Study Title: The clinical and cost effectiveness of surgical repair of partial rotator cuff tears in patients with subacromial shoulder pain: A comparison of surgical repair versus surgery with no repair.
Short title: Partial Rotator Cuff Tear Repair Trial (PRoCuRe Trial)

Ethics Ref: 21/LO/0081

IRAS Project ID: 283908

Date and Version No: V2.0 28Apr2021

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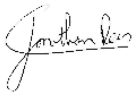
Chief Investigator Signature: 

Statistician Signature: 

Please declare any conflicts of interest: Amar Rangan has declared that his department receives educational and research grants from DePuy J&J Ltd.

Confidentiality Statement: This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, Clinical Trials Unit, Health Research Authority (HRA), host organisation, and members of the Research Ethics Committee (REC), unless authorised to do so.

NIHR funder acknowledgment and DHSC disclaimer: This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (NIHR 128043). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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The Principal Investigator at each, individual site should sign below to document that the protocol has been read and understood before the protocol is filed in the Investigator Site File (ISF)

Study Title: **The clinical and cost effectiveness of surgical repair of partial rotator cuff tears in patients with subacromial shoulder pain: A comparison of surgical repair versus surgery with no repair.**

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The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator: _____
(Please print name)

Signature:

Site name: _____

Date: _____ / _____ / _____ (dd/mon/yyyy)

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1. KEY CONTACTS

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Committees	**Trial Steering Committee (TSC)** Chair: Professor Marion Campbell (University of Aberdeen) **Data Safety Monitoring Committee (DSMC)** Chair: Professor Catherine Hewitt (University of York)

2. LAY SUMMARY

WHAT ARE PARTIAL ROTATOR CUFF TEARS?

Rotator cuff tears are tendon tears in the shoulder that cause pain, weakness and loss of movement. People affected have problems with day to day activities, work, recreation and sleep. These tears can be full tears through the whole tendon or only part way through - a partial tear. Partial tears are first treated in the NHS with physiotherapy and often a steroid injection. Patients who do not get better with these treatments may then choose to have surgery.

WHY IS THIS STUDY IMPORTANT?

The aim of this study is to assess if surgical repair of partial tears, in patients with persistent pain despite physiotherapy, is effective. The study is important because, even though rotator cuff problems are the most common cause of shoulder pain and disability, it remains unknown how best to treat them and whether surgery has any extra value. In particular, we don't know if repairing partial tears prevents bigger full tears and worsening problems. Surgery for full tears is one of the most common shoulder operations in the UK. Prevention of full tears was identified as important by patients and doctors in the 2015 James Lind Alliance Priority Setting Partnership (PSP) for *Surgery for Common Shoulder Conditions* (4 of the top 10 priorities were about rotator cuff problems).

The main aim of this study is therefore to find out if repairing these partial tears is effective, provides lasting benefit and prevents bigger tears.

HOW WILL THE STUDY BE DESIGNED?

We will conduct a study across 20 - 30 NHS hospitals in the UK, recruiting patients aged over 18 years. These patients will have persistent shoulder pain and partial tears of the rotator cuff tendon. They will only be recruited if they have chosen to have surgery after continuing to experience shoulder pain and disability after completing physiotherapy treatment and a steroid injection.

We will conduct a study called a randomised controlled trial to assess any benefit of tendon repair surgery and ensure the other general effects of surgery are taken into account. The trial will compare two similar procedures: Arthroscopic (keyhole) surgery to debride (shave away inflamed tissue, rough tear edges, and bone spurs) and **repair the tear**; compared to Arthroscopic surgery to debride only (shave away inflamed tissue, rough tear edges, and bone spurs) **without any repair**. Repairing the tear involves stitching some of the tendon back to bone. In each participant the type of surgery received will be chosen at random by a computer programme.

We will then monitor how well patients recover from their treatment, and how much benefit they have received using questionnaires about benefit and satisfaction. We will also carry out shoulder scans at 2 years to see whether larger full tears have been prevented. We will determine the costs of the two different surgical procedures and any further treatments over two years. We also plan to assess benefit of each surgery 5 years after the operation using routine information collected by the NHS.

PATIENT INVOLVEMENT

We have conducted patient focus groups and a surgeon survey. Patients and surgeons agreed this is the best and most feasible way to answer this research question. Patients have been central to developing this study and will continue to be involved in the study setup, implementation and dissemination plans. A patient from the 2015 JLA PSP is a co-applicant on this study and another patient representative sits on the Trial Steering Committee.

The trial is supported by the British Elbow and Shoulder Society and we plan to publicise the results of the study widely and use the evidence to influence and improve patient care pathways, including provision of guidelines for primary care and hospital health workers who manage and treat patients with rotator cuff problems.

3. SYNOPSIS

Study Title		The clinical and cost effectiveness of surgical repair of partial rotator cuff tears in patients with subacromial shoulder pain: A comparison of surgical repair versus surgery with no repair.		
Short title		PRoCuRe		
Study registration		ISRCTN60983694		
Sponsor		University of Oxford		
Funder		NIHR HTA		
Study Design		Multi-centre, parallel, patient blinded two arm randomised controlled trial, with integrated QuinteT Recruitment Intervention (QRI) to support recruitment		
Study Participants		Patients with subacromial pain associated with partial tears of the rotator cuff		
QRI component		Patients with subacromial pain associated with partial tears of the rotator cuff and clinicians or researchers involved in trial recruitment		
Sample Size		386 patients (approximately) are anticipated to participate to achieve the required 270 randomised participants.		
QRI component		50 – 100 audio-recordings (patient recruitment discussions) Up to 20 patient interviews Up to 30 interviews with clinicians or researchers involved in trial recruitment		
Planned Study Period		Total study period 92 months RCT will run for 62 months Patient participation 24 months Longer term follow up using routine data at 5 years		
Planned Recruitment period		01 Sep 2020 – 31 Aug 2022 (embedded pilot 01 Sep 2020 – 28 Feb 2021; target recruitment 30)		
		Objectives	Outcome Measures	Timepoint(s)
Primary		To assess and compare patient reported pain and function outcome following arthroscopic debridement and repair of PTT versus arthroscopic debridement only	Oxford Shoulder Score	24 months (+ Baseline)
Secondary	1.	To assess and compare early patient reported pain and function outcomes	Oxford Shoulder Score	6, and 12 months and 5 years (+ Baseline)
	2.	To assess and compare patients' quality of life	EuroQol EQ 5D 5L	6, 12 and 24 months and 5 years (+ Baseline)
	3.	To assess and compare patient resource use	Health resource use	6, 12, and 24 months
	4.	To assess and compare patient satisfaction and perceptions	Patient Satisfaction and Perception Questions	6, 12 and 24 months and 5 years
	5.	To assess and compare tear progression to full thickness tears	Progression to full thickness cuff tears as assessed by MRI imaging	24 months

	6.	To assess and compare long term health care usage, complications, further surgery, patient reported pain and function and quality of life for randomised patients	Readmission for further surgery and associated costs as assessed by routinely collected observational hospital data (HES)	5 years
Exploratory		Objectives	Outcome Measures	Timepoint(s)
	1.	To optimise the accuracy of MRI and USS imaging in diagnosing PTTs	Comparison of imaging reports to arthroscopic findings	During recruitment phase
	2	To assess the long-term health care usage, complications, further surgery, for the non-randomised patients	Readmission for further surgery and associated costs as assessed by routinely collected observational hospital data (HES)	5 years
QRI		Objectives	Outcome Measures	Timepoint(s)
	1.	To understand the recruitment process in the PRoCuRE Trial (Phase I)	The QRI team will present a summary of anonymised findings emerging from the QRI, based upon: 1. Analysis of interviews with the TMG, recruiters and potential participants for PRoCuRe, and of audio recordings of recruitment appointments. 2. Results from the mapping of recruitment processes at PRoCuRe study sites.	Depending on the rate of data collection, it is anticipated that preliminary findings will be obtained within the first three-six months of the QRI
	2.	To develop strategies to optimise recruitment and informed consent (Phase II)	Suggestions will be made to change aspects of design, conduct, organisation or training.	Phase II will continue for the duration of recruitment
Intervention(s)		Arthroscopic Debridement and Arthroscopic Repair (ADAR)		
Comparator		Arthroscopic Debridement Only (No Repair, ADO)		

4. ABBREVIATIONS

ADAR	Arthroscopic Debridement and Arthroscopic Repair
ADO	Arthroscopic Debridement only
CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
DSMC	Data Safety Monitoring Committee
FTT	Full thickness tear
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Episode Statistics
HRA	Health Research Authority
HTA	Human Tissue Authority
(NIHR) HTA	Health Technology Assessment programme
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IEP	Image Exchange Portal
MRI	Magnetic Resonance Imaging
MSK	Musculoskeletal
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OCTRU	Oxford Clinical Trials Research Unit
OSS	Oxford Shoulder Score
PI	Principal Investigator
PIS/PIL	Participant/ Patient Information Sheet/Leaflet
PROM	Patient Reported Outcome Measure
PSP	Priority Setting Partnership
PTT	Partial thickness tear
QRI	QuinteT Recruitment Intervention
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RRAMP	Registration/Randomisation and Management of Product
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Group
USS	Ultrasound Scan

5. BACKGROUND AND RATIONALE

Partial Rotator Cuff Tears

The rotator cuff tendons of the shoulder connect the muscle bellies of Subscapularis, Supraspinatus, Infraspinatus and Teres Minor to the proximal humerus. These muscles play a critical role in the stability and function for the shoulder. Degenerative rotator cuff tendon tears are highly prevalent with increasing age and although some tears can be present without any symptoms, they can lead to subacromial shoulder pain and disability. Degenerative tears usually start at the leading edge of the supraspinatus tendon above the glenohumeral joint and underneath the acromion. Many surgeons and patients believe that these tears start as partial thickness tears (PTTs) and then progress to full thickness tears (FTTs).(1)

Surgical repair of FTTs is very common in the NHS with around 9,000 repairs/year at a cost of £6,628 per operation (£60 million in total) (2, 3). We have already shown in the UKUFF Trial that many repairs of larger FTTs fail (3). Some patients who develop larger FTTs also end up needing more expensive, complex repairs. In recent years, a rapidly increasing number of shoulder replacements are being undertaken for extensive FTTs. These expose patients to greater risks and are of great cost to the NHS (4). Despite these realities, little has been done to investigate whether some PTTs have the potential to heal sufficiently without repair surgery, or whether surgery prevents FTTs. It is therefore important to know if repairing PTTs is worthwhile to patients in improving pain, function and also in preventing FTTs developing.(5)

Current Practice

Patients with a partial rotator cuff tear can present with shoulder pain and disrupted function. Arthroscopic shoulder surgery is offered as an option if physiotherapy and injection treatments have failed to make any improvement (6). As diagnosis of partial rotator cuff tears can only be confirmed during arthroscopic surgery (7), shoulder arthroscopy is commonly performed in the NHS to both confirm the diagnosis and then perform a subsequent therapeutic procedure at the same time. This can include debridement of inflamed bursal tissue and any ragged tear edges, and/or bony decompression, and/or a rotator cuff repair procedure. Physiotherapy and rehabilitation routinely follow surgery.

