferative changes.



The key examination findings were originally described by Codman as restriction of elevation and external rotation.[6] As visual estimation of external rotation has fair to good reliability,[7] restrictions (typically with pain) in both passive and active external rotation have been used as diagnostic criteria in clinical studies.[8-12] Three clinical phases have historically been recognised for this condition,[13] where the duration of each phase is indicative but varies considerably between patients:

(a) Painful phase, which may last three to nine months

(b) Adhesive phase, with stiffness lasting for four to six months

(c) Phase of resolution or 'thawing', lasting for five to 24 months.

These phases have considerable overlap, and therefore the current favoured terminology is that of 'pain predominant' and 'stiffness predominant' phases.[14]

People with this condition may struggle with basic daily activities and have sleep disturbance due to shoulder pain. There is a tendency for spontaneous resolution, but recovery may be slow or incomplete, with around 40% of patients having mild to severe symptoms at five years.[15] Generally, less invasive treatments for pain relief are provided in a primary care setting in the UK for the earlier phases of the disease including oral analgesia; Physiotherapy; Acupuncture; and Glucocorticoid (steroid) injection.[16] There is considerable variation in provision of these treatments, but the modalities of physiotherapy to be used have been previously recommended within the UK national physiotherapy guidelines for frozen shoulder, which were based on a systematic review.[14] The common treatments utilised in hospitals (secondary care), when stiffness becomes more established, were confirmed by a UK survey of health professionals conducted in 2009 as Physiotherapy; Manipulation Under Anaesthesia

(MUA); and surgical Arthroscopic Capsular Release (ACR).[17] Despite lack of good quality evidence, more invasive treatments like MUA and ACR have been increasingly used.[7 16 17] There was therefore a clear need to generate good quality evidence to guide clinical practice in the use of current management strategies for Frozen Shoulder.[7 18]

The dilemma for clinicians in the diagnosis and management of FS involves various aspects of this condition. In the earlier stages when patients present with shoulder pain to a clinician in primary care, the diagnosis may be more difficult to confirm until some stiffness develops. The diagnosis is based mainly on the clinical presentation of pain associated with loss of active and passive movements, typically tested in external rotation with the arm by the side of the body. That is indicative of a capsular contracture in FS and although there tends to be global restriction in shoulder movements, reduced external rotation by at least 50% compared to the contralateral side is normally used to confirm the diagnosis.

When I see patients referred to secondary care with FS, they would have had the condition for a few months and I therefore obtain plain radiographs to exclude glenohumeral joint arthritis [Figure 2] or rarely a locked posterior dislocation [Figure 3] following trauma, as those conditions may present with the same clinical findings.

Figure 2. Anteroposterior and Axillary view X-rays showing glenohumeral osteoarthritis of left shoulder

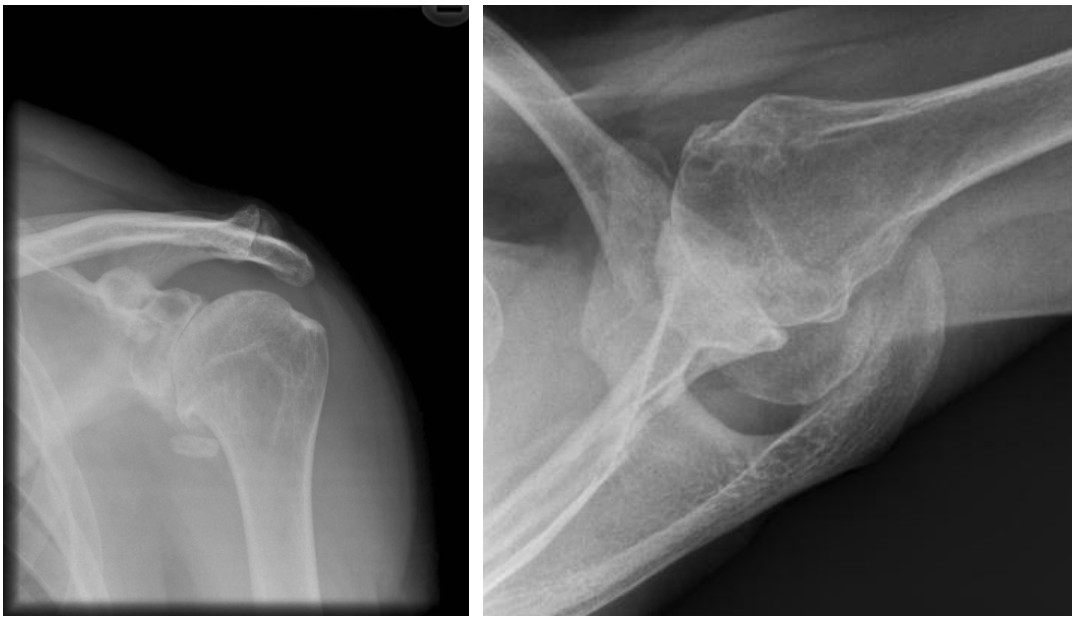
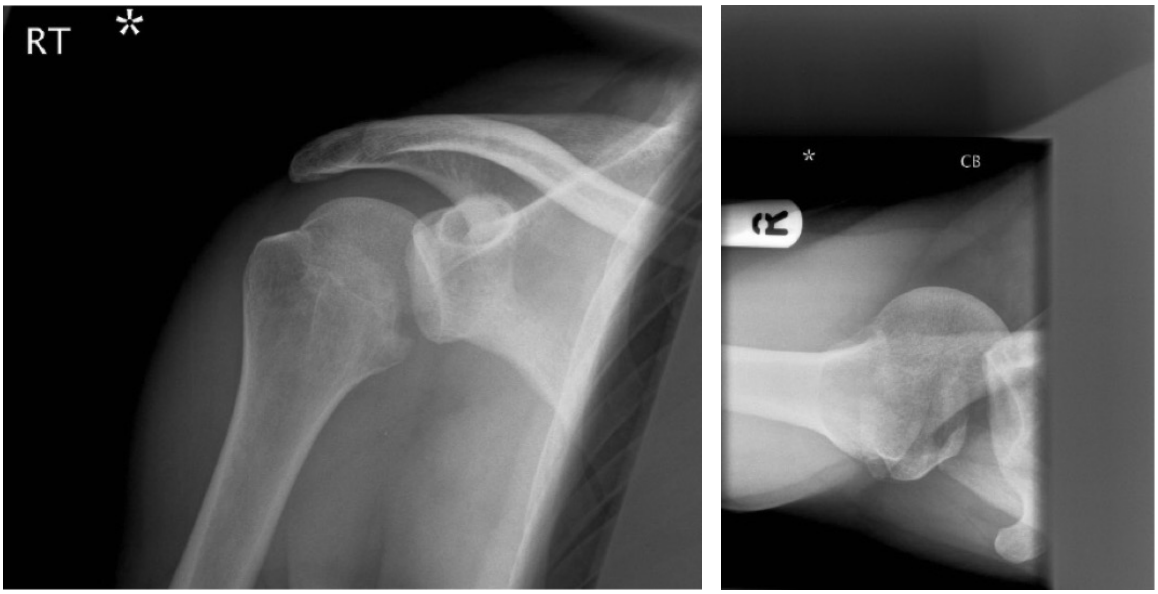


Figure 3. Anteroposterior and Axillary view X-rays showing locked posterior dislocation of right shoulder



Following confirmation of diagnosis of FS, I was faced with the dilemma every time I saw a patient with FS as to which treatment to recommend from the wide choice of treatments available for the condition. There was no strong evidence available for these competing care pathways and treatments to guide clinical decision making. This drove me to close this evidence gap to guide me and my fellow clinicians in our day-to-day clinical practice in managing FS.

Aim

The aim of this thesis is to show how my clinical and research leadership supported a collaborative research endeavour resulting in the generation of good quality research papers to guide clinical practice and to identify important areas for future research in the management of Frozen Shoulder (Adhesive Capsulitis).

Objectives were to:

A. Identify key research priorities in the management of common shoulder problems by engaging key stakeholders, with emphasis on resource intensive surgical interventions
B. Identify gaps in knowledge and uncertainties in the management of Frozen Shoulder to help inform the design of a randomised trial that would address current treatment uncertainties.
C. Describe the development and standardisation of physiotherapy care pathways by consensus for use in the clinical trial

D. Design and deliver a large-scale UK-wide multicentre randomised clinical trial to provide rigorous evidence in the choice of current interventions to manage Frozen Shoulder
E. Outline how the results of the randomised clinical trial drove the need to appraise it in the context of existing evidence to make important recommendations for further research

These objectives developed incrementally as the work progressed and were not defined at the outset of the research programme.

Summary of methods: How the objectives are met by the papers

A. Objective A is met by Paper 1, which describes the James Lind Alliance research priority setting process involving stakeholder engagement and national survey. Important stakeholders including patients, carers and healthcare professionals contributed to a priority setting partnership to identify the top 10 research priorities in the management of common shoulder problems.
B. Objective B is met by Paper 2, which identifies the knowledge gaps and uncertainties in the management of Frozen Shoulder from an in-depth literature review. This paper was a key part of the broader research programme and helped define current treatment uncertainties to inform the design of the randomised trial.
C. Objective C is met by Paper 3, which outlines the UK national Delphi consensus development process that was used to standardise the standalone non-surgical physiotherapy care pathway, and the post-surgical physiotherapy care pathways for the randomised trial.
D. Objective D is met by Paper 4, which reports the main results of a UK-wide multicentred randomised clinical trial to provide evidence comparing three commonly used current interventions in secondary care to manage Frozen Shoulder (United Kingdom FROzen Shoulder Trial or UKFROST). The trial was funded by the NIHR-HTA Programme. 503 participants were recruited and randomised from 35 NHS hospitals. The three treatments compared were manipulation under anaesthesia, keyhole surgery and non-surgical management. Patient reported outcomes, adverse events, serious adverse events, complications, and need for further treatment were collected over a 12 month follow up period. This was a superiority trial to help guide shared decision making in clinical practice.

E. Objective E is met by Paper 5, which is a systematic review of randomised trials on frozen shoulder to contextualise the results of UKFROST and make further research recommendations.

1. Identifying key research priorities

1.1 Stakeholder engagement

As with other causes of shoulder pain, FS is managed by various healthcare professionals from a range of specialties in different settings. It was important to have representation from these healthcare professions alongside patients and carers when identifying important and relevant research priorities. Agreeing on the research priorities for FS was done as part of a broader piece of work to identify research priorities in the use of surgery for common shoulder problems. Shoulder pain is the third most common musculoskeletal cause for presentation to the General Practitioner (GP) in the UK with 2.4% adult prevalence for annual GP consultations.[19-21] Referrals to secondary care are increasing and a 700% increase in the use of some surgical procedures has been reported despite lack of good quality evidence to support that trend.[22] Use of surgical treatment for Frozen Shoulder (FS) was also increasing without justification by evidence.[14 23]

As an academic clinician, my collaborative work with colleagues at the Biomedical Research Centre (BRC) in Oxford led to the commissioning in 2013 of a James Lind Alliance (JLA) Research Priority Setting Partnership (PSP) on the topic of surgery for shoulder pain. I was Chair of the Research Committee of the British Orthopaedic Association (BOA) at the time, which enabled me to leverage support and co-funding from the BOA for the JLA PSP. I worked with the Oxford BRC lead to construct a stakeholder steering group that included patients, physiotherapists, GPs, shoulder surgeons, anaesthetists with pain control expertise, and orthopaedic nurses. A designated lead from the JLA chaired the steering group and ensured that the established JLA methodology was followed.

It was important for us to capture a wide range of 'raw' research questions that relevant stakeholders considered to be important. I worked with members of the steering group to identify a range of individuals and partner organisations within their areas of expertise to bring to a wider stakeholder group meeting. The wider stakeholder group included patients with lived experience of shoulder problems and shoulder surgery, carers, GPs, shoulder

surgeons, nurses, and allied health professionals with experience in managing people with shoulder problems. Each member of the group sought important research questions from partner organisations and individuals ensuring appropriate geographical spread and inclusion. We received 672 questions submitted by 371 respondents. Once the responses were received, I worked with two members of the steering group to collate and merge similar or duplicate responses into a list of 'indicative questions.' Uncertainties not addressed by previous research were then identified, which helped us condense the pool of questions down to a long list of 49 uncertainties [Figure 4]. Uncertainties not addressed by previous research were then added to the UK Database of Uncertainties about the Effects of Treatment (UK DUETS), but that resource is no longer available, and these are currently not hosted in an alternative repository.

1.2. National survey and final consensus meeting

My next step was to reduce the long list to a short list of uncertainties to take forward to final prioritisation. This was done by using an online survey of the steering group and wider stakeholder group for interim prioritisation. The survey was constructed using common and easy to understand language and a traffic light system used by previous PSPs, with green being a response of 'yes' (important), amber being 'unsure,' and red being 'no' (not important). Green light responses to the same question by different stakeholder groups indicated a high level of importance for that uncertainty. The aim of the final stage of the PSP was to prioritise the identified research questions and uncertainties by consensus.

The final prioritisation of the top 10 uncertainties was conducted using a face-to-face meeting of the steering group with representatives from the wider stakeholder group. The shortlist of 25 questions were considered by the group to agree on the final list of top 10 uncertainties. Conflicts of interest were declared by all attendees in advance of the final meeting. The JLA facilitated the final meeting day ensuring transparency, accountability, and fairness. Small group discussions facilitated by JLA advisors and plenary sessions were conducted throughout the day, the groups rotated, and the process repeated until consensus was derived on the final top 10 uncertainties [Table 1].

1.3. Relevance and Impact

The JLA PSP steering group agreed that the top 10 research priorities identified were all equally important and the list provided in Table 1 should not indicate ranking by topic. Research priorities No. 1 and No. 8 are about interventions for treating Frozen Shoulder and

research addressing these priorities forms the basis of the rest of the papers included in this thesis.

The JLA PSP paper has been cited 45 times by other researchers. It was the first JLA PSP to be conducted in orthopaedics and paved the way for PSPs that have subsequently been run in other areas of orthopaedics and musculoskeletal trauma. This work has been influential in guiding the direction of future research on the topic of surgery for common shoulder problems. Research into five of the identified 10 research priorities have so far been commissioned by the National Institute for Health and Care Research (NIHR).

