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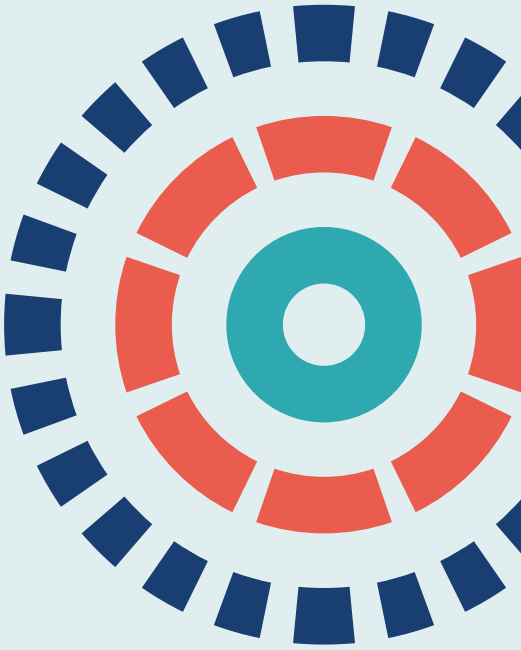

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Patch augmentation surgery for rotator cuff repair: the PARCS mixed-methods feasibility study

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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This report

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Abstract

Patch augmentation surgery for rotator cuff repair: the PARCS mixed-methods feasibility study

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Background: A rotator cuff tear is a common, disabling shoulder problem. Symptoms may include pain, weakness, lack of shoulder mobility and sleep disturbance. Many patients require surgery to repair the tear; however, there is a high failure rate. There is a need to improve the outcome of rotator cuff surgery, and the use of patch augmentation (on-lay or bridging) to provide support to the healing process and improve patient outcomes holds promise. Patches have been made using different materials (e.g. human/animal skin or tissue and synthetic materials) and processes (e.g. woven or mesh).

Objectives: The aim of the Patch Augmented Rotator Cuff Surgery (PARCS) feasibility study was to determine the design of a definitive randomised controlled trial assessing the clinical effectiveness and cost-effectiveness of a patch to augment surgical repair of the rotator cuff that is both acceptable to stakeholders and feasible.

Design: A mixed-methods feasibility study of a randomised controlled trial.

Data sources: MEDLINE, EMBASE and the Cochrane Library databases were searched between April 2006 and August 2018.

Methods: The project involved six stages: a systematic review of clinical evidence, a survey of the British Elbow and Shoulder Society's surgical membership, a survey of surgeon triallists, focus groups and interviews with stakeholders, a two-round Delphi study administered via online questionnaires and a 2-day consensus meeting. The various stakeholders (including patients, surgeons and industry representatives) were involved in stages 2–6.

Results: The systematic review comprised 52 studies; only 15 were comparative and, of these, 11 were observational (search conducted in August 2018). These studies were typically small (median number

of participants 26, range 5–152 participants). There was some evidence to support the use of patches, although most comparative studies were at a serious risk of bias. Little to no published clinical evidence was available for a number of patches in clinical use. The membership survey of British Elbow and Shoulder surgeons [105 (21%) responses received] identified a variety of patches in use. Twenty-four surgeons (77%) completed the triallist survey relating to trial design. Four focus groups were conducted, involving 24 stakeholders. Differing views were held on a number of aspects of trial design, including the appropriate patient population (e.g. patient age) to participate. Agreement on the key research questions and the outline of two potential randomised controlled trials were achieved through the Delphi study [29 (67%)] and the consensus meeting that 22 participants attended.

Limitations: The main limitation was that the findings were influenced by the participants, who are not necessarily representative of the views of the relevant stakeholder groups.

Conclusion: The need for further clinical studies was clear, particularly given the range and number of different patches available.

Future work: Randomised comparisons of on-lay patch use for completed rotator cuff repairs and bridging patch use for partial rotator cuff repairs were identified as areas for further research. The value of an observational study to assess safety concerns of patch use was also highlighted. These elements are included in the trial designs proposed in this study.

Study registration: The systematic review is registered as PROSPERO CRD42017057908.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 13. See the NIHR Journals Library website for further project information.

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List of abbreviations

ASES	American Shoulder and Elbow Surgeons
BESS	British Elbow and Shoulder Society
CENTRAL	Central Register of Controlled Trials
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CRN	Clinical Research Network
CSAW	Can Shoulder Arthroscopy Work?
DARE	Database of Abstracts of Reviews of Effects
EQ-5D	EuroQol-5 Dimensions
GP	general practitioner
HRQoL	health-related quality of life
HTA	Health Technology Assessment
MRI	magnetic resonance imaging
NHS EED	NHS Economic Evaluation Database
OA	osteoarthritis
OSS	Oxford Shoulder Score
PARCS	Patch Augmented Rotator Cuff Surgery
PICO	patient, intervention, control, outcome
PPI	patient and public involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	patient-reported outcome measure
RCR	rotator cuff repair
RCT	randomised controlled trial
ROBINS–I	Risk Of Bias In Non-randomized Studies – of Interventions
RR	risk ratio
SF-12	Short Form questionnaire-12 items
SF-36	Short Form questionnaire-36 items
SIS	small intestinal submucosa
UCLA	University of California, Los Angeles
UKFroST	UK Frozen Shoulder Trial
UKUFF	UK Rotator Cuff Surgery
VAS	visual analogue scale

Plain English summary

Shoulder muscles and tendons allow us to move our arms to carry out daily activities, work and play sports. Disease and injury of these tendons can cause significant long-term disability. Early treatment of these tendon problems usually involves painkillers, injections and physiotherapy. However, many patients whose symptoms do not improve may need surgery to repair these tendons.

Unfortunately, around 40% of surgical tendon repairs fail within 12 months. As such, these operations need to be improved. A promising approach is to use a patch to support the repair while the tendon heals; this patch is often used in a similar way to a plaster. However, it is not yet clear whether or not using a patch improves patient health and, if so, whether or not it makes enough of a difference to justify the additional cost to the NHS.

A scientific study called a randomised controlled trial is needed to fairly assess the value of surgery with a patch in people requiring a tendon repair. This study must be carefully designed so that it is acceptable to patients and surgeons, among others, and feasible to run. We conducted a multistage study to explore whether or not a potential trial design could be achieved.

We searched the scientific literature for previous research that had studied using patches for repairing shoulder tendons. We surveyed shoulder surgeons, including those who had previously been involved shoulder randomised controlled trials. We conducted four focus groups with stakeholders. Initial agreement on the best way to run a randomised controlled trial of patches in shoulder surgery was achieved using online questionnaires. Finally, we held a 2-day meeting to scrutinise the study findings and the relevant issues. Two potential studies were recommended, as was the need for closer monitoring of patch safety.

Scientific summary

Background

A rotator cuff tear is a common, disabling shoulder problem. Symptoms include pain, weakness, lack of shoulder mobility and sleep disturbance. Many patients may require surgery to repair the tear; however, there is a high failure rate. There is a need to improve the outcome of rotator cuff surgery, and the use of patch augmentation to provide support to the healing process and improve patient outcomes holds new promise. Patches have been made using different materials (e.g. human/animal skin or intestine tissue and completely synthetic materials) and processes (e.g. woven or a mesh). Augmentation can be carried out in two main ways: on-lay (placing the patch on top of a completed repair) and bridging (using it to fill a defect that the repair could not address).

Objectives

The aim of the Patch Augmented Rotator Cuff Surgery (PARCS) study was to determine the design of a future definitive randomised controlled trial, assessing the clinical effectiveness and cost-effectiveness of a patch to augment surgical repair of the rotator cuff, that is both acceptable to stakeholders and feasible.

The study objectives were to:

1. review the existing evidence to identify candidate patches for use in a randomised controlled trial and the evidence relating to their clinical use
2. ascertain current NHS clinical practice relating to the use of patches to augment rotator cuff repair
3. explore the acceptability of the proposed trial to patients, surgeons and other stakeholders
4. assess the feasibility of a trial of patch-augmented rotator cuff repair
5. achieve consensus on the key elements of the design of a definitive randomised controlled trial to assess the use of patches to augment rotator cuff repair
6. confirm the scope of the health economic evaluation required in the trial to appropriately assess the cost-effectiveness of patches to augment rotator cuff repair
7. identify areas for further research related to the PARCS study.

Methods

The PARCS feasibility study was a mixed-methods study. It involved six stages: a systematic review of clinical evidence, a survey of the British Elbow and Shoulder Society's surgical membership, a survey of surgeon triallists, focus groups and interviews with stakeholders, a two-round Delphi study administered via online questionnaires and a 2-day consensus meeting. Various stakeholders (including patients, surgeons and representatives from industry) were involved across the six stages.

Systematic review

The MEDLINE, EMBASE and Cochrane databases were searched between April 2006 and August 2018, in accordance with a previously published search strategy for clinical studies of patch use for rotator cuff surgery. No restriction was placed on language. A risk-of-bias assessment was carried out on all comparative studies (Cochrane risk-of-bias tool version 2 for randomised controlled trials and Risk Of Bias In Non-randomized Studies – of Interventions tool for observational studies).

Surveys

An online survey was sent to the surgical membership of British Elbow and Shoulder Society. Questions covered the respondents' demographics, experience with patches, indications for patch augmentation and willingness to be involved in a randomised controlled trial of patch-augmented rotator cuff surgery. A second survey was directed at surgeons who had taken part in previous large, multicentre, UK shoulder trials. It focused on trial-specific implementation issues. The statistical analysis of the surveys was descriptive only.

Qualitative study

Four focus groups covering three stakeholder groups (patient/public, regulatory body and NHS-related administration, and industry representatives) were conducted, with the aim to access a broad range of views and opinions on the feasibility and acceptability of clinical research involving patches in cuff repair. The focus group transcripts were analysed by two members of the PARCS team, alongside data collection, using thematic analysis.

Consensus process

A two-stage online Delphi study, which was informed by the results of the systematic review, surveys and qualitative work, was conducted to develop a consensus on the best way to design a clinical trial of patch-augmented rotator cuff surgery. This was followed by a 2-day consensus meeting with stakeholder representatives and project members to review findings from stages 1–5 of the PARCS study, and to achieve consensus on the feasibility, acceptability and basic design of a randomised controlled trial to address patch use for rotator cuff repair.

Results

Systematic review

Of the 939 articles, 52 studies were included, which consisted of four randomised controlled trials, 11 observational comparative studies and 37 observational non-comparative studies. They varied in terms of study design, inclusion criteria, surgical approach, patch material [human allograft/autograft (46%), xenograft (33%) and synthetic (20%)] and outcome assessed.

All but one study looked at functional outcome measures. The Constant Scale, American Shoulder and Elbow Surgeons and University of California, Los Angeles, Shoulder Scale scores were most commonly used (range 27–48%). Although several studies demonstrated an improved function following patch augmentation, no consistent trends to support a particular patch type or brand were observed. Over two-thirds of studies investigated repair failure, with only one of four randomised controlled trials showing significant reduction in re-tears after patch augmentation. Complications were reported in 21 studies, with a similar complications rate after patch augmentation or non-augmented repair. Only one study in this review had a low risk of bias.

Surveys

For the British Elbow and Shoulder Society surgical membership survey, 105 responses (21%) were received, with over half (58%) stating that they had used a patch to augment rotator cuff surgery and 70% of patch users having undertaken an augmented repair within the last 6 months. A wide surgical experience in augmentation was reported, ranging from 1 to 200 implanted procedures. However, most surgeons reported low-volume use, with a median of five rotator cuff augmentation procedures performed. At least 10 different products were reported as having been used. Most of the patches derived from decellularised dermis tissue, although porcine-derived and synthetic-based patches had also been used. Only 3–5% of respondents stated that they would undertake an augmented repair for small tears across ages, whereas 28–40% and 19–59% would do so for large and massive tears, respectively. When assessing patient suitability, patient age seemed more relevant when considering those with large and massive tears. Half of the surgeons reported an interest in taking part in a randomised controlled trial evaluating the role of patch augmentation for rotator cuff surgery, with a further 22% of respondents undecided.

For the surgeon triallists survey, 24 responses (77%) were received. In total, 20 (83%) used a patch or would be willing to do so in a trial. Views on the importance of assessing the subscapularis state regarding the potential use of a patch were evenly split, with 11 respondents (55%) stating that they considered it. Typical patch used was evenly split between 'on-lay' (45%) and 'bridging' (55%). Responses for age and tear size and revision operation for two- and three-arm trial scenarios regarding willingness to randomise a patient were very similar. With regard to the running of a definitive trial, almost all respondents supported having a standardised operative technique ($n = 18$, 90%) and a standardised postoperative rehabilitation regime ($n = 19$, 95%). Most respondents ($n = 11$, 55%) supported randomising in the operating room, with 12- and 24-month follow-ups supported by almost all respondents ($n = 18$, 90%).

Qualitative study

The four focus groups involved 24 stakeholders. Stakeholders held differing views on a number of aspects, including the appropriate patient population to participate in a trial. For example, some stakeholders felt that all patients having rotator cuff repair surgery should be offered a patch, whereas others felt that the patient population needed to be more specific. There were also differing views on which treatment and control arms to include in a trial and whether or not randomisation was appropriate.

Consensus process

Of the individuals invited to the Delphi study, 29 participated (67%). Initial agreement on five out of six domains was met. The initial proposal based on the Delphi study was revised in the light of discussions at the consensus meeting, which 22 participants attended. The outlines of two potential randomised controlled trials were developed at the consensus meeting. The first related to the use of a patch as an on-lay for patients with a completed rotator cuff repair and the second related to patients with a partial rotator cuff repair using a bridging approach. The two comparisons could potentially be within one more comprehensive trial or conducted separately. In addition, the need for an observational safety study was identified.

Conclusion

Although several experimental and observational studies have demonstrated a decreased failure rate and improved outcome scores following augmented rotator cuff repair, rigorous clinical evaluation of this technology is currently lacking, which prevents firm recommendations for practice. We identified that a variety of patches for rotator cuff repair are available and in clinical use, although few have published evidence for their clinical effectiveness.

Areas for further research identified were randomised comparisons of on-lay patch use where rotator cuff repair has been completed and bridging patch use for partial rotator cuff repairs. The value of a registry was also highlighted.

Study registration

The systematic review is registered as PROSPERO CRD42017057908.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 13. See the NIHR Journals Library website for further project information.

Chapter 1 Background

This report describes the methods and results of the Patch Augmented Rotator Cuff Surgery (PARCS) feasibility study, which assessed the acceptability and feasibility of conducting a randomised controlled trial (RCT) of the clinical effectiveness and cost-effectiveness of patch-augmented rotator cuff repair (RCR). This study was commissioned and funded by the National Institute for Health Research Health Technology Assessment (HTA) programme.[1]

Rotator cuff tears

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 an inability to carry out household activities. It has been estimated that 2.4% of UK general practitioner (GP) consultations are for shoulder complaints.[2] Shoulder pain is frequently caused by problems with the tendons and muscles that surround and stabilise the shoulder joint, known as the rotator cuff. They account for up to 70% of shoulder pain problems and constitute the third most prevalent musculoskeletal disorder, after lower back and neck pain.[3] A common and debilitating rotator cuff problem is a rotator cuff tendon tear, which is found in approximately 25% of people aged ≥ 70 years. Symptoms include pain, weakness, lack of shoulder mobility and sleep disturbance.

Rotator cuff tears refer to a structural failure in the rotator cuff, most commonly involving the supraspinatus (*Figure 1*). It is estimated that the overall prevalence of tears is 34% and that risk increases significantly with age.[5]

Conservative management for rotator cuff tears

Initial management of rotator cuff tears is conservative and includes rest with simple pain management with paracetamol and non-steroidal anti-inflammatory drugs. Physiotherapy combined with advice for home exercises is often included in the package of care. If symptoms persist, patients are usually offered an injection of a corticosteroid into the space between the acromion process of the shoulder blade and the humerus (see *Figure 1*).[6] An ongoing HTA-funded trial, Getting it Right: Addressing Shoulder Pain (GRASP),[7] is aiming to improve conservative treatment for rotator cuff disorders by evaluating the effects of progressive exercise versus best practice advice, with and without subacromial corticosteroid injection, in people with a rotator cuff disorder treated in primary care.

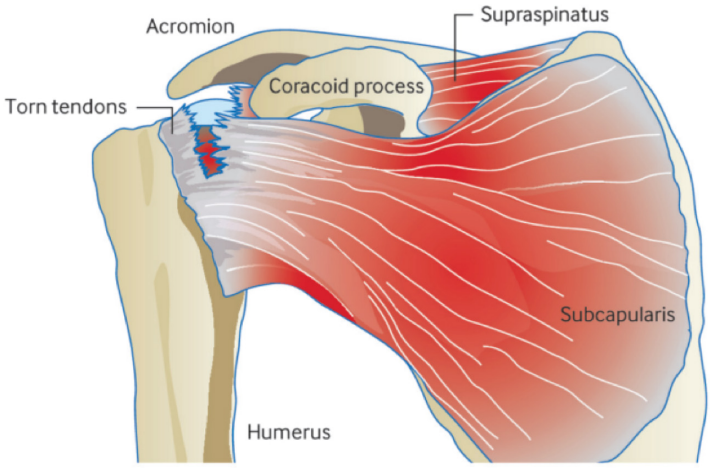


FIGURE 1 Anatomical diagram of the shoulder joint showing rotator cuff tear in the supraspinatus. Reproduced from *Acute Rotator Cuff Tears*, Craig R, Holt T, Rees R, Vol. 359, p. j5366, 2017,[4] with permission from BMJ Publishing Group Ltd.

