Study Title: Patch Augmented Rotator Cuff Surgery Study (PARCS) – A Feasibility Study

Short title: PARCS

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Chief Investigator Signature: 

Declaration of potential conflict of interest

Investigator, Professor Andrew Carr, has applied for a patent that will be considered as part of this work. We have carefully designed a robust research strategy that incorporates substantial independent input throughout to ensure no one individual, whether they be within or out with the project team, can have undue influence on the process.

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1. SYNOPSIS

Study Title	Patch Augmented Rotator Cuff Surgery Study (PARCS) A Feasibility Study	
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Study Design	A six-stage mixed-methods feasibility study.	
Study Participants	Stakeholders: Public, patients, shoulder surgeons, surgeon trialists, NHS Commissioners/procurers, and representatives from regulatory bodies and industry.	
Planned Sample Size	Stage 2: circa 350 members of the British Shoulder and Elbow Society Stage 3: 30+ research active orthopaedic shoulder surgeons Stage 4: 20 – 40 participants in total Stage 5: 50 – 80 participants Stage 6: 20-30 participants	
Planned Study Period	01 April 2017 - 31 Dec 2018 (21 Months)	
	Objectives	**Outcome Measures**
Primary	To determine the design of a definitive randomised trial assessing the effectiveness and cost-effectiveness of a patch to augment surgical repair of the rotator cuff tendon that is both acceptable to stakeholders and feasible.	N/A
Secondary	1) Identify candidate patches and clinical evidence about their use. 2) Determine current practice in the NHS 3) Elicit views on the use of patch-augmented rotator cuff surgery 4) Determine how a randomised trial evaluating patch-augmented rotator cuff surgery that is acceptable and feasible should be carried out, including population, intervention and control groups, surgical techniques, outcomes, follow-up and the type of economic evaluation needed.	1) Systematic Review 2) Surgeon Survey (BESS) 3) Surgeon Survey (trialists) 4) Focus Groups

2. ABBREVIATIONS

BESS	British Elbow and Shoulder Society
BOS	Bristol Online Survey
CI	Chief Investigator
CSAW	Can Shoulder Arthroscopy Work?
EU	Europe/ European
GCP	Good Clinical Practice
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluations
HRA	Health Research Authority
HTA	Health Technology Assessment
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IDEAL	Idea, Development, Exploration, Assessment, Long-term follow-up
JLA	James Lind Alliance
MHRA	Medicines and Healthcare products Regulatory Authority
NHS	National Health Service
NVivo	Qualitative and mixed methods software
RCT	Randomised Controlled Trial
SSC	Study Steering Committee
Stata	Data Analysis and Statistical Software
UK	United Kingdom
UKFRosT	United Kingdom Frozen Shoulder Trial
UKUFF	United Kingdom Rotator Cuff Trial
USA	United States of America

3. BACKGROUND AND RATIONALE

Clinical problem

Shoulder pain is a common problem in the general population and is responsible for prolonged periods of disability, loss of productivity, absence from work and inability to carry out household activities. Rotator cuff conditions which relate to the tendons and muscles surrounding the shoulder joint, account for up to 70% of shoulder pain problems and are the third most prevalent musculoskeletal disorder after lower back and neck pain and 2% of General Practitioner (GP) consultations [1, 2]. A severe but common rotator cuff problem is a rotator cuff tendon tear, found in about 25% of people aged 70 and above. Symptoms include pain, weakness, lack of shoulder mobility and sleep disturbance. Initial management is conservative and includes rest with simple pain management through paracetamol and non-steroidal anti-inflammatory drugs, often followed by an injection of corticosteroid into the space between the acromion process of the shoulder blade and the humerus [3]. Approximately 40% of patients will continue to experience pain despite conservative management and many will require surgery to repair the tear.

Surgery for rotator cuff repair

Surgical repair of the rotator cuff seeks to attach the tendon to the bone to allow the tear to heal and improve patient outcomes. Around 9,000 rotator cuff repairs are performed each year in the NHS in England, at a cost of £6,628 per operation (£60 million per year), and this number is continuing to grow [2, 4]. There is substantial variation in surgical practice, which includes the type of surgery (open or arthroscopic), surgical techniques (for example the use of anchors and type of suture), and type and duration of conservative treatment (including cortisone injections, physiotherapy, rest, advice, analgesia and home exercises). Surgical management of rotator cuff tears was reviewed by Dunn and colleagues [5] , who surveyed members of the American Academy of Orthopaedic Surgeons. At the time only 15% preferred arthroscopic surgery, although this is likely to have since grown. Rotator cuff surgery can have mixed outcomes for patients. It has a high failure rates (25-50% [6-8] within 12 months) and is expensive, invasive and inconvenient to patients. Re-operation is also sometimes necessary. Although there are different views about the key drivers of the health outcome, a number of factors are consistently related to poor outcomes, particularly increasing age and increasing tear size. The recently published UKUFF trial [2] revealed a 40% failure rate of surgical repairs in a wide range of settings using different surgical techniques in the NHS. A healed repair resulted in the best clinical and patient-reported outcomes.

The James Lind Alliance (JLA) Priority Setting Partnership for Surgery for Common Shoulder Problems' (2015) successfully brought together patients, carers and clinicians to identify the ongoing important treatment uncertainties related to shoulder surgery[9]. Four of the top 10 uncertainties for common shoulder problems concerned rotator cuff tears. There is, therefore, a pressing need to progress surgical options for rotator cuff repairs and to improve tendon healing and outcomes for patients [10].