Figure 4. Flow chart indicating the number of questions at each stage of the PSP

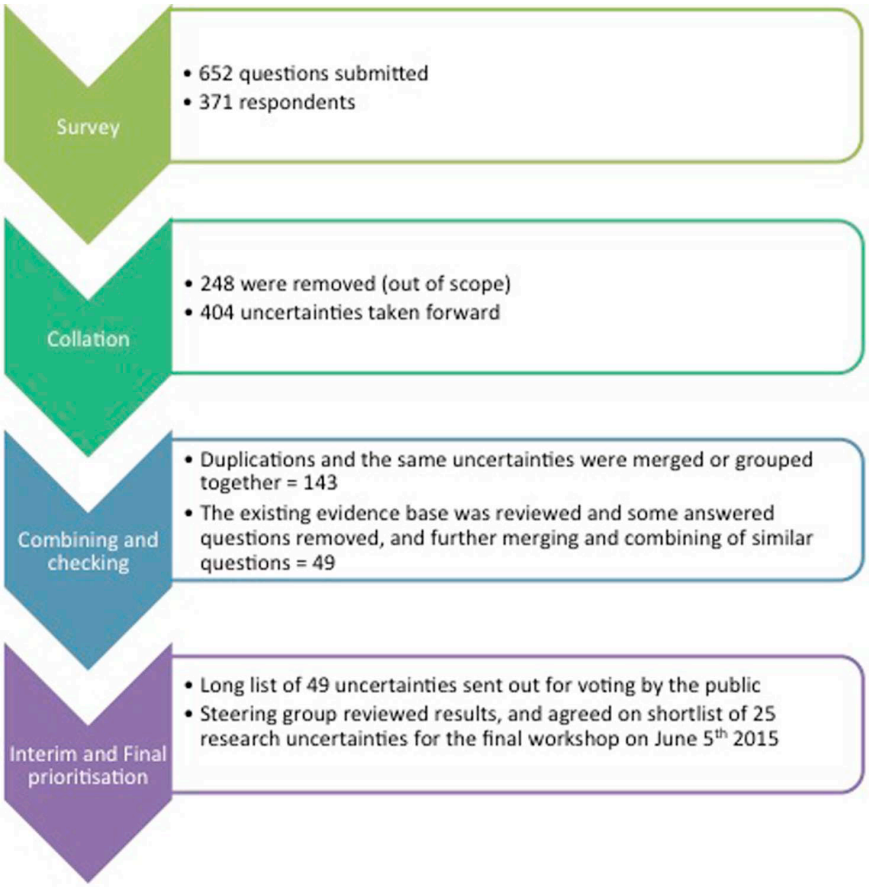


Table 1. Top 10 research priorities: surgery for common shoulder problems

Top 10 questions
1) For the main shoulder conditions of arthritis, frozen shoulder, impingement, rotator cuff tears and instability, can you predict which patients will do well with surgery to help them decide on whether to have surgery or not?

2) In patients with 3- and 4-part proximal humeral fractures, what is the long-term outcome of reverse total shoulder replacement compared to hemiarthroplasty?

3) Does arthroscopic subacromial decompression surgery in patients with degenerative rotator cuff tendon problems improve outcome and prevent further tendon degeneration and tears compared to patients with no surgical intervention?

4) Does early mobilisation and physiotherapy after shoulder surgery improve patient outcome compared to standard immobilisation and physiotherapy?

5) In patients with shoulder arthritis is a hemiarthroplasty or a total shoulder replacement or a reverse replacement most effective?

6) Are patients (including older age groups) with rotator cuff tendon tears in their shoulder best treated with surgery or physiotherapy?

7) How can we ensure that patients see the right doctors and clinicians promptly and correctly, and does this lead to better outcomes?

8) In patients with frozen shoulder, does early surgery improve outcome compared to non-surgery treatments such as injection and dilatation?

9) In patients with newly diagnosed calcific tendinitis (calcium in a shoulder tendon), is early surgical intervention more clinically effective than non-operative treatments?

10) Do patients with partial thickness rotator cuff tendon tears benefit more from a surgical repair compared to a decompression and debridement alone?

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2. Defining the knowledge gaps

I was aware that although interventions for treating Frozen Shoulder (FS), particularly whether early surgery is better than non-surgical treatment was an identified research priority, further work was required to define the knowledge gaps and uncertainties regarding FS and to develop a clear and specific research question to address this research priority. To determine whether surgery was better than non-surgical management, it was essential to conduct a well-designed Randomised Controlled Trial (RCT). There were considerable variations in practice, and it was particularly essential to standardise the interventions to be used in an RCT, and to define the diagnostic criteria to be used for FS. Whilst there were

several interventions being provided in different care settings; it was important to identify which interventions were most commonly used that should be compared in an RCT. This section explains how the uncertainties and interventions to be compared were identified, and how the standardisation of interventions for a subsequent RCT was achieved.

2.1. Summary of evidence: diagnosis of Frozen Shoulder

Clinical criteria used for diagnosis of FS are fairly widely accepted, and these were consistently described in the literature. Symptoms of FS were pain arising insidiously in the Deltoid region with increasing shoulder stiffness. In the earlier stages when pain is the main symptom, the diagnosis may be unclear until stiffness develops. Findings on examination described in the literature were restriction of movements in a 'capsular pattern' that involved loss of both active and passive external rotation of the affected shoulder.[9 10 12] Absence of crepitus on movement would exclude shoulder (glenohumeral) joint arthritis.[11] The clinical diagnosis may be supplemented by obtaining X-rays of the affected shoulder to rule out other diagnoses that present with similar clinical signs like arthritis or a posterior shoulder dislocation. Defining these criteria for diagnosis was an important component of the protocol for the RCT.

2.2. Summary of evidence: treatment uncertainties

Gaps in evidence for interventions to treat FS were identified. We first analysed a previously published systematic review I was involved in that included 28 RCTs, one Quasi-experimental study, and two case series.[7] Most studies had a high risk of bias and were inadequately powered, and few studies reported consistent methods for collecting data on harms.[7] An updated Medline search was conducted for RCTs (up to May 2015) using the search strategy from the review combined with a validated filter for RCTs. The searches only located new studies involving Hydrodilatation. Physiotherapy interventions had been studied in published Cochrane reviews.[24]

A wide range of treatment options were identified for FS, which are listed in Table 2. Overall, there was lack of good quality evidence of superiority, and relative cost-effectiveness, of one treatment over another to guide clinical practice. Oral analgesia, Physiotherapy, and intraarticular steroid injection are usually provided in primary care or in the Musculoskeletal (MSK) 'Tier 2' service, also called 'intermediate care'. Oral corticosteroids are less commonly used. Hydrodilatation, Manipulation Under Anaesthesia (MUA), and Arthroscopic Capsular Release (ACR) are secondary care interventions. MUA and ACR require general anaesthesia

and are considered surgical interventions. A randomised trial comparing surgical vs non-surgical along with an economic evaluation of interventions would therefore need to be in a secondary care setting. I led further preparatory work to determine the feasibility of an RCT by conducting a a survey of 303 healthcare professionals in the UK, which identified three most commonly used treatments in the National Health Service (NHS) that were feasible to test in an RCT: Physiotherapy, Manipulation Under Anaesthesia, and Arthroscopic Capsular Release.[17] Hydrodilatation was only being provided by a small number of centres and was therefore not a feasible intervention to compare within the RCT. The trial design therefore had to be based on addressing gaps in the research base and what was feasible from clinical practice at the time of the trial and in the trial setting.

Table 2. Treatment options for Frozen Shoulder

- Oral analgesia and watchful waiting
- Physiotherapy, typically combinations of advice and education, exercises, manual therapy, thermotherapy, and electrotherapy. Care packages may also include acupuncture or corticosteroid injections
- Acupuncture
- Oral corticosteroid
- Intra-articular corticosteroid injections
- Hydrodilatation (injection of up to 40 mL of sterile saline solution, usually with corticosteroid, to distend the shoulder capsule)
- Manipulation of the shoulder joint under general anaesthesia
- Capsular release (surgical procedure, typically arthroscopic, to release contracted tissue)

When I see patients referred to secondary care with FS, the diagnosis tends to be clearer with the presence of stiffness and a capsular pattern of movement restriction in the shoulder. They are usually in the pain predominant phase that would have not responded adequately to the initial treatment in primary care. Management of pain in the pain predominant phase has been identified as being a priority.[16 25] Outcomes assessed following treatment in most published studies included a combination of pain resolution, functional improvement, and improved quality of life.[7] Identifying these specific uncertainties in FS led to recommendations for further research [Table 3] and helped inform the design of the RCT.

Table 3. Recommendations for further research

Adequately powered randomised controlled trials with:
• Population—Patients with a clinical diagnosis of frozen shoulder
– Studies should specifically address either the pain-predominant phase or the stiffness-predominant phase of frozen shoulder
– The pain predominant phase is the priority, because most patients find this the most trying phase
• Interventions and comparisons:
– Conservative strategies comparing individual and group physiotherapy, home exercises, electrotherapies, and steroid injection in different combinations
– Invasive strategies including distension, manipulation under anaesthesia, and arthroscopic capsular release
• Outcomes—Resolution of pain, improvement of function and quality of life in the short and long term. Patient experience
• Delphi consensus development for physiotherapy interventions

2.3 Standardising the interventions

Physiotherapy treatment that was being used included combinations of advice, exercises, and therapist-applied mobilisation techniques. The modalities of treatment recommended for use were described within the UK national physiotherapy guidelines for frozen shoulder, which were based on a systematic review.[14] These were either provided in isolation, or as a supplement to other interventions such as intra-articular injection of corticosteroid or surgical interventions (MUA or ACR). Intra-articular corticosteroid injection helps improve inflammation of the joint capsule and reduce pain which may facilitate the performance of exercises and hence enhance the effects of physiotherapy. Intra-articular corticosteroid injection has been shown to provide short-term benefit with better improvement in pain, function and range of movement (up to 6-7 weeks) compared to placebo[7] and probably compared to isolated manual therapy and exercise.[14] It was important to reduce variations in practice and standardise the physiotherapy intervention to be compared in the trial. Whilst standardising physiotherapy would not be 'pragmatic' in the sense that it was not standard NHS practice before the trial, it would lead to a reduction in the variation which would arguably lead to better generalisation of the results. Including an intraarticular steroid injection as part of the

physiotherapy was important[14] and a structured physiotherapy pathway was developed using a national Delphi consensus process. This intervention could be accessed relatively quickly within the participating centres in the trial and therefore the intervention was termed 'Early Structured Physiotherapy' (ESP).[26]

The components and standardisation of the surgical trial interventions were informed by a survey of 53 surgeons who were Principal Investigators (PIs) for two multi-centre shoulder surgical RCTs.[27 28] Whilst it was recognised that a pragmatic approach was important to allow additional individualised treatment, there was unanimous agreement that core components of Manipulation Under Anaesthesia (MUA) and Arthroscopic Capsular Release (ACR) could be defined. There was agreement that MUA should be performed under General Anaesthesia, where an intraarticular steroid injection is administered, and the shoulder manipulated to stretch and 'tear' the tight capsule to overcome the contracture. That should be followed by a course of physiotherapy to maintain the mobility achieved with MUA. The surgical procedure ACR, performed under a General Anaesthetic, should incise and surgically release the contracted shoulder capsule in the rotator interval using 'keyhole' surgery. The shoulder should then manipulated to ensure good release of the capsular contracture has been achieved. That should then be followed by a course of physiotherapy to maintain the mobility achieved with ACR. These were defined as the core components of MUA and ACR that should be delivered for these interventions in an RCT. The physiotherapy following MUA and ACR was also standardised using a Delphi consensus process and was termed 'Post-Procedural Physiotherapy' (PPP).[26]

2.4 Developing consensus for the Physiotherapy interventions

Physiotherapy protocols were developed for the RCT incorporating best evidence but recognising uncertainty and allowing flexibility by using a composite methodology. Firstly, we screened a UK Department of Health systematic review and UK evidence-based guidelines[14] for recommendations, and previous surveys of UK physiotherapists[29 30] for strong consensus. The systematic review and guideline recommended including steroid injection and manual mobilisations in non-operative care, and consensus in the pre-existing surveys strongly favoured advice, education and home exercises.

Secondly, we conducted a two-stage, questionnaire-based, modified Delphi survey of shoulder specialist physiotherapists in the UK NHS. The aim was to rationalise development and

implementation of the physiotherapy protocols in the RCT, to make the interventions relevant and acceptable beyond the trial. This involved:

- developing physiotherapy protocols incorporating 'best practice' insofar as this could be established, while recognising uncertainty and accommodating clinical adaptability.
- implementing these protocols for stand-alone and post-operative physiotherapy, whereby any possible physiotherapy intervention would fall into one category on an ordinal scale of 'mandatory', 'optional' or 'not allowed'; and
- gauging the optimal duration of a course of physiotherapy based on clinical considerations.

The main interventions considered to fall under the umbrella of 'Physiotherapy' were patient education, prescribing home exercise programmes, intra-articular steroid injection, hands-on techniques including manual mobilisations, exercises, thermo/electro-therapies, neural dynamics, and acupuncture related techniques. Aromatherapy and Occupational therapy were not considered to be 'Physiotherapy' but were included in the Delphi process for the sake of completeness to derive consensus on the treatment modalities.

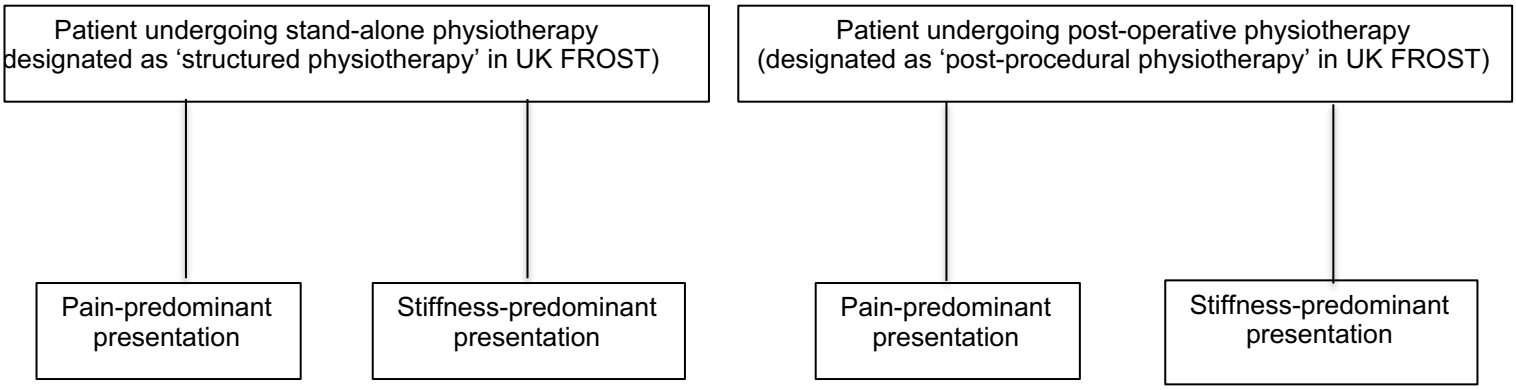
There were three fundamental standards established *a priori*: Physiotherapy in the RCT (1) should be delivered by qualified physiotherapists (2) should be delivered in hospital settings and (3) post-operative physiotherapy should ideally commence within 24 hours of the procedure. Each intervention had to be categorised in four clinical contexts [Figure 5], which accounted for whether physiotherapy was stand-alone or post-operative and whether the presentation was 'pain-'or 'stiffness-predominant'.