Some patients with rotator cuff tears have few, if any, symptoms. A combination of conservative management approaches may allow the inflammation to settle, undamaged muscles to adapt and good function to be restored.

However, there are limitations to conservative treatments. Approximately 40% of patients will continue to experience pain despite conservative management. There is also emerging evidence suggesting that multiple injections may increase the chance of a rotator cuff tear occurring, leading to long-term harm.[8,9]

Surgery for rotator cuff repair

Generally, if symptoms of severe pain and lack of function continue to disrupt daily activities, despite conservative treatment for a minimum of 3 months, surgery is considered for the patient. Around 9000 RCRs were performed per year in the NHS in England from 2000 to 2010, at a cost of around £2600 per operation (£23M per year), and this number would appear to be growing.[2,10]

Surgical repair of the rotator cuff seeks to re-attach the tendon to the bone, allow the tear to heal and improve patient outcomes (*Figure 2*). The form of the repair depends on the nature of the tear and which tendons are involved. If the tendon is not able to be fully restored to its original position, a partial repair is often conducted to help encourage further healing.

There is substantial variation in surgical practice. This can include the type of surgery (open or arthroscopic), the surgical techniques used (e.g. the use of anchors and type of suture) and the type and duration of conservative treatment before surgery.[11] A review of surgical management of rotator cuff tears published by Dunn *et al.*[11] in 2005 surveyed members of the American Academy of Orthopaedic Surgeons. At the time, 15% preferred arthroscopic surgery, but this is likely to have grown since.

Rotator cuff surgery can have mixed outcomes for patients, with failure rates between 25% and 50% within 12 months.[12–14] The UK Rotator Cuff Surgery trial (UKUFF)[2] revealed a 40% failure rate of surgical repairs in a wide range of settings using different surgical techniques in the NHS. RCR surgery is expensive, invasive and inconvenient to patients, and reoperation is sometimes necessary.

Although there are different views about the key drivers of patient outcomes, a number of factors are consistently related to poor outcomes, particularly increasing age and tear size.[15] Repairs also commonly fail because of poor tissue and bone quality or inadequate fixing of the tendon to the bone, allowing the two to pull away.

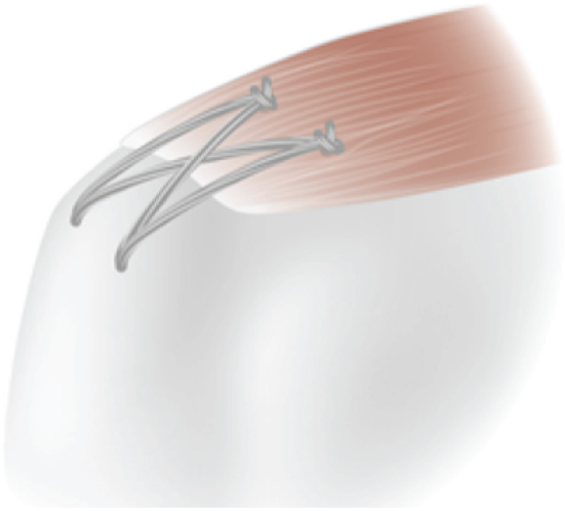


FIGURE 2 Surgically repaired rotator cuff (supraspinatus) tear. Reproduced with permission (Carr Group, Botnar Research Centre, University of Oxford, 2020, personal communication).

A healed repair results in the best clinical and patient-reported outcomes. As a result, a number of surgical approaches have tried to improve RCR; unfortunately, these have been unsuccessful.[2,14,16,17] For example, the UKUFF trial found that minimally invasive (arthroscopic) surgery had no benefit over open surgery.[18]

A Cochrane review,[16] published in 2008, identified only two RCTs that evaluated surgery for a rotator cuff tear;[19,20] both were judged to be susceptible to bias. An updated systematic search performed in 2014 to set the UKUFF trial findings in context revealed five more trials comparing two surgical interventions.[19–24] These RCTs were single-centre trials and were relatively small, with between 73 and 114 participants per trial and a mean participant age of around 60 years. They included participants with full-thickness rotator cuff tears and small and medium rotator cuff tears.[20–25] The studies mainly compared surgical approaches with arthroscopic, mini-open and open repair, with or without acromioplasty or subacromial decompression.[21–24] One study[19] evaluated a minor variation in the suture used and not the surgical technique.

Attention has recently focused on improving the biology of the torn tendon at the time of surgery and for the critical 8-week period after surgery when effective healing is needed.[21]

Patch-augmented rotator cuff surgery

A promising area for further advancement in rotator cuff surgery is the use of a patch to provide a support structure or 'scaffold' for the repair. The aim is to improve the fixing of the tendon to the bone and, thus, tendon healing.[26,27] A patch can be defined as an implantable human, synthetic or animal material that is used with the aim of improving tissue healing and/or patient outcome via some form of mechanical support. These implants are also referred to as an extracellular or acellular 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 produce the patch). Some preclinical studies suggest that augmentation patches may have value in reducing the rate of repair failure and in improving patient outcomes.[28–31]

A patch can be used for one of two surgical indications (*Figure 3*). The patch can be surgically sutured on top of the tendon-to-bone repair, a technique known as 'on-lay', to strengthen the repair and aid tendon healing.[32] Some authors refer to this as 'augmentation', although the use of terminology to date has been far from consistent. Terminology such as reinforcement, bridging, reconstruction and interposition has been used, as well as augmentation.[27]

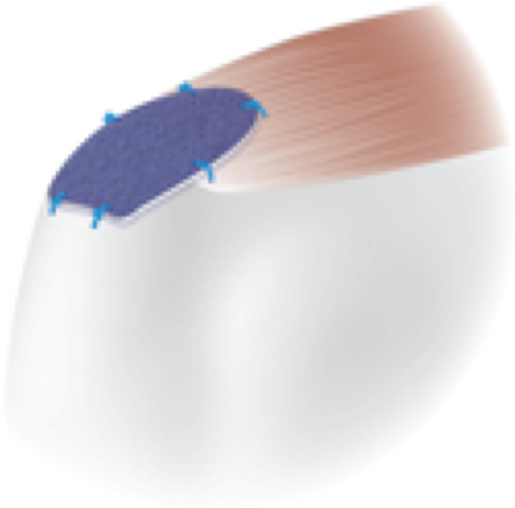


FIGURE 3 Surgical RCR augmented with a patch using the on-lay surgical approach. Reproduced with permission (Carr Group, Botnar Research Centre, University of Oxford, 2020, personal communication).

Alternatively, a patch can be sutured into the exposed area following a partial repair, known as 'bridging', to provide a scaffold for the regeneration of the tendon.[33] In this report we use the terms on-lay and bridging to refer to the two surgical approaches, and augmentation is used as an inclusive term for either approach. There are variations in how these approaches are carried out, such as the fixation approach and equipment used.

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), as well as in different sizes.[27,29] They can be designed to be absorbable, avoiding the possibility of later surgical removal. Patches differ in how they respond to tendon tissue and their mechanical properties.[28] Some have been designed specifically or can be tailored in size and shape for specific uses in rotator cuff surgery ('on-lay' or 'bridging'), whereas others were initially developed for other soft-tissue contexts.

At the time of developing this study, > 20 patches (see *Chapters 2* and *3*) have received regulatory approval for use in surgical repair of the rotator cuff in the USA and/or by an EU-notified body.[34] A number of centres in the UK were using patches in RCR for private and/or NHS patients at the time of study set-up. Patches currently in use in the UK reflect different materials and original purposes. One example is the GRAFTJACKET (Wright Medical Group, Memphis, TN, USA); made from human cadaver dermis, originally developed for RCR, it is available in different sizes and thicknesses. Another is LARS™ ligament (Corin, Gloucestershire, UK), which is a completely synthetic material originally developed for anterior cruciate ligament reconstructions and is available in various versions, including specifically for RCR. A final example is Permicol™ (Warsaw, IN, USA), which is made from pig dermis and originally developed for hernia repair. Later, a version for rotator cuff was produced called the Zimmer® collagen repair patch (Zimmer, Warsaw, IN, USA)]. The use of a patch to augment rotator cuff surgery appears to be increasing.

The use of patches has not been without negative impact. One patch [Restore Orthobiologic Implant™ (DePuy Orthopaedics, Warsaw, IN, USA)] was withdrawn from the market following a clinical study that identified a severe autoimmune response.[35] In addition to safety concerns, the use of a patch, if not effective, is a waste of precious resources in terms of staff, time and the cost of the implant.

Recent advances in patches include the development of electrospun materials and exploration of the concurrent use of growth factors.[32] 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.[35] Augmenting surgical repair with a patch may also enable the repair of tears that are currently considered irreparable.[26,33,35,36]

The need for research

The pressing need to improve surgical options for RCRs and to improve outcomes for patients has been demonstrated.[37] The James Lind Alliance Priority Setting Partnership for Surgery for Common Shoulder Problems brought together patients, carers and clinicians to identify the ongoing important treatment uncertainties related to shoulder surgery.[38] Four of the top 10 uncertainties for common shoulder problems concerned rotator cuff tears.[38]

At the time of inception of the PARCS study, only a handful of small, single-centre, predominantly North America-based, comparative studies had been carried out for a subset of the available patches, with mixed findings. Three relevant reviews had been carried out. The first review was a literature review of preclinical and clinical studies on candidate patches for use in rotator cuff surgery.[34] The review considered clinical and preclinical studies on > 20 available patches that can be used for rotator cuff surgery, including the Restore Orthobiologic Implant, which had been withdrawn from the market

because of safety concerns.[29,30] It identified a variety of studies, but little clinical or comparative evidence. The second and third reviews were both recently published systematic reviews of clinical studies [identified through a search of the PROSPERO online registry and the Centre for Reviews and Dissemination (CRD) database], assessing patch-augmented rotator cuff surgery.[27,39] They collectively identified 16 clinical studies, of which only two were RCTs and two were observational comparative studies.[26,35,40,41] These four comparative studies assessed only four patches and one of these, a retrospective study, compared only two patches.[40] Two of the studies assessed the Restore Orthobiologic Implant.[35,41]

In addition to the above reviews, there are a further three published comparative studies evaluating 'irreparable' rotator cuff tears: a RCT evaluating an autograft (self-donor) and two observational comparative studies assessing different biological patches.[33,42,43] During the conduct of the PARCS study, a third systematic review was published that included additional studies (although not all of the previous studies identified in the previous systematic reviews).[44]

Study design

At the time of conduct, to our knowledge no comprehensive systematic review or health technology assessment of patch-augmented surgery for RCR had been performed. It is not clear whether or not patch use improves outcomes for patients following RCR. To establish certainty for patients in the UK, this needs to be evaluated in a large multicentre RCT that is relevant to the NHS setting. Existing studies in this clinical area have shown that a RCT of this kind is possible. For example, the UKUFF trial has demonstrated that a rotator cuff RCT can be conducted.[18] It offers valuable learning about recruiting patients undergoing rotator cuff surgery with regard to the timing and nature of the approach.

However, there remained uncertainty about how a RCT should be designed to evaluate patch augmentation specifically. Major uncertainties related to patch augmentation trial design include the patient population, which patches should be evaluated, the intervention and control groups, the associated surgical technique and the acceptability of such a trial to stakeholders, particularly patients and surgeons. Surgical trials are generally difficult to conduct owing to varied patient pathways throughout the NHS, surgical equipoise being difficult to establish and portray, and patients' reservations about being recruited.[45–47] These uncertainties and difficulties are compounded by the sporadic introduction of the use of patches into the NHS and the variety of patches available.

It became apparent that a feasibility study would be necessary to address all of these concerns. However, an unnecessarily long feasibility study could miss the optimal timing for evaluating this innovation in a surgical trial, as stated in Buxton's law:[48] 'It's always too early for a rigorous evaluation until suddenly it's unfortunately too late'. A multistage mixed-methods research study was used to address the uncertainties related to the conduct of a RCT of patch-augmented rotator cuff surgery.[1] The aim and objectives of the study are described in the following section. The methods and findings of the six stages of research that are part of the PARCS feasibility study are described in *Chapters 2–5*.

Aim and objectives

The aim of the PARCS study was to determine the design of a future definitive RCT assessing the clinical effectiveness and cost-effectiveness of a patch to augment surgical repair of the rotator cuff that is both acceptable to stakeholders and feasible.[1]

The approach built on work by the Idea, Development, Exploration, Assessment, Long-term Follow-up (IDEAL) collaboration for evaluating surgical innovation and devices on early evaluations and RCTs.[49,50]

Methodology was adapted from that for achieving expert consensus in guideline and core outcome sets for trials.[51–53] This feasibility study used a mixed-methods approach to assess current evidence and practice, and to achieve consensus on the optimal randomised trial design.[1]

The study objectives were to:

1. review existing evidence to identify candidate patches for use in a RCT and the evidence relating to their clinical use
2. ascertain current NHS clinical practice relating to the use of patches to augment RCR
3. explore the acceptability of the proposed trial to patients, surgeons and other stakeholders
4. assess the feasibility of a trial of patch-augmented RCR
5. achieve consensus on the key elements of the design of a definitive RCT to assess the use of patches to augment RCR
6. confirm the scope of the health economic evaluation required in the trial to appropriately assess the cost-effectiveness
7. identify areas for further research related to PARCS.

Chapter 2 Systematic review

Introduction

It is critical to review the current evidence when designing a future RCT. Systematic reviews are a useful tool for this because they identify, collate and summarise results from individual studies, which makes the existing evidence easier to evaluate. Having a systematic review as the first stage in a mixed-methods feasibility study gives a foundation from which to generate new evidence.

It was particularly important to provide a systematic review of the clinical evidence (including non-comparative observational studies) on the use of patches in RCR. The growing number of available patches (made from different materials and originally for different purposes), mixed clinical and preclinical results and recent concerns over safety, including adverse immunological responses, had generated a clouded and uncertain landscape.[54]

The aim of this systematic review was to identify and critically appraise those studies reporting on the clinical effectiveness and safety of patch-augmented surgical repair in adults with rotator cuff tears.[1] The key objectives of the systematic review were to:

- undertake evidence synthesis using systematic review methodologies, including meta-analysis, to evaluate the relative effectiveness of patch-augmented RCR
- undertake a review of safety/adverse events associated with all identified patches
- identify the most clinically effective and safe candidate patches, as well as other key parameters that can inform a future definitive RCT.

Methods

Protocol and registration

Evidence synthesis was carried out in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews[55] and the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care, and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[55–57] The review protocol and search strategy has been previously been registered and published in full.[58]

Search strategy

A previous Cochrane systematic review had carried out a comprehensive search prior to April 2006.[16] Based on this search we searched the following databases between April 2006 and February 2017 (and updated our search in August 2018): EMBASE, MEDLINE, the Cochrane Library, incorporating Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), the HTA database and the NHS Economic Evaluation Database (NHS EED). In addition, the reference lists of all identified articles and reviews were checked for relevant articles.[17,27,39,44,59] The search strategy was initially developed for EMBASE (see *Appendix 1*) and has previously been published.[58] Our strategy was subsequently modified for use in MEDLINE and the Cochrane Library databases.

Inclusion and exclusion criteria

Population

The review incorporated studies of adult patients (aged ≥ 18 years) who required surgical repair of a rotator cuff tear. No restrictions were applied to tear type (partial or full thickness), size (small through to massive), tendon involvement (supraspinatus, infraspinatus, teres minor or subscapularis), primary or recurrent tears, or the presence of medical comorbidities. For the purpose of this review, small (< 1 cm), medium (1 cm to < 3 cm) and large (3 cm to 5 cm) tears were classified according to the DeOrio and Cofield classification.[60] Because of the large number of classification systems available, tears were also considered massive if they met one of the following criteria: (1) measured > 5 cm in the anteroposterior dimension, (2) involved two or more tendons[61] or (3) were described as being massive by the study authors.[60,61]

Interventions

All studies in which at least one treatment arm included the use of patches to augment rotator cuff surgery were included. A patch was defined as an implantable human, synthetic or animal material that is used with the aim of improving tissue healing and/or patient outcome via some form of mechanical support. Patch types were grouped into xenograft, allograft, autograft or synthetic. There was no restriction placed on the type of surgery received or the experience of the surgeon. The type of patch surgery was classified as either 'on-lay' or 'bridging' in accordance with previously reported definitions.[27] We excluded studies that investigated the use of sutures or anchors in isolation and studies that investigated drug therapy or physiotherapy, except when used as a comparator group or in addition to patch augmentation.