A number of unsuccessful surgical approaches have been tried to improve the outcome of rotator cuff repair [2, 8, 11, 12]. The UKUFF trial found that minimally invasive (arthroscopic) surgery had no benefit over open surgery [13] . At the time only two randomised controlled trials (RCTs) which evaluated surgery for a rotator cuff tear, were identified by the current Cochrane review, published in 2008 [11, 14, 15] . Both were judged to be susceptible to bias. An updated systematic search performed in March 2014 to set the UKUFF trial findings in context revealed six more trials comparing two surgical interventions [14-19]. These RCTs were single centre and were relatively small, with between 73 and 114 participants per trial and a mean participant age of around 60 years. The trial mainly included participants with full thickness rotator cuff tears [15, 16, 18, 19] and two those with small and medium rotator cuff tears [17, 20].One further ongoing study was identified [20]. There was no evidence that the use of suture anchors or alternate methods of suturing improve healing rates. Attention has recently focused on improving the biology of the torn tendon at the time of surgery and for the critical 8-12 week period after surgery, when effective healing is needed [21]. Repairs commonly fail due to poor tissue and bone quality or inadequate fixing of the tendon to the bone, allowing the tendon to pull away from the bone.

Patch-augmented rotator cuff surgery

A promising, yet to be fully evaluated, area for further assessment is the use of a patch to provide a support structure or 'scaffold' for the repair, to improve the fixing of the tendon to the bone and tendon healing [22, 23]. These implants are also referred to as an extra- or a-cellular matrix (when made from human or animal cells) or as a graft (e.g., an allograft, autograft or xenograft, depending on the source material used to manufacture the patch). The patch is surgically sutured on top of the tendon-to-bone repair to strengthen the repair and aid tendon healing, thereby reducing the likelihood of failure and improving patient outcomes. [24]

Patches have been made using different materials (human/animal heart, skin or intestine tissue, and completely synthetic materials) and processes (e.g. woven or mesh approaches) and to different sizes. They can be designed to be absorbable, avoiding the possibility of later surgical complications or surgical removal. [9] Patches differ in how they respond to tendon tissue and their mechanical properties. [25] Some have been designed specifically or can be tailored in size and shape for specific use in rotator cuff

surgery, whereas others were developed for other soft-tissue contexts (e.g., anterior cruciate ligament reconstruction in the knee or for hernia repair). Recent advances include the development of electrospun materials [24] and exploration of the concurrent use of growth factors. Electrospun materials have a structure that closely resembles the surrounding tissue; they provide biological cues to encourage cell growth and tissue healing. The aim of these and other biomimetic materials is to avoid adverse immunological responses, which some tissue-based patches have provoked [26]. Augmenting surgical repair with a patch may also enable the repair of tears that are currently considered unrepairable [9, 22, 27-29]. Over 20 patches have received regulatory approval in the USA and/or by an EU-notified body for use in surgical repair of the rotator cuff. The Graftjacket™ (Wright Medical Group), Inc.), for example has been on the market for over 10 years. There are more patches in development and they are being used in a number of centres in the UK for private and NHS patients.

The use of a patch to augment rotator cuff surgery is increasing. There is currently a window of opportunity to design, gain stakeholder buy-in for, and conduct a timely RCT before widespread adoption of these medical devices for rotator cuff surgery. However, the design and feasibility of such a trial is not clear. The aim of this study (PARCS) is address this gap in knowledge by determining, using consensus methods, the design of a definitive randomised trial to assess the effectiveness and cost-effectiveness of a patch to augment surgical repair of the rotator cuff, and to assess this trial's acceptability and feasibility.

4. AIM AND OBJECTIVES

Aim/Research Questions	Objectives
To determine the design of a definitive randomised trial assessing the effectiveness and cost-effectiveness of a patch to augment surgical repair of the rotator cuff tendon that is both acceptable and feasible.	• Review existing evidence to identify candidate patches for use in a randomised trial and the evidence relating to their clinical use. • Determine current practice in the NHS relating to the use of patches to augment rotator cuff repair. • Assess the acceptability of the trial's design to patients and surgeons. • Assess the feasibility of a trial of patch-augmented rotator cuff repair. • Achieve consensus on the key elements of the design of a definitive randomised trial to assess

	the use of patches to augment rotator cuff repair. • Confirm the scope of the health economic evaluation required in the trial to appropriately assess its cost effectiveness. • Identify areas for further research related to patch augmented rotator cuff surgery.

5. STUDY DESIGN

PARCS is a mixed methods feasibility study consisting of 6 stages. This protocol pertains to Stages 2-6. The design of each stage is summarised below.

This consensus methods approach builds on the work by the IDEAL Collaboration for evaluating surgical innovation and devices in early-stage and randomised trial assessments [30] and adapts the methodology used for achieving expert consensus in guideline development and development of core outcome sets [31-33] to the broader scope of trial design.

See Appendix A for a summary flow diagram.

Stage 1: Systematic Review of candidate patches and related clinical evidence

The Systematic Review will be performed according to a separate protocol. Refer to protocol: Systematic review of the surgical management of rotator cuff repair with augmentative patch: a feasibility study. This protocol is available on the PARCS study webpage: https://www.ndorms.ox.ac.uk/clinical-trials/current-trials-and-studies/parcs

Stages 2 & 3: Surveys of surgical practice and acceptability and feasibility of a randomised trial.

The aim of the two surveys is to ascertain current NHS clinical practice relating to the use of patches to augment rotator cuff repair. PARCS will also explore the acceptability of the proposed trial to surgeons and assess the feasibility of a trial of patch augmented rotator cuff repair.