2.4.1. Delphi questionnaire and sampling frame

The target population and sampling frame were NHS shoulder specialist physiotherapists from three major shoulder RCTs in the NHS: CSAW,[31] ProFHER,[28] and UKUFF.[27] A full list of potentially relevant treatment interventions (Table 4) was used to populate a Delphi questionnaire in which respondents would be required to categorise the respective interventions as 'should always be used' (mandatory), 'should not be used' (not allowed) or 'optional' in each of the four study contexts defined in Figure 5.

Certain interventions were pre-categorised based on recommendations of evidence-based clinical guidelines and HTA systematic review,[7 14] on strong, previously established expert consensus,[30] or both. Spaces were provided for respondents to add any unlisted treatment interventions that they thought important. Round two questionnaires replicated those of round one but reminded respondents of their respective round-one categorisations as well as presenting the modal categorisations for all respondents. Thus, individual responses were informed by those of the group and could be modified at this stage. The Delphi was structured to deliver the best possible consensus over 2 rounds.

Figure 5. Four clinical contexts in UKFROST



As a Surgeon and Chief Investigator, I had worked with the site Principal Investigators of CSAW, ProFHER and UKUFF, and I personally emailed each of them (N = 113) to ask that they forward the email with Participant Information Sheet and the first-round questionnaire to the appropriate physiotherapists at their site. It was estimated that the sampling frame comprised between 70 and 100 physiotherapists. Consensus criteria that were defined *a priori* are shown in Table 5.

Table 4. Interventions considered in the Delphi questionnaires (including those added by respondents).

Category	Intervention
Education and re-education	*Advice and education (±. PT, (Post-op), Pain, Stiff)*
	Alexander technique
	CBT
	Explain pain
	Graded motor imagery
	Mirror therapy

	Posture re-education
	Relaxation techniques
Injection	*Intra-articular steroid injection (†, ǂ, PT, Pain)*
Hands-on techniques	*Manual mobilisations (†, ǂ, PT, Pain, Stiff)*
	Bowen therapy
	Craniosacral therapy
	Effleurage for pain
	Mobilisations with Movement (MWMs)
	Muscle energy techniques
	Myofascial release
	PNF
	Spinal/scapulothoracic manual therapy
	Therapist-assisted end range mobilisations
	Tool-assisted soft tissue techniques
Exercises	1-to-1 function based exercises
	1-to-1 gentle active exercises
	1-to-1 sustained stretching exercises
	Active assisted exercises with scapula control
	Facilitation/strength training of rotator cuff/scapula
	Gentle pulley exercises
	Hydrotherapy
	Land-based exercise class
	Pain-relieving self-mobilizations
	Passive assisted exercises
	Scapula setting
Neural dynamics	Neural dynamics
Electro- and thermotherapies	Laser
	Interferential
	Shortwave diathermy
	Shockwave therapy
	Superficial cold
	Superficial heat
	TENS
	Ultrasound
Acupuncture and related	Acupressure
	Acupuncture
	Dry needling
	Electro-acupuncture
	Trigger-point therapy
	Deep tendon friction
	Effleurage

	Myofascial release
Taping techniques	Conventional taping
	Kinesiotaping
Immobilization	Brace
Other	Aromatherapy
	OT or combined assessment

Pre-specified mandatory interventions are in italics, where † is based on empirical evidence and ≠ on previous questionnaire surveys; *PT* is stand-alone physiotherapy, *post-op* post-operative physiotherapy, *Pain* to pain- predominant and *Stiff* to stiffness-predominant.

Table 5. Consensus criteria.

Definition of consensus	Consensus threshold	Implementation of intervention in a Trial protocol	
'Should always be used'	100%	Mandatory	
'Should always be used'*	80%	Encouraged	Optional
—	—	—	
'Should not be used'*	80%	Discouraged	
'Should not be used'*	90%	Not allowed	

*"Don't know" responses were excluded from the consensus calculations.

2.4.2. Delphi results and their application

There were 46 responses to round one (41% response rate) and 42 to round two, demonstrating good retention (91%). A potential limitation of this approach was the relatively narrow sampling frame that included only secondary-care based physiotherapists. Whilst this achieved the objective of defining physiotherapy for the randomised trial within the secondary care setting, including responses from community-based physiotherapists would have gathered wider views and helped develop broader consensus across healthcare settings. No interventions achieved the 100% consensus criterion for 'should always be used', but some, all exercise-related, reached or exceeded 80%. Some interventions met or exceeded our 90% consensus criterion for 'should not be used', for example, deep friction, laser and provision of a brace. There was also > 90% consensus that craniosacral therapy, interferential and shockwave therapy 'should not be used' in the stiffness- predominant phase. Some other interventions met or exceeded our 80% consensus criterion for 'should not be used' in one or

more of the four clinical contexts, and the protocol discouraged their use in those contexts. Summary of the responses are provided in Appendices A, B, C, and D.

This work enabled the development of Physiotherapy treatment log sheets for recording key session characteristics, one for standalone Early Structured Physiotherapy and one for Post-Procedural Physiotherapy. The treatment modalities to be delivered were categorised as 'must be given', 'not essential but encouraged', 'discouraged', and 'not allowed' for both pain predominant and stiffness predominant presentations [Appendices E & F]. There were two key considerations in implementing the physiotherapy protocols within an RCT. First, the data collection instrument had to capture interventions in sufficient detail to enable comprehensive reporting as recommended by the TiDIER guidelines[32] and be navigable by clinicians and researchers alike. Second, in order to optimise participating physiotherapists' adherence and the reliability of their recording, it had to be clearly presented and quick and easy to complete, requiring little more than routine record keeping. This would help optimise recording, monitoring and reporting of the physiotherapy interventions in the trial. Alongside guidance on the number and distribution of physiotherapy sessions, this would provide a clearly defined treatment framework and facilitate monitoring of treatment fidelity as well as recording of the interventions given. This approach is broadly commensurate with the strategy for standardising complex surgical interventions that has been recommended.[33] The stand-alone physiotherapy and the post-procedural physiotherapy programmes were thus developed using evidence from a systematic review,[7] UK guidelines,[14] previous surveys of UK physiotherapists[29 30] and consensus from expert shoulder physiotherapists in secondary care derived from a Delphi survey.[26]

3. The United Kingdom Frozen Shoulder Trial (UKFROST)

3.1 Design considerations

The design of the trial was informed by the preparatory work described in the previous sections. The three most commonly used treatments for FS when stiffness sets in were Physiotherapy, Manipulation Under Anaesthesia, and Arthroscopic Capsular Release, and these were confirmed as important to compare in a Randomised Controlled Trial (RCT).[17] Only 6% of respondents in the national survey conducted suggested Hydrodilatation as a comparator

they could use in a trial, which did not make this a feasible intervention to test within an RCT. As MUA and ACR were surgical interventions that are provided in secondary care, the setting of the trial had to be in secondary care NHS hospitals. The standalone Physiotherapy intervention could be provided earlier than the surgical interventions in secondary care and therefore this was called Early Structured Physiotherapy (ESP). Achieving pain control was crucial to enable patients to perform their shoulder exercises and therefore provision of intraarticular steroid injection at the start of ESP was important.

My own perceptions from my clinical practice, which are verified by the literature[7 34] is that the priority for patients with FS is relief from shoulder pain. Key outcomes from interventions assessed in an RCT would therefore need to include patient reported pain levels in addition to shoulder function and general quality of life. These aspects would best be captured by validated Patient Reported Outcome Measures (PROMs). One of the challenges for the RCT would be the different waiting times in the NHS for delivery of the three interventions. There was likely to be a longer wait to receive ACR than MUA, and the waiting time for both was longer than for ESP. In addition to collecting PROMs at baseline at the time of randomisation, collecting the primary outcome at the start of delivery of the interventions would help explore the impact of the different waiting times on outcomes. Follow up of 12 months from randomisation would be desirable to allow recovery from any complications or further treatment and that in turn would allow more credible comparisons of outcomes from the three trial treatment pathways. A multicentre RCT with a pragmatic design was important to ensure subsequent generalisability and applicability of trial findings to practice in the NHS.

The United Kingdom FROzen Shoulder Trial (UKFROST) was commissioned and funded by the NIHR-HTA programme NIHR-HTA Project 13/26/01). I led the grant application and was the Chief Investigator with overall responsibility for trial conduct and reporting. NRES Committee North East – Newcastle and North Tyneside 2 approved the study on the 18 November 2014 (REC reference 14/NE/1176). Health Research Authority (HRA) approval for the study with an existing UK wide review was granted on 15 June 2016.

3.1.1. Objective

The main objective of the trial, underpinned by the key treatment uncertainties, was to evaluate the effectiveness and cost-effectiveness of Early Structured Physiotherapy (ESP)

versus MUA versus ACR for patients referred to secondary care for the treatment of primary frozen shoulder.

3.1.2. Trial design

This was a pragmatic, multi-centre, stratified (diabetes present or not), superiority trial comparing three parallel groups (MUA versus ACR versus ESP, with unequal allocation [2:2:1]) in adult patients referred to secondary care in England, Wales and Scotland for the treatment of primary frozen shoulder, and for whom surgery was being considered. An internal pilot, from which the data contributed to the final analyses, confirmed the trial feasibility. Alternative study designs (e.g., two level comparison of surgery vs ESP and MUA vs ACR; superiority of surgery vs ESP and non-inferiority of MUA vs ACR) were considered but in view of the increasing degree of invasiveness of the three interventions that are sufficiently different, demonstrating superiority with the three-way comparison would be important to justify higher potential risks and invasiveness. The same logic applies when comparing the two surgical interventions MUA and ACR, where ACR is more invasive than MUA.

3.1.3. Participants

Patients with primary frozen shoulder were identified through clinical examination and plain radiographs.[35] To minimise diagnostic uncertainty, the clinical examination included the key diagnostic assessment of restriction of passive external rotation in the affected shoulder[36] for which there is evidence of good inter-rater agreement on whether restriction is present[37] and a high threshold (50% restriction) for inclusion. Plain radiographs (antero-posterior and axillary projections) were obtained routinely for all patients to see whether they were normal and could exclude glenohumeral arthritis and other pathology that could lead to similar clinical presentation (e.g. locked posterior dislocation).

Table 6. Participant inclusion and exclusion criteria

Inclusion criteria
Patients, including diabetics, were eligible if: • they were aged 18 year or older • they presented with a clinical diagnosis of frozen shoulder characterised by restriction of passive external rotation in the

affected shoulder to less than 50% of the contralateral shoulder; and • they had radiographs to exclude other pathologies.
Exclusion criteria
Patients were excluded if: • they had a bilateral concurrent frozen shoulder • their frozen shoulder was secondary to trauma which necessitated hospital care e.g. fracture, dislocation, rotator cuff tear • their frozen shoulder was secondary to other causes e.g. recent breast surgery, radiotherapy • any of the trial treatments (e.g. unfit for anaesthesia or corticosteroid injection) were contraindicated • they were not resident in a catchment area of a trial site • they lacked the mental capacity to understand the trial.

3.1.4. Setting

The trial recruited from the orthopaedic departments of 35 National Health Service (NHS) hospitals in the UK across a range of urban and rural areas. This included 28 hospitals in England, six in Scotland and one in Wales. There were two additional hospitals in England that screened for patients but did not recruit into the trial. Recruitment started in April 2015 and the final follow-up was in December 2018.

3.1.5. Intervention delivery

Whilst there was standardisation of core components of each intervention, a pragmatic approach was taken for delivery of the interventions at the trial sites. Physiotherapy was delivered by qualified physiotherapists (i.e. not students or assistants) and participating surgeons were familiar with the surgical procedure(s). There was no minimum number of surgical procedures that the surgeon had to have performed, and no grades of surgeon were excluded. Which surgeon operated on participants and whether the individual surgeon needed to be supervised by a consultant was at the discretion of the participating site and followed normal care pathways and practices. The experience of physiotherapists and surgeons

delivering the trial treatments was recorded in terms of their salary bands and number of frozen shoulder patients treated in a typical month.

ESP: The development of the physiotherapy programmes are available on-line.[26] Whilst physiotherapy is a common treatment in NHS practice, the ESP intervention was a specifically designed and standardised physiotherapy pathway to test the optimal delivery of physiotherapy in the NHS based on the best available evidence and expert consensus.[26] Participants received up to 12 sessions of ESP over a period of up to 12 weeks. The physiotherapy package included an information leaflet containing education, advice on pain management and function; supervised exercises; home exercise programme; an intra-articular steroid injection; and hands-on mobilisation techniques.[25 38] Control of pain with a steroid injection to enable performing the shoulder exercises was an integral part of ESP. Steroid injections were administered with or without imaging guidance depending on the usual practice of the hospital site. Available evidence did not support the superiority of either approach.[39] Participants who did not improve with ESP were referred for further treatment to the treating surgeon following a 12-week assessment and any further treatment provided was recorded. The ESP given at each session was recorded in the Physiotherapy logbook.

Participants assigned to either MUA or ACR were placed on the surgical waiting list and underwent routine pre-operative screening. The procedures were performed under general anaesthesia and were expected to be day cases. Post-operative analgesia including nerve blocks were provided as per usual care in the treating hospital.

MUA: The affected shoulder was manipulated to stretch and tear the tight capsule and to improve range of movement and injection of corticosteroid to the glenohumeral joint was performed. In the unlikely event that the MUA was judged to be incomplete it was recommended that the surgeon should not cross-over intra-operatively to capsular release. The need for this was to be reviewed at another clinic appointment to allow assessment of outcome of the MUA and the need for any further intervention.

ACR: Arthroscopic release of the contracted rotator interval and anterior capsule was performed, followed by MUA to complete the release. Additional procedures like posterior capsular release or subacromial decompression and steroid injection (which may carry a higher risk of infection) were permitted at the surgeon's discretion.[40]

Post-Procedural Physiotherapy (PPP): Following MUA or ACR, participants underwent up to 12 weeks of physiotherapy commencing within 24 hours of the procedure. The aim was to reduce pain and aid with regaining/maintaining the mobility achieved by the operation.

Adherence to the trial treatments was monitored in the internal pilot phase to check the feasibility of delivering the ESP programme, surgical interventions, and PPP. Every month extracted data from the hospital Case Report Forms (CRFs) was reviewed by me as the Chief Investigator (CI), and the Lead Trial Physiotherapist for treatment adherence. This was further monitored by the Trial Management Group (TMG), independent Trial Steering Committee (TSC) and the Data Monitoring Ethics Committee (DMEC).

3.1.6. Outcomes

I wanted to capture patient reported pain levels, shoulder function, and general quality of life as key outcomes. Following discussions within the trials team, we agreed on Oxford Shoulder Score (OSS), a patient-reported measure, as the primary outcome. OSS captures both pain and functioning and additional work has confirmed it does not have a 2-factor structure.[41] The development and validation of OSS included patients with frozen shoulder[42] and has been used in the follow-up of these patients.[15] OSS is a 12 item measure with five response categories and a range of scores from 0 (worst) to 48 (best).[43] The OSS was completed by the participant at the hospital at baseline prior to randomisation, and by postal questionnaires at 3, 6 and 12 months after randomisation. OSS was also collected at the start of intervention delivery. The primary endpoint was 12 months after randomisation allowing the interventions and co-treatment interventions to be delivered and the majority of any ensuing complications to be treated.