Comparators

No restriction was placed on the type or number of control groups.

Outcomes

The primary outcomes of interest in this review were:

1. shoulder-specific function and pain – measured using a previously validated scale
2. shoulder pain – measured using validated tools, such as the visual analogue scale (VAS) or non-validated scales
3. health-related quality of life (HRQoL) – measured using Short Form questionnaire-36 items (SF-36), EuroQol-5 Dimensions (EQ-5D) or other assessment measures
4. patch-related adverse events.

Secondary outcomes of interest were recurrence of rotator cuff tear (re-tear), radiological assessment of postoperative rotator cuff integrity, revision rates of the surgery, time to surgical revision and patient satisfaction.

Study types

We considered all relevant RCTs and observational studies (comparative and single group) that included at least five patients. No language restrictions were applied. In vitro studies, animal studies, review articles, editorials and studies involving five or fewer patients were excluded.

Study selection

Two authors (MB and NSN) independently screened all of the titles and abstracts identified from the search strategy. Full reports for all relevant studies identified were then reviewed and assessed against the eligibility criteria. A third independent reviewer (GG) was available to resolve any disagreements regarding study inclusion. Reasons for exclusion are detailed in the PRISMA flow diagram (*Figure 4*).

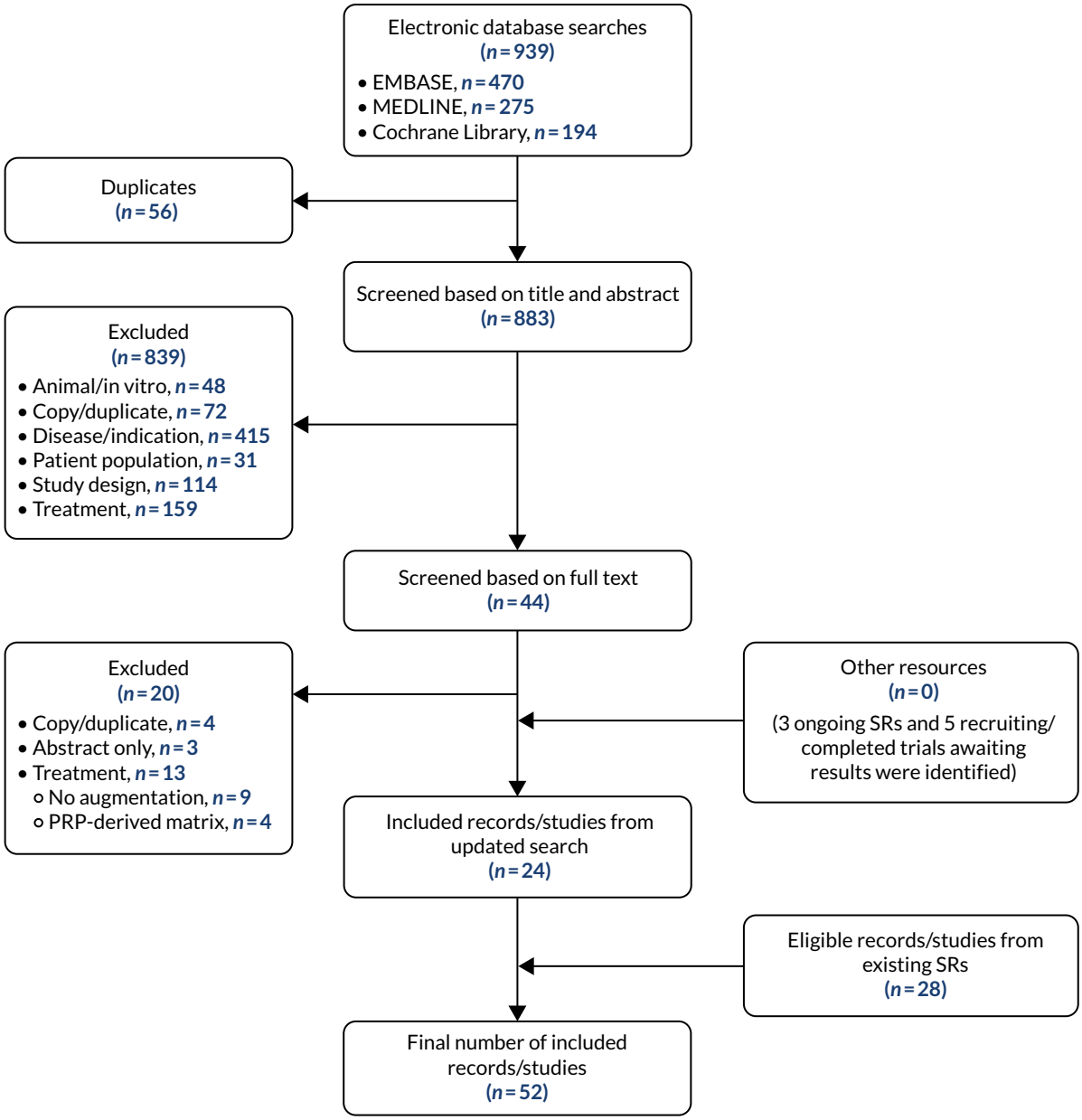


FIGURE 4 The PRISMA flow chart of study selection. PRP, platelet-rich plasma; SR, systematic review.

Data extraction

Two authors (MB and NSN) extracted the following data from all eligible studies: general study information (authors, publication year and study location), study population (sample size, age, sex and tear size), study characteristics (study design, inclusion/exclusion criteria, duration of clinical and radiological follow-up, surgical technique and patch characteristics), all primary and secondary outcomes for each study and adverse events or complications. Each reviewer independently checked the results of the data extraction process.

Risk-of-bias assessment

The risk of bias was independently assessed by two authors (MB and NSN) and discrepancies were discussed with a third reviewer (GG), allowing resolution based on unanimous decision. RCTs were assessed using the risk-of-bias tool (2011 update) provided by the Cochrane Collaboration.[55] Each domain was rated as having a 'low', 'high' or 'unclear' risk of bias before the study was assessed as a whole. Observational comparative studies were assessed using the Risk Of Bias In Non-randomized

Studies – of Interventions (ROBINS–I) tool.[62] The risk of bias for each domain was judged as low, moderate, serious, critical or no information, followed by an overall judgement of bias based around the judgements from each individual domain. Single-arm studies were not formally assessed for risk of bias.

Data analysis

Identified studies were grouped (RCTs, observational comparative and non-comparative) and a narrative summary of results was reported in accordance with the standards set out in the PRISMA checklist.[20] Data from all available studies were utilised in the quantification of complications. All studies that compared the outcomes of RCR with graft augmentation with standard RCR were considered for meta-analysis. A meta-analysis was conducted only for outcomes consistently reported across studies and reported using Review Manager version 5.3 (RevMan, the Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Regardless of the observed statistical heterogeneity, we conducted an analysis for each patch type (xenograft, allograft, autograft or synthetic) when each type was represented by at least two comparative studies. Given the known controversy surrounding xenograft isolated from small intestinal submucosa (SIS), the analysis for xenografts was further divided into SIS-derived and non-SIS. There were insufficient study numbers to permit further subdivision based on graft configuration (on-lay or bridging). Complications (including patch-related adverse events) were grouped together given how they were reported across the included studies. They were not formally meta-analysed and only crudely summarised as overall numbers for augmentation and non-augmentation groups across all variations in patches and non-patches and reported events.

Statistical analysis

For dichotomous parameters included in the meta-analysis, the risk ratio (RR) with 95% confidence interval (CI) was calculated for each graft type. For continuous variables, such as shoulder-specific functional outcome scores, the effect was reported as the mean difference with 95% CI. Owing to the significant heterogeneity in the specific functional shoulder scores utilised between studies, a meta-analysis was conducted using the most frequently used score across all studies at final follow-up. In each patch type, if no single functional outcome score was consistently used, scores were combined and a standard mean difference was reported with 95% CI. Studies in which no standard deviation was calculable, or in which only subcomponents of functional outcome scores were reported, were reported only descriptively. Heterogeneity was characterised by use of the I^2-statistic and a random-effect analysis used to incorporate heterogeneity among studies.

Patient involvement

Patient representatives were full members of the PARCS Study Steering Committee and provided critical feedback on the study protocol.[1]

Results

Study selection

The search strategy identified 939 articles, of which 56 were duplicates (see *Figure 4*). A total of 883 abstracts were reviewed in detail, with 44 appearing to meet inclusion criteria. After full-text review, 27 articles were excluded based on the following criteria: included an abstract only ($n = 3$), treatment was a platelet-rich plasma-derived matrix lacking the structural properties of patch augmentation ($n = 4$), RCR did not involve any form of augmentation ($n = 9$) and the article was a duplicate ($n = 4$). A further 28 articles were identified from existing systematic reviews, which generated a total of 52 studies for inclusion. No economic evaluations of patch-augmented rotator cuff surgery were identified.

Study characteristics

Comparative studies

Four RCTs and 11 observational comparative studies involving 896 patients were identified. Most comparative studies assessed a single patch against standard repair, with some studies having up to three treatment arms.[40,63,64] Across all the comparative studies a total of 12 different patches were utilised. Study population sizes ranged from 30 to 89 patients (age range 29–82 years) for RCTs and from 21 to 152 patients (age range 36–83 years) for observational comparative studies, with a predominance of male participants across all studies. Only two studies included the full spectrum of full-thickness tear sizes, with most studies instead restricting recruitment to large or massive tears of the supraspinatus and infraspinatus. Other eligibility criteria were highly heterogeneous; however, the exclusion of patients with significant glenohumeral osteoarthritis (OA) ($n = 10$) emerged as a common theme (*Table 1* and see *Appendix 2*, *Table 19*).

The RCTs employed various time points for data collection. One RCT collected data preoperatively and at 6 weeks, 3, 6, 12 and 24 months postoperatively. Another RCT collected data at 12 and 24 months, and a third at 14 months.[26,35,65] In terms of health-related quality-of-life outcomes, the SF-36 was collected in two RCTs and one comparative study.[35,42,65]

Non-comparative studies

A total of 37 observational single-group studies involving 700 patients were identified. The study populations ranged from 5 to 61 patients (age range 26–89 years), with the majority ($n = 28$) recruiting patients with large or massive full-thickness tears only. Petriccioli *et al.*[96] was the only study to have reported on the use of patch augmentation in the treatment of isolated subscapularis tears, whereas Schlegel *et al.*[103] recruited patients with partial-thickness supraspinatus tears only.

None of the identified studies carried out a formal economics evaluation of patch use for rotator cuff surgery. Adverse events and their associated procedures were captured in all RCTs. Only one RCT reported information about patients' capacity to return to work, as well as capacity to continue their recreational activities and medication utilisation at 6 weeks, 3 months and 6 months post surgery.[65]

Surgical characteristics

Comparative studies

Across all the comparative studies, a total of 12 different patches were utilised. Decellularised xenograft patches were the most commonly investigated ($n = 6$; Restore, $n = 4$). Surgical techniques could be classified as fully arthroscopic (46%, $n = 7$), open (40%, $n = 6$) or a mixture of both (13%, $n = 2$). The method of patch utilisation was split fairly evenly between the categories of 'on-lay' (53%, $n = 8$) or 'bridging' (47%, $n = 7$).

Non-comparative studies

A full spectrum of patch materials [human allograft (32%, $n = 12$), human autograft (11%, $n = 4$), xenograft dermal (22%, $n = 8$), xenograft intestinal (11%, $n = 4$) and synthetic (24%, $n = 9$)] and surgical techniques were reported [on-lay (51%, $n = 19$), bridging (41%, $n = 15$) and mixed (8%, $n = 3$)].

Shoulder pain and function

Comparative studies

Eight different outcome scores were used to assess shoulder function (see *Appendix 2*, *Table 19*). The Constant Scale (60%), American Shoulder and Elbow Surgeons (ASES) (47%) and the University of California, Los Angeles (UCLA), Shoulder Scale (33%) scores were the most commonly reported, with most studies reporting multiple functional scores.

TABLE 1 Patch type and population demographics

Study (first author and year of publication)	Patch type							Group	Surgical approach	Surgical patch technique	Tear size	Patient demographics	
	Xenograft			Human		Synthetic						Age at surgery (years), mean (range or ± SD)	Sex, *n* male (%)
	Dermal	Intestinal	Other	Allograft[a]	Autograft	Resorbable	Non-resorbable						
Randomised comparative studies													
Barber 2012[26]				✓				GRAFTJACKET	Arthroscopic	On-lay	Small to massive[b]	56 (43–69)	18 (82)
								Control			Small to large[b]	56 (34–72)	13 (65)
Bryant 2016[65]		✓						[c]Restore®	Open	On-lay	Small to massive[b]	55 (29–40)	29 (85)
								Control			Small to massive[b]	58 (40–81)	22 (79)
Iannotti 2006[35]		✓						[c]Restore®	Open	On-lay	Large to massive[b]	58 (NR)	11 (73)
								Control			Large to massive[b]	57 (NR)	12 (80)
Leuzinger 2016[63]				✓				GRAFTJACKET	Arthroscopic		Massive[d]	66 (51–81)	20 (71)
						✓		[e]Artelon®		On-lay	Massive[d]	68 (52–79)	23 (22)
		✓						[c]Restore®			Massive[d]	68 (50–82)	20 (69)
Non-randomised comparative studies													
Ciampi 2014[40]							✓	Repol Angimesh[f]	Open	On-lay	Massive[d]	66 (57–77)	41 (79)
			✓[g]					[h]TUTOPATCH®			Massive[d]	66 (58–76)	38 (78)
								Control			Massive[d]	67 (58–77)	35 (69)
Gilot 2015[42]				✓				[i]Arthroflex®	Arthroscopic	On-lay	Large to massive[b]	58 (± 6.2)	8 (60)
								Control			Large to massive[b]	62 (± 4.6)	7 (47)

Study (first author and year of publication)	Patch type							Group	Surgical approach	Surgical patch technique	Tear size	Patient demographics	
	Xenograft			Human		Synthetic						Age at surgery (years), mean (range or ± SD)	Sex, *n* male (%)
	Dermal	Intestinal	Other	Allograft[a]	Autograft	Resorbable	Non-resorbable						
Ito 2003[66]				✓				Fascia lata	Open	Bridging	Large to massive[b]	63 (49–70)	6 (67)
								Control			Large to massive[b]	52 (36–66)	10 (83)
Jeon 2017[67]					✓			Biceps (long-head)	Arthroscopic	Bridging	Medium[b]	62 (46–82)	14 (45)
								Control			Medium to large[b]	63 (46–82)	16 (48)
Maillot 2018[64]	✓							[j]Conexa™	Open	On-lay	Medium to massive[b]	56 (46–63)	5 (45)
								Standard repair	Arthroscopic		Medium to massive[b]	58 (45–71)	5 (42)
								Debridement	Arthroscopic		Medium to massive[b]	60 (54–76)	3 (33)
Mori 2013[33]					✓			Fascia lata	Arthroscopic	Bridging	Medium to massive[b]	65 (± 8.9)	17 (71)
								Control			Medium to massive[b]	65 (± 9.2)	10 (42)
Mori 2015[68]					✓			Fascia lata + grade 1–2 atrophy	Arthroscopic	Bridging	Large to massive[b]	65 (± 9.0)	18 (69)
					✓			Fascia lata + grade 3–4 atrophy			Large to massive[b]	67 (± 6.2)	11 (58)
Tempelaere 2017[69]					✓			Quadriceps tendon	Open	Bridging	Massive[k]	NR	18 (78)
								Control	Arthroscopic		Massive[k]	NR	15 (56)
Vitali 2015[43]					✓		✓	Repol Angimesh + biceps (long-head)	Open	Bridging	Massive[d]	66 (55–78)	15 (25)
								Control			Massive[d]	67 (56–77)	18 (30)

continued

TABLE 1 Patch type and population demographics (*continued*)