Electronic surveys will be conducted using the Bristol Online Survey (BOS) tool [34]. Prior to finalising, each survey will be piloted internally amongst the study investigators and a number of external individuals as appropriate. The number of responses and feedback received on completing the Stage 2 survey will be taken into account when finalising the Stage 3 survey.

Surgeons will be invited via email to participate in the survey. Information about the study and a hyperlink to the relevant survey will be provided. If necessary, a maximum of two e-mail reminder messages will be sent per survey. If there is no response by the time the survey closes, we will assume that the surgeon does not wish to take part in that stage of the study. Refer to section 7.3 for informed consent procedures.

- British Elbow and Shoulder Society (BESS) Membership Survey (Stage 2)

  The aim of this survey is to identify current UK clinical practice and gather information on surgeon opinion relating to the factors that influence their choice of patch, and patient suitability. This survey will also explore the general attitude of the orthopaedic surgical community towards a randomised controlled trial of patch augmented rotator cuff repair.

  To avoid unnecessary sharing of personal data, invitations to take part in this (stage 2) survey will be coordinated and managed in collaboration with the administrator at the BESS office. Therefore, if reminder e-mails are needed, they will be sent to the entire sample.

  Members of BESS attending the 2017 annual meeting will be offered an opportunity to complete the survey during the meeting. A member of the PARCS study team will provide verbal and, where appropriate, written study information. If the surgeon is agreeable, they will be given access to the on-line survey for completion at the meeting.

  The survey will take approximately 10 minutes to complete. There is no minimum number required.

- Survey of Shoulder Surgeon Trialists (Stage 3).

  This survey will be directed at surgeons who are trial active and, therefore, most likely to participate in a randomised controlled trial of patch-augmented rotator cuff surgery. It will therefore include more trial specific focus and concern the practicalities of running such a trial. We will invite a network of surgeon trialists who have participated in previous NHS-based shoulder surgical trials. This will include a number of surgeons who acted as Principal Investigator for the UKUFF, CSAW and UKFroST trials [2, 35, 36].

  For stage 3, e-mail correspondence (invites/reminders) will be personalised.

  The survey will take approximately 15 minutes to complete. During the survey, participants will be asked to register their interest in taking part in further stages of the PARCS study.

Stage 4: Focus Groups

Focus Groups allow participants to speak freely about their concerns and offer their views about the existing and proposed evaluation of a new approach to surgical treatment. They are particularly useful for helping to identify issues that resonate with lay people and the public at large in matters of healthcare [37, 38]. Focus groups are widely used in health services research.

Using a number of focus groups we aim to access a broad range of stakeholder views and opinions on the acceptability of the use of patches in the augmentation of rotator cuff repair, and the trial design options that may be used to test them. Themes and issues identified from the surgeon surveys (stages 2 and 3) will help to form topics for discussion.

Focus group members will be recruited to separate focus groups, each reflecting the various key stakeholder groups:

A) Public/ Patients with current or previous rotator cuff problems.
    - Two focus groups; each will be conducted in a different region of the UK (Thames Valley and South Tees)
B) Regulatory body representatives, NHS managers, commissioners, and other staff involved in surgical equipment procurement.
C) Representatives from Industry.

Group A is considered to be the key stakeholder group. However, the introduction of patches in to the NHS has regulatory and cost implications, therefore, it is relevant to include the views and opinions of groups B, and C in the study. Refer to section 7.0 for recruitment strategy.

Each focus group will aim to involve 4 to 8 participants and will be held at a location best suited to the participants.

Focus groups sessions will last for a maximum of 2 hours. There will be breaks for refreshment of at least 15 minutes per hour of discussion. Refreshments will be provided during the focus group session.

Refer to section 11.6 for details of associated expenses and benefits.

Each focus group will be facilitated by an appropriately trained member of the PARCS study team. Discussions will be audio recorded, and one or two observers will take notes to aid in the transcription of audio files and analysis.

Ahead of the focus group session, potential participants will be provided with a study information sheet (specifically tailored to their stakeholder group) that describes the aim of the focus group, how to take

part, and the consent procedure. Depending on individual preference, this information will be supplied by either hand, e-mail or post. As soon as they are confirmed, arrangements for the focus group (date, time and location) will be provided.

During the focus group session, the aim of the focus group and the PARCS project will be briefly introduced, participants will be asked to consider a number of scenarios or vignettes. These will be in the form of brief narratives that contain key items of information about the possible trial design options such as; the different kinds of patches available and their acceptability; the choice of comparative study arms; most appropriate outcome measures; and methods of data collection. The way in which this information is delivered may be adapted according to participant group.

We will ask focus group participants to provide some basic background information on themselves (gender, age, relevant experience, and treatment routes used). This information will be anonymous. Participants will be provided with a plain opaque envelope in which to place the completed 'background information form', they will be instructed to place the envelope to in a box as they leave.

Data collected at the focus groups will be analysed by appropriately trained researchers from the University of Oxford.

If a participant is unable to attend their focus group on the proposed date, they will be offered an opportunity to respond to the topics discussed at the meeting in writing.

If it is not feasible to conduct a focus group meeting due to insufficient interest, participants may be offered an individual face-to-face interview, or telephone interview instead.

Stage 5: Consensus Building: Delphi Study

We will use a Delphi study to develop a consensus on the best way to design a clinical trial of patch-augmented rotator cuff surgery. The Delphi method is a structured process of obtaining information from a group of experts using a series of related questionnaires, each one refined using respondents' feedback from a previous version [39]. Delphi is a well-known and increasingly common method in the clinical setting to establish a consensus [37, 39, 40].