Secondary outcomes collected at 3, 6, and 12 months from randomisation were Quick Disabilities of Arm, Shoulder and Hand (QuickDASH),[44] EuroQuol-5 Dimensions-5 levels (EQ-5D-5L),[45-48] Numeric Rating Scale for pain.[49] Complications during trial follow up were collected at 12 months. Non-serious Adverse Events (AE) and Serious Adverse Events (SAE) were collected throughout the trial follow up period.

3.1.7. Sample size

The primary trial outcome was the OSS and was assessed for three treatment comparisons: ESP compared with MUA, ESP compared with ACR and MUA versus ACR. There are data to suggest a 4 to 5-point improvement can be found on the OSS[50-52] (standard effect size of 0.33 to 0.42), with a stable standard deviation of 12 points across different populations. The larger effect size of 0.42 was required to justify the greater costs and potential risks associated with surgery when comparing ESP with MUA and ESP with ACR.[43] A smaller difference of 4 points on the OSS (effect size of 0.33) was expected to distinguish between MUA and ACR. To observe these effect sizes with 90% power and 5% two-sided significance, adjusting for a moderate estimate (r=0.4) of the correlation between OSS over 12 months and allowing for 20% attrition, a total sample size of 500 patients was required (MUA: 200, ACR: 200, ESP: 100).

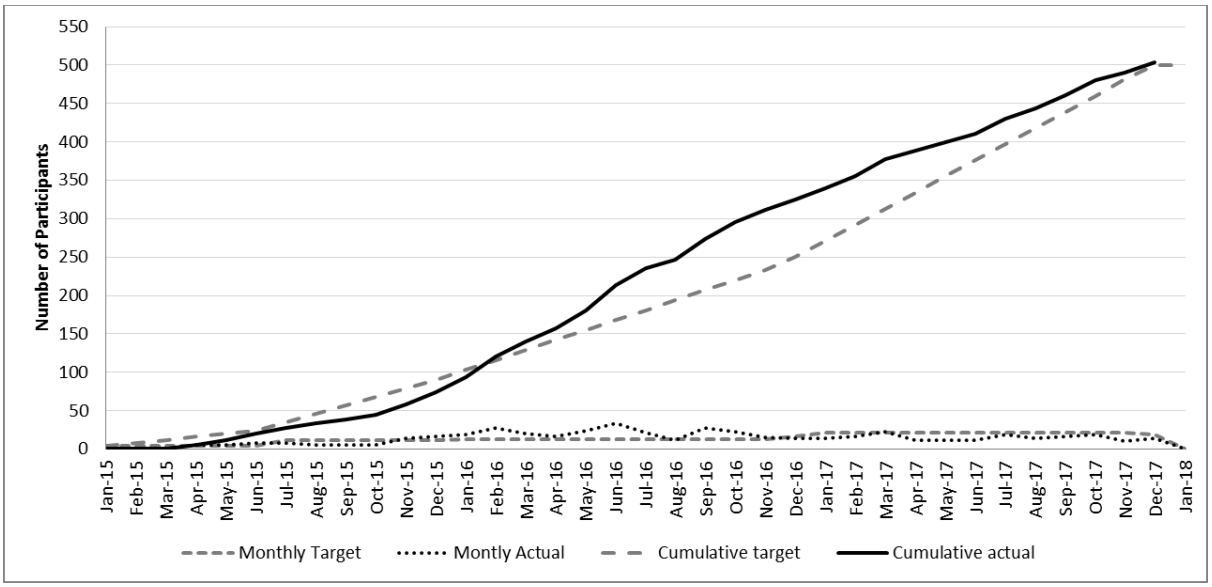
3.1.8. Randomisation

Computer-generated remote randomisation (telephone or online access) was provided by York Trials Unit (YTU), University of York. The unit of randomisation was the individual patient, allocated to MUA:ACR:ESP in the ratio of 2:2:1, stratified by the presence of diabetes,[53] using random blocks sizes of 10 and 15. Research staff from trial sites used the remote randomisation service to register eligible and consenting patients before computer generation of the allocation. This ensured treatment concealment and immediate unbiased allocation. Given the nature of the trial treatments, comparing surgical and non-surgical treatment options, the blinding of participants and clinicians to treatment allocation was not possible or desirable in this pragmatic trial.

3.1.9. Recruitment

I secured engagement of clinicians from 35 NHS hospitals that regularly treated patients with frozen shoulder, and all of those 35 sites recruited to the trial. Hospital Episode Statistics (HES) data from NHS hospitals in England in 2009/2010 and 2010/2011 confirmed a stable rate of 210 per million patients treated for frozen shoulder. Assuming 50% of frozen shoulder patients presenting in secondary care met the inclusion criteria, and of whom 40% consented, we estimated at least 25 hospitals each serving half a million population would be needed to recruit 500 participants. Successful recruitment was a particular highlight and was completed precisely to time and target within budget [Figure 6].

Figure 6. Trial recruitment: Apr 2015 to Dec 2017 (35 centres); Screened: 914 Recruited: 503 (MUA=201; ACR=203; ESP=99)



Of the 914 patients screened who met the inclusion criteria, 95 were excluded for genuine clinical reasons, and a further 21 excluded for other reasons. Review of the baseline characteristics confirmed the inclusion of appropriate trial participants who were in their sixth decade of life and slightly more women.[54 55] There were comparable characteristics between 295 eligible patients who did not consent and eligible patients who consented to take part. The characteristics (age, gender, diabetes, symptom duration, laterality and patient preferences) of ineligible and non-consenting patients were comparable to the randomised patient population. The baseline characteristics of included trial participants were well balanced across the three groups (both 'as randomised' and 'as analysed'). Sensitivity analysis confirmed that small chance baseline imbalances (e.g., employment status) did not impact on the main trial results. The flow of participants from eligibility, randomisation to follow-up and analysis of the trial is presented in a CONSORT flow diagram [Figure 7]

3.2 Statistical methods

Analyses were conducted for the three treatment comparisons of interest: ACR vs ESP, MUA vs ESP and ACR vs MUA according to the principle of intention to treat. All analyses were conducted in Stata Version 15[56] using two-sided statistical significance at the 0.05 level. The

Statistical Analyses Plan was completed prior to completion of data collection on 12 February 2019 and agreed with the trial oversight committees.

3.2.1 Primary outcome (Oxford Shoulder Score) analysis

The primary analysis was conducted on intention to treat (ITT) basis, including patients in the groups to which they were randomised. The primary analysis compared OSS between treatment groups at 12 months. The primary outcome OSS was analysed using a covariance pattern linear mixed model, including assessments at all available time points with reference to the date of randomisation (3, 6 and 12 months, thereby increasing power) and treating patients as a random effect. The model was adjusted for OSS at baseline and included as further fixed effects: treatment arm, time, arm by time interaction, age, gender and diabetes. Differences in local practice and expertise were accounted for by including recruitment site as a random effect in the model. For all three treatment comparisons, the model provided estimates at individual time points (the estimate at the 12-month time point served as the primary endpoint for each of the three treatment comparisons), as well as an overall treatment effect over 12 months. These are reported as mean differences between treatment groups with 95% confidence intervals and associated p-values.

3.2.2 Secondary analyses

Complier Average Causal Effect (CACE) analysis was carried out for compliance with ESP (minimum of 8 ESP sessions *or* participant / physiotherapist satisfied with progress). The analysis adjusted for covariates of the primary analysis model. Analysis adjusting for waiting time was conducted with a separate secondary ITT random intercept linear mixed model including pre-treatment OSS and OSS 6 months from the start of treatment in addition to the three- and six-month post-randomisation data. Continuous secondary outcomes were reported descriptively (unadjusted mean, standard deviation, median, minimum and maximum). ITT linear mixed models were conducted for each outcome, adjusting for the same covariates as the primary analysis. A logistic regression model was used to determine treatment group differences in having experienced at least one adverse event if the number of participants with one or more events exceeded 10 in each arm. The same covariates used in the primary analysis were adjusted for.

3.2.3 Subgroup analyses

In order to explore differences in treatment response for different participant populations, three planned exploratory sub-group analyses were conducted: (1) influence of whether the participant was diabetic (yes/no); (2) whether the participant had previously received physiotherapy (yes/no); (3) treatment preferences at baseline (allocated to preferred treatment / not allocated to preferred treatment / had no preference); and (4) length of frozen shoulder symptoms at baseline (median of less/more than nine months as cut-off).

3.3 Main results

At the primary end point at 12 months, none of the comparisons reached the prespecified minimum clinically important effect sizes. Participants randomised to ACR were shown to have on average statistically significantly higher (better) OSS scores than MUA (2.01 points, 95% CI 0.10 to 3.91) and ESP (3.06 points, 95% CI 0.71 to 5.41). Although statistically significant, mean estimates were short of the sought minimal clinically important effect size of 4 to 5 OSS points. Table 7 provides the adjusted estimates of group means and mean differences for each treatment comparison, and Figures 8, 9, and 10 show the Group Means with Confidence Intervals (CI). Group Means and CI for the secondary outcomes are in Figures 11 and 12. At 3 months post-randomisation, ACR was shown to have lower (worse) outcomes compared with the other two interventions, but this was an artefact of waiting times, as many participants randomised to ACR had not yet received their allocated treatment at that timepoint.

In addition to questionnaires completed at post-randomisation follow-ups, participants were asked to complete the OSS just before and 6 months following receipt of treatment in order to account for the differential waiting times for each trial treatment. The OSS between randomisation and start of treatment remained stable, including in the ACR arm where the waiting times for treatment were the longest. Estimated Mean differences by treatment arm are provided in Table 8. Compared with the primary analysis model, group differences 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). The 95% CI interval still included the minimal clinically important difference for this comparison of 5 OSS points.

Figure 7. UKFROST CONSORT flow diagram

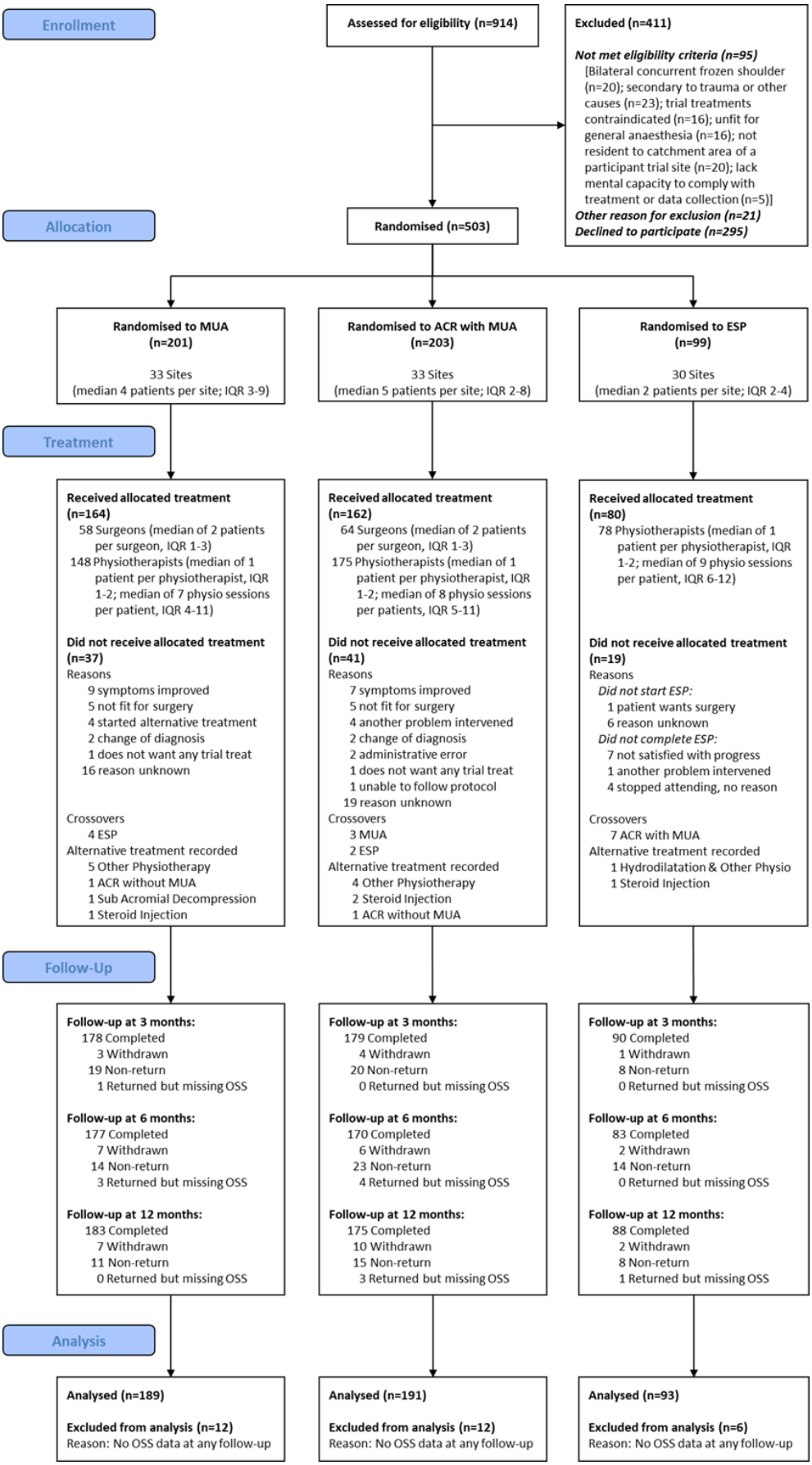


Table 7. Estimated Mean OSS Differences by Treatment Arm (Primary Analysis Model[a])

	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	p-value
	MUA	**ESP**	**Difference**	
3 months	30.2 (28.8 to 31.6)	31.6 (29.7 to 33.5)	-1.36 (-3.70 to 0.98)	0.25
6 months	37.1 (35.7 to 38.4)	34.9 (33.0 to 36.8)	2.15 (-0.12 to 4.42)	0.06
12 months[b]	38.3 (36.9 to 39.7)	37.2 (35.3 to 39.2)	1.05 (-1.28 to 3.39)	0.38
Average	35.2 (34.0 to 36.4)	34.6 (33.0 to 36.2)	0.61 (-1.31 to 2.53)	0.53
	ACR	**ESP**	**Difference**	
3 months	26.9 (25.5 to 28.3)	31.6 (29.7 to 33.5)	-4.72 (-7.06 to -2.39)	<0.01
6 months	35.9 (34.6 to 37.3)	34.9 (33.0 to 36.8)	0.98 (-1.31 to 3.26)	0.40
12 months[b]	40.3 (38.9 to 41.7)	37.2 (35.3 to 39.2)	3.06 (0.71 to 5.41)	0.01
Average	34.4 (33.2 to 35.5)	34.6 (33.0 to 36.2)	-0.23 (-2.15 to 1.70)	0.82
	ACR	**MUA**	**Difference**	
3 months	26.9 (25.5 to 28.3)	30.2 (28.8 to 31.6)	-3.36 (-5.27 to -1.45)	<0.01
6 months	35.9 (34.6 to 37.3)	37.1 (35.7 to 38.4)	-1.17 (-3.02 to 0.67)	0.21
12 months[b]	40.3 (38.9 to 41.7)	38.3 (36.9 to 39.7)	2.01 (0.10 to 3.91)	0.04
Average	34.4 (33.2 to 35.5)	35.2 (34.0 to 36.4)	-0.84 (-2.41 to 0.72)	0.29