Current Evidence

There is limited evidence available on the effectiveness of repairing PTTs surgically. It is not currently known if this practice improves pain, function and prevents FTTs from developing. There is the possibility that debridement surgery alone might help, or that symptoms can improve without surgical intervention, but the evidence for best treatment, and the natural history of painful PTTs, remains uncertain (8, 9).

The only evidence that exists assessing outcomes from PTT surgical repair is from a multitude of surgical technique case studies and small cohort studies showing favourable outcomes for surgery (4, 5, 10). Previous systematic reviews support surgery but unfortunately contain low quality studies (11, 12). Other studies were not direct assessments of the surgical repair intervention, however these focused more on surgical technique. These also showed no difference in outcomes with different techniques and concluded that the best treatment method for this patient group is unknown (13-16).

To add further to complexity of the choice of treatment for PTTs, there is evidence indicating that imaging quality in diagnosis rotator cuff problems is insufficient. A 2013 Cochrane Review by Lenza et al on the accuracy of shoulder imaging for rotator cuff problems reports the sensitivity and specificity of Magnetic Resonance Imaging (MRI) to be 74% and 93% respectively (7). Ultrasound scans also showed problematic sensitivity and specificity rates, with 52% and 93% respectively. Therefore, in most cases, confirmation of PTT diagnosis can only be confirmed during an arthroscopic procedure. This issue of diagnostic inaccuracy (outside of arthroscopy) also needs careful consideration in any formal evaluation of PTT surgical intervention.

Evidence Based Surgery

The provision of any treatment of unknown efficacy or value is problematic for both individual patient wellbeing and the health service in general and this work fits with the current initiative (NHS England and RCS) to scrutinise and fully evaluate the efficacy of surgical procedures. As symptomatic FTTs requiring surgery are now highly prevalent in the UK (17) knowledge on the effectiveness of treatment in reducing pain and disability, and proof that PTTs progress to FTTs is needed. FTT's cause a significant health burden and their prevention should be a priority (2, 13). The 2015 James Lind Alliance Priority Setting Partnership on shoulder surgery highlighted this research question and priority (5).

Study Rationale Support

The limited work in this area highlights the uncertainty around whether there is a benefit to PTT repair. Responses from a survey of the shoulder surgeon community confirmed the existence of community equipoise and a willingness to engage in the provision of evidence based practice.

Given the lack of quality evidence and the potential effects of progression on NHS resources, a robust trial is required to address the issues that surrounds PTTs and their management.

The PRoCuRe Trial seeks to answer whether arthroscopic surgical repair of PTTs is clinically and cost effective by comparing it to arthroscopic debridement surgery with no repair. The study will provide

evidence on this patient population in relation to the short-medium term effects on pain and disability, and the longer-term effects including preventing progression to symptomatic FTTs.

Choice and Justification of Treatment Arms

In the NHS, surgeons treat PTTs with a variety of surgical options including cuff repair, debridement, subacromial decompression/acromioplasty, and any combination of these interventions.

The primary research question surrounds the efficacy and cost effectiveness of arthroscopic repair of PTT. The treatment arms for the study are detailed in section 9.6 and can be summarised as:

- Intervention(s) Arthroscopic Debridement and Arthroscopic Repair (ADAR)
- Comparator (control) Arthroscopic Debridement Only (No Repair) (ADO)

The treatment chosen for comparison against surgical repair (arthroscopy and debridement only - ADO) is a routine surgical procedure that some surgeons perform for PTT. It consists of all elements of the definitive repair intervention, but without the "*critical surgical element*" of that procedure, the repair itself. This high fidelity treatment control is also useful from a design point of view as it will confirm or refute the theoretical mechanism for benefit by accounting for any placebo effects of surgery. (18).

The previously outlined issue of diagnostic inaccuracy for PTTs without undergoing arthroscopy means that a non-operative arm is neither appropriate or possible (7). Any comparison study employing a non-surgical intervention would be compromised by inclusion of incorrectly diagnosed PTTs. Moreover, previous experience in surgical versus non-surgical treatment trials using similar populations (and recent patient involvement work), indicate a non-surgical intervention would be difficult to recruit to and therefore not feasible (3). Conducting a two-arm surgical trial in which both groups undergo arthroscopic surgery allows for essential confirmation of diagnosis, secure patient blinding and represents the most efficient design to assess efficacy of repairing PTTs.

6. OBJECTIVES AND OUTCOME MEASURES

Research Question: In patients with suspected PTT listed for arthroscopic surgery, is ADAR more beneficial than ADO as measured by pain reduction and functional restoration at 24 months post operation?

Objectives	Outcome Measures	Timepoint(s)
Primary Objective		
To assess and compare patient reported pain and function outcome following arthroscopic debridement and repair of PTT versus arthroscopic debridement only	Oxford Shoulder Score	24 months (+ Baseline)

Secondary Objectives			
1.	To assess and compare early patient reported pain and function outcome	Oxford Shoulder Score	6 and 12 months, and 5 years (+Baseline)
2.	To assess and compare patients' quality of life	EuroQol EQ-5D-5L	6, 12, and 24 months and 5 years (+Baseline)
3.	To assess and compare patient resource use	Health resource use	6, 12, and 24 months
4.	To assess and compare patient satisfaction and perceptions	Patient Satisfaction and perception questions	6, 12 and 24 months and 5 years
5.	To assess and compare tear progression	Progression to full thickness cuff tears as assessed by MRI imaging	24 months
6.	To assess and compare long term health care usage, complications, further surgery, patient reported pain and function and quality of life for randomised patients.	Readmission for further surgery and associated costs as assessed by routinely collected observational hospital data (HES)	5 years
Exploratory Objectives			
1	To optimise the accuracy of MRI and USS imaging in diagnosing PTTs	Comparison of imaging reports to arthroscopic findings	During recruitment phase
2.	To assess the long-term health care usage, complications, further surgery, for the non-randomised patients	Readmission for further surgery and associated costs as assessed by routinely collected observational hospital data (HES)	5 years
QRI Objectives			
Refer to section 7.2.1			

7. STUDY DESIGN

PRoCuRe is a multicentre superiority randomised controlled trial using a two-arm parallel group design with 1:1 allocation ratio and with an internal pilot phase and a Quintet Recruitment Intervention (QRI). Participants will remain unaware (blinded) as to whether they have had their PTT repaired or not.

Participants will be recruited to the study in hospitals across England. The study overall is modelled on participation from 20 centres, but additional sites may be included depending on recruitment rates in the 6-month pilot phase.

Participants (patients) are expected to be enrolled in the study for up to 5 years. During this time, participants will complete questionnaires as per the schedule in Appendix A and flow diagram (Figure 1). They will also be asked to have an MRI scan two years after their surgery. Routine healthcare data will be collected up to five years to assess for any longer- term shoulder diagnoses and healthcare resource use following the repair. Participants will also receive a short questionnaire at 5 years to assess patient reported outcomes, so that long-term clinical and cost effectiveness can be estimated.

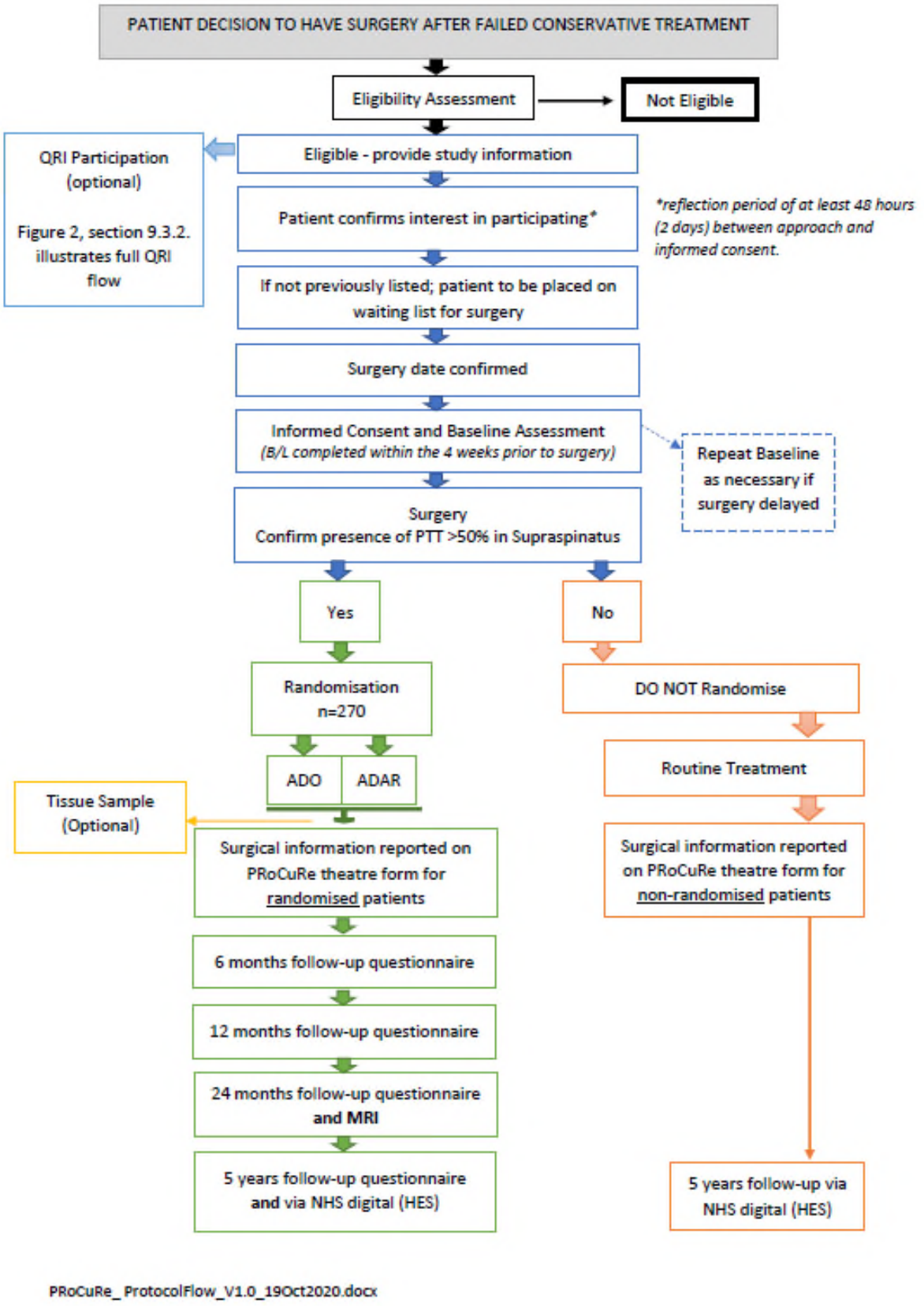

Figure 1: Patient flow diagram for PRoCuRe

7.1. Pilot Phase

Incorporated within the PRoCuRe study design is a pilot phase, which will involve up to six centres with a staggered initiation over a six-month period. The aim of the pilot is to assess the following criteria: recruitment rate; randomisation process and adherence to allocated treatment. The initial six centres will be used as a basis for revising aspects of trial conduct.