We will conduct a multi-stage on-line Delphi survey consisting of at least two but no more than three rounds. The survey will be developed and conducted using the Bristol Online Survey (BOS) System [34].

Participants involved in stages 2 to 4 of the PARCS Study will be invited to take part in stage 5 where appropriate according to stakeholder group and background, as detailed in section 7.0. Those who

respond positively to invite will be included. Given the nature of the study there has been no formal sample size calculation but around 50-80 are anticipated.

Delphi study participants will have their name and contact e-mail address entered in to the BOS system [34]. An e-mail will be sent to each participant containing a personalised link that enables access for survey completion. Refer to section 7.3 for informed consent procedures.

Findings from Stages 1 to 4 will determine the individual elements to be included in the first round of the Delphi survey.

During completion of the first round, survey participants will be asked to supply some basic demographic information (for example; age, background, current employment & position, and number of years of relevant experience) and will be allocated a unique identifier used for administrative and data analysis purposes.

Responses are stored securely on the BOS system and will be downloaded on to a secure file space at the University of Oxford.

During the survey, participants will be presented with aspects of the proposed trial design and asked to score each using an adapted version of the Grading of Recommendations Assessment, Development and Evaluations (GRADE) scale of 1-9, where 1 represents complete disagreement and 9 represents complete agreement [41] . Participants will be given the opportunity to communicate their personal suggestions with regards to any additional design elements they feel should be included in future round in order to achieve consensus. All design elements will be carried forward to round two of the Delphi survey.

New design elements suggested by participants in round one of the Delphi survey will be reviewed and coded by two members of the PARCS study team. The wider project team will be consulted if there is any uncertainty.

Subsequent rounds: Participants will receive an e-mail containing a summary of the findings from the previous round. They will be asked to reflect on their own response and also the collated responses. Participants will then score each design again using the BOS system.

The final set of proposals, areas of provisional consensus, and remaining disagreement and uncertainty will then be brought forward to the consensus meeting in Stage 6 and used as the basis for discussion.

Where necessary, at each round of this Delphi survey non-responders will receive a maximum of two reminder messages. The final reminder will contain a specific deadline for survey closure [42].

Each survey will take approximately 20 minutes to complete.

Stage 6: Consensus Building: Consensus Meeting

Findings from Stages 1 – 5 will feed in to, and inform the structure of, a two day face-to-face meeting where we will seek to agree a final consensus on an acceptable and feasible trial design for a definitive randomised trial to assess the effectiveness and cost-effectiveness of a patch to augment surgical repair of the rotator cuff tendon.

This meeting will involve a range of stakeholders (including patient and public representatives, surgeons and trialists) who took part in stages 2 – 5 of the study. Participants will be selected for invite based on their perspectives, experience and background. To ensure a robust decision is made, approximately 30 stakeholders will take part in this meeting.

Ahead of the consensus meeting, participants will be sent, by email, a summary of findings from earlier stages of the project. Participants will be advised that reasonable travel expenses will be reimbursed, and accommodation provided where appropriate.

The meeting will be structured to ensure key areas of uncertainty and/ or disagreement are identified. We will seek consensus on key elements of trial design; patient eligibility; intervention and control definitions; surgeon requirements; outcomes and target difference. Draft guidance, options and recommendations for a randomised trial assessing patch –augmented rotator cuff surgery will be developed from previous work updated in light of the findings from Stage 1 (Systematic Review). In order to maximise the available time and enable the inclusion of more stakeholder-specific topics, we may conduct small parallel group sessions if appropriate on more stakeholder specific aspects (e.g. inclusion/exclusion criteria for surgeons).

The meeting will last for a maximum of 6 hours per day and will include breaks for refreshment of at least 15 minutes per hour of discussion. There will also be a lunch break of an hour. The meeting will be fully catered for.

To ensure robustness and to avoid any potential conflicts of interest, the meeting will be chaired by an independent surgeon from a different surgical speciality who also has expertise in surgical trials.

A post-meeting report will be drafted and circulated to participants for their review and comments. The report will detail the key design decisions and will be divided into sections on methods, study design issues (e.g. the definition of comparison groups) and special topics (e.g. allowable variation in surgical technique). The scope of the trial health economic evaluation and areas for further research will also be included in this report.

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Study participants (stages 2-6) will be adult members of the public who are currently experiencing, or have a history of, problems involving the rotator cuff, orthopaedic shoulder surgeons who are actively practicing shoulder surgery in the United Kingdom, and surgeons with experience specific to shoulder surgery trials (surgeon trialists). We will also invite participants because of their specific knowledge and experience relevant to an aspect of the study topic (such as NHS commissioning and procurement, industry and regulatory bodies), there is no specific inclusion/ exclusion criteria relating to these participants.

6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Adult (18 yrs or older).
- Ability to understand and communicate (read, speak, write) in English at a level that permits effective interaction.

BESS Membership (Stages 2, 5, 6)

- Practicing orthopaedic shoulder surgeon (UK).

Surgeon trialist (Stage 3, 5, 6)

- Practicing orthopaedic shoulder surgeon.
- Active or previous Investigator for a Randomised Controlled Trial of shoulder surgery.
- Substantive involvement in a Randomised Controlled Trial i.e. with experience in recruitment, trial treatments, completion of case report forms etc.

Patients/ Public (Stages 4, 5, 6)

- Active or previous shoulder problem.

6.3. Exclusion Criteria

- <18yrs of age.
- Unable to provide informed consent for themselves.