[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

Figure 8. Treatment effects from ITT mixed model analysis (1)

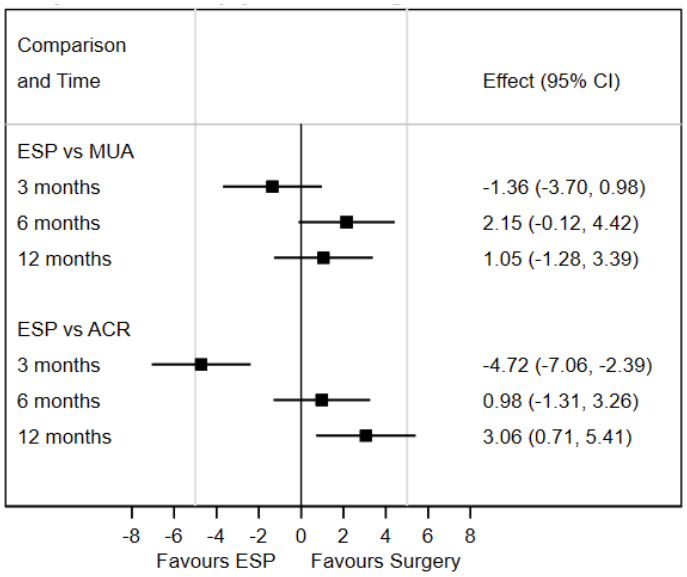


Figure 9. Treatment effects from ITT mixed model analysis (2)

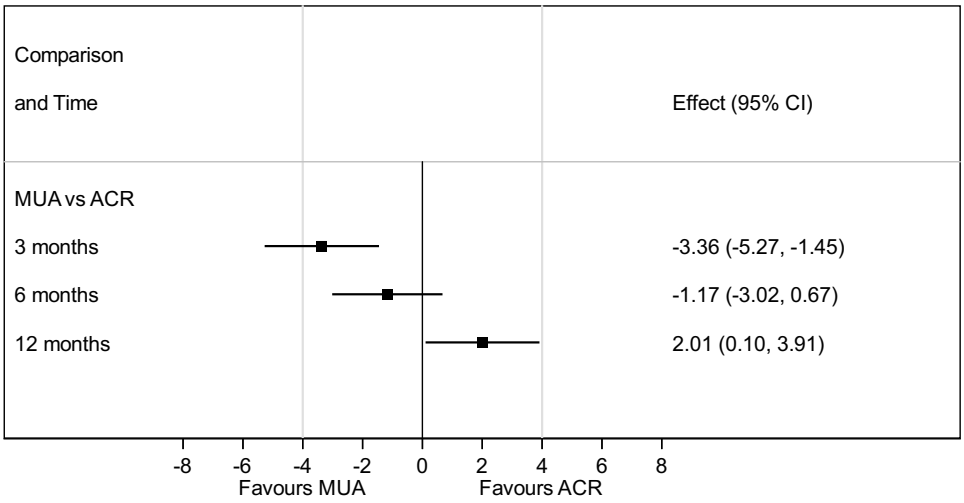


Figure 10. Raw OSS Means and 95% CI

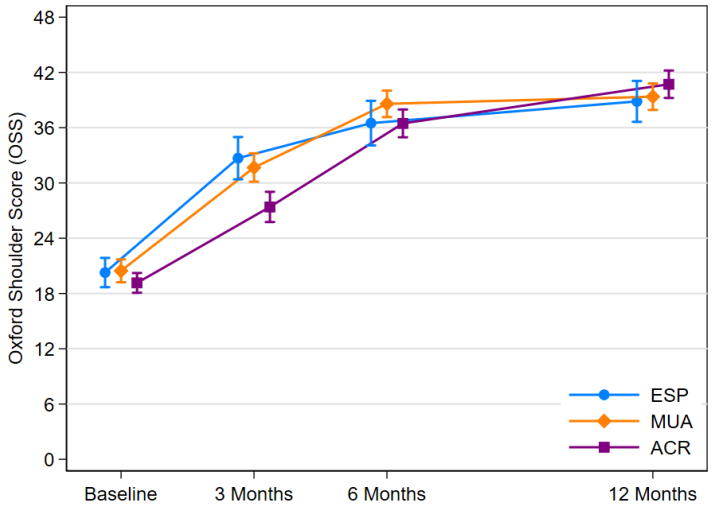


Figure 11. Raw QuickDASH Means and 95% CI

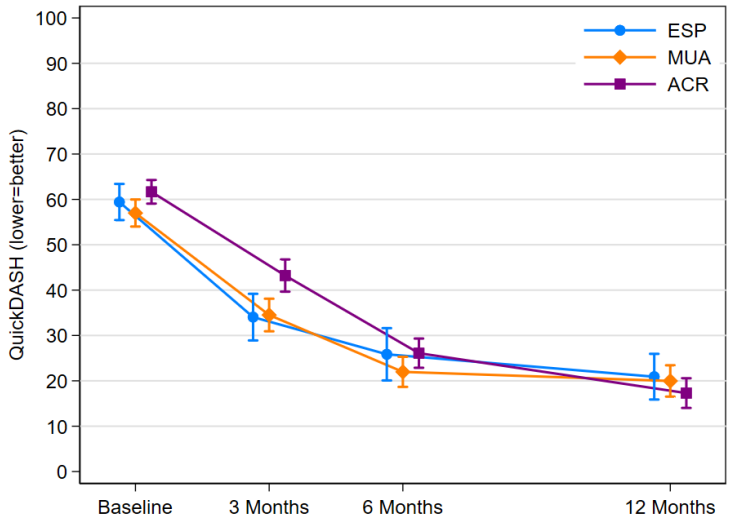


Figure 12. Raw Pain NRS Means and 95% CI

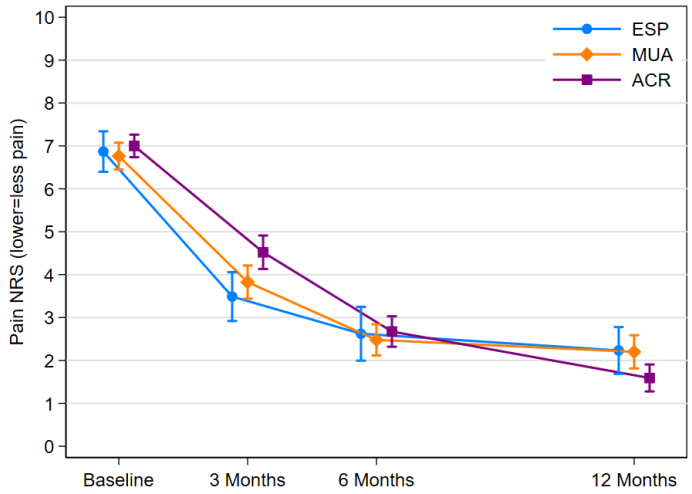


Table 8. Estimated Mean OSS Differences by Treatment Arm (Estimates from Model incorporating follow-ups before and after treatment in addition to post-randomisation outcomes[a])

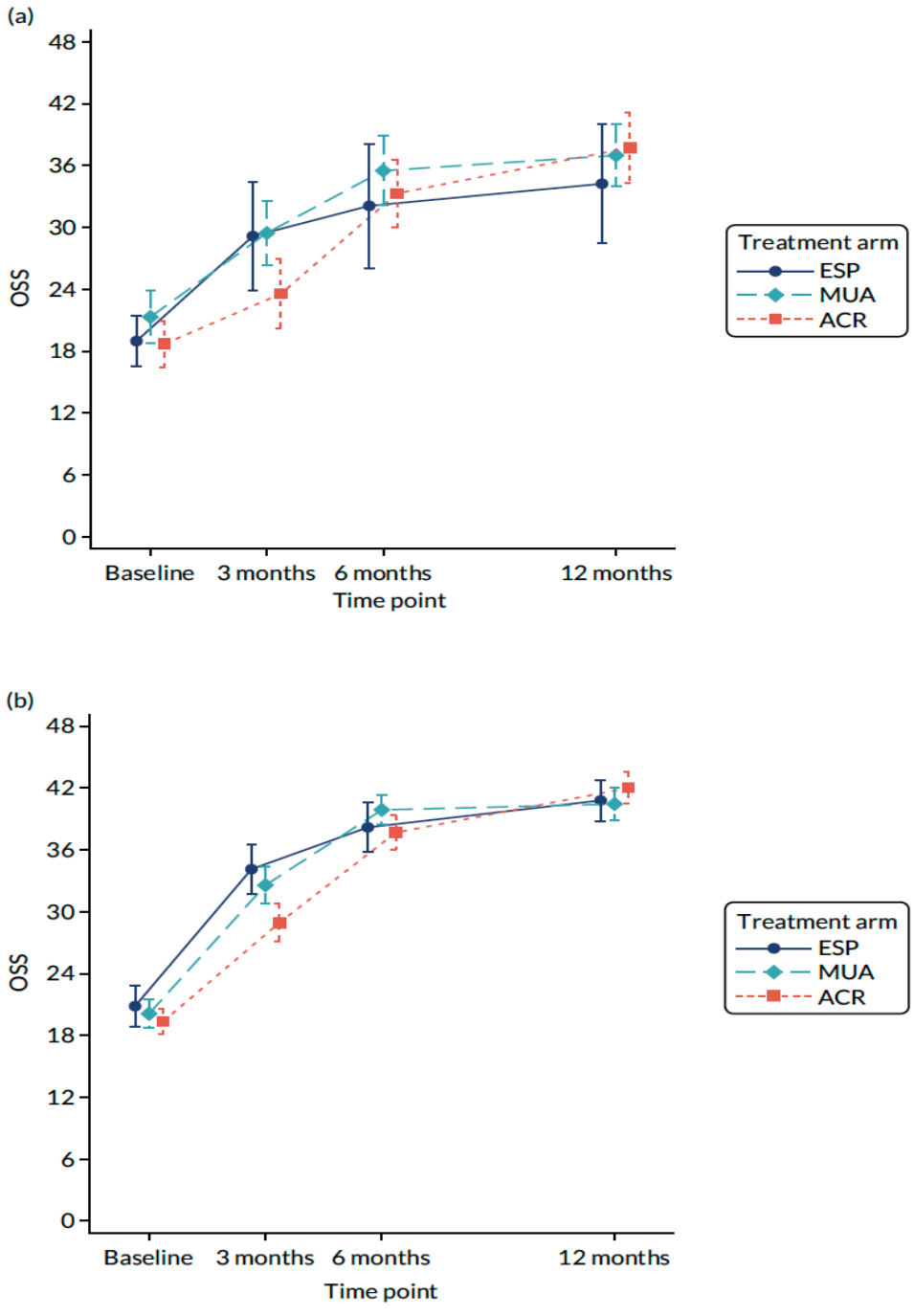
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	p-value
	MUA	**ESP**	**Difference**	
3 months	28.2 (27.1 to 29.3)	29.4 (27.8 to 30.9)	-1.18 (-3.10 to 0.73)	0.23
6 months	32.5 (31.5 to 33.5)	32.7 (31.2 to 34.1)	-0.15 (-1.90 to 1.60)	0.87
12 months	41.1 (40.0 to 42.3)	39.2 (37.5 to 40.9)	1.92 (-0.16 to 4.00)	0.07
	ACR	**ESP**	**Difference**	
3 months	26.0 (24.9 to 27.2)	29.4 (27.8 to 30.9)	-3.33 (-5.25 to -1.40)	<0.01
6 months	31.5 (30.5 to 32.5)	32.7 (31.2 to 34.1)	-1.13 (-2.88 to 0.62)	0.21
12 months	42.5 (41.3 to 43.7)	39.2 (37.5 to 40.9)	3.26 (1.18 to 5.35)	<0.01
	ACR	**MUA**	**Difference**	
3 months	26.0 (24.9 to 27.2)	28.2 (27.1 to 29.3)	-2.14 (-3.71 to -0.57)	0.01
6 months	31.5 (30.5 to 32.5)	32.5 (31.5 to 33.5)	-0.98 (-2.40 to 0.44)	0.18
12 months	42.5 (41.3 to 43.7)	41.1 (40.0 to 42.3)	1.35 (-0.33 to 3.02)	0.12

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

Diabetic patients tended to have poorer outcomes compared with non-diabetic patients at all time-points [Figure 13]. Patients who had previous physiotherapy tended to have worse

outcomes if randomised to ESP, whereas patients who indicated a prior preference for physiotherapy tended to have better outcomes if randomised to ESP and worse outcomes if randomised to either surgical treatment. Participants who reported frozen shoulder symptoms for 9 months or more prior to entering the trial, tended to have worse outcomes at 3 months if randomised to ACR and better outcomes at 3 months if randomised to ESP.

Figure 13. Unadjusted Mean OSS by treatment arm and (a) diabetic; and (b) non-diabetic



There were 10 serious adverse events and 33 non-serious adverse events [Table 9]. The relatively low numbers of these in each intervention arm provides further reassurance of competence in delivery of the trial interventions. A higher proportion of participants who received ESP accessed further treatment when compared with MUA or ACR [Table 10].

Table 9. Serious and Non-Serious Adverse Events (as treated)

	MUA N=167	ACR N=169	ESP N=86	Other N=17	None N=64
Serious Adverse Events					
Total number of events	2	6	0	1	1
Patients	2 (1%)	5 (3%)	0 (0%)	1 (6%)	1 (2%)
Potentially long lasting consequences					
DVT	-	-	-	1	-
Stroke	-	1	-	-	-
Septic Joint Arthritis	1	-	-	-	-
Likely anterior dislocation	1	-	-	-	-
Non-Serious Adverse Events					
Total number of events	15	12	4	2	0
Patients	14 (8%)	11 (7%)	4 (5%)	2 (12%)	0 (0%)

Table 10. Further treatment

	MUA N=164 completed	ACR N=162 completed	ESP N=80 completed
Required Further Treatment	20 (12%)	10 (6%)	19 (24%)
Received Further Treatment	14 (9%)	8 (5%)	15 (19%)
ACR	4	-	4
ACR without MUA	3	-	1
Arthroscopic arthrolysis and decompression	-	-	1
MUA	1	1	3
Injection	5	4	4
Physiotherapy	2	3	6
Rheumatology clinic	-	-	1

3.4 Conclusions

UK FROST provided robust clinically relevant evidence that none of the three treatments were clearly superior on patient-reported shoulder pain and functioning at 12 months. Our specifically designed ESP pathway can be accessed quickly in the NHS, is relatively safe and is less invasive, but may carry a higher likelihood of needing further treatment. The surgical treatments are more invasive with higher risks but may carry a lower likelihood of needing further treatment. The results of this trial should help inform shared decision making in clinical practice.