During the pilot, screening forms detailing information on eligibility criteria, reasons for exclusion and patients declining to participate will be completed. To identify and understand any challenges to recruitment, a QuinteT Recruitment Intervention (QRI) is integrated into the pilot phase (19). The QRI is a well-established intervention involving rapid data collection and analysis, with feedback to the trial management team, the development of action plans and provision of tailored recruitment support and training. Further information about the QRI is detailed in section 7.2

Any obvious barriers to recruitment will be assessed at six months, with on-going QRI support. The overall recruitment target for the pilot is 30 patients, based on one participant per site per month with staggered initiation.

The pilot phase will also include close monitoring of discrepancies between suspected diagnosis from imaging and true diagnosis from operation. Any patterns in these errors and inaccuracies based on imaging type, imaging sequencing, content or seniority of reporting will form part of feedback to centres, and surgeons in order to make improvements during the full recruitment phase (20, 21) (please see section 7.3 below). Once PTTs are confirmed at the time of surgery, we expect in excess of 90% adherence with protocol as the intervention occurs immediately. However, this will also be assessed as part of the pilot.

The TMG and oversight committees will monitor progress and success during the pilot phase using the following traffic light system for progression; green light for 30 recruited patients, no other action needed, trial continues. Amber light for between 15-30 recruits, the following actions will be taken; auditing of centres, analysis and implementation of QRI results (see section 7.2 below), refresher training, amendment of study procedures. Red light for less than 15 recruits, next steps and measures will be discussed with the funder.

7.2. QuinteT Recruitment Intervention (QRI) 'Information Study'

The QRI will proceed in two iterative stages: a detailed understanding of the recruitment process will be developed in stage I, leading to tailored interventions to improve recruitment in stage II.

- **Stage I: Understanding Recruitment**

  A multi-faceted, flexible approach will be used to investigate site-specific or wider recruitment obstacles. These will comprise the following:

  1. Mapping of eligibility and recruitment pathways: This will identify points at which patients do not continue with recruitment to the Randomised Controlled Trial (RCT) and will closely monitor numbers of patients being screened, assessed as eligible/ineligible and approached for the study. Logs of eligible and recruited patients will be assembled using simple flow charts and counts to display numbers and percentages of patients for each stage of the eligibility and recruitment processes. These figures will be compared across centres and considered in relation to estimates specified in the grant application/study protocol. The screening log data used during this process is not identifiable.
  2. In-depth interviews*:* These will be conducted and audio-recorded with
     (i) members of the Trial Management Group (TMG) (n=3-5),
     (ii) clinicians or researchers involved in trial recruitment, (n=12-20), and
     (iii) eligible patients who have been approached to take part in the trial (n=5-10).

     Interviews provide data about recruiters' equipoise and commitment to the study, their acceptance and interpretation of eligibility criteria, the presentation of the trial, the practical implementation of the trial in clinical centres, and insights about recruitment barriers. Patient interviews provide insights into their understanding and acceptability of study participation, and the processes involved in taking part. Patients will be purposefully sampled for maximum variation on the basis of age, study centre, and the final decision about trial participation (i.e. accept or decline), and treatment selected. A purposeful sampling strategy will also be used to ensure that views of PRoCuRe and recruitment are captured from a range of health care professional's perspectives. This will include sampling by professional role (e.g. surgeons, research nurses) and recruitment site, and recruitment rate (i.e. high to low recruitment)

     Interviewees will be contacted by a researcher from the University of Bristol. Interviews will be arranged for a time and place convenient to the interviewee and may be in person or over the telephone (whichever is preferable).
  3. Audio-recording of recruitment appointments: The recruitment appointment(s) where the trial is presented and consent is taken for participation will be audio-recorded with consent. These appointments identify recruitment difficulties and provide the basis for feedback and/or training as required. Recordings will be sought from a range of recruiting centres/surgeons to ensure maximum variation. (Target n = c50 consultations from across 5-10 centres).

4. Study documentation*:* Patient Information Sheets (PIS) and consent forms will be reviewed following analysis of interviews and audio recordings and may identify aspects that are unclear or potentially open to misinterpretation, and thus make recommendations for amendments.

- **Stage II: Feedback to CI/TMG and plan of action**

  The QRI researcher will present summaries of anonymised findings to the PRoCuRe Chief Investigator (CI) and TMG, identifying the factors that appear to be hindering recruitment with supporting evidence. A plan of action will then be drawn up to try to improve recruitment.

  The QRI has successfully identified common recruitment challenges in previous studies (22, 23)) and this knowledge, combined with empirical analysis of PRoCuRe data, will be applied to the plan of action and thus to support ongoing recruitment. The content of the action plan may include 'tips' about how to explain study design and processes. Supportive feedback will be a core component of the plan of action, with the exact nature and timing of feedback dependent on the issues that arise. Centre-specific feedback may cover institutional barriers, while multi-centre group feedback sessions may address widespread challenges that would benefit from discussion. All group feedback sessions will be aided by displaying anonymised data extracts from interviews and audio-recorded consultations. Individual confidential feedback will also be offered – particularly when recruiters experience specific difficulties, or where there is a need to discuss potentially sensitive issues. The responsibility for deciding on the details of the plan of action and implementing changes and facilitating the QRI team's work will lie with the CI.

  In the main trial the QRI researcher will provide training for new centres, based on evidence derived from the pilot stage.

7.2.1. QRI Objectives and Outcome Measures

Objectives	Outcome Measures	Time point(s)
To understand the recruitment process in the PRoCuRE Trial (Phase I)	The QRI team will present a summary of anonymised findings emerging from the QRI, based upon: 1. Analysis of interviews with the TMG, recruiters and potential participants for PRoCuRe, and of audio recordings of recruitment appointments. 2. Results from the mapping of recruitment processes at PRoCuRe study sites 3. Review of information given to patient in information sheets and through the recording of informed consent discussions.	Depending on the rate of data collection, it is anticipated that preliminary findings will be obtained within the first three-six months of recruitment.
To develop strategies to optimise recruitment and informed consent (Phase II)	Suggestions will be made to change aspects of design, conduct, organisation or training.	Phase II will continue for the duration of recruitment

7.2.2. Information Study Inclusion Criteria

- Patients approached for participation in the PRoCuRe study
- HCPs involved in management, operation or recruitment for the PRoCuRe study

7.2.3. Information Study Exclusion Criteria

- Patient exclusions are the same as for the PRoCuRe study
- HCPs who do not meet the Information study inclusion criteria

7.3. Assessment of imaging and role of diagnostic uncertainty

Diagnostic uncertainty related to low reliability and accuracy of imaging is expected to lead to a considerable number of false positive results for identifying eligible patients in this trial. To counteract this we have opted to only randomise participants once diagnosis is confirmed at operation. It could have been argued that a more pragmatic design, reflecting usual care for this condition including diagnostic uncertainty, would have been to include all patients with a suspected diagnosis of PTT based on imaging. Our design ensures that only patients with PTT are randomised and imaging inaccuracy does not negatively impact the aim of the trial. It also provides an opportunity to explore the magnitude, variation and potential reasons for any imaging inaccuracy, and facilitate better and more uniform recruitment during the trial. This is achieved by minimising variability between centres in the false positive rate of diagnostic

imaging in patients with suspected PTT by monitoring and offering feedback to centres regarding imaging type, imaging sequences, and methods of assessing presence and size of tears.

This design will also allow the following additional sub questions to be addressed:

(1) What recommendations can be made for future NHS routine practice that decrease false positive rates within the current imaging model?

(2) What is the subsequent impact of NHS diagnostic errors (false positive findings) on rates of any further shoulder surgery?

For all patients considered eligible based on diagnostic imaging and who have consented to take part in the trial (during pilot phase and the remainder of the trial), we will collect the following information:

- *Patient characteristics:* All baseline data collected as part of the trial.
- *Diagnosis of PTT*: The diagnostic imaging (MRI or USS) as part of this trial will be the normal pathway investigations in each recruiting centre. Data regarding the results of imaging (MRI or ultrasound scan) will be collected from each participating centre, including the estimated site and size of the supraspinatus PTT, and any other relevant findings from the imaging report (e.g. calcification, bursal fluid). We will also collect information regarding the type of imaging, imaging sequencing used, and any methods used to determine presence and size of any tear. We will also record the staff level of the operator and/or clinician reporting the scans, and details of the hardware equipment used. Following arthroscopy: the presence and size of tear as determined intraoperatively; other intra-operative findings; decision regarding eligibility; and randomisation number will be collected.
- *Monitoring and feedback:* Based on previous research of the accuracy of imaging for identifying PTTs compared to the gold standard of arthroscopy (2-4), we expect up to 30% false positive results (ineligible patients) from imaging. We will monitor results every six months during the recruitment period and provide feedback to centres regarding their false positive rates against the overall rate, with the first round of feedback planned at the end of the internal pilot study. If false positive rates for individual centres are consistently higher than average at 6 months (at the end of the internal pilot and/or at 12 months when all sites are actively recruiting) information regarding characteristics of ineligible vs eligible patients, scanning protocols and methods for assessing rotator cuff tears will be shared, with guidance for optimal procedures based on centres with the lowest false positive rate. Monitoring will continue throughout the 2nd year of recruitment and any impact of feedback on variations in false positive rates and trial recruitment will be recorded.
- *Follow-up (see section 9.9.1)*: Information regarding treatment received, the primary outcome (2-year OSS score), satisfaction with treatment, and quality of life will be collected as well as 5 year HES data for all randomised participants as part of the main trial. We will also extend the 5 year

HES data collection to include those who consented but were not deemed eligible during arthroscopy for randomisation (false positive results). This will provide valuable insight into subsequent surgery rates as a consequence of imaging errors in patients with suspected PTTs.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Patients aged over 18 years with subacromial shoulder pain and a partial thickness rotator cuff tear, for whom their normal pathway management of physiotherapy, steroid injection over a six month period has failed, and have decided to pursue surgical treatment.

8.2. Inclusion Criteria for potential recruitment into trial

- Over 18 years of age
- Willing and able to provide informed consent
- An understanding of the English language sufficient to receive written and verbal information about the trial, its consent process and complete study questionnaires
- MRI or USS suggesting a PTT diagnosis in Supraspinatus

8.3. Inclusion Criteria for randomisation (confirmed in surgery)

- PTT more than 50% tendon thickness confirmed in Supraspinatus during arthroscopy.