- Significant cognitive or behavioural issues.
- Does not meet the inclusion criteria specific to relevant stakeholder group.
- Unable or unwilling to;
    - speak, read or write English to a sufficient level;
    - correspond using e-mail;
    - receive electronic documents as e-mail attachments;
    - access and complete on-line survey (stages 2, 3, 5).

7. STUDY ACTIVITIES

See Appendix B for schedule of activities.

7.1. Recruitment

Participants will be invited and recruited for each stage of the study separately, rather than for all stages at once. This is because the type of participant and the participant numbers required at each stage differs, and participants may wish to/be eligible to take part in one stage but not another.

At any stage, potential participants will be able to contact the PARCS study team in a number of ways (e-mail, phone, post) to ask questions and/or express an interest in taking part.

Recruitment of potential participants will occur through a number of routes depending on the stage of the study:

Stage 2: BESS Membership Survey

An invite to participate in this on-line survey will be sent to all surgeon members of the British Elbow and Shoulder Society (BESS).

Stage 3: Survey of Surgeon Trialists

Eligible participants will be identified by the PARCS Project Management Group and recruited through a personalised, email or face-to-face, invitation. These surgeons will be invited based on their previous experience in shoulder surgical trials.

Stage 4: Focus Groups

Potential participants will be invited and recruited using various avenues.

Public/ Patients

Consultant orthopaedic surgeons (and PARCS investigators) based at the Nuffield Orthopaedic Centre, Oxford and the James Cook University Hospital, South Tees will approach potential participants though outpatient clinics.

Poster advertisement in the local community such as Libraries, Community Centres, Supermarkets, Hospitals, GP Surgeries etc. may also be used. If necessary, the geographical area may be extended. Advertisements may also be placed on local or national websites set-up to increase public and patient involvement in clinical research such as www.makingresearchbetter.co.uk and www.patientsactiveinresearch.org.uk.

Those who respond positively and meet the inclusion criteria will primarily be included in the PARCS study focus groups in principle on a 'first come first served' basis within stakeholder group until the required sample size is met.

Other Stakeholder Groups

Regulatory body representatives, NHS commissioners, NHS procurers, representatives of industry and other individuals with relevant experience and knowledge will be identified, approached and invited to participate directly. This may be through professional or personal acquaintance.

If necessary, the technique of snowballing may be utilised i.e. respondents may be asked to pass on information to other potential participants[43].

Stage 5: Delphi Study – Survey

Those stakeholders who participate in stages 2 to 4 may be invited to take part in stage 5. To ensure balanced stakeholder representation, participants will be selected for invite based on their previous input.

Where appropriate, stakeholders who have relevant experience but did not take part in previous stages may be invited to participate. We will identify and recruit these participants using a similar approach as described in stages 3 and 4.

Stage 6: Delphi Study – Consensus Meeting

A purposive sample of participants from stages 2 - 4 will be selected and invited to participate such that a diverse range of perspectives, experiences and stakeholders are represented at the meeting.

For each stage of the study, eligible potential participants will receive an invite to participate and information on the study that is relevant to the stage of the study they are invited to take part in, and their stakeholder group. Depending on the stage of the study these documents will be available in either paper or electronic format, or both. Study information will also be accessible on the PARCS webpage on the Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences (NDORMS) website: https://www.ndorms.ox.ac.uk/clinical-trials/current-trials-and-studies/parcs

7.2. Informed Consent

Prior to taking part in any stage appropriate study information will be presented to potential participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol and any risks involved in taking part. This information will be presented in a written format, verbal information will be provided at face-to-face meetings and on request.

At all stages of the study it will be clearly stated that the participant is free to withdraw themselves and/or their response data at any time where it can be identified and removed (this is not likely to be feasible for responses to stage 2), and for any reason (that does not need to be disclosed). There will be no adverse consequence and without prejudice to future care if this is done.

Where relevant (see below for further details), written Informed Consent will be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtains the consent will be a suitably qualified and experienced member of the PARCS team. They will be authorised by the Chief/Principal Investigator to undertake Informed Consent activities.

The participant will be allowed as much time as they wish (within the constraints of the project timelines) to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study.

Stages 2 and 3 (Surgeon Surveys)

Participant consent will be implied by completion and submission of the on-line survey. Study information and details on how the data is collected, processed and used will be detailed in the e-mail correspondence (invite and reminders).

Stage 4 (Focus Groups)

Participants attending focus group discussions will be required to personally sign and date a consent form. The participant will be provided with a copy of their signed consent form.

The original (signed form) will be retained and filed securely at the study management office (University of Oxford). Original consent forms for participants of the focus group held in South Tees will be forwarded to Oxford for filing. A copy will be held by the PARCS study team at South Tees Hospitals NHS Foundation Trust, the Oxford office will acknowledge receipt of each consent form by email. Copies held at South Tees Hospitals NHS Foundation Trust will be confidentially destroyed at the end of the study.

Stage 5 (Delphi Study)

Those taking part in this on-line survey will be required to provide electronic consent to participate at the first round. The system will be organised so that survey completion is prohibited if the participant has not provided consent. Surveys will be directly linked to participants to ensure traceability.

Continued consent will be implied by the completion and submission of subsequent rounds. Checks will be in place to ensure that only participants who have consented have access to subsequent rounds.

Stage 6 (Consensus Meeting)

Consent will be implied through voluntary attendance and participation in this meeting. The name of attendee may be reported later in study outputs and participants will be made aware of this at the start of the meeting. A group photograph of the meeting attendees will be taken of individuals who verbally consent to take part (participation in this optional and attendees will be made aware of this). An electronic audio recording of the meeting for note taking purposes may be taken but only if all attendees verbally consent. Cases where verbal consent is provided (or not provided) will be minuted in the meeting notes.