4. Context and relevance of UKFROST

A systematic review of randomised trials helped place UKFROST in context of the existing randomised evidence for the management of primary frozen shoulder. The review protocol was prospectively developed and registered: International Prospective Register of Systematic Reviews (PROSPERO) registration number: CRD42019122999. The protocol for this review and the findings were reported in alignment with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist and the PRISMA guidance, respectively.[57 58]

4.1. Literature search

We adapted the search strategy used in our 2012 review[7] to search for any new RCTs of the interventions of interest. The searches for the 2012 review were conducted in March 2010, and we therefore used a start date of January 2010 for the updated searches with some overlap, allowing for delays in adding articles to the bibliographic databases. MEDLINE, Embase, PEDro, Science Citation Index, Clinicaltrials. gov, CENTRAL, and the World Health Organization (WHO) International Clinical Trials Registry were searched in December 2018. Eligible studies were RCTs comparing the effectiveness of MUA, ACR, Physiotherapy with Steroid Injection (PTSI), and hydrodilatation against each other, or supportive care or no treatment, for the management of primary frozen shoulder. Randomized clinical trials (RCTs) including people aged 18 years or older and with over 90% of participants with idiopathic (primary) frozen shoulder (adhesive capsulitis), with or without diabetes, were included. Studies treating general shoulder conditions were only included if outcomes were reported separately for participants with a frozen shoulder. The study selection is summarised in Figure 14. Literature search results were uploaded to Clarivate's EndNote referencing software (Clarivate Analytics, USA) and exported to Covidence, an online systematic review programme to remove duplicates and facilitate collaboration.[59] A data extraction form was developed in Microsoft Excel, piloted and adjusted using a small selection of studies.

4.2. Risk of bias assessment

The Cochrane Risk of Bias Tool was used to assess the risk of bias in included RCTs.[60] All studies were marked as high risk of bias for 'blinding of participants and personnel' and 'blinding of outcome assessment'. Studies with high attrition rate (i.e. over 30% in any single

arm) were marked as high risk of bias for 'incomplete outcome data'. [61-63] Three studies did not provide clear reasons for non-consent and drop outs; [62 64 65] one study only followed-up patients for 20 weeks; [66] one was from a single institution.[67] These studies were marked as 'unclear' for other risk of bias. [Figure 15]

Figure 14. Flow diagram of study selection

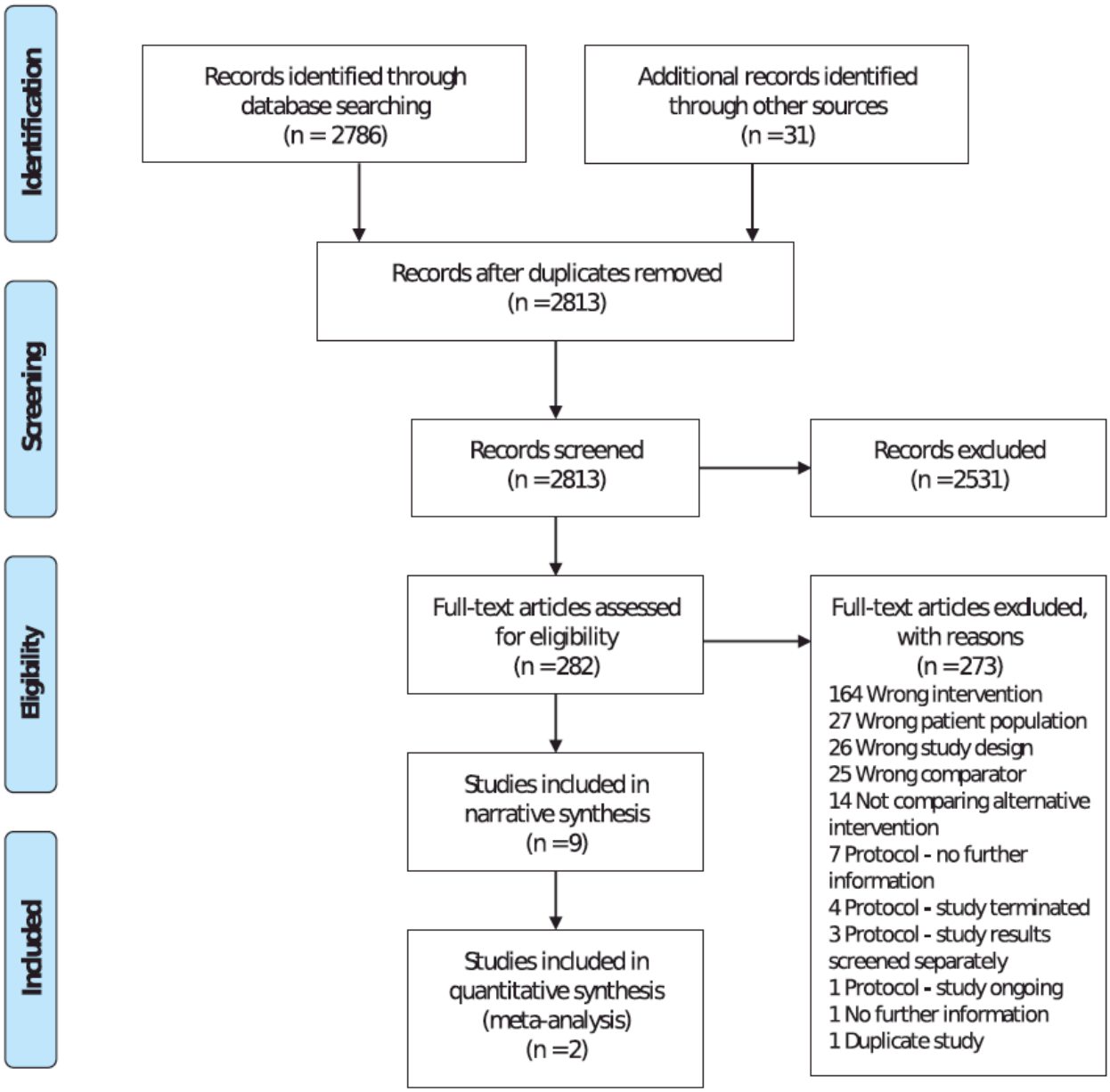
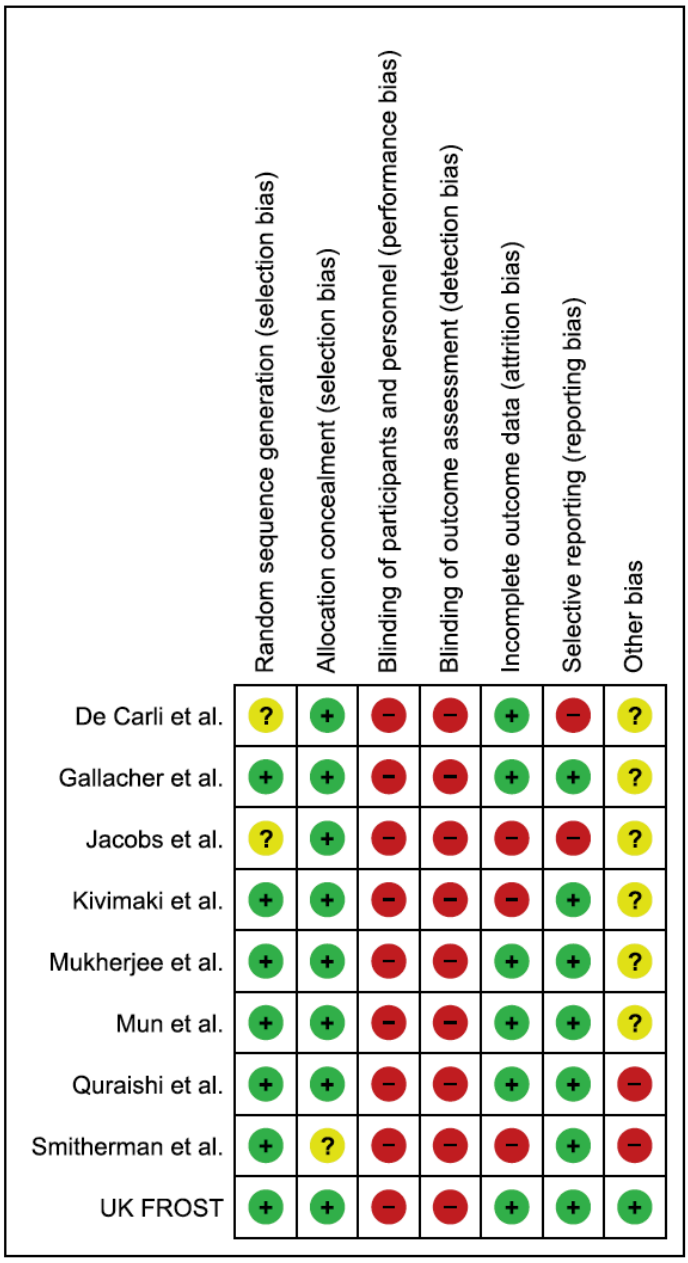


Figure 15. Risk of bias assessment of included studies



4.3. Synthesis of results

Studies were grouped by intervention and comparator. At baseline, the average age of patients in all RCTs was the sixth decade of their life. The percentage of females ranged from 54% to 70%. Seven of the nine RCTs were known to include diabetics. Duration of symptoms ranged from four to eleven months. Summary of the main study characteristics are provided in Table 11. The primary outcome of shoulder function score was reported for five studies comparing six combinations of interventions. The summary of results in Table 12 shows the

Mean Difference (MD, when same scales were used) and Standardised Mean Difference (SMD, when different measurement scales were used) for patient reported shoulder pain and function in the included studies. Of the nine RCTs included in the systematic review, five reported no complications in any of the treatment groups,[61 68-70] and one did not report whether complications were assessed.[71] One trial reported that there were no major complications in the MUA group but that small injuries of the joint were possible, as verified on arthroscopy.[62] One case of articular cartilage scuffing of glenoid, and one case of the humeral head were reported in the ACR group.[72] UK FROST reported more complications in the ACR group compared to MUA and PTSI.[73] A single pooled meta-analysis of two studies, UKFROST & De Carli et al, yielded an SMD of 0.32 in favour of ACR over PTSI. In view of a small number of centres providing Hydrodilatation as an intervention for FS when UKFROST was designed and commissioned, it was not feasible to formally test that intervention in the trial. Four RCTs that evaluated Hydrodilatation were included in this review, and the evidence was inconclusive with limited sample sizes ranging from 20 to 60 patients in the Hydrodilatation arm. Given the limited number of eligible RCTs, it was not feasible to perform a sub-analysis on studies with and without diabetic patients.

Table 11. Summary of study characteristics

Description	Country	Number randomised	Interventions	Number of sites	Number dropped out	Age in years Mean (SD)	Females in %	Included diabetic patients?	Diabetic patients (%)	Duration of symptoms (months)
Rangan et al., UK FROST 2020[74]	UK	503	1) MUA 2) ACR 3) Steroid and Physio	35	57 (11.33%)	54.3 (7.7)	63.42%	Yes	150 (29.82%)	10.9
De Carli et al., 2012[64]	Italy	46	1) ACR 2) Steroid and physio	1	2 (4.35%)	55.6	54.35%	Yes	6 (13.04%)	-
Gallacher et al., 2018[65]	UK	50	1) ACR 2) Hydrodilatation	1	11 (22%)	53.9 (9)	70.00%	Yes	8 (16%)	-

Description	Country	Number randomised	Interventions	Number of sites	Number dropped out	Age in years Mean (SD)	Females in %	Included diabetic patients?	Diabetic patients (%)	Duration of symptoms (months)
Jacobs et al., 2009[61]	UK	53	1) MUA 2) Hydrodilatation	1	10 (18.87%)	56.75	66.04%	No	0	4.4
Kivimaki et al., 2007[62]	Finland	125	1) MUA 2) Supportive care	3	46 (36.8%)	53 (8.5)	68.00%	Yes	18 (14.4%)	7.2
Mukherjee et al., 2017[66]	India	60	1) ACR 2) Steroid and physio	1	4 (6%)	50.4 (8.8)	58.93%	Yes	16 (28.57%)	6.3
Mun et al., 2016[67]	Korea	136	1) Steroid and physio 2) Hydrodilatation	1	15	53.01 (6.15)	62.81%	Unknown	-	6.5
Quraishi et al., 2007[71]	UK	36	1) MUA 2) Hydrodilatation	1	3	54.87	58.33%	Yes	6 (16.67%)	8.9
Smitherman et al., 2015[63]	USA	26	1) ACR 2) Supportive care	1	9	51.75 (9.2)	-	Yes	-	-

Table 12. Summary of results

Study	Scale	Short term (≤ 3 months)	Medium term (> 3 and ≤ 6 months)	Long term (>6 and ≤ 12 months)
ACR vs Hydrodilatation				
Oxford Shoulder Score (Higher is better)				
Gallacher et al[65], 2018 (ACR: n=25, Hydro: n=25)	MD		5.3 (1.16 to 9.44)	
	SMD		0.77 (0.12 to 1.42)	
ACR vs MUA				
Oxford Shoulder Score (Higher is better)				
UK FROST[74] (ACR: n=203, MUA: n=201)	MD	-3.36 (-5.27 to -1.45)	-1.17 (-3.02 to 0.67)	2.01 (0.1 to 3.91)
	SMD	-0.35 (-0.56 to -0.14)	-0.13 (-0.34 to 0.08)	0.21 (0.00 to 0.42)
Numerical Rating Scale - Pain (Lower is better)				
UK FROST[74] (ACR: n=203, MUA: n=201)	MD	0.59 (0.1 to 1.07)	0.05 (-0.43 to 0.52)	-0.73 (-1.2 to -0.25)
	SMD	0.24 (0.03 to 0.44)	0.00 (-0.21 to 0.21)	-0.32 (-0.53 to -0.11)
ACR vs Supportive care				
Shoulder Pain and Disability Index (Lower score is better)				
Smitherman et al., 2015[63] (ACR: n=13, Supportive care: n=13)	MD	-5 (-29.16 to 19.16)		-2 (-15.39 to 11.39)
	SMD	-0.20 (-1.17 to 0.77)		-0.13 (-1.10 to 0.83)
ACR vs PTSI				
Oxford Shoulder Score (Higher is better)				
UK FROST[74] (ACR: n=203, PTSI: n=99)	MD	-4.72 (-7.06 to -2.39)	0.98 (-1.31 to 3.26)	3.06 (0.71 to 5.41)
	SMD	-0.50 (-0.76 to -0.24)	0.11 (-0.15 to 0.38)	0.33 (0.07 to 0.59)