8.4. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Patient has not had six months of physiotherapy
- Patient has not had at least one steroid injection
- Steroid injection within six weeks of planned surgery date
- PTT less than 50% tendon thickness
- Any FTTs on imaging or at surgery
- Inflammatory arthritis (e.g. rheumatoid)
- Glenohumeral Osteoarthritis
- Current active malignancy of any kind
- Tears associated with acute fractures
- Tears associated with shoulder dislocations
- Upper limb neurological deficit on either side

- Unable to undergo an MRI
- Unable to complete the written follow up questionnaires

9. PROTOCOL PROCEDURES

Refer to Appendix A for schedule of study procedures.

9.1. Recruitment

The study will take place across NHS hospitals in England. Potential participants will be recruited at routine shoulder appointments. The clinical team will identify potential participants and, if trained, discuss the trial before referring the patient to the research team for further information. QRI intervention(s) will be used to support recruitment and training; clinical team members who have not received training should advise the patient of their potential eligibility for PRoCuRe and refer them on appropriately.

In addition to verbal information, potential participants will be given written study information to take home. They will be informed that participation in the trial is optional and will not affect their medical or legal rights. All patients will be made aware of the trial's aims, anticipated benefits and potential risks. A reflection period of at least 48 hours will be given to allow the patient to decide whether they would like to consent to take part in the trial or not. No delay to surgery will be incurred as a result of being invited to take part in the study i.e. patients with a surgery date that would not allow for the minimum reflection period will not be approached.

During their outpatient clinic appointment, a patient may decide to pursue surgical treatment; making them potentially eligible for PRoCuRe. All patients who decide on surgery are routinely added to the waiting list at this point. This will include the patients who express interest in taking part in PRoCuRe, but they will not be prioritised for surgery above those who are not participating. They will proceed through the standard clinical pathway as per routine care. Participation in the trial will only influence the type of procedure.

9.2. Screening and Eligibility Assessment

Eligibility assessment forms a 2-stage process.

<u>Stage 1:</u> Initial eligibility assessment; confirm patient as potentially eligible for randomisation

This initial stage of the assessment will take place in outpatient clinics and will depend on routine shoulder examination and MRI or USS imaging conducted as part of normal care (as per local hospital policy), to confirm the initial diagnosis and rule out any exclusion criteria. Details relating to the scan report such as

reviewer staff level and information on the type of scanner, methods and sequences used will also be collected at this stage. Screening forms will be completed for each potential participant, with reasons for ineligibility and non-participation documented.

Stage 2: Confirmation of eligibility for randomisation

This stage of the eligibility assessment will be conducted and finalised in theatre. During surgery, via arthroscopic exploration of the shoulder tendons the surgeon will either confirm or refute the presence of a partial tendon thickness tear of >50% in Supraspinatus. Patients who do not meet the inclusion criteria will receive the appropriate surgical management for their problem and will not be randomised.

This 2-step process is highlighted in the study information and consent procedures.

9.3. Informed Consent

Informed consent will take place prior to the Baseline assessment being undertaken, and before surgery. The participant must personally sign and date the latest approved version of the Informed Consent Form (ICF) before any study specific procedures are performed.

The Principal Investigator (PI) at each site assumes overall responsibility for consenting patients but can delegate this task to an appropriately trained member of the local research team. The research team at each site will comprise of clinical researchers and other appropriately trained research staff such as nurses, physiotherapists, practitioners etc. who will be included on the delegation log according to their delegated responsibilities.

Patients who consent but are found to have an injury or problem that does not meet inclusion criteria during the operation (i.e. any condition that is not a supraspinatus PTT of more than 50% tendon thickness), will not proceed to be randomised. The informed consent process highlights this to patients and that they will then receive the appropriate surgical management for their problem. The consent will also include following up of this non-randomised cohort of patients using HES data at 5 years post-surgery. Follow up of the non-randomised participant group will help to inform the prognostic consequences of such imaging inaccuracies in the NHS.

Prior to consent, written versions of the PIS and ICF will be presented and verbally communicated to the patient detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that participants are free to withdraw from the study at any time for any reason

without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. The patient will be given a reflection period of at least 48 hours (2 days), prior to their surgery date, to consider the study information and have the opportunity to question the Investigator, their General Practitioner (GP) or other independent parties to help them decide whether they will participate in the study.

9.3.1. Written Informed Consent

Written Informed Consent will be obtained by means of a dated signature of the participant and of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the local Chief/Principal Investigator. A copy of the signed Informed Consent Form will be given to the participant. The original signed form will be retained at the study site and participant consent will be recorded in the PRoCuRe study database via the Consent notification form.

9.3.2. QRI Consent

Patient participants: A separate PIL and ICF specific to the QRI will be prepared and may be sent to patients prior to their clinic appointment, or if this is not possible, given to them at the time of their out-patient appointment. Patients will be asked to consider consent for the QRI – to either take part in an interview, an audio recording of their PRoCuRe consultation, or both, in clinic, by a member of the local research team. It will be clearly stated in the Information Study PIS for patients that participants are free to withdraw from the study at any time and without giving a reason. For the QRI, where possible, patients will be given a reflection period of at least 24 hours to consider whether to participate. Where the period of reflection is less than 24 hours, patients will only be enrolled if they confirm that they feel they have had enough time to consider their participation and fully understand the QRI and its requirements. Staff at site will make this judgement on a case-by-case basis. A copy of the signed Information Study Informed Consent Form for patients will be given to the participant. The original signed form will be retained at the study site , a copy will be filed in the patient medical record, and participant consent will be recorded in the PRoCuRe study database.

Staff participants: Consent from staff to audio record their consultations will be discussed and sought as part of the site set up processes. Staff may consent to an interview only, to be audio recorded only or to both. They may also decline to participate in the QRI. Where the recruiting member of staff has not consented to participate in the QRI audio-recordings, their patients will not be invited to take part in the Information Study. It will be clearly stated in the Information

Study PIS for HCPs that participants are free to withdraw from the study at any time and without giving a reason. Where possible, HCPs will be given a reflection period of at least 24 hours to consider whether to participate. Where the period of reflection is less than 24 hours, HCPs will only be enrolled if they confirm that they feel they have had enough time to consider their participation and fully understand the QRI and its requirements. The member of staff (central study team) receiving consent will make this judgement on a case-by-case basis. A copy of the signed Information Study Informed Consent Form for HCPs will be given to the participant. The original signed form will be retained at the study site and participant consent will be recorded in the PRoCuRe study database.

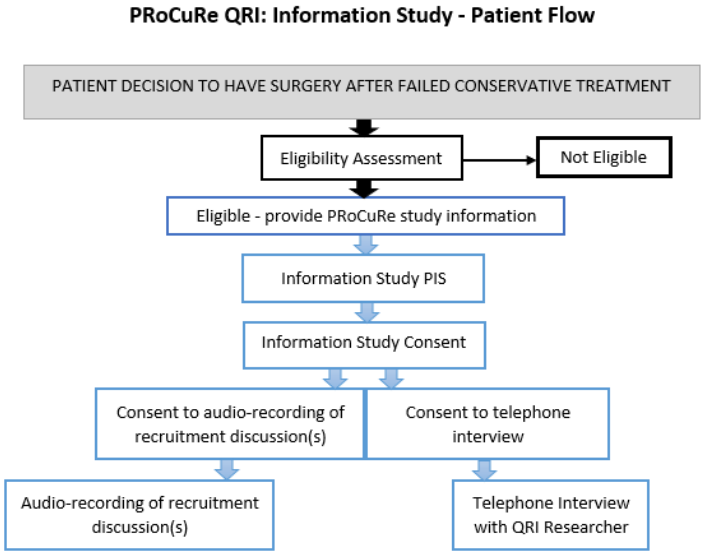

Figure 2: Information Study Flow (Patients)

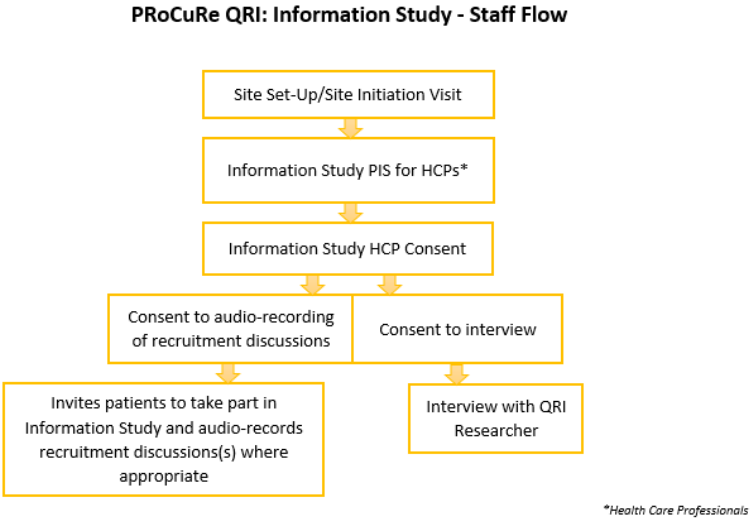

Figure 3: Information Study Flow (Health Care Professionals)

9.4. Randomisation

Participants will be randomised in theatre after confirmation of a partial tendon tear (PTT) in supraspinatus that is more than 50% thickness of the tendon. The randomisation will follow a 1:1 allocation ratio and use a minimisation algorithm; initially simple randomisation seeding will be used and minimisation will also incorporate a "random twist" element to protect allocation concealment throughout. Randomisation will be minimised according to age, type of tear and study site.

Randomisation will be performed using a web based automated computer-generated system. The allocation system will be generated by the trial statistician and will be programmed into the Oxford Clinical Trials Research Unit (OCTRU) computer randomisation system, Registration/Randomisation and Management of Product (RRAMP). The research team at each site will conduct the randomisation via secure logins to the web-based system. An emergency randomisation list prepared by the trial statistician and held securely by the trial manager will be used if RRAMP is not available.

A member of the clinical research team delegated to treatment allocation (randomising) will enter the relevant data into the online randomisation system when the patient is in theatre and inform the operating surgeon of the allocation details. If for some rare reason the patient is not under general anaesthetic, this will need to be done carefully without revealing the intended treatment to protect the blinding.

9.5. Blinding and code-breaking

Participants will be blinded to the randomised allocation. It is not possible to blind theatre staff nor the surgeon. Those in the clinical team and the central trial team will not be blinded to the allocation, so no code break procedure for clinical care or safety reporting is needed. Post-operative rehabilitation and exercises will be the same in both groups which means therapists can remain blinded. All participants will be provided with the same study specific guide to rehabilitation. The participants GP will be notified and asked not to disclose the treatment allocation to the participant.

24 months after randomisation, patients will be asked which surgical treatment they think they underwent to assess success of patient blinding.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

All procedures described below are a one-off treatment. Any further treatments will be sought as per routine NHS pathways.