Study (first author and year of publication)	Patch type							Group	Surgical approach	Surgical patch technique	Tear size	Patient demographics	
	Xenograft			Human		Synthetic						Age at surgery (years), mean (range or ± SD)	Sex, *n* male (%)
	Dermal	Intestinal	Other	Allograft[a]	Autograft	Resorbable	Non-resorbable						
Walton 2007[41]		✓						[c]Restore®	Open	On-lay	Large to massive[l]	60 (± 3.5)	10 (67)
								Control			Large to massive[l]	59 (± 3.1)	11 (69)
Yoon 2016[71]				✓				[m]Allocover™	Arthroscopic	Bridging	Large to massive[b]	64 (± 8.7)	9 (43)
								Control			Large to massive[b]	62 (± 6.7)	26 (48)
Non-comparative studies													
Agrawal 2012[72]				✓				[n]Allopatch HD™	Arthroscopic	On-lay	Large to massive[b]	54 (47–69)	10 (71)
Audenaert 2006[73]							✓	[o]MERSILENE®	Open	Bridging	Massive[d]	67 (51–80)	23 (56)
Badhe 2008[74]	✓							Zimmer collagen repair patch	Open	Bridging	Massive[b,d]	66 (46–80)	5 (50)
Bektaser 2010[75]					✓			Coracoacromial ligament[q]	Open	On-lay	Medium to massive[b]	54.3 (39–66)	4 (9)
Bond 2008[76]				✓				GRAFTJACKET	Arthroscopic	Bridging	Massive[b,d]	54 (39–74)	13 (81)
Burkhead 2007[77]				✓				GRAFTJACKET	Open	On-lay	Massive[d]	56 (NR)	12 (71)
Cho 2014[78]	✓							[r]Permacol™	Open	On-lay	Massive[b,d]	53 (45–57)	3 (60)
Consigliere 2017[79]	✓							DX reinforcement matrix[s]	Arthroscopic	On-lay	Large to massive[d]	74 (65–82)	6 (40)

Study (first author and year of publication)	Patch type							Group	Surgical approach	Surgical patch technique	Tear size	Patient demographics	
	Xenograft			Human		Synthetic						Age at surgery (years), mean (range or ± SD)	Sex, *n* male (%)
	Dermal	Intestinal	Other	Allograft[a]	Autograft	Resorbable	Non-resorbable						
Encalada-Diaz 2011[80]							✓	Polycarbonate polyurethane patch[t]	Open	On-lay	Small to large[b]	56 (44–65)	0
Flury 2012[81]				✓				GRAFTJACKET or Arthroflex	Arthroscopic	On-lay	Medium to large[b]	57 (50–68)	5 (63)
Giannotti 2014[82]	✓							Zimmer collagen repair patch	Open	Mixed	Massive[l]	66 (50–80)	4 (44)
Gupta 2012[83]				✓				GRAFTJACKET	Open	Bridging	Massive[l]	63 (45–83)	12 (50)
Gupta 2013[84]	✓							Conexa	Open	Bridging	Massive[d]	60 (45–77)	12 (46)
Hirooka 2002[85]							✓	GORE-TEX® PTFE[u]	Open	Bridging	Small to massive[b]	62 (44–75)	20 (74)
Lederman 2016[86]	✓							Conexa	Open	On-lay	Large[b]	56 (40–69)	NR
Lenart 2015[87]						✓		X-repair[v]	Open	On-lay	Massive[d]	57 (42–68)	9 (69)
Malcarney 2005[54]		✓						[c]Restore®	Open	Mixed	NR	NR	NR
Marberry 2013[88]						✓		Artelon	Open	On-lay	Massive[d]	65 (45–76)	5 (29)
Metcalf 2002[89]		✓						[c]Restore®	Open	On-lay	Massive[l]	NR	NR
Modi 2013[90]				✓				GRAFTJACKET	Open	Bridging	Large to massive[b]	62 (47–72)	41 (67)
Moore 2006[91]				✓[w]				Cadaveric allograft	Open	Bridging	Massive[d]	59 (34–81)	23 (72)
Nada 2010[92]							✓	Dacron[x]	Arthroscopic	Bridging	Massive[b,d]	66 (55–85)	14 (67)

continued

TABLE 1 Patch type and population demographics (*continued*)

Study (first author and year of publication)	Patch type										Patient demographics	
	Xenograft			Human		Synthetic						
	Dermal	Intestinal	Other	Allograft[a]	Autograft	Resorbable	Non-resorbable	Group	Surgical approach	Surgical patch technique	Tear size	Age at surgery (years), mean (range or ± SD)	Sex, *n* male (%)
Neumann 2017[93]	✓							Conexa	Open	Bridging	Massive[b,d]	62 (38–82)	21 (35)
Petrie 2013[94]							✓	[y]LARS™	Open	Bridging	Massive[l]	67 (NR)	21 (70)
Petri 2016[95]				✓				Arthroflex	Open	On-lay	Large to massive[l]	57 (26–68)	11 (85)
Petriccioli 2013[96]						✓		[z]SportMesh™	Open	On-lay	Subscapularis tears	61 (51–68)	8 (80)
Phipatanakul 2009[97]		✓						[c]Restore®	Open	On-lay	Massive[l]	48 (31–62)	9 (82)
Proctor 2014[98]						✓		X-Repair	Arthroscopic	On-lay	Massive[d]	66 (52–89)	NR
Rhee 2008[99]					✓			Biceps (long-head)	Mixed	Bridging	Massive[b,d]	61 (46–79)	11 (35)
Rotini 2011[100]				✓				Acellular human dermal matrix	Mixed	On-lay	Large to massive[l]	48 (37–55)	5 (100)
Sano 2010[101]					✓			Biceps (long-head)	Open	Bridging	Massive[d]	64 (48–79)	12 (86)
Scheibel 2007[102]					✓			Periosteum	Open	On-lay	NR	59 (44–71)	16 (70)
Schlegel 2018[103]			✓					Collagen sheet[h]	Arthroscopic	On-lay	N/A: partial thickness	54 (34–75)	19 (58)
Sclamberg 2004[104]		✓						[c]Restore®	Open	Mixed	Large to massive[b]	67 (52–79)	7 (64)

Study (first author and year of publication)	Patch type							Group	Surgical approach	Surgical patch technique	Tear size	Patient demographics	
	Xenograft			Human		Synthetic						Age at surgery (years), mean (range or ± SD)	Sex, *n* male (%)
	Dermal	Intestinal	Other	Allograft[a]	Autograft	Resorbable	Non-resorbable						
Sears 2015[105]				✓				GRAFTJACKET	Arthroscopic	On-lay			
	✓							Tissuemend[aa]			NR	50 (37–70)	NR
	✓							Conexa					
Venouziou 2013[106]				✓				GRAFTJACKET	Open	Bridging	Massive[l]	54 (33–64)	9 (64)
Wong 2010[32]				✓				GRAFTJACKET	Arthroscopic	Bridging	Massive[l]	53 (39–67)	36 (80)

NR, not reported; PTFE, polytetrafluoroethylene.
a Allograft patches constructed from decellularised human dermis.
b DeOrio and Cofield.[60]
c Depuy Synthes, Johnson & Johnson, Warsaw, IN, USA.
d Gerber *et al.*[61]
e Artelon, Marietta, GA, USA.
f Angiologica, Martino Siccomario, Pavia, Italy.
g Patch constructed from decellularised bovine pericardium.
h RTI Surgical, Alachua, FL, USA.
i Arthrex GmbH, Munich, Germany. Arthroflex is a registered trademark of LifeNet Health – Virginia Beach, VA, USA.
j Tornier, Minneapolis, MN, USA. Tornier is now part of Wright Medical Group (Memphis, TN, USA).
k Defined as a grade 3 retraction according to the Patte classification.[70]
l Size of tear as reported by study authors. No details were provided on the classification utilised and there were insufficient details to enable post-hoc classification by review authors (MB and NN).
m Hans Biomed, Seoul, Republic of Korea.
n HD Conmed, Utica, NY, USA.
o Ethicon, Johnson & Johnson, Somerville, NJ, USA.
p Patch derived from bovine Achilles tendons.
q No reference to brand in publication.
r Medtronic, Watford, UK.
s Arthrex GmbH, Munich, Germany.
t Polycarbonate polyurethane patch Biomerix, Somerset, NJ, USA.
u Gore Medical, Flagstaff, AZ, USA.
v Synthasome, San Diego, CA, USA.
w Cadaveric source of allograft, irradiated but not decellularised.
x Xiros, Leeds, UK.
y The Corin Group, Cirencester, UK.
z Arthrotek, Warsaw, IN, USA.
aa Stryker, Kalamazoo, MI, USA.
Control refers to RCR without augmentation. For definitions of 'on-lay' and 'bridging' see *Methods* section.

Among RCTs, only one study found a statistically meaningful improvement in ASES and Constant scores, but not the UCLA scale, following implantation of an allograft patch (see *Appendix 2*, *Table 20*).[26] The two RCTs investigating decellularised porcine small intestine submucosa (Restore)[35,65] failed to demonstrate an improvement in patient-reported outcomes at 1- and 2-year follow-up, whereas the study by Leuzinger *et al.*[63] undertook only intragroup comparisons between preoperative and post-operative Constant scores, reporting similar improvements following implantation of an allograft, xenograft or synthetic patch.

Only three non-randomised comparative studies reported a significant improvement in functional shoulder scores for synthetic, human allograft and fascia lata autografts.[33,40,42] The remaining studies found no significant improvement, whereas the studies by Ito and Morioka[66] and Vitali *et al.*[43] did not undertake intergroup comparisons.

Non-comparative studies

Of the non-comparative observational studies, 35 collected patient-reported outcome scores, with 25 reporting a statistically significant temporal improvement (see *Appendix 2*, *Table 20*).

Re-tear (including radiological assessments)

The integrity of the surgical repair was assessed by all RCTs and seven observational comparative studies, with a re-tear rate ranging from 10% to 73% following patch implantation and from 18% to 65% following a standard RCR (see *Appendix 2*, *Table 21*). Magnetic resonance imaging (MRI) was the commonest imaging modality (62%) utilised to diagnose recurrent tears, with a magnetic resonance arthrogram utilised in a further 23% of studies. The majority of studies undertook postoperative imaging after 1–2 years; however, there was considerable heterogeneity existing in the radiological classification of re-tears, and four studies did not provide any details. Definitions of re-tears could be broadly categorised into two themes: the presence of any tear or the presence of tears greater than the residual intraoperative defects. Five studies also attempted to subcategorise recurrent tears into 'partial' or 'complete'. For example, the study by Iannotti *et al.*[35] described a third 'partially healed' group, which was defined as a smaller rotator cuff lesion than that observed during preoperative imaging.

Although the RCT investigating human allograft (GRAFTJACKET) demonstrated a significantly lower failure rate in the augmentation arm, neither of the RCTs investigating the xenograft patch Restore found any reduction in re-tear rate.[26,35,65] In conflict with these findings, a multipatch comparative study found no difference in failure rate between three different patches: xenograft (Restore), human allograft (GRAFTJACKET) or synthetic (Artelon).[30] Among the observational comparative studies, significantly lower rates of re-tears were reported after augmentation with synthetic (Repol Angimesh), autograft (fascia lata) or allograft patches (Arthroflex and Allocover), whereas no improvement in re-tears was observed following augmentation with a long head of biceps tendon autograft or for the Restore patch.[33,39–43,67,71]

Non-comparative studies

Re-tear rate was assessed by 31 non-comparative studies, with a wide range of re-tear rates reported for each graft type [human allograft (0–25%, $n = 7$), human autograft (7–100%, $n = 4$), xenograft dermal (0–63%, $n = 8$), xenograft intestinal (8–90%, $n = 4$) and synthetic (7–62%, $n = 8$)].

Shoulder pain

Comparative studies

Only two studies (Gilot *et al.*,[42] Athroflex; Mori *et al.*,[33] fascia lata) reported a significant reduction in pain when compared with standard repair (see *Appendix 2*, *Table 22*). The remaining nine studies either did not provide intergroup comparisons ($n = 3$) or found no significant difference in pain scores between treatment arms ($n = 6$). Interestingly, the study by Walton *et al.*,[41] which utilised a 'mean activity pain score', found an increase in pain for the first 3 months following implantation of the Restore patch, which subsequently normalised by 6 months.

Non-comparative studies

In contrast to the comparative studies, of the 24 non-comparative observational studies reported pain scores, 22 reported a significant temporal improvement following augmented RCR.

Health-related quality of life

Comparative studies

Only three comparative trials reported the use of either the Short Form questionnaire-12 items (SF-12) or the SF-36 scores (see *Appendix 2*, *Table 23*). When compared with standard repair, two RCTs investigating porcine SIS xenograft (Restore) found no difference in the physical or mental components of the SF-36.[35,65] Conversely, an observational comparative study using human allograft (Athroflex) reported a significant improvement in both of these components at 6 months and 2 years postoperatively.[42]

Non-comparative studies

Three non-comparative studies reported significant improvements in SF-12 scores at final follow-up (32–36 months postoperatively). Conversely, the study by Encalada-Diaz *et al.*[80] found no improvement in the physical or mental components of the SF-12 at 12 months, following implantation of a synthetic rotator cuff patch.

Patch-related adverse events

A total of 43 studies provided data on complications, of which 21 studies reported the occurrence of complications in a total of 73 patients. The more commonly reported events across the studies included superficial and deep infections, and inflammatory response. Other reported complications were shoulder bursitis, biceps rupture, fibrosis, unexplained fever, shoulder manipulation, wound erythema, shoulder stiffness, persistent pain, skin reaction, biceps deformity, ossification, cardiac event and possible inflammatory response. One study,[69] which used a quadriceps autograft-based patch, reported knee-related problems and nerve injury.

Other secondary outcomes

No data on other secondary outcomes of interest were reported.

Meta-analysis

Shoulder pain and function scores

Of the 15 comparative studies, nine (eight observational and one RCT) provided sufficient data on post-operative functional outcome scores to be included in the meta-analysis (*Figure 5*). A 10-point improvement on the UCLA scale was observed for synthetic patches at 36 months postoperatively (mean difference 9.81, 95% CI 9.10 to 10.51; $I^2 = 0\%$) but not in the ASES score of studies of autografts (mean difference 4.18, 95% CI −3.22 to 11.58; $I^2 = 78\%$). Studies of allografts or xenografts derived from dermis or pericardium (non-SIS) used differing measures. No difference was found when the allograft studies were combined (standardised mean difference 0.54, 95% CI −0.23 to 1.31; $I^2 = 80\%$). There did not appear to be a difference between the sole RCT[26] in this meta-analysis and the other studies. For studies of xenografts versus surgery, there was also no evidence of a difference (standardised mean difference −0.05, 95% CI −0.41 to 0.30; $I^2 = 0\%$, respectively). Insufficient data were available for xenografts derived from intestinal submucosa (SIS).

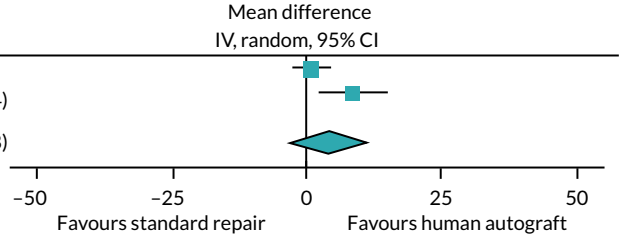
Shoulder pain

Eight observational comparative studies had sufficient data for a meta-analysis of postoperative pain (*Figure 6*). A small, probably non-clinically significant[107] improvement in postoperative pain was observed for synthetic patches only (mean difference −0.46, 95% CI −0.74 to −0.17; $I^2 = 0\%$). For studies of non-SIS xenografts, there was no evidence of a difference in postoperative pain scores (standardised mean difference 0.26, 95% CI −0.16 to 0.68; $I^2 = 16\%$). There was substantial statistical heterogeneity between

(a)

Study (first author and year of publication)	Human autograft patch Mean	SD	Total	Standard repair Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Jeon 2017[67]	88.2	6.9	31	87.4	7.2	33	55.5%	0.80 (−2.65 to 4.25)
Mori 2013[33]	94.1	5.4	24	85.7	14.1	24	44.5%	8.40 (−2.36 to 14.44)
Total (95% CI)			55			57	100.0%	4.18 (−3.22 to 11.58)

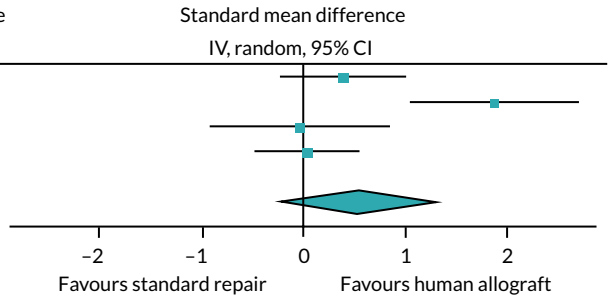
Heterogeneity: $\tau^2 = 22.58$; $\chi^2 = 4.58$, df = 1 ($p = 0.03$); $I^2 = 78\%$
Test for overall effect: $z = 1.11$ ($p = 0.27$)



(b)

Study (first author and year of publication)	Human allograft patch Mean	SD	Total	Standard repair Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Barber 2012[26]	98.9	4.2	22	94.8	14.2	20	26.3%	0.39 (−0.22 to 1.00)
Gilot 2015[42]	88.9	4.8	20	72.6	11.9	15	23.3%	1.86 (1.05 to 2.67)
Ito 2003[66]	91.7	7	9	92	7.6	12	22.6%	−0.04 (−0.90 to 0.83)
Yoon 2016[71]	82.5	11.2	21	82	15.3	54	27.8%	0.03 (−0.47 to 0.54)
Total (95% CI)			72			101	100.0%	0.54 (−0.23 to 1.31)