Study	Scale	Short term (≤ 3 months)	Medium term (> 3 and ≤ 6 months)	Long term (>6 and ≤ 12 months)
Simple Shoulder Test (SST) (Higher is better)				
De Carli et al., 2012[64] (ACR: n=25, PTSI: n=21)	MD	1.44 (0.08 to 2.8)	1.18 (-0.18 to 2.54)	0.59 (-0.77 to 1.95)
	SMD	0.61 (0.01 to 1.22)	0.50 (-0.10 to 1.11)	0.25 (-0.34 to 0.85)
Note: SST score was reported as a percentage so was converted to original scale. Standard deviation (SD) was not provided so was imputed by taking the average SD reported by Yoon et al.[75]				
Numerical Rating Scale - Pain (Lower is better)				
UK FROST, 2020[74] (ACR: n=203, PTSI: n=99)	MD	1.02 (0.42 to 1.61)	-0.14 (-0.74 to 0.45)	-0.81 (-1.39 to -0.23)
	SMD	0.38 (0.13 to 0.64)	-0.09 (-0.36 to 0.18)	-0.38 (-0.64 to -0.12)
Visual Analogue Scale – Pain (Lower is better)				
Mukherjee et al., 2017[66] (ACR: n=30 PTSI: n=30)	MD	-1.2 (-2.04 to -0.36)	-1.2 (-2.04 to -0.36)	
	SMD	-0.74 (-1.28 to -0.20)	-0.74 (-1.28 to -0.20)	
Hydrodilatation vs PTSI				
Visual Analogue Scale – Pain (Lower is better)				
Mun et al., 2016[67] (Hydro: n=67, PTSI: n=69)	MD	-0.9 (-1.16 to -0.64)		-0.1 (-0.39 to 0.19)
	SMD	-1.23 (-1.62 to -0.84)		-0.12 (-0.48 to 0.23)
MUA vs Hydrodilatation				
Visual Analogue Scale – Pain (Lower is better)				
Jacobs et al., 2009[61] (MUA: n=28, Hydro: n=25)	MD	-0.02 (-1.15 to 1.11)		
	SMD	-0.01 (-0.61 to 0.59)		

Study	Scale	Short term (≤ 3 months)	Medium term (> 3 and ≤ 6 months)	Long term (>6 and ≤ 12 months)
Quraishi et al., 2007[71] (MUA: n=17, Hydro: n=19)	MD	2.3 (1.51 to 3.09)	1 (0.21 to 1.79)	
	SMD	1.90 (1.08 to 2.73)	0.83 (0.12 to 1.53)	
Note: VAS Pain SD was not reported by Quraishi et al., 2007. This value was imputed by taking the average SD reported from other VAS scores reported.				
MUA vs Supportive care				
Shoulder Disability Questionnaire Score (Lower score is better)				
Kivimaki et al., 2007[62] (MUA: n=65, Supportive care: n=60)	MD	0.3 (-2.69 to 2.75)	-1.7 (-5.3 to 1.9)	0 (-3.2 to 3.2)
	SMD	0.04 (-0.35 to 0.43)	-0.2 (-0.63 to 0.23)	0 (-0.44 to 0.44)
MUA vs PTSI				
Oxford Shoulder Score (Higher is better)				
UK FROST[74] (MUA: n=201, PTSI: n=99)	MD	-1.36 (-3.7 to 0.98)	2.15 (-0.12 to 4.42)	1.05 (-1.28 to 3.39)
	SMD	-0.15 (-0.4 to 0.10)	0.24 (-0.02 to 0.51)	0.12 (-0.14 to 0.37)
Numerical Rating Scale - Pain (Lower is better)				
UK FROST[74] (MUA: n=201, PTSI: n=99)	MD	0.43 (-0.17 to 1.03)	-0.19 (-0.78 to 0.4)	-0.08 (-0.66 to 0.5)
	SMD	0.17 (-0.09 to 0.42)	-0.09 (-0.35 to 0.18)	-0.04 (-0.30 to 0.21)

4.4 Implications

UKFROST is the largest multi-centre RCT comparing three of the treatments of interest, while most of the other comparisons between treatments are informed by single site studies with limited sample sizes. UKFROST provided unbiased evidence except for blinding which can be argued to be neither feasible with the interventions being evaluated nor necessarily desirable in a pragmatic trial design that reflects the real world delivery of care.[76] In comparison, other

RCTs were susceptible to additional bias concerning, for example, incomplete outcome data or selective reporting of outcomes.

5. Final remarks and recommendations

The body of work presented in this thesis has helped further the knowledge and generated good quality primary evidence to guide clinical practice in the management of Frozen Shoulder (FS). The need for work in this area was driven by my clinical experience of treating this condition. Similar to other specialists managing shoulder problems, I was unable to rely on existing scientific evidence to guide patients referred to my secondary care clinic with FS about which treatment to choose, particularly whether surgical treatment was superior to competent non-surgical management. Patients and clinicians also confirmed it was an important research priority to find out if surgery led to better outcomes than non-surgical treatments. This work has addressed that research priority by standardising the non-surgical physiotherapy intervention and comparing it with commonly used surgical treatments in a rigorous multicentre randomised clinical trial (UKFROST), which is the largest trial to date of secondary care interventions for FS. Whilst all three interventions led to significant improvements over 12 months, none were clearly superior. The more invasive surgical treatment (ACR) that carries higher risks and costs was being increasingly used despite lack of high-quality evidence. Following the results of UKFROST, it is logical to avoid surgery and consider providing the less invasive structured physiotherapy intervention used in the trial, as it also carries lower risks and costs. The results of the trial should help inform shared decision making in clinical practice.

The different elements of the research presented in this thesis were designed to generate new knowledge and the evidence base to help guide clinical practice. Rather than move straight to an RCT, it was important to identify the key issues and priorities from the perspective of patients, clinicians and other stakeholders. Wide engagement with patients, healthcare professionals, and other relevant stakeholders followed by a national stakeholder survey and a final consensus development meeting led to identifying the important research priorities. That was supplemented by a national survey of healthcare professionals who regularly treat FS to gauge the level of interest within the secondary care clinician community to collaborate in a multicentre RCT comparing common interventions in use within their practice, i.e., Physiotherapy, MUA and ACR. It was recognised that there was a need for some

standardisation of physiotherapy provision in view of considerable variations in practice. A Delphi consensus development process helped standardise physiotherapy interventions for FS including a structured non-surgical pathway. This preparatory work for an RCT helped me work collaboratively with a multidisciplinary team of experts in research methodology, clinicians, and patient representatives to develop the study protocol for a pragmatic multicentre RCT (UKFROST) to evaluate clinical effectiveness and cost-effectiveness of the interventions along with a nested qualitative study. Input from a strong team that included trial methodologists, health economists, and qualitative researchers ensured rigorous conduct and successful delivery of the trial. A systematic review then helped place the results of UKFROST in context of the currently available evidence.

Successful conduct of UKFROST inspired a nested qualitative study seeking the views of a purposive sample of study participants and healthcare professionals on their attitudes to the condition and its treatment. The qualitative study, which has been published separately, confirmed that the clear priorities for patients were early diagnosis and early access to treatment. Further, a full health economic evaluation alongside UKFROST showed that the more invasive and costly ACR is not cost-effective. MUA is cost-effective, but the structured physiotherapy used in the trial could be accessed earlier than the other trial interventions in the NHS. These findings, along with the main results of UKFROST, should help inform treatment choices and commissioning decisions.

Future research and new treatments

The setting for UKFROST was secondary care as that is the NHS setting where the surgical interventions are delivered. The ESP non-surgical pathway used in the trial can be provided in a pre-hospital setting, particularly where Musculoskeletal (MSK) services provided by First Contact Practitioners and Physiotherapists are available. It is likely that resourcing and embedding this pathway in such pre-hospital care settings may avoid the need for patients with FS to be seen in secondary care hospitals for more invasive treatments. The applicability and effectiveness of this intervention in the pre-hospital setting needs further evaluation.

Hydrodilatation is an intervention that has gained popularity after UKFROST was commissioned, but the evidence to support its use remains limited and of low quality as confirmed by the systematic review. This is recommended as an area for future research. It is uncertain whether Hydrodilatation is superior to the ESP pathway used in UKFROST and the

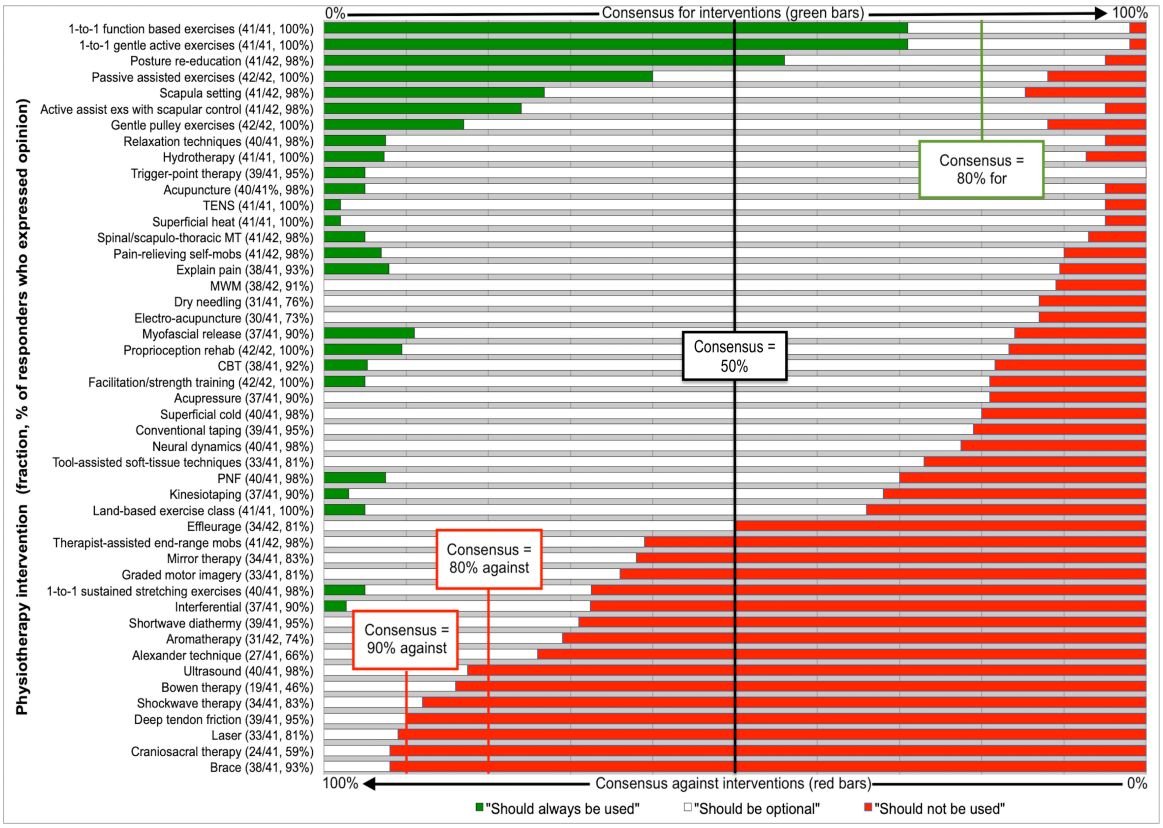
UKFROST ESP intervention should therefore be used as the comparator for a future randomised trial, ideally following evaluation of ESP in the pre-hospital setting where both interventions can be delivered. Whilst current interventions lead to improvements in pain and function, they do not address the underlying biological process leading to the capsular disease and contracture. A capsular tissue sub-study, which is not included in this thesis was also conducted in UKFROST to study the biological disease process in FS within the shoulder capsule.[77] Further research to better understand the biological disease processes within the shoulder capsule is crucial, as ultimately the definitive treatment for FS would need to fundamentally address the underlying capsular disease.

Route to impact

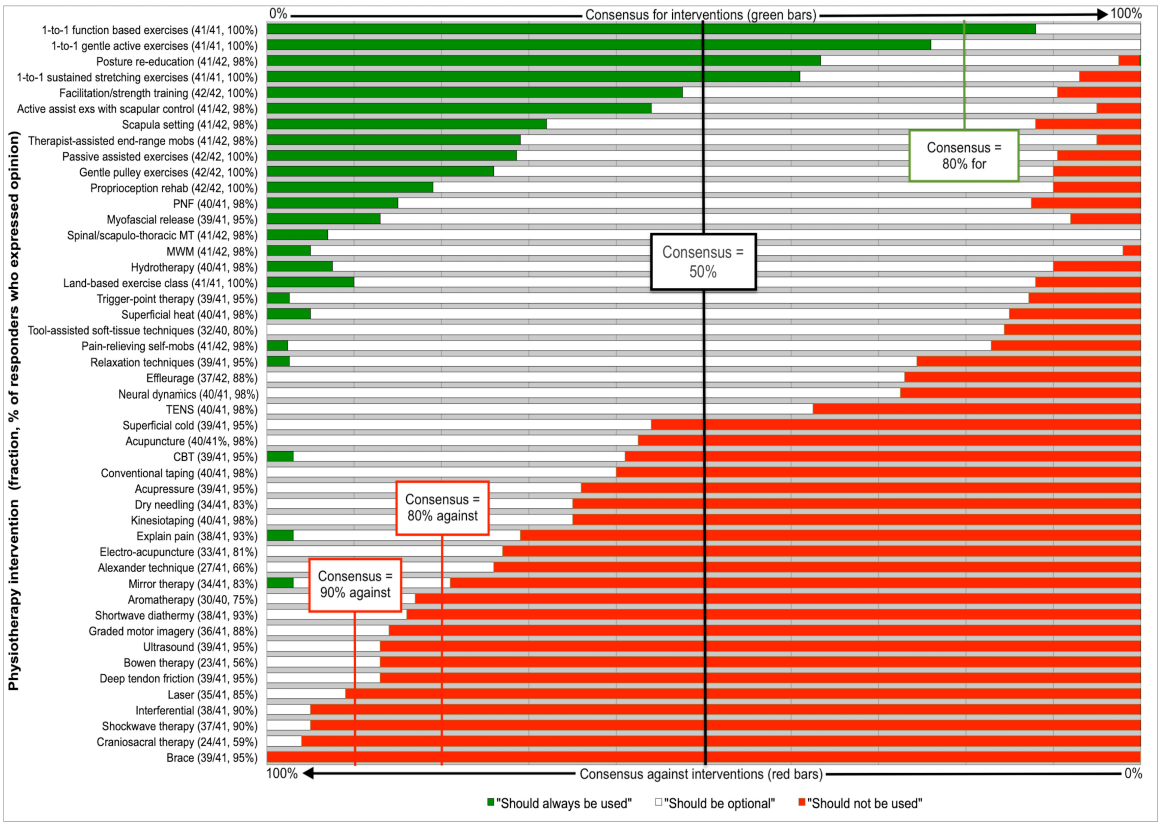
The UKFROST is widely acknowledged as the largest trial to date comparing surgical interventions in secondary care. The main trial report published in the Lancet continues to be referred to in discussions at national and international scientific meetings of shoulder specialists and has been cited by other researchers in 178 indexed publications so far. A short animation video (90 seconds) explaining the results of UKFROST and a home exercise video for patients have been produced, which are hosted in the webpages of the British Elbow & Shoulder Society (BESS) and are being used by clinicians and patients:
https://bess.ac.uk/uk-frost-study/ ; https://bess.ac.uk/frozen-shoulder/
Further resources for patients and physiotherapists have been developed for use in the NHS to aid shared decision making on treatment and to guide non-surgical management. I have personally presented the results of UKFROST at national and international meetings including the BESS annual scientific meeting, European Shoulder & Elbow Society (SECEC), and the International Congress of Shoulder & Elbow Surgical Societies (ICSES). The trial results have informed the BESS national clinical guidelines on Frozen Shoulder, and FS guidelines in Germany. Feedback from surgeons in professional societies and a preliminary review of Hospital Episode Statistics (HES) data from England indicates reduced use of the more invasive and costly ACR for FS following publication of UKFROST. That should in turn lead to considerable cost savings for the NHS. The results of the trial have led to wider stakeholder consultation involving patients and the public, healthcare professionals, healthcare commissioners, and policymakers to develop a Frozen Shoulder care pathway that is currently under consideration for implementation within the NHS. The stakeholder consultation (report submitted for publication) has also recommended updating the NICE guidelines on Frozen Shoulder by incorporating the results of UKFROST.