9.6.1. Surgical Preparation

The procedures will be undertaken as per NHS practice by specialist shoulder surgeons. They will be done either as a day case or as an overnight stay; any extended stays involving randomised participants will be recorded. The operations are usually conducted under a general anaesthetic with an accompanying nerve block.

The arthroscopy will be carried out in the standard sterile environment of an operating theatre with standard arthroscopic equipment as per routine practice. The shoulder glenohumeral joint will be assessed for evidence of arthritis or frozen shoulder or biceps problems or any other condition that might be causing the patients symptoms. The rotator cuff will then be assessed for evidence of an articular sided partial thickness tears (PTTs) or a full thickness tear (FTT). Surgeons will then routinely inspect the rotator cuff from its upper surface in the subacromial bursa for evidence of a bursal sided tear. This part of the arthroscopy can involve debriding bursal tissue, bone spurs and any ragged tear edges. This procedure is done routinely in the NHS in order to fully inspect, evaluate and confirm the presence and size of a PTT on either side of the tendon. Many surgeons also regard it as a therapeutic symptomatic treatment and possibly a tendon healing one and so would not add in an additional formal tendon repair. Other surgeons do believe in a benefit of an additional tendon repair and so would proceed to do this.

In the PRoCuRe Trial, patients with PTTs (of more than 50% tendon thickness) present will be randomised in theatre to receive the additional tendon repair procedure or not i.e. either the intervention or the control as below in sections 9.6.2 and 9.6.3. Patient blinding can be maintained, as both these surgical procedures will include only two to three arthroscopic portal skin incisions that are similar.

9.6.2. Arthroscopic Debridement and Arthroscopic Repair (ADAR)

A PTT in the supraspinatus rotator cuff tendon either on the joint side or bursal side of the tendon randomised for repair will be repaired using either of the following techniques, whichever is the surgeon's preference for that tear:

- "take-down" repair which involves the surgeons converting the partial tear to full thickness tear first before repair, or
- "in-situ" repair where the surgeon directly repairs the partial tear, without converting it to a full thickness tear

Such partial tendon repairs are performed completely arthroscopically. The small amount of tendon tissue removed during tear edge debridement, and regarded as clinical waste, may, with the participant's consent, be used for further research. Following repair, sutures or steristrips are

used to close the keyhole wounds and dressings and a sling are applied as per routine practice at all sites.

9.6.3. Arthroscopic Debridement Only (ADO)

This surgical procedure is the same as above, but without the tendon repair. It includes the assessment and confirmation of diagnosis and can involve debriding bursal tissue, bone spurs and any ragged tear edges. The small amount of tendon tissue removed during tear edge debridement, and regarded as clinical waste, may, with the participant's consent, be used for further research. The characteristics of the tear will be recorded but no formal repair is undertaken. The procedure will be finished at this point with the same routine closure and dressings applied.

The ADO group consists of patients who are undergoing the same arthroscopic surgery as the intervention (repair) group but with the established critical surgical element of tendon tissue repair omitted. The control group are undergoing surgery which exhibits moderate fidelity to the intervention group but importantly have all other characteristics of the procedure which will account for any placebo effect of undergoing surgery.

9.6.4. Post-operative Rehabilitation

The post-operative rehabilitation will be pragmatic and the same in both treatment groups. Participants will receive a sling for up to two weeks for comfort and healing with instructions to mobilise the arm as pain allows and begin standard NHS care physiotherapy exercises. The rehabilitation is simple and routine after this type of surgery. It will be further enhanced with standard information and standard exercises in a rehabilitation booklet for the trial. The information and standard exercises have been checked and agreed by UK leading shoulder physiotherapy experts from the British Elbow and Shoulder Society. Patients commonly request these booklets after their operations and so this booklet will be given on discharge after surgery, and it will also help standardise rehabilitation in both groups. This will be available on the study website, as well as printed copies provided to participants.

9.7. Baseline Assessments

Routine care involves patients attending a pre-admission surgical clinic usually within 4 weeks of their surgery. Baseline assessments will therefore be completed within 4 weeks prior to the patient's surgery date; this can include the day of surgery. Ideally, consent and baseline activities will take place after a surgery date has been confirmed and as close to surgery as is practicable e.g. at pre-op appointment or

day of surgery. The assessment involves patient reported questionnaires on shoulder pain and function and quality of life.

In order to ensure there is an accurate comparison, it is important that the baseline information provided refers to the patient condition up to a maximum of 8 weeks prior to surgery. Therefore, where a patient's surgery date is considerably delayed and rescheduled we will seek to complete a repeat Baseline assessment, if the initial data collection was to fall outside of the 4 week window. This will be communicated to the patient in the PIS and verbally during recruitment. The Baseline assessment is not onerous and does not involve an extra visit. We do not anticipate that the 'extra' step of repeating the baseline assessments, if needed, will result in any negative effect on patient recruitment and will enhance the reliability of any study findings.

9.8. Operative Assessment

At the time of surgery, the operating surgeon will confirm the diagnosis of a supraspinatus PTT that is more than half the thickness of the patient's tendon thickness and fulfils the inclusion criteria for randomisation to ADAR or ADO. Further details of all arthroscopic findings and procedure details will be recorded. This will include adherence to the randomised allocation, the extent of any concomitant conditions and any complications.

9.9. Follow up Assessments

9.9.1. Patient Questionnaires

The following questionnaires will be sent to participants at pre-determined timepoints post randomisation. These will be sent by the central study team and can be completed by post or online:

- Oxford Shoulder Score (OSS)

  This patient reported outcome measure (PROM) is a validated questionnaire for measuring outcomes of rotator cuff surgery in the NHS (24, 25).

- EuroQoL EQ-5D-5L

  This questionnaire will be completed in order to estimate a health utility index (using UK population preference weights) and from this estimate quality-adjusted life years for trial-based economic evaluation (26, 27).

- Health Resource Use and patient reported events

Postoperative costs and lost productivity costs attributable to the shoulder condition will be collected during the follow-up period. Information on outpatient visits, community care provision, days off work due to their shoulder problem, and patient reported adverse events will be collected.

- Patient Satisfaction and Perception questions
  OSS transition and satisfaction questionnaire and a simple Likert scale will be used to assess participant satisfaction (28, 29).

Reminders will be sent to participants who do not respond to the initial request for follow-up data within 10 days. If there is still no response, the central study team will use other means of contact including by telephone. This may be done in conjunction with re-posting of the questionnaire.; In the case of telephone follow-up, participants will be asked to provide OSS data as a minimum. Where needed, up to a maximum of 5 attempts will be made.

As required, local research teams will be expected to provide support for follow-up data collection.

9.9.2. MRI Assessment

For randomised participants, an MRI is required two years after surgery to evaluate the tendon appearance and to assess if a FTT has developed. This assessment will determine the structural outcome of the surgical procedures. Identification of progression to FTT over time will indicate the mechanical failure in the surgical repair group, or progression of unrepaired PTTs to FTTs, as well as providing insight into whether progression to FTTs correlates to poorer clinical outcomes. Standard MRI images will be taken at the participants' local hospital and performed according to the NHS Trust's policies and procedures. An anonymised copy of the scan will be collected centrally and reported by independent radiology experts to evaluate for any FTTs. This method of assessment has been used in previous trials of this patient population (3).

Sites will refer to study specific instructions on the transfer of MRI images. Where available, de-identified MRI scans will be transferred using the NHS trust secure Image Exchange Portal (IEP). If IEP is not available at a recruiting centre, the anonymised image will be copied to CD and sent to the PRoCuRe office, Oxford, where the image will be uploaded to the OUH NHS Trust PACS system. Staff at site will be responsible for removing identifiable data from the image and labelling with

the relevant study ID prior to transfer. Sites will follow local Information Governance process to ensure patient confidentiality.

MRI is commonly used every day within the NHS and all hospital Trusts have robust policies and procedures in place to ensure patient safety. Many patients will have undergone such an MRI scan(s) prior to their participation in the PRoCuRe study.

Participating sites will assume responsibility for coordinating the follow up MRI appointment for their randomised participants. The scan should take place 24 months post-randomisation (+/- 2 weeks) and the scan image transferred to Oxford as soon as possible after.

9.9.3. Long Term Follow Up

To obtain long term data about randomised participants beyond the 24-month timepoint, data will be collected via Hospital Episode Statistics (HES) data from hospitals in England, and a simple questionnaire will be sent to participants, involving questions on patient satisfaction, and perception of their treatment. A repeat OSS and EQ5D will also be collected.

HES data will be collected for the non-randomised participants; this group will not be asked to complete a questionnaire at 5 years post-surgery.

- HES Data - Routinely-collected data will be used to determine re-operation rates on trial participants up to five years following initial surgery. A bespoke HES extract provided by NHS Digital and linked to the Office of National Statistics data is required. This will include all events and outcomes associated with any further shoulder surgery using a pre-agreed list of procedure (OPCS 4.7) and clinical diagnosis (ICD10) codes and including but not limited to: primary rotator cuff repair, revision rotator cuff repair, augmented rotator cuff repair, arthroscopic debridement, biceps tenotomy, shoulder replacement. Consent will be collected from patients during recruitment to use their HES data in this way.

9.10. Tissue Samples

All participants will be invited to consent to providing a very small sample of tendon tissue that is otherwise usually routinely removed and discarded during debridement or repair preparation; it is possible to decline and remain a participant in the study. For all participants who consent to provide a sample, tissue will only be collected from those who are eligible for randomisation. Information relating to tissue sampling will be included in the PIS.

Once patients are deemed to have the appropriate PTT and eligible for randomisation then a tissue sample can be considered. Tissue will be collected from the patients who either undergo a tear debridement or those that undergo a takedown repair and have consented to provide a sample. Only the small amount tissue that would otherwise be debrided and discarded during the procedure will be collected. The volume of tissue collected would be around the size of a grain of rice.

The tissue samples will be analysed by a variety of laboratory techniques to allow us to characterise how the diseased tissue looks at a cellular and molecular level. Examples of techniques to be used include transcriptomic, metabolomic and proteomic analysis and subsequent validation using RT-qPCR, FACs and immunostaining. These methods will allow us to identify cells and molecules characteristic of disease and that may predict outcome from surgery. We will also be able to compare data to healthy tendon samples we have collected from other separate studies. Some tendon samples will be processed so that we can study the cells from the tissues in the laboratory and test which surgical biomaterials or drugs best change their behaviour so that they look like healthy tendons – this will identify promising treatments for partial rotator cuff tears.

The tissue samples are small and each sample will only be processed for one laboratory application. The samples will be transferred from the clinical collection sites in appropriate and safe containers and received and stored in a secure laboratory area within The Botnar Research Centre in accordance with Human Tissue Authority (HTA) guidance. Access will be restricted to authorised personnel associated with the study.