Heterogeneity: $\tau^2 = 0.49$; $\chi^2 = 15.36$, df = 3 ($p = 0.002$); $I^2 = 80\%$
Test for overall effect: $z = 1.37$ ($p = 0.17$)



(c)

Study (first author and year of publication)	Human allograft patch Mean	SD	Total	Standard repair Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Barber 2012[26]	98.9	4.2	22	94.8	14.2	20	0.0%	0.39 (−0.22 to 1.00)
Gilot 2015[42]	88.9	4.8	20	72.6	11.9	15	32.4%	1.86 (1.05 to 2.67)
Ito 2003[66]	91.7	7	9	92	7.6	12	31.7%	−0.04 (−0.90 to 0.83)
Yoon 2016[71]	82.5	11.2	21	82	15.3	54	35.9%	0.03 (−0.47 to 0.54)
Total (95% CI)			50			81	100.0%	0.60 (−0.55 to 1.75)

Heterogeneity: $\tau^2 = 0.89$; $\chi^2 = 15.36$, df = 2 ($p = 0.0005$); $I^2 = 87\%$
Test for overall effect: $z = 1.03$ ($p = 0.30$)

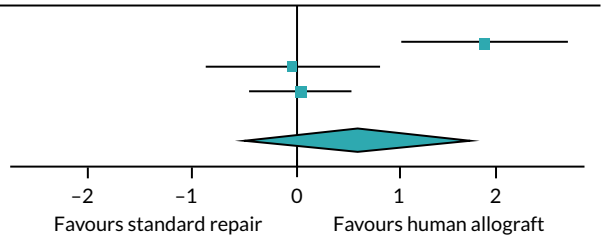


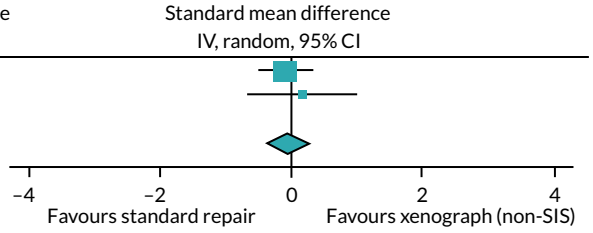
FIGURE 5 Forest plot comparing shoulder-specific pain and function outcome scores at final follow-up between (a) autograph patches and standard repair; (b) allograft patches and standard repair; (c) allograft patches and standard repair (observational studies only); (d) xenografts (non-small intestine submucosa) and standard repair; and (e) synthetic patches and standard repair. (*continued*)

(d)

Study (first author and year of publication)	Xenograft (non-SIS) patch Mean	SD	Total	Standard repair Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Ciampi 2014[40]	14.7	2	49	14.9	2	51	81.4%	−0.10 (−0.49 to 0.29)
Maillot 2018[64]	75.8	8.6	11	74.7	4.3	12	18.6%	0.16 (−0.66 to 0.98)
Total (95% CI)			60			63	100.0%	−0.05 (−0.41 to 0.30)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.31$, df = 1 ($p = 0.58$); $I^2 = 0\%$

Test for overall effect: $z = 0.28$ ($p = 0.78$)



(e)

Study (first author and year of publication)	Synthetic patch Mean	SD	Total	Standard repair Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Vitali 2015[43]	24.6	3.3	60	14.7	2	60	52.6%	9.90 (8.92 to 10.88)
Ciampi 2014[40]	24.6	3.2	52	14.9	2	51	47.4%	9.70 (8.67 to 10.73)
Total (95% CI)			112			111	100.0%	9.81 (9.10 to 10.51)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.08$, df = 1 ($p = 0.78$); $I^2 = 0\%$

Test for overall effect: $z = 27.14$ ($p < 0.00001$)

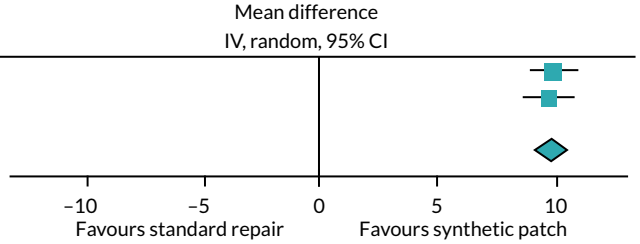
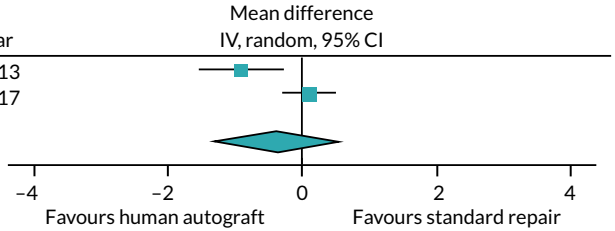


FIGURE 5 Forest plot comparing shoulder-specific pain and function outcome scores at final follow-up between (a) autograph patches and standard repair; (b) allograft patches and standard repair; (c) allograft patches and standard repair (observational studies only); (d) xenografts (non-small intestine submucosa) and standard repair; and (e) synthetic patches and standard repair.

(a)

Study (first author and year of publication)	Human autograft patch Mean	SD	Total	Standard repair Mean	SD	Total	Weight	Mean difference IV, random, 95% CI	Year
Mori 2013[33]	0.3	0.5	24	1.2	1.5	24	46.8%	−0.90 (−1.53 to −0.27)	2013
Jeon 2017[67]	1	0.8	31	0.9	0.8	33	53.2%	0.10 (−0.29 to 0.49)	2017
Total (95% CI)			55			57	100.0%	−0.37 (−1.35 to 0.61)	

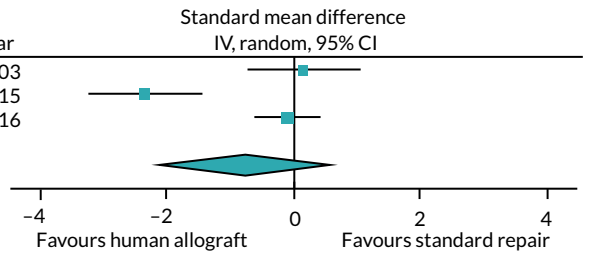
Heterogeneity: $\tau^2 = 0.43$; $\chi^2 = 6.93$, df = 1 ($p = 0.008$); $I^2 = 86\%$
Test for overall effect: $z = 0.74$ (p 0.46)



(b)

Study (first author and year of publication)	Human allograft patch Mean	SD	Total	Standard repair Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI	Year
Ito 2003[66]	−27.8	3.6	9	−28.3	3.3	12	32.4%	0.14 (−0.73 to 1.01)	2003
Gilot 2015[42]	1.3	1.2	20	4.1	1.1	15	32.2%	−2.36 (−3.25 to −1.47)	2015
Yoon 2016[71]	1.6	1.7	21	1.8	1.9	54	35.3%	−0.11 (−0.61 to 0.40)	2016
Total (95% CI)			50			81	100.0%	−0.75 (−2.15 to 0.64)	

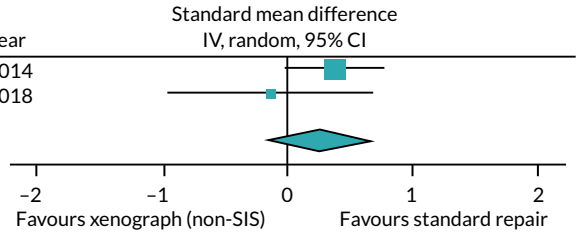
Heterogeneity: $\tau^2 = 1.37$; $\chi^2 = 21.21$, df = 2 ($p < 0.0001$); $I^2 = 91\%$
Test for overall effect: $z = 1.06$ ($p = 0.29$)



(c)

Study (first author and year of publication)	Xenograft (non-SIS) patch Mean	SD	Total	Standard repair Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI	Year
Ciampi 2014[40]	4.1	1	49	3.7	1.1	51	76.2%	0.38 (−0.02 to 0.77)	2014
Maillot 2018[64]	0.6	0.7	11	0.7	0.8	12	23.8%	−0.13 (−0.95 to 0.69)	2018
Total (95% CI)			60			63	100.0%	0.26 (−0.16 to 0.68)	

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 1.18$, df = 1 ($p = 0.28$); $I^2 = 16\%$
Test for overall effect: $z = 1.20$ ($p = 0.23$)



(d)

Study (first author and year of publication)	Synthetic patch Mean	SD	Total	Standard repair Mean	SD	Total	Weight	Mean difference IV, random, 95% CI	Year
Ciampi 2014[40]	3.3	1.1	52	3.7	1.1	51	43.9%	−0.40 (−0.82 to 0.02)	2014
Vitali 2015[43]	3.2	1.1	60	3.7	1	60	56.1%	−0.50 (−0.88 to −0.12)	2015
Total (95% CI)			112			111	100.0%	−0.46 (−0.74 to −0.17)	

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.12$, df = 1 ($p = 0.73$); $I^2 = 0\%$
Test for overall effect: $z = 3.17$ ($p = 0.002$)

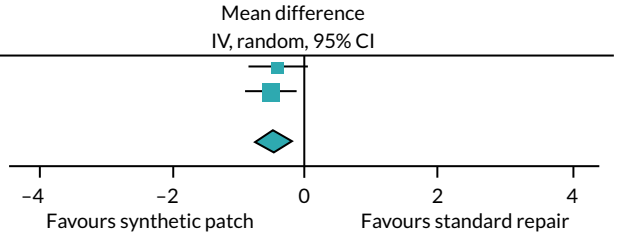


FIGURE 6 Forest plot comparing shoulder pain at final follow-up between (a) autograft patches and standard repair; (b) allograft patches and standard repair; (c) xenografts (non-small intestine submucosa) and standard repair; and (d) synthetic patches and standard repair.

the studies of both autograft and allograft patches (mean difference −0.37, 95% CI −1.35 to 0.61, $I^2 = 86\%$; and standardised mean difference −0.75, 95% CI −2.15 to 0.64, $I^2 = 91\%$, respectively). Insufficient data were reported for a meta-analysis of shoulder pain following augmentation with xenograft patches derived from SIS.

Health-related quality of life

Only three comparative studies (two RCTs and one observational study) provided data on HRQoL, but there were insufficient data available to meta-analyse.[35,42,65]

Surgical re-tear rate

In total, 11 comparative studies (four RCTs and seven observational studies) could be included in a meta-analysis for re-tear rate (*Figure 7*). A significantly lower re-tear rate was seen for an allograft patch (RR 0.34, 95% CI 0.18 to 0.64; $I^2 = 0\%$). The one RCT evaluating an allograft[26] appears to have a consistent finding with the three observational studies. There was evidence from two observational studies for a lower re-tear rate with synthetic patches (RR 0.40, 95% CI 0.25 to 0.64; $I^2 = 0\%$).[41] There was no evidence of a difference for autografts (RR 0.69, 95% CI 0.40 to 1.18; $I^2 = 0\%$), based on two observational studies, or SIS-derived xenografts (RR 0.97, 95% CI 0.72 to 1.30; $I^2 = 0\%$), based on two RCTs and one observational study (the meta-analysis of only the two RCTs had similar findings). Insufficient data were available for non-SIS derived xenografts to meta-analyse.

Complications (including patch-related adverse events)

A total of 43 studies provided data on complications, of which 21 studies reported the occurrence of 77 complications in a total population of 1381 patients undergoing any form of augmentative surgery and 372 patients receiving a standard rotator cuff repair. The overall crude complications rates were 4.8% for patients undergoing any form of patch augmentation and 1.9% following non-augmentative surgery. However, by excluding five studies in the augmentation group that had particularly high rates of complications (20–74%, following quadriceps tendon, Restore patch or humeral periosteal-augmented repair[35,41,69,97,102]), the overall rate of complications following patch augmentation was 2.9%. An inflammatory response was recorded in fifteen patients (see *Appendix 2*, *Table 21*). The majority of these events ($n = 11$) occurred in patients who received a SIS xenograft (Restore) patch but with reactions also reported after implantation of bovine-derived, irradiated, decellularized human allograft and synthetic patches. Excluding all adverse events concerning the Restore patch, which has been withdrawn from the marketplace, the crude complication rate for patches in potential clinical use was 2.3%.

Risk of bias

Assessment of bias was conducted for all RCTs and comparative studies (*Tables 2* and *3*). Only the study by Bryant *et al.*[65] was at a low risk of bias, with the remaining RCTs assessed as having an unclear risk. These findings are based on a lack of study methodology detail, in particular surrounding blinding of patients and outcome assessors. All observational comparative studies had a serious risk of bias, which centred around the potential for confounding, bias in patient selection and outcome measurement.

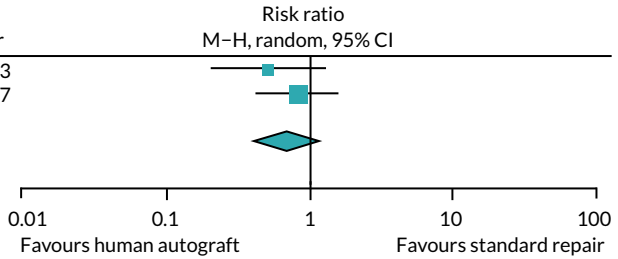
Discussion

The use of medical implants has recently come under increasing scrutiny. Surgical repair of the rotator cuff with patch augmentation has been proposed as a method of improving rates of tendon healing and patient outcomes. To the best of our knowledge, this systematic review is the largest and most comprehensive systematic appraisal of the clinical effectiveness and safety of such implants to date. Overall, the current evidence is not sufficiently robust to determine the effectiveness of patch-augmented RCR compared with standard repair alone. Interestingly, the consistently observed improvement in functional scores and pain observed in non-comparative observational studies was often not reflected when the same patch was tested in a controlled fashion, reinforcing the importance of well-designed clinical trials in the assessment of novel health technologies.

(a)

Study (first author and year of publication)	Human autograft patch Events	Total	Standard repair Events	Total	Weight	Risk ratio M–H, random, 95% CI	Year
Mori 2013[33]	5	24	10	24	34.5%	0.50 (0.20 to 1.25)	2013
Jeon 2017[67]	10	31	13	33	65.5%	0.82 (0.42 to 1.59)	2017
Total (95% CI)		55		57	100.0%	0.69 (0.40 to 1.18)	
Total events	15		23				

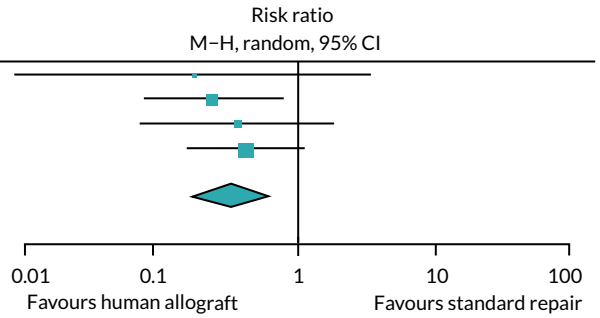
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.74$, df = 1 ($p = 0.39$); $I^2 = 0\%$
Test for overall effect: $z = 1.35$ ($p = 0.18$)



(b)

Study (first author and year of publication)	Human allograft patch Events	Total	Standard repair Events	Total	Weight	Risk ratio M–H, random, 95% CI	Year
Ito 2003[66]	0	13	3	17	4.9%	0.18 (0.01 to 3.27)	2003
Barber 2012[26]	3	20	9	15	32.0%	0.25 (0.08 to 0.77)	2012
Gilot 2015[42]	2	20	4	15	16.6%	0.38 (0.08 to 1.78)	2015
Yoon 2016[71]	4	21	24	54	46.5%	0.43 (0.17 to 1.09)	2016
Total (95% CI)		74		101	100.0%	0.34 (0.18 to 0.84)	
Total events	9		40				

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.72$, df = 3 ($p = 0.87$); $I^2 = 0\%$
Test for overall effect: $z = 3.34$ ($p = 0.0008$)



(c)

Study (first author and year of publication)	Human allograft patch Events	Total	Standard repair Events	Total	Weight	Risk ratio M–H, random, 95% CI	Year
Ito 2003[66]	0	13	3	17	7.2%	0.18 (0.01 to 3.27)	2003
Barber 2012[26]	3	20	9	15	0.0%	0.25 (0.08 to 0.77)	2012
Gilot 2015[42]	2	20	4	15	24.4%	0.38 (0.08 to 1.78)	2015
Yoon 2016[71]	4	21	24	54	68.5%	0.43 (0.17 to 1.09)	2016
Total (95% CI)		54		86	100.0%	0.39 (0.18 to 0.84)	
Total events	6		31				

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.31$, df = 2 ($p = 0.86$); $I^2 = 0\%$
Test for overall effect: $z = 2.39$ ($p = 0.02$)