For all on-line surveys; if there is no response by the time the survey closes, we will assume that the person does not wish to participate in that stage of the study.

7.3. Screening and Eligibility Assessment

Where necessary, responders (potential participants) will be asked to verbally confirm that they meet any relevant eligibility criteria before being accepted to participate. At Stage 4 (Focus Groups) participant eligibility will be further confirmed by a member of the PARCS study team prior to requesting/ receiving Informed Consent.

7.4. Subsequent Visits

Focus Groups (Stage 4)

This stage will involve one visit.

Focus Group sessions will be held in a place that best suits the people taking part. If a participant is unable to attend the focus group on the proposed date, they may be offered the opportunity to respond to the focus groups questions in writing.

If there is insufficient interest and it is not feasible to conduct a focus group discussion, participants may be offered an individual interview instead (face-to-face or telephone).

Consensus Meeting (Stage 6)

This stage will involve one visit (lasting a maximum of two days) per participant. The meeting will likely be held in Oxford.

Stages 2, 3 and 5 are on-line surveys and visits are therefore not applicable.

Due to the nature of the PARCS study, not all participants will take part in every stage. Therefore, the maximum number of visits that a participant will undertake is two.

7.5. Discontinuation/Withdrawal of Participants from Study

All participants have the right to withdraw from the study at any time. Participants who withdraw will be offered the option to; withdraw all of their data from the study where it can be identified and removed from the rest of the data; or allow the investigator team to keep any study data they have already provided for inclusion in the analysis. If the participant freely provides a reason for withdrawal, this will be recorded.

- In addition, the Chief Investigator may discontinue a participant from the study at any time if they consider it is necessary for any reason such as;
    - significant non-compliance with study requirements
    - conflict of interest identified

The reason for withdrawal by the study team (and by participant, if this information is volunteered) will be recorded in a study file. Where the Chief Investigator deems it necessary to discontinue a participant, they will discuss this with the participant and provide justification for their decision.

7.6. Definition of End of Study

The end of study is the will be once the grant funding has ended and the mandatory reporting period has finished (scheduled for one month post end of the funding).

8. ANALYSIS

8.1. Description of Analytical Methods

Stage 1: Refer to Systematic Review Protocol.

Stages 2 and 3: The surveys will be analysed separately. The response rate will be defined as the number of responding participants divided by the number of eligible people invited. The statistical analysis will be descriptive only. Responses will be summarised quantitatively or narratively, as appropriate (e.g. using Microsoft Excel and/or Stata).

Stage 4: The data will initially be analysed alongside data collection using thematic analysis [44]. The emphasis of the analysis will be on the acceptability of the proposed trial and on factors that might facilitate or impede such acceptability. Thematic content analysis will consist of:

(1) familiarisation with the focus group transcript;

(2) coding the transcript text under relevant themes using NVivo Version 10 (qualitative data analysis software);

(3) agreeing a thematic framework;

(4) applying the framework to subsequent focus group transcripts; and

(5) interpreting and summarising the data within each theme, including implications for trial design and stages 5 to 6 of the feasibility study.

Stage 5: During each round, scores (1 – 9) will be calculated as a percentage of the total responses. We will define consensus for the design elements proposal as >70% of responses rating the element 7 or greater and not more than 15% of responses rating the element <3 [24]. Median and ranges will also be produced for the scores. We will explore similarities and differences across stakeholder groups. Textual responses will summarised narratively.

Stage 6: The aim of this stage is to agree a consensus. There will be no statistical analysis. Decisions will be made through a group decision making process.

8.2. The Number of Participants

There is no formal sample size calculation.

Stage 1: Not Applicable

Stage 2: The membership of the British Shoulder and Elbow Society will be invited to take part. The BESS membership is approximately 350 members who are predominantly clinically active shoulder surgeons. The whole of this surgical membership will be invited to participate given that this will not add to the burden of the study conduct and will potentially increase the generalisability of findings. There is no minimum number required.

Stage 3: At least 30 research active orthopaedic shoulder surgeons will be invited to take part. This is considered large enough to meet the aim of this component of the project and ensuring a range of surgeons and centres are included.

Stage 4: 20 – 40 participants in total are anticipated. (Five focus groups, four stakeholder groups, between four and eight participants per group). This number has been suggested to be sufficient for a study of this kind. No strict minimum or maximum number will be applied.

Stage 5: 50 – 80 participants from Stages 2 to 4.
There are generally no accepted guidelines for the optimal sample size needed to achieve consensus in a Delphi studies [45]. We will aim to recruit 80 participants to the first round of the Delphi consensus survey; this sample size is based on previous experience of conducting these surveys and anticipated attrition rates at each round. (substantial loss from the initial to final round is not unusual [40, 46])

Stage 6: Around 20-30 participants from stages 2 - 5 to ensure a range of perspectives from different stakeholder groups.

8.3. Data Analysis

Analysis of all data will be descriptive and narrative. No statistical analyses will be carried out. Simple summaries (e.g. percentage of people state X) will be used

9. DATA MANAGEMENT

9.1. Access to Data

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

9.2. Data Recording and Record Keeping

Electronic surveys managed by the PARCS study team will be conducted using the Bristol Online Survey Tool. This system is fully compliant with UK data protection laws and meets UK accessibility requirements, it is robust and tested system that is commonly used by academic researchers at around 130 UK Universities [34].