In summary, my leadership in the collaborative research presented in this thesis has generated high quality evidence to help guide clinicians and patients with shared decision making in the management of FS. It has also helped identify important research questions to guide the direction of further research. My research has been patient centred to ensure relevance, and I have involved patients and clinicians from the outset to identify the research priorities for FS. My clinical insight and methodological skills have helped guide the further work in confirming key commonly used interventions to be evaluated and in standardising physiotherapy interventions, and subsequently progressing to an RCT. The evidence generated from this work should help make a significant difference in guiding clinical practice which should consequently benefit several thousands of patients worldwide.

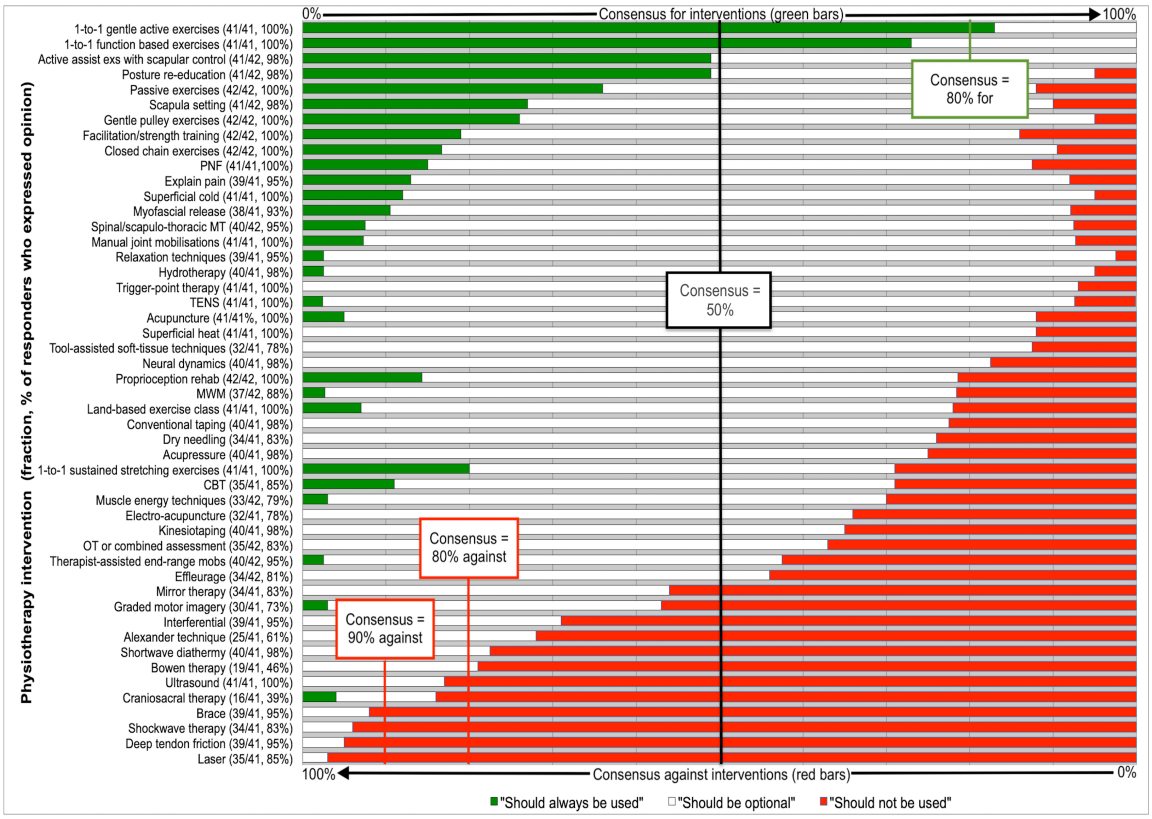
Appendix A: Standalone physiotherapy for pain predominant phase



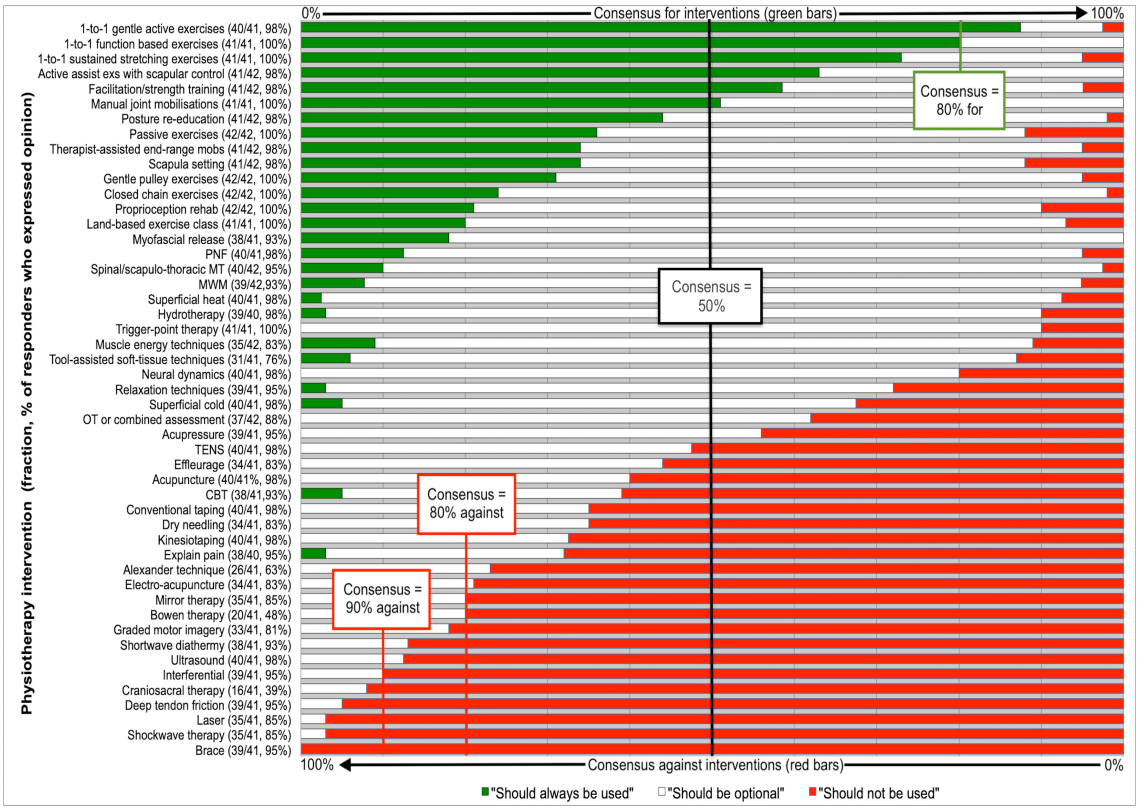
Appendix B: Standalone physiotherapy for stiffness predominant phase



Appendix C: Post-procedural physiotherapy for pain predominant phase



Appendix D: Post-procedural physiotherapy for stiffness predominant phase



Appendix E

Structured Physiotherapy (SP) Treatment Log

Please complete this form as soon as possible after each treatment session.

Date ☐☐ / ☐☐ / ☐☐☐☐ (day / month / year) Session No ☐☐ Duration of session (mins) ☐☐☐

Name of physiotherapist _____ Staff grade *(Please cross one box only)* 5 ☐ 6 ☐ 7 ☐ ≥8 ☐

How many non-surgical frozen shoulders do you treat in a typical month? *(Please place a cross in one box only)* 0 - 1 ☐ 2 - 3 ☐ 4 or more ☐

Ask the patient which of the following is their main problem today. *(Please place a cross in one box only and proceed as indicated.)*

☐ Pain more than stiffness? ☐ Pain and stiffness equally? ☐ Stiffness more than pain?

PAIN IS PREDOMINANT **Use the YELLOW column**

STIFFNESS IS PREDOMINANT **Use the GREEN column**

IMPORTANT! Interventions marked ★ ★ **must** be given as part of the overall SP package (but not necessarily at every session) unless contraindicated. Interventions marked ★ are not essential but are encouraged.

Please place a cross in the box beside any treatments given in this session. To record any treatments that are not listed, please use the free-text box provided.

Use this column if PAIN IS PREDOMINANT

- ☐ **Advice and education** ★ ★
- ☐ **Manual shoulder mobilization** ★ ★
- ☐ **Home exercises (instruction/review)** ★ ★
- ☐ Acupuncture, TENS or trigger-point therapy
- ☐ Hydrotherapy
- ☐ Posture correction
- ☐ Relaxation techniques
- ☐ Spinal/scapulothoracic manual therapy
- ☐ Superficial heat
- ☐ Supervised exercises (function-based)
- ☐ Supervised exercises (gentle active/self-assisted)

TREATMENTS THAT ARE NOT ALLOWED:
Brace, craniosacral therapy, deep friction, laser.
TREATMENTS THAT ARE DISCOURAGED:
Bowen therapy, shockwave therapy, ultrasound.

Use this column if STIFFNESS IS PREDOMINANT

- ☐ **Advice and education** ★ ★
- ☐ **Manual shoulder mobilization** ★ ★
- ☐ **Home exercises (instruction/review)** ★ ★
- ☐ **Supervised exercises (function-based)** ★
- ☐ Hydrotherapy
- ☐ Posture correction
- ☐ Soft-tissue techniques
- ☐ Spinal/scapulothoracic manual therapy
- ☐ Supervised exercises (active/self-assisted)
- ☐ Supervised exercises (strengthening)
- ☐ Supervised exercises (sustained stretching)

TREATMENTS THAT ARE NOT ALLOWED:
Brace, craniosacral therapy, deep friction, interferential, laser, shockwave therapy.
TREATMENTS THAT ARE DISCOURAGED:
Bowen therapy, graded motor imagery, mirror therapy, SWD, ultrasound.

Please record any other treatments given
(e.g. gym class, neural dynamics, referral to another specialty such as Occupational Therapy).

Do you feel the patient has done his /her home exercises adequately? *(Please place a cross in one box only)* ☐ Yes ☐ No Comments:

Please record any serious adverse effects of treatment (e.g. joint infection) and notify the Research Nurse:

Please record and give reasons for any substantial deviation from the UK FROST SP Instructions (in terms of treatments given/not given, or number of sessions) and notify the Research Nurse:

Appendix F

Post-Procedural Physiotherapy (PPP) Treatment Log

Please complete this form as soon as possible after each treatment session.

Date ☐☐ / ☐☐ / ☐☐☐☐ (day / month / year) Session No ☐☐ Duration of session (mins) ☐☐☐

Name of physiotherapist _____ Staff grade *(Please cross one box only)* 5 ☐ 6 ☐ 7 ☐ ≥8 ☐

How many post-surgical frozen shoulders do you treat in a typical month? *(Please place a cross in one box only)* 0 - 1 ☐ 2 - 3 ☐ 4 or more ☐

Ask the patient which of the following is their main problem today. *(Please place a cross in one box only and proceed as indicated.)*

☐ Pain more than stiffness? ☐ Pain and stiffness equally? → PAIN IS PREDOMINANT **Use the YELLOW column**

☐ Stiffness more than pain? → STIFFNESS IS PREDOMINANT **Use the GREEN column**

IMPORTANT! Interventions marked ★ ★ **must** be given as part of the overall PPP package (but not necessarily at every session) unless contraindicated. Interventions marked ★ are not essential but are encouraged.

Please place a cross in the box beside any treatments given in this session. To record any treatments that are not listed, please use the free-text box provided.

Use this column if PAIN IS PREDOMINANT

- ☐ **Advice and education** ★ ★
- ☐ **Home exercises (instruction/review)** ★ ★
- ☐ **Supervised exercises (gentle active/self-assisted)** ★
- ☐ Supervised exercises (function-based)
- ☐ Hydrotherapy
- ☐ Relaxation techniques
- ☐ Manual shoulder mobilization
- ☐ Superficial cold
- ☐ TENS
- ☐ Trigger point therapy
- ☐ Posture correction

TREATMENTS THAT ARE NOT ALLOWED:
Brace, deep friction, laser, shockwave therapy.
TREATMENTS THAT ARE DISCOURAGED:
Craniosacral therapy, ultrasound.

Use this column if STIFFNESS IS PREDOMINANT

- ☐ **Advice and education** ★ ★
- ☐ **Home exercises (instruction/review)** ★ ★
- ☐ **Supervised exercises (active/self-assisted)** ★
- ☐ **Supervised exercises (function-based)** ★
- ☐ Supervised exercises (sustained stretching)
- ☐ Supervised exercises (strengthening)
- ☐ Manual shoulder mobilization
- ☐ Soft-tissue techniques
- ☐ PNF
- ☐ Spinal/scapulothoracic manual therapy
- ☐ Posture correction

TREATMENTS THAT ARE NOT ALLOWED:
Brace, craniosacral therapy, deep friction, interferential, laser, shockwave therapy
TREATMENTS THAT ARE DISCOURAGED:
Bowen therapy, electroacupuncture, graded motor imagery, mirror therapy, SWD, ultrasound.

Please record any other treatments given
(e.g. gym class, neural dynamics, referral to another specialty such as Occupational Therapy).

Do you feel the patient has done his /her home exercises adequately? *(Please place a cross in one box only)* ☐ Yes ☐ No Comments:

Please record any serious adverse effects of treatment, including surgery (e.g. joint infection, nerve injury), and notify the Research Nurse:

Please record and give reasons for any substantial deviation from the UK FROST PPP Instructions (in terms of treatments given/not given, or number of sessions) and notify the Research Nurse:

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