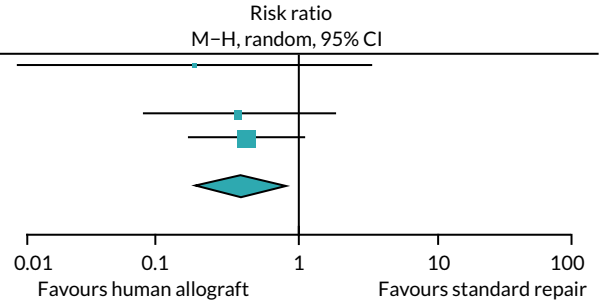


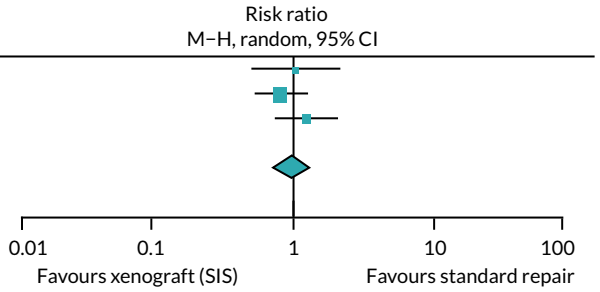
FIGURE 7 Forest plot comparing re-tear rates at final follow-up between (a) autograft patches and standard repair; (b) allograft patches and standard repair; (c) allograft patches and standard repair (observational studies only); (d) xenografts (small intestine submucosa) and standard repair; (e) xenografts (small intestinal patches) and standard repair (RCTs only); and (f) synthetic patches and standard repair. M–H, Mantel–Haenszel. (*continued*)

(d)

Study (first author and year of publication)	Xenograft (SIS) patch Events	Total	Standard repair Events	Total	Weight	Risk ratio M–H, random, 95% CI	Year
Walton 2007[41]	6	10	7	12	18.0%	1.03 (0.51 to 2.06)	2007
Bryant 2016[65]	18	34	17	26	48.9%	0.81 (0.53 to 1.24)	2016
Iannotti 2006[35]	11	15	9	15	33.1%	1.22 (0.73 to 2.04)	2016
Total (95% CI)		59		53	100.0%	0.97 (0.72 to 1.30)	
Total events	35		33				

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.51$, df = 2 ($p = 0.47$); $I^2 = 0\%$

Test for overall effect: $z = 0.21$ ($p = 0.83$)

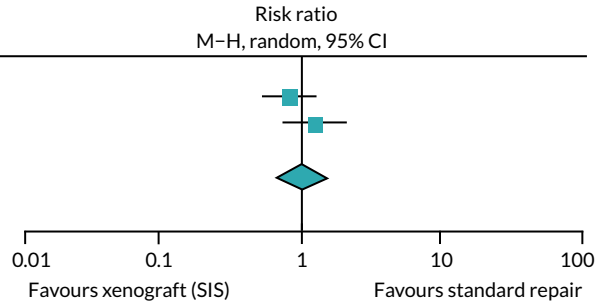


(e)

Study (first author and year of publication)	Xenograft (SIS) patch Events	Total	Standard repair Events	Total	Weight	Risk ratio M–H, random, 95% CI	Year
Walton 2007[41]	6	10	7	12	0.0%	1.03 (0.51 to 2.06)	2007
Bryant 2016[65]	18	34	17	26	56.5%	0.81 (0.53 to 1.24)	2016
Iannotti 2006[35]	11	15	9	15	43.5%	1.22 (0.73 to 2.04)	2016
Total (95% CI)		49		41	100.0%	0.97 (0.65 to 1.45)	
Total events	29		26				

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 1.48$, df = 1 ($p = 0.22$); $I^2 = 32\%$

Test for overall effect: $z = 0.16$ ($p = 0.88$)



(f)

Study (first author and year of publication)	Synthetic patch Events	Total	Standard repair Events	Total	Weight	Risk ratio M–H, random, 95% CI	Year
Ciampi 2014[40]	9	52	21	51	49.9%	0.42 (0.21 to 0.83)	2014
Vitali 2015[43]	9	60	24	60	50.1%	0.38 (0.19 to 0.74)	2015
Total (95% CI)		112		111	100.0%	0.40 (0.25 to 0.64)	
Total events	18		45				

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.05$, df = 1 ($p = 0.82$); $I^2 = 0\%$

Test for overall effect: $z = 3.78$ ($p = 0.0002$)

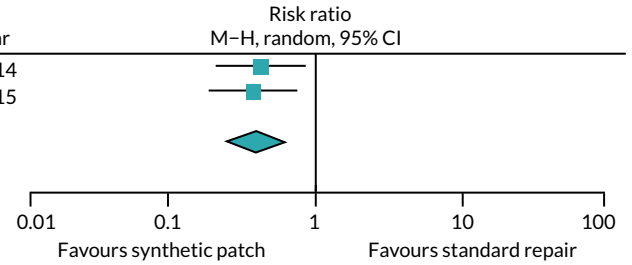


FIGURE 7 Forest plot comparing re-tear rates at final follow-up between (a) autograft patches and standard repair; (b) allograft patches and standard repair; (c) allograft patches and standard repair (observational studies only); (d) xenografts (small intestine submucosa) and standard repair; (e) xenografts (small intestinal patches) and standard repair (RCTs only); and (f) synthetic patches and standard repair. M–H, Mantel–Haenszel.

TABLE 2 Risk of bias for RCTs

Study (first author and year of publication)	Type of bias							Overall assessment
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other sources of bias	
Barber 2012[26]	Unclear	High	Unclear	Unclear	Unclear	Low	High[a]	Unclear
Byrant 2016[65]	Low	Low	Low	Low	Low	Low	Low	Low
Iannotti 2006[35]	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Leuzinger 2016[63]	Unclear	Unclear	Unclear	Unclear	Low	High	Low	Unclear

a Classified as 'high' because of the risk of sponsor bias.

TABLE 3 The ROBINS-I risk of bias (non-randomised comparative trials)

Study (first author and year of publication)	Type of bias							Overall assessment
	Bias due to confounding	Bias in participant selection	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	
Ciampi 2014[40]	Serious	Moderate	Low	Low	No information	Serious	No information	Serious
Gilot 2015[42]	Serious	Serious	Low	Low	Serious	Serious	Serious	Serious
Ito 2003[66]	Serious	Serious	Moderate	No information	No information	Serious	Moderate	Serious
Jeon 2017[67]	Moderate	Serious	Moderate	No information	No information	Serious	Moderate	Serious
Maillot 2018[64]	Moderate	Serious	Low	No information	Low	Serious	Serious	Serious
Mori 2013[33]	Serious	Serious	Low	Low	Serious	Serious	Serious	Serious
Mori 2015[68]	Serious	Serious	Moderate	Low	Moderate	Serious	Serious	Serious
Tempelaere 2017[69]	Serious	Serious	Moderate	No information	Serious	Serious	Moderate	Serious
Vitali 2015[43]	Serious	Serious	Low	No information	Serious	Serious	Serious	Serious
Walton 2007[41]	Moderate	Serious	Low	No information	Serious	Serious	Low	Serious
Yoon 2016[71]	Serious	Serious	Low	No information	Serious	Serious	Serious	Serious

Although our meta-analysis suggests a small improvement in pain and shoulder function for synthetic patches and a moderate reduction in re-tear rate for synthetic and human allograft patches, study bias and heterogeneity mean that these results must be interpreted very cautiously. Furthermore, it is unclear if the observed 10-point improvement in UCLA score for the synthetic patches is clinically meaningful. To date, the minimal clinically important difference for the UCLA score following RCR has not been established.[108] However, a threshold of 30 UCLA points at 2 years has been proposed as an absolute cut-off point signifying treatment success for RCR.[109] In the studies investigating synthetic polypropylene patches, augmentation failed to meet this threshold.[40,43] Similarly, the small 0.46-point reduction in VAS pain scores is unlikely to be clinically meaningful.[107]

Across 43 studies with a combined safety population of 1753 participants, complications rates were similar between augmented repairs (2.3%) and standard repairs (1.9%), with specific safety concerns associated with certain patches (Restore) or techniques (such as quadriceps allograft, humeral periosteal allograft).[37,38,45,69,102]

Most studies reported on the use of patch augmentation for large to massive tears in patients aged 50–70 years. This demographic is similar to that reported by British shoulder surgeons (see *Chapter 3*), in which only 10% of respondents would consider augmentation for small and medium-sized tears. Only four studies were identified that included patients with small or medium-sized tears and none assessed the effect of tear size on outcome. It is interesting to note that small tears in patients aged 80 years are predicted to have a similar chance of repair failure as massive tears in patients aged 50 years.[15] It is, therefore, unclear why a dichotomy between small to medium and large to massive tears has emerged. Rather than viewing the degree of structural incompetence as the primary indication for patch augmentation, we would instead encourage a biological perspective, applying augmentation to cases in which tendon healing is the most impaired.

Interestingly, radiological findings seemed to closely echo patient-reported outcome measures (PROMs). Three studies[35,65,67] found no significant improvement in either PROMs or rate of re-tear, whereas a further five studies[26,33,40,42,68] reported significant improvements in both functional outcome scores and radiologically defined repair failure. This lends support to the notion that repair success is intimately linked with symptom resolution. Indeed, a subgroup analysis by Iannotti *et al.*[35] identified a significant association between tendon healing and postoperative improvements in the PENN score and SF-36 physical component. Similar findings have previously been reported by the UKUFF study,[2] in which those with healed repairs had a better Oxford Shoulder Score (OSS) than patients with re-tears but with the worst results among those with an irreparable tear.

The systematic literature review lacked evidence of economic evaluation of patch use for rotator cuff surgery. The few RCTs that were found evaluated the clinical effectiveness rather than the cost or cost-effectiveness of patch use. However, the studies considered and collected resource utilisation related to the complications following a rotator cuff surgery and medication use, which can both be transformed into monetised units and, hence, considered as a further cost of the surgery. Evidence of the methods of patient data collection was revealed in one study.[65] The SF-36 was the preferred instrument of capturing HRQoL in the population under consideration. From a societal point of view, rotator cuff surgery is expected to have an impact on patients' capacity to return to their daily activities following a rotator cuff operation. The return to daily activities, as well as capacity to return to work, was captured in a study by Bryant *et al.*[65]

Strengths and limitations of the study

Strengths of this review include a priori published protocol,[58] a comprehensive search strategy, inclusion of non-English language articles, duplicate assessment of eligibility, a risk-of-bias assessment and data extraction. Nonetheless, there remain several limitations to the current review, which are mainly a reflection of the quality of the published primary research available. Only four RCTs have been published, of which two relate to a product (Restore) that has now been withdrawn from market

because of safety concerns.[26] In addition, substantial heterogeneity between studies was observed, with the majority of studies also judged to have a high risk of bias, which seriously limited our ability to draw firm recommendations. An exhaustive exploration of the heterogeneity has not been undertaken and indeed such an analysis was not declared a priori in our protocol paper.[58] However, separating studies by patch type did influence the degree of heterogeneity and we would, therefore, recommend that patch type should be considered in the design of future reviews.

In comparison with previous systematic reviews, we have included one additional RCT[63] and three observational comparative studies representing 278 patients not otherwise identified.[27,44,59,63,66,67,71] Results from our meta-analysis are, in part, consistent with a previous analysis that found an overall reduction in re-tear rate and improved ASES scores following patch augmentation.[44] The substantial number of additional studies included in this current review provide greater precision and, although a subgroup analysis was not originally specified in our protocol, they have allowed us to hypothesise that patch type may have an effect on patient outcomes. The occurrence of adverse events with only certain patch types adds some credibility to this notion. Previous reviews of augmented RCR have, on the basis of a presumed effect on patient outcome, excluded studies based on the size of rotator cuff tear or surgical technique (on-lay or bridging).[27] It is possible that each technique reflects different patient cohorts; for example, the use of bridging scaffolds may represent larger, more chronic or even recurrent rotator cuff tears. However, we were unable to detect any overall difference in patient-reported outcomes, re-tear rate or pain scores between studies reporting on-lay or bridging techniques. It should be noted that differences in terminology makes comparison of these surgical techniques challenging; the terms 'irreparable', 'bridging', 'interposition' or 'reconstruction' were used interchangeably in a number of studies or to refer to the same approach. To help facilitate the future interrogation of the relationship between surgical technique and outcomes we would suggest that only the terms 'on-lay' (defined as repair augmentation) or 'bridging' (defined as repair reconstruction/augmentation) be utilised in accordance with previously published definitions.[27]

There are a growing number of patches available for the augmentation of RCR. Despite the safety-related withdrawal of certain patches, as well as wider concerns surrounding medical device and mesh implantation, rigorous clinical evaluation of patch augmentation is lacking.[41,110] We were particularly concerned by the absence of publicly available research for several patches currently in clinical use [e.g. dCELL® (Tissue Regenix Group plc, Leeds, UK) and Leeds–Kuff™ (Neoligaments, Leeds, UK)]. Although some studies have indicated promise for specific patches, firm recommendations in terms of patch type or surgical technique cannot be made at present. There remains a need for well-designed comparative studies (preferably multicentre RCTs) that are capable of robustly evaluating the effectiveness and safety of multiple patch types. Furthermore, routine reporting of patch registry data could address the current lack of robust safety data for cuff-augmented RCR.[111]

Chapter 3 Surveys

Introduction

When planning a RCT of patch use for rotator cuff tears, considering current practice alongside current evidence is critical. It is particularly important to understand practice in the setting in which a trial would be carried out. The constraints that potential investigators would have to work within are a key issue that will affect the conduct of a RCT. Two surveys were undertaken with surgeons to address these concerns, as stages 2 and 4 of this mixed-methods feasibility study. The first was a survey of the surgical membership of the British Elbow and Shoulder Society (BESS), also known as the BESS membership survey. The second was a survey of surgeons who had previously participated in large UK shoulder surgery trials, known as the surgeon triallist survey.[1]

The aims of the surveys were to:

- identify the current UK clinical practice of patch use
- gather information on surgeon opinion of patch choice and patient suitability
- explore the general attitude towards a RCT of patch-augmented RCR
- explore the acceptability of proposed trial design elements to surgeons and to assess the feasibility of a RCT of patch-augmented RCR.

Methods

The surveys were developed and distributed using the Online Surveys tool (Jisc, Bristol, UK) (previously known as Bristol Online Surveys). Prior to finalising, each survey was reviewed and piloted internally among the study investigators and external individuals as appropriate.

Participant consent was implied by the completion and submission of the online survey. Information about the study and how the data would be collected and processed was explained in e-mail correspondence (invite and reminders) and at the start of the survey.

The response rate for the surveys was defined as the number of responding participants divided by the number of eligible people invited. Responses were summarised quantitatively or narratively as appropriate [using Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) (version 16.12) and GraphPad Prism (GraphPad Software Inc., CA, USA) (version 7.0)].

The methodology, findings and discussion for each survey are detailed separately below.

Stage 2: British Elbow and Shoulder Society membership survey

The BESS members are predominantly clinically active shoulder surgeons. The BESS office used the e-mail list to invite participants to complete the survey, avoiding the unnecessary sharing of personal data. Information about the PARCS study and a hyperlink to the survey was provided. There was no minimum number of responses required as the study was opportunistic in terms of sample size and was not driven by statistical testing.

The e-mail invitation was sent out in April 2017 and available to complete until the end of August 2017. Surgeon members of the BESS attending the annual meeting in June 2017 were also offered an opportunity to complete the survey at an exhibition stand. To assess respondent demographics, participants were asked about their grade (i.e. consultant, trainee or other) and place of work (i.e. district general hospital, university

teaching hospital, private practice or other). To determine their familiarity with and experience of augmented RCR, participants were asked about their preferred surgical technique for RCR (predominantly open, predominantly arthroscopic or substantial amount of both open and arthroscopic repairs), whether or not they had previously used patch-augmented rotator cuff surgery (i.e. no, yes within 6 months or yes but not within 6 months) and the total number of augmented cuff repairs that they had undertaken. Further questions sought to determine the types of patch commonly in use and to investigate the factors influencing patch selection. Two separate free-text questions were posed: 'Which patches have you used?' and 'Why did you use these specific patches?'. A final free-text box was provided to allow further comments about the choice of patch to be recorded.

To gather opinion on patient selection for augmented RCR, respondents were asked to consider discrete patient subgroups. Four different tear sizes (i.e. small, medium, large and massive) were combined with different four different ages (50, 60, 70 and 80 years) to produce 16 combinations. Participants were asked if they considered each patient combination appropriate for patch augmentation. An answer of 'yes', 'no' or 'unsure' could be provided for each scenario. A free-text box was also provided to capture further comments relating to patient suitability.

Respondents were then asked to consider participation in a future clinical trial in augmented RCR. Responders were asked if they would be interested in participating in a RCT of patch-augmented surgery (i.e. yes, no or maybe). Members were asked what factors could be addressed to encourage participation in a RCT.

The survey was piloted with four members of the shoulder and elbow surgical team who perform patch repair. The survey took approximately 10 minutes to complete.