9.11. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may, where it is still possible, choose to withdraw early from the randomised intervention or other trial procedures at any time. This may happen for several reasons, including but not limited to:

- Investigator decision
    - Ineligibility (either arising during the study or retrospectively, having been overlooked at screening)
    - Other clinical reasoning
    - Significant protocol deviation
    - Significant non-compliance with treatment regimen or study requirements
- Participant decision
    - The occurrence of what the participant perceives as an intolerable adverse event

- Inability to comply with study procedures

The type of withdrawal and reason for withdrawal will be recorded in the relevant Case Report Form (CRF). If the participant is withdrawn due to an adverse event, the Investigator will arrange follow up until the event has resolved or stabilised. Withdrawal (from any or all aspects of the study) will managed via the Oxford office.

Participants may decide any of the following types of withdrawal:

- Withdrawal from follow up MRI assessment but willing to complete questionnaires at home
- Withdrawal from follow up MRI assessment and completing questionnaires, but willing for the study team to access medical records and any relevant hospital data that is recorded as part of routine care. These patients may also be willing to be followed up via HES
- Withdrawal from all follow-up, but willing for data collected up to the point of withdrawal to be included in the final study analysis
- Complete withdrawal, with data collected not being used in the final study analysis. Where available, this will include tissue samples and/or audio-recordings that are still identifiable. (There are limits to this, for example when data has already been integrated into interim results)

All patients who withdraw from the study will continue to receive routine clinical care.
Participants will not be replaced, as withdrawal and loss to follow-up has been accounted for in the estimated sample size. Analysis will be performed as per intention-to-treat, irrespective of compliance with treatment allocation.

9.12. Definition of End of Study

The end of the initial follow-up is defined as the final participant assessment at 24 months, and after all data has been entered and queries resolve. The end of the trial is defined as 3 years after this point when all longer term (5 year) follow-up data has been collected and queries resolved.

10. SAFETY REPORTING

The study involves no additional risks to participants beyond those of routine standard care. Participants will be informed of the standard risks associated with the anaesthetic and surgery.

Adverse Events (AEs)

Complications (adverse events) that the clinicians deem associated with the patient population and the trial treatments will be collected via the REDCap database. Examples of expected adverse events that can occur with this type of surgery include, but are not limited to:

- Infection
- Frozen Shoulder
- Tendon Re-tear
- Ongoing Pain with minimal clinical improvement
- Further shoulder surgery (requiring inpatient hospitalisation)
- Recurrence of same problem
- Conversion to open surgery
- Poor movement
- Cartilage damage
- Future arthritis
- Instrument breakage
- Nerve or vessel injury
- Fracture needing further surgery
- Scar tenderness
- Bleeding
- Complications of anaesthetic and nerve block

Sites will use the Complications eCRF to record information on AEs occurring from the day of surgery to 24 months post-randomisation; sites will also conduct a notes review at the 24 months post-randomisation timepoint. Information on complications experienced by randomised participants will also be solicited from the follow-up questionnaires up to 24 months. Complications occurring during surgery (randomised participants) will be collected from sites via the theatre form eCRF.

Adverse events experienced by randomised participants will be periodically reviewed by the Data Safety Monitoring Committee (DSMC) and any unusual increased patterns of serious adverse events (i.e. complications defined as serious) compared to what is expected for such patients and interventions will be notified to the Research Ethics Committee (REC).

Serious Adverse Events (SAEs)

SAEs occurring to a randomised participant, from surgery and up to 24 months post-randomisation, clinically judged by the PI as being related to the intervention will be reported via the PRoCuRe SAE form

for review by the nominated person. All deaths, related or unrelated, will be reported. Sites will report any events meeting these criteria to the central study team within 24 hours of the PI becoming aware of the event. The central study team will review the submission reports of related and unexpected SAEs will be submitted within 15 working days of the Chief Investigator becoming aware of the event.

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

11. MAIN STATISTICAL ANALYSIS

11.1. Statistical Analysis Plan (SAP) for the trial analyses

The statistical aspects of the trial analyses are summarised here (Section 11.1-11.8) with details of the trial analyses fully described in a statistical analysis plan that will be finalised before the final analysis takes place and agreed by the Trial Steering Committee (TSC). Information on the imaging and diagnostic uncertainty statistical analyses and Health economic analyses are summarised in Sections 12.1 and 12.2 below. A single main set of analyses will be performed at the end of the follow-up. The main analyses will be according to randomised groups irrespective of non-compliance, "as randomised" population (See Section 11.4) and based upon the data up to and including the 24 months timepoint. Details of the 5-year HES analysis are given in Section 12.4.

Analyses will be carried out using Stata (Stata: Release 15. Statistical Software. College Station, TX: StataCorp LP; 2017.15).

11.2. Description of the Statistical Methods

Baseline, treatment, study process, and outcomes data will be summarised using appropriate statistical summarises (e.g. number of observations and percentages for binary measures). The primary outcome will be compared using generalised estimating equation (GEE) model with adjustment for the randomisation variables (age, type of tear & site), baseline OSS and time point using fixed effects. A secondary unadjusted analysis will also be carried out by an independent t-test. Secondary outcomes will be analysed using generalised linear multilevel models with adjustment for minimisation and baseline variables as appropriate. Exploratory subgroup analyses will explore the possible treatment effect modification of patient age and type of tear, through the use of treatment by factor interaction, and will be interpreted cautiously.

The impact of missing data and non-compliance on the findings will also be explored in sensitivity analyses of the primary outcome utilising appropriate methods (e.g. the rctmiss Stata command for assessing the impact of missing not at random for OSS using a pattern mixed-model based approach) (30) and complier average causal effect (CACE) (31) type approaches respectively.

11.3. Sample Size Determination

A recent systematic review of shoulder PROMs found a minimum important difference (MID) in the OSS to be around 4-5 points for patients with shoulder conditions (32, 33). The observed SD of the OSS at 12 and 24 months in the CSAW & UKUFF trials was 9 & 8 points respectively (3, 34) To detect a target difference of 4 OSS points & assuming a SD of 9 with 2- sided 5% significance level & 90% statistical power, requires 108 participants per group (216 overall). Allowing for 20% attrition (16% observed in the UKUFF trial at 24 months) (3) (the final sample size is 135 per group (270 overall). Allowing for 30% ineligibility in theatre at time of arthroscopy means 386 patients will be recruited.

11.4. Analysis populations

The main analyses (to be conducted once the 24 months data is available) will be according to randomised groups irrespective of non-compliance, “as randomised” population. This is akin to intention to treat or a treatment policy population; however, no imputation of missing data will be carried out under the main analyses. For complications and further surgery an “as treated” population where individuals will be grouped according to whether they received ADAR or ADO will also be used. An “as randomised” population summary will also be produced.

11.5. Stopping rules

An independent Data Safety Monitoring Committee (DSMC) will meet early in the course of the trial to agree terms of reference and will review confidential interim reports of accumulating data. No formal stopping rules are incorporated and accordingly no formal interim analyses planned.

11.6. The Level of Statistical Significance

The statistical significance will be assessed at 5% for two-sided tests and reported for p-values less than 5% (p values of less than 0.05). All p values will be reported to 3 decimal places. 95% confidence intervals will be reported throughout. Subgroup analyses will be considered exploratory though nominally at the same 2-sided 5% significance level.

11.7. Procedure for Accounting for Missing, Unused, and Spurious Data

The number and percentage of individuals in the missing category will be presented by treatment arm. No data will be considered spurious in the analysis since all data will be checked and cleaned before statistical analyses. Prior to any statistical analysis, missing data pattern will be investigated and reasons for missing data obtained and summarised where possible. The impact of missing data on the findings will also be explored in a sensitivity analysis (see Section 11.2)

11.8. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Substantive deviations from the original SAP will be documented in the statistical report and justification for each deviation provided.

12. OTHER ANALYSES

12.1. Imaging and diagnostic uncertainty analyses

Descriptive statistics will be used to report the total number (%) of patients where PTT is not confirmed during arthroscopy (false positive rate for MRI), overall and for each participating site. The characteristics of this group of ineligible patients will be described and compared with those who were eligible for the trial. Logistic regression will be used to explore for any patient and disease characteristics associated with the probability of a false positive result from imaging.

False positive rates (proportions of ineligible patients with no tear, FTT or PTT less than 50% tendon thickness) as well as trial recruitment rates will be graphically presented for the 24-month recruitment period to visually present trends and fluctuations over time. Joinpoint regression will used to determine the mean monthly percentage change in false positive rates and recruitment rates over time and to assess if a significant change occurred at 12 months, after targeted feedback to those recruiting centres with higher false positive rates.

12.2. Health Economics Analysis

The cost-effectiveness of ADAR compared to ADO will be assessed by a full within-trial economic evaluation where both relevant costs and outcomes for each alternative will be considered. As the main statistical analyses, the economic analysis will be performed according to randomised groups irrespective of non-compliance, “as randomised” or “as allocated” population, i.e. on an intention-to-treat basis. The economic evaluation will follow a Health Economics Analysis Plan (HEAP) agreed in advance by the TSC. The analysis will be conducted from an NHS and personal social services perspective to estimate the relative difference in healthcare costs and quality-adjusted life years (QALYs) between the two arms of the trial. Costs will mainly include primary and hospital healthcare services collected via CRFs and resource use questionnaires at six, 12 and 24 months. Benefits will be reported in terms of QALYs, which will be calculated from answers to the EQ-5D questionnaire and the corresponding social value set of preferences. Although there are no definitive set of valuations for the health states in the EQ5D-5L questionnaire for England or the UK yet, the most up-to-date position statement from NICE (35) suggests using the EQ5D-5L and an algorithm to map to 3L valuations (36). We will use the most up-to-date recommendation on how to value health states measured using the EQ5D-5L instrument at the time of analysis. The valuation will allow to produce health utility estimates at baseline, six, 12 and 24 months, with QALYs estimated using the area under the curve method. Given the number and nature of resource use data collection methods and time points, we expect some missing data in both costs and outcomes. Multiple imputation methods will be used as the base case analyses to impute missing cost and QALY data and avoid biases associated with a complete case analysis.

The results of the economic evaluation will be reported in terms of incremental net monetary benefits using the NICE recommended thresholds of £20,000 and £30,000 per QALY. If no arm is dominant (i.e., reporting both lower costs and better outcomes), we will also report the incremental cost-effectiveness ratio (ICER), i.e. the additional cost per QALY gained by undertaking ADAR compared to ADO. We will consider producing results by subgroups if specific subpopulations such as by demographic (e.g. age) or clinical characteristics are found to be relevant and if allowed by statistical power. Sensitivity analyses will be conducted to explore the implications of uncertainty around key inputs in the analysis. As a sensitivity analysis, the economic evaluation will be conducted from the societal perspective (i.e. including costs for absenteeism from work).

For the long-term (five-year) analysis, cost-effectiveness will be assessed based on hospital costs obtained from routinely HES collected data and long-term health-related quality of life (EQ-5D-5L) collected at 5 years follow-up following the procedures in each trial arm. A series of sensitivity analyses will be undertaken to explore the implications of uncertainty around the costing and methodological assumptions on overall results.