All study data will be stored on the secure University of Oxford IT Network, which is automatically backed up once a day. Each participant will be allocated a unique study specific number. Identifying information (name, contact details, institution, organisation etc.) will be entered in to an Excel spreadsheet. This Excel spreadsheet will be password protected, encrypted and stored in the PARCS study File. Any electronic data will be labelled with the participants study specific ID number only and these data will be held separately to any information that may identify participants. Only approved members of the PARCS study team will be able to access both identifying information and data. Other members of the team may be allowed access to either the identifying dataset or research datasets according to need.

Focus groups, and where it is appropriate, the consensus meeting, will be audio recorded in the field using a digital recording device; the resulting audio files (and accompanying field notes) will be transcribed for storage, and the original file deleted from the recording device, as soon as is practicably possible. Any identifying information appearing in focus group transcripts will be removed as soon as possible following transcription to minimise risk of participant identification. Transcription will be performed by appropriate individual and checked by a researcher at the University of Oxford. Any transfer of data that is required between the PARCS study team and the qualitative researchers will be

logged. Data will be transferred using OxFile, the University of Oxford's secure file sharing system: Link to OxFile: https://oxfile.ox.ac.uk/oxfile/work/intro?execution=e2s1

During the study period, paper consent forms will be stored in a locked filing cabinet at the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford. Consent forms will also be scanned and stored securely as PDF files within the PARCS study file.

Participants identifying information will be retained after the end of the study as an audit trail. We will regularly review the need for this information and it will be securely destroyed when no longer needed and within 3 years of the end of the study.

Following publication of our findings, anonymised individual participant data (as far as is feasible according to the nature of the data) will be permanently archived. We will ensure that archived data complies with the current Data Protection Act by having transcript speech and survey free text reviewed by a data protection expert prior to archiving. Archiving methods and services approved by the University of Oxford will be used.

Anonymised data may be shared with legitimate internal and external researchers. Access to the data will be controlled through the use of a Data Request procedure. All data request form submissions will be reviewed by the Chief Investigator. The requester will be required to sign a Data Use Agreement prohibiting them from sharing the data outside of their specified research team, using the data for any purpose other than that stated or attempting to re-identify participants. The Chief Investigator will have responsibility for deciding on a case-by-case basis whether or not the data may be shared. If the data will not be shared, the Chief Investigator will provide the data requester with justification for this decision.

The study information sheet will inform participants that their anonymised data will be archived and may be shared with other legitimate researchers.

Audio files will be treated as identifying data and will be excluded from archiving and sharing.

In order to facilitate appropriate use of the archived data by others, metadata will be documented alongside data collection, including methods used to generate the data, detailed descriptions of records and variables, who created and contributed to the data and when, and under what conditions it can be accessed.

The Chief Investigator will act as Data Custodian for this study.

10. QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, relevant regulations and standard operating procedures.

During data cleaning and processing, any changes made to the data will be logged on a secure database, accessible only by approved members of the PARCS study team.

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

The independent Study Steering Committee (SSC) will oversee study conduct and progress.

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

11.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

11.3. Approvals

This project has been reviewed and approved to proceed by the University of Oxford Joint Research Office (JRO) study classification group (ref: PID13023). The JRO determined that the PARCS study falls outside of the definition of research that requires Health Research Authority (HRA) ethical approval and is therefore not subject to the Department of Health's Research Governance Framework for Health and Social Care (2005). It does not therefore require further assessment or approval prior to commencement.

11.4. Reporting

Progress reports will also be submitted to the study funder (NIHR HTA Programme) as requested.

11.5. Participant Confidentiality

Study staff will ensure that the participants' anonymity is maintained. Participants will be identified by a study-specific ID number in any electronic research dataset. All documents will be stored securely and only PARCS study staff and authorised personnel will have access. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so. Only de-identified data will be included in publications.

11.6. Expenses and Benefits

Patient/ Public focus group participants will be offered a payment of £20 in the form of a shopping voucher for their participation in the research.

Patients and members of the public who take part in stage 6 (consensus meeting) will be offered a single payment of £100 in the form of a shopping voucher as a thank you for their time and participation.

All stakeholder groups: Reasonable travel expenses for focus group and consensus workshop attendance will be reimbursed on the production of original receipts, or a mileage allowance provided as appropriate.

Refreshments will be provided free of charge during focus groups and consensus workshops.

11.7. Other Ethical Considerations

There are minimal ethical considerations as this is not an interventional study and the population, in general, is not vulnerable.

Prior to participating, patients/ public shall be advised that they will be asked to share information relating to their general health and shoulder problem. There is a small possibility that some patients could find the sharing of this information upsetting. Participants will have the right to leave questions or

requests for information unanswered if they find them distressing. We will reassure these participants, and inform them that there will be no adverse consequences from this.

12. FINANCE AND INSURANCE

12.1. Funding

This study is funded by the National Health Service (NHS) National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme.

12.2. Insurance

The University of Oxford maintains Public Liability and Professional Liability insurance which will operate in this respect.

13. PUBLICATION POLICY

The primary outputs of this project will be:

1) The funders report in the form of the HTA Monograph
2) A Systematic Review publication of candidate patches and evidence of their clinical use.
3) A summary of current practice in the NHS.
4) A proposed trial design and assessment of its acceptability to stakeholders and its feasibility.

A report containing the methodology and findings of this study will be published as a HTA monograph (freely accessible on the HTA webpage). We also plan to publish shorter journal articles on different aspects of the findings of the study. We will aim to publish in high-impact speciality and methodological journals as open-access publications.