Stage 4: surgeon triallist survey

The surgeon triallist survey was directed at surgeons who had taken part in previous large multicentre NHS shoulder trials and, therefore, the subset of surgeons who were most likely to participate in a RCT of patch-augmented rotator cuff surgery. Eligible participants were identified through a network of surgeon triallists who have participated in previous NHS-based shoulder surgical trials [i.e. Can Shoulder Arthroscopy Work (CSAW)?, UK Frozen Shoulder Trial (UKFroST) and UKUFF].[18,112,113] They were invited to complete the survey by the PARCS project management group through a personalised e-mail or face-to-face invitation. The survey was open between June and August 2018. Non-responders received up to two e-mail reminders asking them to complete the survey.

The intention was to invite at least 30 research-active orthopaedic shoulder surgeons. This was considered large enough to meet the aim of this component of the project and ensured that a range of surgeons and centres were included. This would also be close to the number of surgeons needed to participate in a future trial of patch-augmented rotator cuff surgery.

The surgeon triallist survey was developed based on previous stages, including the systematic review, the above BESS membership survey and the stakeholder focus groups. Uncertainties related to the patient population, intervention, control and outcome (PICO) elements, and trial practicalities were incorporated into the survey design.

The survey started by asking if the triallists currently used a patch to augment a RCR on any of their patients. If they answered yes, the surgeons were then invited to respond to questions on how they typically used a patch (bridge, on-lay or other) and whether or not the state of the subscapularis affected their decision to use a patch. The next section included questions about a trial of patch-augmented rotator cuff surgery and which patients they would be willing to randomise. Other questions included what the comparator in a trial would be and more detail about patient characteristics, including tear size, age ranges, presence of atrophy, glenohumeral OA and cuff arthropathy. The survey also asked questions

about logistical trial procedures, including the timing of randomisation, surgical repair technique, types of patch they would be willing to use, postoperative rehabilitation and length of patient follow-up.

The survey was reviewed and tested by members of the study team, including surgeons and trainees. The survey took approximately 15 minutes to complete. During the survey, participants were asked to register their interest in taking part in further stages of the PARCS study.

Results

Stage 2: British Elbow and Shoulder Society membership survey

A total of 550 medically qualified members of the BESS (of whom 481 were consultant orthopaedic surgeons) were invited to participate, with 105 (19%) responding. The respondents were mostly consultant surgeons (97%), with the majority working at district general hospitals (48%) (*Table 4*). Most participants (95%) worked within the NHS but with some reporting additional work within the private sector (32%).

Most respondents undertook arthroscopic RCRs (66%), with only a minority solely undertaking open repairs (14%) (*Table 5*). When asked whether or not they had ever used a patch to augment rotator cuff surgery, over half (58%) had done so. The majority of patch users had undertaken an augmented repair within the last 6 months (70%). The utilisation of patches among surgeons performing open repairs was slightly lower (40%) than for those reporting an arthroscopic (56%) or mixed open and arthroscopic practice (76%).

A varied surgical experience was reported among those who had performed patch-augmented RCR. Most surgeons reported low use, with a median of five rotator cuff augmentation procedures performed; however, the maximum reported was 200 procedures.

Responses relating to the patch types used can be seen in *Table 6*. When asked about the patch types and products utilised during RCR, 13 different products were reported. Decellularised dermis accounted for 85% of the different patches used, and non-degradable synthetic meshes made up the remaining 15%. Human decellularised products were more frequently used, with only 13% of decellularised patches being porcine derived (the rest being human, except for one for which it was not clear what the source material was). All synthetic scaffolds that were reported were non-degradable and produced from a variety of polymers (i.e. polyester, polypropylene and polyurethane). Overall, GRAFTJACKET was the most commonly reported device (55%) with the Leeds-Kuff Patch (10%), Arthroflex (8%) and dCELL (8%) the next most common.

TABLE 4 The BESS membership survey respondents' characteristics

Category	*n* (%) (*N* = 105)
Training grade	
Consultant	102 (97)
Other	3 (3)
Place of work	
DGH	50 (48)
Teaching hospital	44 (42)
Mixed (DGH and teaching hospitals)	6 (6)
Private hospital	5 (5)

DGH, district general hospital.

TABLE 5 The BESS surgeons' survey responses regarding experience with patch augmentation

Category	*n* (%)
***Preferred repair technique* (N = *105*)**	
Arthroscopic	69 (66)
Open	15 (14)
Open or arthroscopic	21 (20)
***Use of patch augmentation* (N = *105*)**	
Yes: within 6 months	43 (41)
Yes: not within 6 months	18 (17)
No	44 (42)
***Number of patches implanted* (N = *61*)**	
1–5	32 (30)
6–10	15 (14)
11–15	0 (0)
16–20	6 (6)
> 20	8 (8)

TABLE 6 Patch types reported in the BESS membership survey

Category	*N* (%)	*n*
Decellularised patches		
Porcine derived	10 (13)	
Arthrex DX reinforcement matrix		1
Conexa reconstructive matrix		5
Restore		1
Zimmer collagen repair patch		2
Manufacturer not specified		1
Human derived	56 (71)	
Arthroflex®		6
dCELL		6
GRAFTJACKET		44
Type not specified	1 (1)	1
Synthetic patches	***12 (15)***	
Artelon		2
Leeds–Kuff patch		8
Vypro®		1
Manufacturer not specified		1

Reported factors influencing patch selection are given in *Table 7*. The device's perceived efficacy was an important theme, with clinical evidence (24%) and personal and peer experience (8% and 4%, respectively) cited as important determinants. Product characteristics formed another dominant theme, with patch usability, strength and material influencing selection. A product's cost and availability within the local hospital was also important. In addition, the specific characteristics of a rotator cuff tear may also determine patch choice.

Participants responded with their opinions on patient selection for a RCT of patch-augmented RCR (*Figure 8*). Responses for patients aged 50 or 60 years tended to be similar regarding patient suitability for receiving a patch. However, the effect of age on patient suitability was clearly influenced by tear size. Among older patients (aged 70 or 80 years) with small and medium-sized tears, a greater (although still relatively small) proportion of upper limb surgeons either would consider augmentation or were unsure (12–26%).

Conversely, the reverse trend was observed in large and massive tears, with a greater proportion of surgeons considering augmentation appropriate in the 50 or 60 years age groups (39–59%).

Overall, tear size seemed to be more important than age in assessing patient suitability. Just over half of respondents (range 19–59%) would use augmentation in large and massive tears, compared with $\leq$ 10% (range 3–11%) for small and medium-sized rotator cuff tears. However, it is worth noting that considerable uncertainty remains. Around one-fifth (range 19–27%) of respondents were unsure as to the role of augmentations in medium, large and massive tears.

Additional free-text comments were provided by 48 participants, with six dominant themes emerging (*Table 8*). Tear characteristics remained an important consideration during patch augmentation. As well as tear size, the degree of fatty atrophy, the intraoperative ability to mobilise the tendon and the tension of the repair were often mentioned as important factors during tear classification. Surgical assessment of tendon quality was reported as important by 17% of respondents. A lack of glenohumeral OA (13%)

TABLE 7 The BESS membership survey responses regarding patch selection

Category	*n* (%)
***Product efficacy* (N = *29*)**	
Clinical evidence	19 (24)
Personal experience	6 (8)
Peer experience	3 (4)
Regulatory approval	1 (1)
***Product characteristics* (N = *18*)**	
Material type	9 (11)
Strength	5 (6)
Usability	4 (5)
***Product access* (N = *17*)**	
Cost	6 (8)
Local availability	11 (14)
***Tear characteristics* (N = *15*)**	
Type of tear	14 (18)
Tissue quality	1 (1)

A total of 61 participants provided written responses to the question 'Why did you use these specific patches'. Each answer could fit into multiple categories. Percentages are expressed against the total number (*n* = 79) of extracted themes.

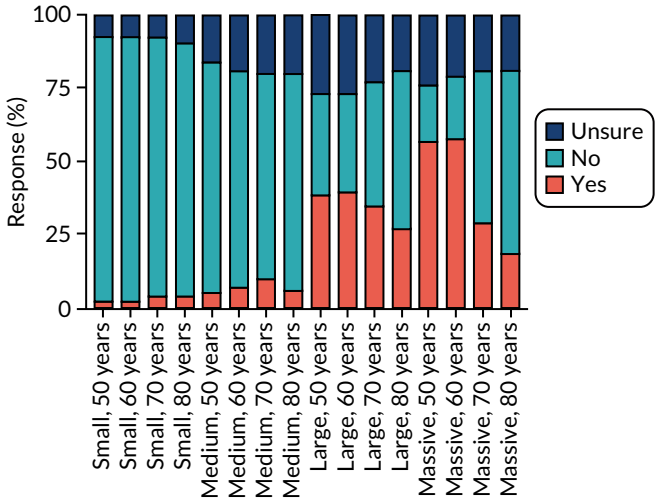


FIGURE 8 The BESS membership survey responses relating to suitability on patient selection. Reproduced with permission from Baldwin *et al.*[114] © 2020 Baldwin *et al.* This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited (https://creativecommons.org/licenses/by/4.0/). This includes minor additions and formatting changes to the original figure.

TABLE 8 Factors influencing patch selection from BESS surgeons' survey responses

Category	*n* (%) (*N* = 48)
Tear characteristics	28 (58)
Patient population	17 (35)
Previous repair failure	13 (27)
Tissue quality	8 (17)
No OA	6 (13)
Supportive evidence or experience	5 (10)

and the failure of a standard repair (27%) were provided as other important qualifiers during augmented repair consideration. For older patients (aged ≥ 70 years) with large tears, 10% of respondents justified avoiding augmented repair because of the perceived success of reverse shoulder arthroplasty.

When asked if they would actively participate in a RCT of patch augmentation, half of the respondents confirmed an interest, with a further 22% undecided and the remainder not interested. Twelve respondents provided additional comments that explored barriers to participation. Further trial details were mentioned in almost half (46%) of comments and specific limits were placed on the inclusion/exclusion criteria by 23%, for example 'no compulsion to use patch in small/medium tears'. A further 31% of comments listed concerns over the type of intervention or comparison that would be utilised. For example, 'compared to balloon interposition' or 'comparing reverse [total shoulder arthroplasty] with patch repair' were suggested.

Stage 4: surgeon triallist survey

Of the surgeons invited, 24 out of 31 (77%) completed the survey. All of the surgeons who responded had acted as the principal investigator for at least one of the UKUFF,[2] CSAW[112] and UKFroST[113] trials.

Patch use was not as common in this population of surgeons as implied in the BESS membership survey (*Table 9*). Only 11 of the 24 surgeons (46%) regularly used patches. Nine (38%) do not currently use patches but would be willing to for the purpose of a trial and four do not use patches at all and would

TABLE 9 Surgeon triallists' patch use for RCR

Category	*n* (%)
***Patch use to augment RCR* (N = *24*)**	
Yes	11 (46)
No, but I would be willing to for a trial of patch augmentation with suitable support	9 (37)
No, and I would not be interested in being involved in a trial where I would have to carry out patch augmentation	4 (17)
***Typical use of patch (for those currently using a patch)* (N = *11*)**	
Bridge	6 (55)
On-lay	5 (45)
***Subscapularis state considered* (N = *20*)[a]**	
Yes	11 (55)
No	9 (45)

a Responses are reported for those ($n = 20$) who indicated that they would consider using a patch in a trial setting.

not consider using them in a trial setting. Responses from the four surgeons unwilling to use a patch in a trial have been excluded from the analysis. How the surgeons used a patch varied: six out of the 11 surgeons used patches as a bridge to fill a persistent defect after a standard repair and five used it as on-lay to reinforce a standard repair.

Among the 20 surgeons, there was a division of opinion related to the question on whether or not the state of the subscapularis muscle would affect their decision to use a patch, with 11 (55%) stating yes and 9 (45%) stating no. Comments related to these answers indicated that some surgeons would use a patch only if the subscapularis was intact or repairable, whereas others would make the decision based on other patient characteristics. Furthermore, some stated that they would never consider the state of the subscapularis when making a decision to use a patch.

Surgeons were asked to consider which patients they would be prepared to randomise in a number of given scenarios. The first scenario proposed a two-arm study, comparing RCR plus a patch with a cuff repair with no patch. The patient characteristics for consideration within this design included patients with medium, large or massive tears, patients having revision surgery, patients aged between 50 and 60 years, 60 and 70 years, 70 and 80 years and those aged ≥ 80 years. The second scenario proposed a three-arm study, comparing a standard RCR plus a specific patch (patch A) with a standard RCR plus a different patch (Patch B) versus a standard RCR with no patch. The same patient characteristic options were given as for the two-arm trial (*Table 10*). Surgeons had the option of indicating if they would not randomise any patients into either study.

Large and massive tears were the most popular tear size group in both trial scenarios, with $> 50\%$ of surgeons opting for these patient groups to be included in a study. Revision surgery would also be considered within a trial patient population. Patients aged between 50 and 70 years make up the most common age range, with patients aged > 80 years being the less favoured to be included in a trial.

Further questions were asked about specific patient characteristics that surgeons felt should be excluded from a trial of patch-augmented RCR surgery. These included what degree of muscle atrophy would need to be present to consider exclusion. The grading of atrophy was based on the Goutallier Classification.[115] Surgeons were also asked to consider the degree of glenohumeral OA that would determine patient exclusion. This grading was based on the Kellgren–Lawrence Classification.[116,117] The presence of cuff arthropathy was also considered in this section of the survey.

TABLE 10 Surgeon triallists' willingness to randomise patient characteristics

Category	Two-arm trial scenario, *n* (%)	Three-arm trial scenario, *n* (%)
N	24 (100)	24 (100)
Medium tear	9 (37)	9 (39)
Large tear	17 (71)	15 (65)
Massive tear	15 (62)	14 (61)
Revision surgery	14 (58)	14 (61)
50–60 years	19 (79)	18 (78)
60–70 years	17 (71)	16 (70)
70–80 years	9 (37)	8 (35)
≥ 80 years	1 (4)	1 (4)
Would not randomise any patients into such a study	4 (17)	4 (17)

Of the responses, 50% indicated the exclusion of patients with grade 3 and 4 atrophy (> 50% of fatty muscle atrophy). However, additional comments provided in this question implied that patients with a degree of atrophy could be included if other characteristics indicated patch use. Three of the responses indicated that atrophy was not an important consideration for patches (*Table 11*). Over half of the surgeons felt that patients with glenohumeral OA greater than grade 2 should be excluded from a trial of patch use. The presence of cuff arthropathy provided a definitive response as 86% of surgeons indicated that these patients should be excluded from a trial assessing patches in rotator cuff surgery. Additional comments suggested that surgeons would opt for a reverse total shoulder replacement procedure on patients with cuff arthropathy.

TABLE 11 Surgeon triallists' exclusion criteria for a RCT

Exclusion criteria category	*n* (%)
Degree of atrophy ($N = 20$)	
Grade 0 – normal muscle	1 (5)
Grade 1 – some fatty streaks	2 (10)
Grade 2 – < 50% fatty muscle atrophy	0 (0)
Grade 3 – 50% fatty muscle atrophy	1 (5)
Grade 4 – > 50% fatty muscle atrophy	9 (45)
Not answered	7 (35)
Degree of glenohumeral OA present ($N = 20$)	
Grade 0 – no radiographic evidence of OA	2 (10)
Grade 1 – marginal osteophytes of doubtful importance	1 (5)
Grade 2 – definite osteophytes	7 (35)
Grade 3 – moderate joint space narrowing, subchondral sclerosis	8 (40)
Grade 4 – severe joint space narrowing, cyst formation	2 (10)
Presence of cuff arthropathy ($N = 20$)	
Yes	17 (86)
No	3 (14)

Responses are reported for those ($n = 20$) who indicated that they would consider using a patch in a trial setting.

Following on from patient characteristics that surgeons felt should be excluded from the trial, participants were asked questions related to the practical elements involved in designing a trial (*Table 12*). Surgeons were varied in their responses about the timing of randomisation: prior to the day of surgery was favoured by 35% and a further 40% opted for during the operation, once the shoulder pathology had been assessed. The remainder mostly favoured either in the anaesthetic room (5%) or at the start of the operation (15%). One surgeon (5%) suggested that randomisation should be completed at the time that patients are listed for surgery. There were practical reasons listed in the additional comments for wanting randomisation to be completed prior to the day of surgery. Most of the surgeons (85%) felt that an agreed standardised repair technique was optimal for a trial of this nature. However, they also indicated that uptake of this may be dependent on what the technique involves. Use of a specific brand of patch was supported by 75% of surgeons. There was 95% support to standardise postoperative rehabilitation in a trial. There was a fairly even split between opinions on the length of follow-up, with 50% of surgeons suggesting that 12 months would be sufficient and another 40% believing that 24 months would be more appropriate.

A few respondents stated that they were currently involved in or planning a study on patch augmentation.