12.3. Qualitative Data Analysis

All qualitative data will be audio-recorded using digital encrypted recorders, transcribed verbatim and edited to ensure anonymity of respondent. Interview data will be managed using NVivo software (QRS International) and analysed thematically using constant comparative approaches derived from Grounded Theory methodology. Consultation data will be analysed using novel approaches, including targeted conversation analysis (37) and appointment timing (the 'Q-Qat method') (38). There will be a focus on aspects of information provision that are unclear, disrupted, or potentially detrimental to recruitment and/or adherence. Analysis will be led by the qualitative researcher, with a sample of transcripts independently coded by a second qualitative methodologist.

12.4. HES 5-year Data Analysis

The effect of treatment on HES-based outcomes will be analysed separately in the linked dataset by members of our group with specific expertise in such analyses.

A HES working dataset will be produced by a senior data manager with expertise in such procedures. Under supervision from the application team, the data manager will develop ad-hoc code in Python and SQL to produce a dataset that can be analysed using standard statistical packages such as Stata. This will be carried out using pseudo-anonymised linked datasets.

Outcomes of interest in this long-term data analysis will be analysed as time-to-event data, and will include all related hospital admissions and procedures, including further surgery and any associated complications requiring hospital admissions. Patients will be followed up from randomisation to the earliest of each of the events of interest, death, loss to follow-up (e.g. migration out of England) or 5 years after randomisation. Incidence rates and 95% confidence intervals and 5-year cumulative incidence will be estimated stratified by treatment allocation (intention-to-treat/"as allocated') and separately by actual receipt of the allocated intervention (per protocol). The non-randomised group will be followed up in a similar way 5 years post intervention to assess the subsequent impact of diagnostic errors (false positive findings) on rates of any further shoulder surgery.

Finally, Cox regression models will be fitted to estimate Hazard Ratios (HR) and 95 % Confidence Intervals according to treatment allocation in an intention-to-treat analysis. Similar analyses but with HR estimated using a "per protocol" population will be conducted. Separate models will be fitted for each of the events of interest. The proportionality of hazards assumption will be tested using visual inspection of Nelson-Aalen plots and formal testing using the Schöenfeld's residuals test. Competing risk modelling (cause-specific Cox) will be conducted if there is evidence of substantial differential mortality between treatment groups.

13. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

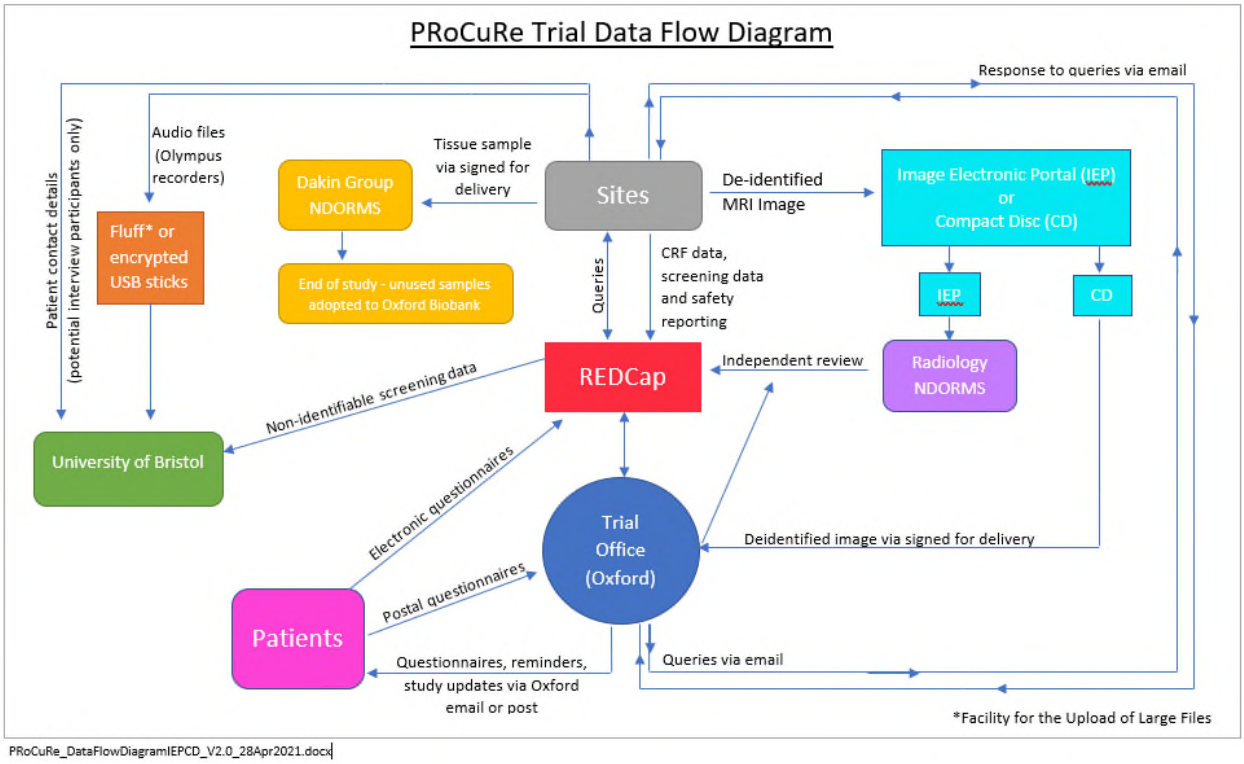

Figure 4: Data Flow Diagram

13.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consents, the participant will be referred to by the study participant number/code, not by name.

13.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

On completion of the study, and with appropriate participant consent, de-identified data may be shared with other organisations at the behest of the funder. All requests for the use of the data from the PRoCuRe

study will be approved by the CI, Trial Management Group (TMG) and where necessary the Trial Steering Committee (TSC). A data request form should be completed detailing the decision as to whether the request is accepted. In cases where individual site data is requested, only summary data would be provided with caveats for dissemination, to emphasise that trial data should be interpreted as a whole.

13.3. Trial Data Recording and Record Keeping

A Data Management and Sharing Plan will be produced for the trial, which will describe the methods of data collection, entry and management, including details of data management tools and the study-specific database. All data will be processed in accordance with the Sponsor's policy for data protection.

All trial-specific documents, except for the signed consent forms and follow-up contact details, will refer to the participant with a unique study participant number/code and not by name. Participant identifiable data will be stored securely in accordance with OCTRU Standard Operating Procedures (SOPs).

Site teams will enter data directly into the study-specific database, which will be validated and queried by central trial team. The central team will control access to the database in accordance with OCTRU SOPs. Any paper questionnaires returned by participants will be stored securely in offices only accessible by swipe card by the central coordinating team staff in Oxford and authorised personnel.

13.4. QRI Data

Audio files, made using encrypted audio-recorders, will be extracted by a research nurse or member of the research team directly on to the local Trust secure servers. To ensure safe and secure transfer of digital data, the Bristol University encrypted 'FLUFF' electronic data transfer system will be used. Electronic data (audio files) will then be transferred to the University of Bristol servers via an encrypted 'FLUFF' electronic data transfer method. Data sent via this method is encrypted via a HTTPS link preventing any third party to read the exchanged data; folders will also benefit from the added security of password protection. All data will be destroyed/returned to Oxford on completion of the study. Non-identifiable data will be retained on the Bristol University's secure Research Data Storage Facility (RDSF) for 20 years in line with the study's ethical approval.

Digital data, transferred from the Trust, will be uploaded onto the University of Bristol secure severs. All files will be labelled under participants' unique ID numbers and secured in password protected files. Oxford will retain a links document containing personal identifiers. This will not be shared with the University of Bristol. Interview data will be transcribed in-house by University of Bristol employees.

Although the transcripts can be fully de-identified, there may be aspects of the audio-recordings that contain personal/identifiable information (such as participants' voices in the recordings). Only authorised members of staff involved in the research will be able to access the data. University of Bristol may use this

data as part of publications, teaching and presentations at academic meetings. All quotes will be completely anonymised. If a section of audio is played (i.e. for training), voices will be modified voices and any personal information will be removed. Information about how the data are stored and used is provided in the information leaflet, and participants will confirm they consent for their data to be used in this manner.

14. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, Good Clinical Practice (GCP), relevant regulations and standard operating procedures.

14.1. Risk assessment

OCTRU conducted a risk assessment prior to the study starting. Issues raised have been addressed within the final protocol and procedures have been planned to monitor the ongoing risks of the trial. A risk proportionate approach will be utilised within this trial. The risk assessment will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

14.2. Study monitoring

Regular central monitoring of trial procedures will be imbedded into the trial conduct and management, according to a study specific Monitoring Plan. The trial will be subject to audit by the OCTRU Quality Assurance team, according to its Audit Programme. The trial will also undergo a process of review before it is granted the green light to begin recruiting patients.

14.3. Study Committees

The Trial Management Group, Trial Steering Committee and Data Safety Monitoring Committee will be set up and run in accordance to their Charters. All members have to sign to agree to the conditions of the Charter before sitting on a committee.

15. PROTOCOL DEVIATIONS

A study related deviation is a departure from:

- the ethically approved study protocol
- other study document or process (e.g. consent process or administration of study intervention)
- GCP
- any applicable regulatory requirements

Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file. OCTRU SOPs will be followed for the procedure of identifying non-compliances, escalation to the central team and assessment of whether a non-compliance/deviation may be a potential serious breach.

16. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree;

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

17. ETHICAL AND REGULATORY CONSIDERATIONS

Participants will be supported by their routine care providers over the duration of the study. The trial intervention is a one-off procedure and all subsequent care will be sought through and provided by routine care.

17.1. Clinical Trials Unit (CTU) Involvement

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

17.2. Compliance Statement

The trial will be conducted in compliance with the approved protocol and standard operating procedures (SOPs), the Declaration of Helsinki, the principals of Good Clinical Practices (GCP, UK Data Protection Act) and other applicable regulatory and governance frameworks including the UK policy framework for health and social care research.

17.3. Approvals

Following Sponsor approval of the protocol, informed consent form, patient facing documentation will be submitted to an appropriate Research Ethics Committee (REC), and Health Research Authority (HRA) (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

17.4. Other Ethical Considerations

The follow-up MRI scan is for research purposes only and results will not routinely be fed back to the local PI. However, if the independent reviewer (Consultant MSK Radiologist) happens to notice an abnormality that they think might be potentially serious, we will contact the PI who will assume responsibility for contacting both the patient and the patient's GP.

17.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress Report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

17.6. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database. Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

17.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of some CRFs, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

17.8. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

18. FINANCE AND INSURANCE

18.1. Funding

The study is funded by the National Institute of Health Research, Health Technology Assessment (NIHR128043). The Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences at the University of Oxford will manage the finances and budget.

Activities specific to tissue samples are funded by the NIHR Oxford Biomedical Research Centre.