The findings will be disseminated widely to those involved in the delivery and management of shoulder surgery care (surgeons, commissioners of health and NHS procurers) and other relevant stakeholders (the funder and the Medicines and Healthcare products Regulatory Agency, MHRA). Results may be

disseminated through presentation at national and international conferences, orthopaedic meetings, patient and public group meetings, and relevant department webpages. We will also be guided by our patient representatives regarding other means of dissemination to patients and the public.

The systematic review will be registered on the International Prospective Register of Systematic Reviews (PROPSERO).

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 the study funder using the following wording: *This project was funded by the National Institute for Health Research Health Technology Assessment Programme (project number 15/103/03).*

Authors will include the following disclaimer: *The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Health Technology Assessment Programme, NIHR, NHS or the Department of Health. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged*.

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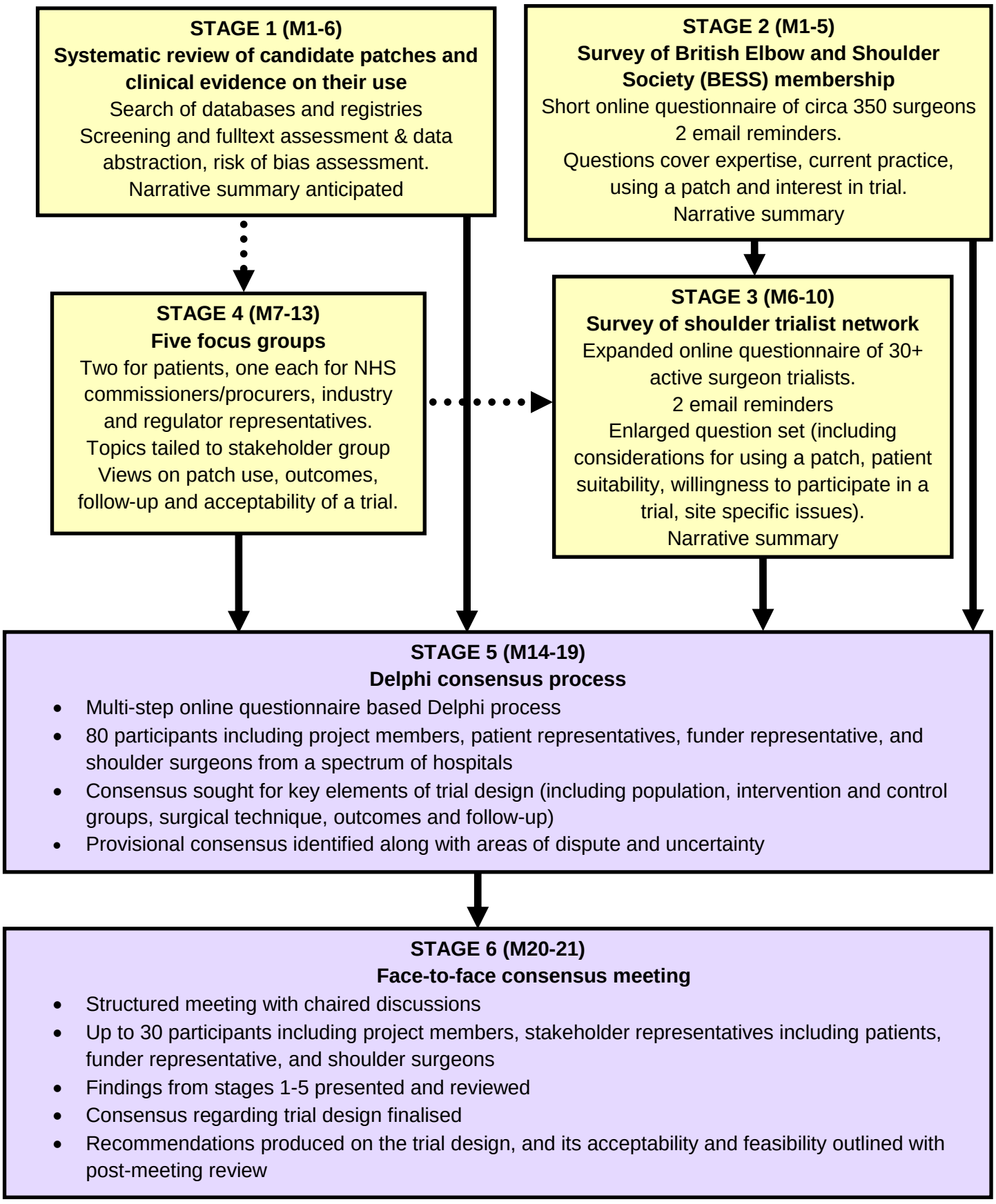
15. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

16. APPENDIX A: STUDY FLOW CHART

PATCH AUGMENTED ROTATOR CUFF REPAIR STUDY (PARCS)



17. APPENDIX B: SCHEDULE OF ACTIVITIES

Procedures	Months	Date
Stage 1: Systematic Review	1 to 6	01 Apr 2017- 30 Sep 2017
Stage 2: BESS Membership Survey		
Stage 3: Survey of Surgeon Trialists	6 to13	01 Sep 2017 – 30 Apr 2018
Stage 4: Focus Groups		
Stage 5: Delphi Study -Survey	14 to19	01 May 2018 – 31 Oct 2018
Stage 6: Delphi Study - Consensus Meeting	20	01 Nov 2018 – 30 Nov 2018
Post-meeting follow-up and Final Report	21	01 Dec 2018 – 31 Dec 2018