18.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

18.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

19. PUBLICATION POLICY

Authorship of the Primary Publication shall be in accordance with normal academic practice. The Project Lead shall have final say on all publications related to the Project. The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by NIHR Heath Technology Assessment Programme. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University unless otherwise stated in the collaboration agreement between Oxford, Bristol and Keele. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

20. ARCHIVING

The Trial Master File including all essential documents must be retained for at least 5 years after the completion of study-related activities. The Sponsor File will be archived centrally, and the Investigator Site Files will be archived at site.

21. REFERENCES

1. Keener JD, Patterson BM, Orvets N, Chamberlain AM. Degenerative Rotator Cuff Tears: Refining Surgical Indications Based on Natural History Data. J Am Acad Orthop Surg. 2019;27(5):156-65.
2. Carr AJ, Cooper CD, Campbell MK, Rees JL, Moser J, Beard DJ, et al. Clinical effectiveness and cost-effectiveness of open and arthroscopic rotator cuff repair [the UK Rotator Cuff Surgery (UKUFF) randomised trial]. Health Technol Assess. 2015;19(80):1-218.
3. Carr A, Cooper C, Campbell MK, Rees J, Moser J, Beard DJ, et al. Effectiveness of open and arthroscopic rotator cuff repair (UKUFF): a randomised controlled trial. Bone Joint J. 2017;99-B(1):107-15.
4. Craig RS, Lane JCE, Carr AJ, Furniss D, Collins GS, Rees JL. Serious adverse events and lifetime risk of reoperation after elective shoulder replacement: population based cohort study using hospital episode statistics for England. Bmj. 2019;364:l298.
5. 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;6(4):e010412.
6. Kulkarni R, Gibson J, Brownson P, Thomas M, Rangan A, Carr AJ, et al. BESS/BOA Patient Care Pathways: Subacromial shoulder pain. Shoulder & Elbow. 2015;7(2):135-43.
7. Lenza M, Buchbinder R, Takwoingi Y, Johnston RV, Hanchard NC, Faloppa F. Magnetic resonance imaging, magnetic resonance arthrography and ultrasonography for assessing rotator cuff tears in people with shoulder pain for whom surgery is being considered. Cochrane Database Syst Rev. 2013;9:CD009020.
8. Karjalainen TV, Jain NB, Page CM, Lahdeoja TA, Johnston RV, Salamh P, et al. Subacromial decompression surgery for rotator cuff disease. Cochrane Database Syst Rev. 2019;1:Cd005619.
9. Vandvik PO, Lahdeoja T, Ardern C, Buchbinder R, Moro J, Brox JI, et al. Subacromial decompression surgery for adults with shoulder pain: a clinical practice guideline. Bmj. 2019;364:l294.
10. Kim YS, Lee HJ, Bae SH, Jin H, Song HS. Outcome Comparison Between in Situ Repair Versus Tear Completion Repair for Partial Thickness Rotator Cuff Tears. Arthroscopy. 2015;31(11):2191-8.
11. Kim YS, Lee HJ, Kim JH, Noh DY. When Should We Repair Partial-Thickness Rotator Cuff Tears? Outcome Comparison Between Immediate Surgical Repair Versus Delayed Repair After 6-Month Period of Nonsurgical Treatment. Am J Sports Med. 2018;46(5):1091-6.
12. Ranalletta M, Rossi LA, Atala NA, Bertona A, Maignon GD, Bongiovanni SL. Arthroscopic in Situ Repair of Partial Bursal Rotator Cuff Tears Without Acromioplasty. Arthroscopy. 2017;33(7):1294-8.
13. Katthagen JC, Bucci G, Moatshe G, Tahal DS, Millett PJ. Improved outcomes with arthroscopic repair of partial-thickness rotator cuff tears: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2018;26(1):113-24.
14. Osti L, Buda M, Andreotti M, Osti R, Massari L, Maffulli N. Transtendon repair in partial articular supraspinatus tendon tear. Br Med Bull. 2017;123(1):19-34.
15. Ono Y, Woodmass J, Bois A, Boorman R, Thornton G, Ian K. Arthroscopic Repair of Articular Surface Partial-Thickness Rotator Cuff Tears: Transtendon Technique versus Repair after Completion of the Tear—A Meta-Analysis. Advances in Orthopedics. 2016;2016:1-7.
16. Sun L, Zhang Q, Ge H, Sun Y, Cheng B. Which is the best repair of articular-sided rotator cuff tears: a meta-analysis. J Orthop Surg Res. 2015;10:84.
17. Judge A, Murphy RJ, Maxwell R, Arden NK, Carr AJ. Temporal trends and geographical variation in the use of subacromial decompression and rotator cuff repair of the shoulder in England. Bone & Joint Journal. 2014;96-B(1):70-4.
18. Beard DJ, Campbell MK, Blazeby JM, Carr AJ, Weijer C, Cuthbertson BH, et al. Considerations and methods for placebo controls in surgical trials (ASPIRE guidelines). The Lancet. 2020;395(10226):828-38.
19. Donovan JL, Rooshenas L, Jepson M, Elliott D, Wade J, Avery K, et al. Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention (QRI). Trials. 2016;17(1):283.

20. Rooshenas L, Elliott D, Wade J, Jepson M, Paramasivan S, Strong S, et al. Conveying Equipoise during Recruitment for Clinical Trials: Qualitative Synthesis of Clinicians' Practices across Six Randomised Controlled Trials. PLoS Med. 2016;13(10):e1002147.
21. Jepson M, Elliott D, Conefrey C, Wade J, Rooshenas L, Wilson C, et al. An observational study showed that explaining randomization using gambling-related metaphors and computer-agency descriptions impeded randomized clinical trial recruitment. J Clin Epidemiol. 2018;99:75-83.
22. Rooshenas L, Elliott D, Wade J, Jepson M, Paramasivan S, Strong S, et al. Conveying Equipoise during Recruitment for Clinical Trials: Qualitative Synthesis of Clinicians' Practices across Six Randomised Controlled Trials. PLoS medicine. 2016;13(10):e1002147-e.
23. Jepson M, Elliott D, Conefrey C, Wade J, Rooshenas L, Wilson C, et al. An observational study showed that explaining randomization using gambling-related metaphors and computer-agency descriptions impeded randomized clinical trial recruitment. Journal of Clinical Epidemiology. 2018;99:75-83.
24. Dawson J, Fitzpatrick R, Carr A. Questionnaire on the perceptions of patients about shoulder surgery. J Bone Joint Surg Br. 1996;78(4):593-600.
25. Dawson J, Hill G, Fitzpatrick R, Carr A. Comparison of clinical and patient-based measures to assess medium-term outcomes following shoulder surgery for disorders of the rotator cuff. Arthritis Rheum. 2002;47(5):513-9.
26. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.
27. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013;22(7):1717-27.
28. Moosmayer S, Lund G, Seljom U, Svege I, Hennig T, Tariq R. Comparison between surgery and physiotherapy in the treatment of small and medium-sized tears of the rotator cuff: a randomised controlled study of 103 patients with one-year follow-up. 2010;92:83-91.
29. Rees JL, Dawson J, Hand GC, Cooper C, Judge A, Price AJ, et al. The use of patient-reported outcome measures and patient satisfaction ratings to assess outcome in hemiarthroplasty of the shoulder. J Bone Joint Surg Br. 2010;92(8):1107-11.
30. White IR, Kalaitzaki E, Thompson SG. Allowing for missing outcome data and incomplete uptake of randomised interventions, with application to an Internet-based alcohol trial. Statistics in medicine. 2011;30(27):3192-207.
31. Dunn G, Emsley R, Liu H, Landau S, Green J, White I, et al. Evaluation and validation of social and psychological markers in randomised trials of complex interventions in mental health: a methodological research programme. Health technology assessment (Winchester, England). 2015;19(93):1-115, v-vi.
32. Hao Q, Devji T, Zeraatkar D, Wang Y, Qasim A, Siemieniuk RAC, et al. Minimal important differences for improvement in shoulder condition patient-reported outcomes: a systematic review to inform a BMJ Rapid Recommendation. BMJ Open. 2019;9(2):e028777.
33. van Kampen DA, Willems WJ, van Beers LW, Castelein RM, Scholtes VA, Terwee CB. Determination and comparison of the smallest detectable change (SDC) and the minimal important change (MIC) of four-shoulder patient-reported outcome measures (PROMs). J Orthop Surg Res. 2013;8:40.
34. Beard DJ, Rees JL, Cook JA, Rombach I, Cooper C, Merritt N, et al. Arthroscopic subacromial decompression for subacromial shoulder pain (CSAW): a multicentre, pragmatic, parallel group, placebo-controlled, three-group, randomised surgical trial. Lancet. 2018;391(10118):329-38.
35. NICE. Position statement on use of the EQ-5D-5L valuation set for England (updated November 2018). 2018.
36. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2012;15(5):708-15.

37. Wade J, Donovan JL, Athene Lane J, Neal DE, Hamdy FC. It's not just what you say, it's also how you say it: Opening the 'black box' of informed consent appointments in randomised controlled trials. Social Science & Medicine. 2009;68(11):2018-28.
38. Paramasivan S, Strong S, Wilson C, Campbell B, Blazeby JM, Donovan JL. A simple technique to identify key recruitment issues in randomised controlled trials: Q-QAT - Quanti-Qualitative Appointment Timing. Trials. 2015;16:88.

22. APPENDIX A: SCHEDULE OF STUDY PROCEDURES

Procedures x = site team # = central team	**Visits/Follow-up**						
	Screening	**Prior to operation**	**Operation**	**6 months ***	**12 months ***	**24 months ***	**5 years**
Eligibility assessment	x		x				
Baseline imaging review	x						
QRI Informed Consent	x						
PRoCuRe Informed Consent		x					
Demographics		x					
Details of tendon status	x		x				
Randomisation			x				
Surgery details			x				
OSS		X**		#	#	#	#*
Patient satisfaction and perception questions				#	#	#	#*
EQ-5D-5L		X**		#	#	#	
Health resource use questionnaire				#	#	#	
Patient reported adverse events				#	#	#	
PRoCuRe MRI						x	
PRoCuRe MRI Review						#	
Notes review						x	
HES Data Review							#

* Randomised participants only

** Baseline assessments will be completed within the 4 weeks prior to the patient's surgery date; this includes the day of surgery. Where a patient's surgery date is delayed and rescheduled a repeat Baseline assessment will be completed, if the initial data collection was to fall outside of the 4 week window. Refer to section 9.7.

23. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	V2.0	28Apr2021	Naomi Merritt	Planned recruitment period dates amended to reflect original period approved by the HTA programme. NIHR reference number corrected. References to 'DMC' changed to 'DSMC'. Figure 4 updated to reflect the 2-way data flow between Trial Office and REDCap. Notes review at 24 months post-randomisation added to Appendix A. Minor text corrections and clarifications.

Details of all protocol amendments will be listed here whenever a new version of the protocol is produced.

Protocol amendments will be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).