TABLE 12 Surgeon triallists' perspectives on practical elements of trial design

Category	*n* (%)
Timing of randomisation	
Prior to the day of surgery (e.g. pre-surgery assessment)	7 (35)
In the anaesthetic room	1 (5)
In the operating room (at the start of the operation)	3 (15)
In the operating room (once the shoulder pathology has been assessed)	8 (40)
Other	1 (5)
Standardised repair technique	
Use an agreed standardised repair technique	17 (85)
I would not want to use a standardised repair technique, I prefer to use my own repair technique	2 (10)
Not answered	1 (5)
Use of a specific brand of patch	
Yes	15 (75)
No	4 (20)
Not answered	1 (5)
Standardised postoperative rehabilitation regime	
Yes	19 (95)
No	0
Not answered	1 (5)
Length of follow-up to assess the outcome of the operation	
6 months	0
12 months	10 (50)
24 months	8 (40)
Other	1 (5)
Not answered	1 (5)

Responses are reported for those ($n = 20$) who indicated that they would consider using a patch in a trial setting.

Discussion

Two surveys were conducted with surgeons to inform the acceptability and feasibility of a RCT of patch-augmented rotator cuff surgery. The findings of the two surveys are discussed in turn below.

The BESS membership survey demonstrated a number of insights into surgeons' use of and opinions around augmentation of RCRs. It also began to explore the acceptability of a RCT in this area.

Overall, 58% of surgeons had used patches, with 41% of all surgeons using these in the last 6 months. Although responders may not be fully representative of the wider surgical community, this survey suggests that a there was a substantial uptake of patch-augmented repair. The majority of surgeons had used the GRAFTJACKET device, which currently has the highest number of studies published to support its efficacy (see *Chapter 2*). This is consistent with the fact that the evidence base and product usability were cited as the most influential factors when choosing a device for augmented repair. However, there was a broad range of other patches (12 in total) currently in use. Reviews of the evidence have shown that, for many of these patches, there is very limited robust clinical data for surgeons to base their decisions on. There remains a clear need for more rigorous evaluation of current and future patches in a randomised trial. It would also appear to be a good time to undertake a RCT assessing the clinical effectiveness and cost-effectiveness of patch use, before use and acceptance of patches becomes so widespread as to become prohibitive. The difficulty in getting the timing right has been well articulated by Buxton's law,[48] whereby it is always too early for such an evaluation, until it is suddenly too late.

Many respondents commented that data on patch evidence and safety are needed. This is not surprising given the highly publicised adverse reactions of biomaterials, such as metal-on-metal hip replacements[118] and vaginal mesh implants,[119] as well as the adverse reactions resulting in the market withdrawal of the Restore patch.[35,54]

There was a preference for arthroscopic interventions in those surveyed from university teaching hospitals and district general hospitals, which is in keeping with the general trends towards greater arthroscopic intervention. Surgeons who undertook RCR arthroscopically or reported a mixed open/arthroscopic practice were more likely to use patch augmentation, which might be reflective of a greater willingness among this cohort to adopt new technologies.

The survey also shed light on the relationship between tear size and use of an augmented RCR. Patches were more likely to be considered for use in large and massive, rather than small or medium, tears. The driving force behind this dichotomy remains unclear. It may be that large and massive tears are viewed among surgeons as requiring the most supportive healing environment. However, small tears in patients aged $\geq$ 80 years are predicted to have a similar chance of repair failure as massive tears in patients aged 50 years. Given that symptom resolution is linked with repair success, the use of patch augmentation with small to medium tears may gain traction in the future.[5]

Involving surgeons in the early stages of trial design is integral to the participation and success of a trial.[120] The surgeon triallist survey allowed the surgical triallists to have an input into the trial question and protocol design. Involving them in this way allows the surgeon community to embrace research and provide evidence for their practices and for changing practices.[121] McCulloch *et al.*[122] state that surgeons tend to rush to learn new procedures or techniques, apparently not questioning the possible effects on patient care. The surgeons responding to this survey appeared more conservative, and their answers indicated that further exploration and discussion was required before 'rushing' forward to fully utilise patches in their practice. Furthermore, this perhaps is reflected in the surgeons' positive response regarding potential participation in a RCT in the BESS membership survey, and through the proportion of triallist surgeons stating their willingness to conform to standard practice for a trial to provide clinically relevant evidence. Initially, half of the BESS respondents being willing to participate in a RCT may not seem an impressive number, particularly after considering the potential for responders

being unrepresentative. However, the reality is that the number of surgeons who have been involved in a RCT of shoulder surgery in the past has been a very small proportion of the overall surgical community, making this number seem much better.

Patient characteristics and indications for surgery have not been well described in previous research of RCR.[123] Issues such as difficulties with daily function, failure of non-operative treatment, a history of night pain, age and tear size have been widely described as indications of repair failure.[2,15,123] Patients with a degree of muscle atrophy and with glenohumeral OA present have often not been included in previous studies looking at the integrity of RCR surgery. These characteristics are already perceived as an indication of failed surgical repair.[15,124]

Responses to the triallist survey suggested that surgeons would be unwilling to augment RCRs on patients with the above characteristics in a two- or three-arm trial setting; however, there was some discrepancy among these answers. It could be that the range of responses reflect a misreading of the question, meaning that some participants answered with 'patients to be included' rather than 'patients to be excluded'. If this was not the case, the surgeons' answers could vary according to their assumption of tear size or repair technique. Perceived discrepancy was increased by some of the surgeons who ticked more than one response. In this case, the least amount of atrophy and OA selected as a response was reported in *Table 11*, under the assumption that any higher levels would also be excluded. Seven participants did not answer this question, indicating in the free-text box that this presentation is not important to them when deciding whether or not to use a patch. Not all surgeons use or refer to the Goutallier classifications,[115,125] and a recent paper[126] suggests that atrophy is reversible and, therefore, the classification may be seen irrelevant.

There was documented variation in how surgeons use a patch in RCR surgery. The technique of on-lay or bridging needs further exploration in a trial setting and may be determined by other factors. The systematic review conducted as part of this study suggests that the different techniques reflect different patient populations and characteristics, for example the use of bridging may be for larger or revision tears. This systematic review also highlighted the differences in the terminology and the meaning of the different techniques. How a patch is used and what patient population it will be used in will raise challenges when confirming the PICO elements of a trial. This will require further exploration in the later stages of this project.

The responses to the questions on practical aspects of trial design and set-up appeared to provide more cohesive results. However, there were still some conditions to full agreements. For some surgeons, the uptake of an agreed standardised repair technique would be dependent on the components involved. Surgeons generally undertake operations differently and have differing levels of skill that can influence the procedure, meaning that standardisation of any surgical intervention may prove challenging.[127] This is especially the case for any pragmatic trial in an NHS setting, and any standardisation would require monitoring, which may be difficult to conduct and report on.

The timing of randomisation showed great variation in surgeon perspective. Ideally, as some of the responses indicated, intervention should be conducted as soon after randomisation as possible.[128] However, the comments in the survey indicated the need to consider the availability of resources and time needed to conduct surgery involving patches when agreeing the point of randomisation. For example, it may be that the theatre team need more preparation if a patch is to be used and the procedure may take longer. This issue will need further exploration as the trial design emerges.

Strengths and limitations of the surveys

As with all survey-based data collection, there is potential for a response bias. In addition, the survey options potentially limit the generalisability of the findings of this survey. The achieved response rate to the BESS membership survey was low, but not dissimilar to that achieved in similar surveys of clinical professional groups. It is also consistent with responses to other surveys sent to the BESS

surgical membership in the experience of the PARCS study team. BESS members, in particular those who are more likely to respond to this survey, are not necessarily representative of the wider upper-limb surgical community and may include more research-oriented surgeons. In this case, respondents may be more familiar with and supportive of patch use in RCR. Although steps were taken to ensure that there was anonymity, it is possible that respondents may have answered questions in a way that did not exactly reflect their personal beliefs. Few respondents were clearly not in favour of patch use. Moving forward, a wider range of upper-limb surgeons could be consulted to increase the robustness of studies such as this. The proportion who participated are probably more interested and perhaps more positive about the use of patches than the BESS surgical community as a whole.

The triallist survey sample was as expected (approximately 20 surgeons) and surgeons were invited personally, based on their previous experience in surgical trials. Their responses should not be taken as indicative of the surgical community as they were selected intentionally to be the subgroup of surgeons who would, in principle, be more likely to participate in a RCT. Furthermore, there may have been other research-active surgeons willing to participate but could not as they were unknown to the PARCS study team. This is a key limitation of the method. The survey was designed to be deliberately short and concise to keep surgeons engaged while also providing relevant data. Patient characteristics that indicate failure in standard RCR surgery could have been explored further in the surgeon triallist survey. Results suggest that surgeons would not be willing to conduct patch-augmented surgery on patients with muscle atrophy nor with glenohumeral OA present, yet it is unknown whether or not these patients would benefit from an augmented repair.

Conclusion

Despite the aforementioned limitations, there were a number of important findings from both of the surveys. It was clear that there are a substantial number of patches in clinical use across the NHS and that this includes patches of different types. Furthermore, a strong theme from the respondents was the lack of evidence to inform current practice, and the need for multicentre clinical trials. There was appetite to partake in a prospective RCT and emphasis that patches commonly used within the NHS (e.g. GRAFTJACKET) needed to be included. The general opinion was that more research is required to inform the use of patch augmentation, with a focus on assessing patient safety and efficacy. From the triallist survey, there was some agreement in the patient population and outcome timings, but what the final trial design incorporates remains uncertain. How a patch is used and at what point the decision is made to use one were also highlighted as questions requiring further exploration. The uncertainty around these aspects was taken forward into the consensus process.

Chapter 4 Focus groups

Introduction

Focus groups are widely used in health services research. They allow interactions between individuals, from which more information is generated than in individual interviews.[129] Focus groups enable participants to speak freely about their concerns and offer their views about the existing and proposed evaluation of a new approach to surgical treatment.[130,131] They are particularly useful for helping to identify issues that resonate with lay people and the public in matters of health care.[130,131]

Using a set of focus groups, our aim was to access a broad range of stakeholder views and opinions on the acceptability of the use of patches in the augmentation of RCR and the trial design options that may be used to test them. Themes and issues identified from the BESS survey (see *Chapter 3*) helped to form topics for discussion.[1]

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

- patients/public with current or previous rotator cuff problems (carers were also invited)
    - two focus groups, each conducted in a different region of the UK (Thames Valley and South Tees)
- regulatory body representatives, NHS managers, commissioners and other staff involved in surgical equipment procurement [e.g. members of research ethics committees and staff members from the local clinical research network (CRN) support service]
- representatives from industry.

Group A was considered to be the key stakeholder group. However, the introduction of patches in the NHS has implications for industry, regulatory approvals and NHS costs; therefore, it was relevant to include the views and opinions of groups B and C in the study.[1]

Where attending the same focus group was not practical, stakeholders were offered the possibility of individual or group interviews.

Methods

Potential participants were invited and recruited using various avenues according to the relevant stakeholder group(s).

Recruitment of patients and carers

Consultant orthopaedic surgeons (and PARCS investigators) based at the Nuffield Orthopaedic Centre in Oxford and the James Cook University Hospital in South Tees approached potential participants through their units. Patients had to meet the following inclusion criteria to be approached: willing and able to give informed consent for participation in the study; aged $\geq$ 18 years; have the ability to understand and communicate (read, speak, and write) in English at a level that permits effective

interaction; and have active or previous shoulder problems involving the rotator cuff. Patients were invited regardless of whether or not they had undergone surgery, and their carers were also invited if available. At each site, a balance of men and women, and of patients and carers, was sought. A convenience sampling approach for recruitment was used from the Oxford-based patient clinics. At South Tees, potential participants were identified from (1) a list of patients who had previously registered interest to be involved in future patient and public involvement (PPI) activity as part of the pre-grant submission PPI evaluation conducted for the PARCS study, (2) a list of patients who received treatment for rotator cuff in the past 3 years within the unit and (3) a small number identified by prospective convenience sampling of patients attending the investigator surgeons' outpatient clinic. Once identified, all participants were approached directly at their outpatient/physiotherapy appointments or via telephone by the PPI co-applicant at this site.

Those who responded positively and met the inclusion criteria were included in the PARCS study focus groups. Identification of potential participants continued until the target number of participants had been recruited (between four and eight participants per focus group).

Recruitment of other stakeholder groups

Representatives of regulatory bodies and industry were identified via local networks, approached and invited to participate directly. We also used snowballing as information was passed on to potential participants via professional acquaintances.[132]

Focus groups

Ahead of the focus group session, potential participants were provided with a study information sheet specifically tailored to their stakeholder group, describing the aim of the focus group and what to expect. Each focus group lasted around 2 hours, with a break for refreshments. The cost of travel was reimbursed, and participants were offered a shopping voucher to the value of £25 as a token of appreciation. Each participant was asked to personally sign and date a consent form, of which they were given a copy.

During each focus group session, the aims of the PARCS study, and focus groups specifically, were briefly introduced. Participants were asked to consider a number of key issues, scenarios or vignettes. These included 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, the most appropriate outcome measures, and the methods of data collection. The way in which this information was delivered was adapted according to participant group. For example, a more technical approach was used for the industry stakeholders. Participants were provided with the following definition of a patch: 'an implantable human, synthetic or animal material which is used with the aim of improving tissue healing and patient outcome'.

We also asked focus group participants to provide some basic background information about themselves (i.e. sex, age, relevant experience and previous treatments). This information was anonymous. Participants were provided with a plain opaque envelope in which to place the completed 'background information form'. They were asked to place this envelope into a box as they left.

The focus groups were facilitated by an appropriately trained member of the PARCS study team (NM). Discussions were audio-recorded and one or two observers (LK, JCC or CC) took notes to aid in the transcription of audio files and analysis. The resulting audio files and accompanying field notes were transcribed verbatim. Transcription was performed by an external transcription company. Any identifying information appearing in focus group transcripts was removed as soon as possible following transcription to minimise the risk of participant identification. The audio files and transcripts were encrypted for secure storage.

Analysis

The focus group transcripts were analysed by two members of the PARCS team (CC and JCC) using thematic analysis.[133] The following steps were followed:

1. Analysts familiarised themselves with the transcript.
2. One analyst (CC) initially coded the transcripts by hand, both deductively (guided by themes included in the focus group topic guides) and inductively (allowing unanticipated themes and subthemes to emerge). The first three transcripts were also independently coded by a second analyst (JCC). The codes were subsequently compared, discussed and agreed with the first analyst. The emphasis of the analysis was on the acceptability of the proposed trial and on factors that might influence such acceptability.
3. Analysts reviewed the coding and agreed a working thematic framework. This was applied to subsequent transcripts using QSR NVivo 10 software (QSR International, Warrington, UK) and evolved as analysis progressed. In accordance with the study design objectives, the themes were grouped into PICO elements, that is their relationship to patient population, intervention, control and/or outcome (including timing of measurements). The framework also included practical considerations to take forward.

The final thematic framework and its content were used to inform the questions posed in the triallist survey, which followed the focus groups (see *Chapter 3*).

Results

Focus group participants

A total of 24 people took part in the focus groups (*Table 13*). Thirteen participants were patients who had previously been treated in the NHS for their shoulder problem. Ten of the patients had undergone shoulder surgery. Five patients reported ongoing shoulder problems (of whom three had had surgery), whereas two reported that their problems had resolved (of whom one had had surgery). Two carers (partners) of patient representatives also participated.

TABLE 13 Focus group characteristics

Variable	Patients and carers	Industry	NHS Research Ethics Committee members	CRN representatives
Attendees	15	4 (from 3 companies)	2	3
Thames Valley region	7 (2 carers)		2	3
South Tees region	8			
Sex				
Female	4	1	1	3
Male	11	3	1	0
Age (years)				
46–55	2			
56–65	6			
66–75	7			

Views on patient population for a trial assessing patches in rotator cuff repair surgery

Patients and regulatory body representatives were eager to discuss which characteristics patients would need to be present for the patch to be a treatment option:

> *To me it's got to go on the size of the tear and how much discomfort they're getting because you can't treat everyone the same.*
>
> *P504 – patient, South Tees*

> *Would age be a big factor in this?*
>
> *P505 – patient, South Tees*

> *So, the surgery, the inclusion criteria, would you say that they've done everything possible, like physio?*
>
> *P401 – regulatory representative, Ethics*

Some patients felt that all patients having RCR surgery should be offered a patch:

> *. . . so you're going to get . . . you're getting a high percentage [of success] at the moment, 60% [success rate after standard RCR] as against 40% [re-tear rate after standard RCR], so you've already got that percentage of success so my argument is if you've got that surely anybody that's prepared to take the trial should just go for the patch . . .*
>
> *P101 – patient, Thames Valley*

> *It seems silly, like you said, why aren't they just using [patches] now, if they're using [patches] elsewhere in the body . . .*
>
> *P506 – patient, South Tees*

Other participants felt that the patient population needed to be more specific. Industry representatives were strong in their opinion that, for a patch's effectiveness to be assessed, confounding factors and certain patient characteristics should be excluded:

> *. . . in the end it's a clinical decision and also the patient, patient age, bone quality, tissue quality, smoker or not, again . . . keep them out of the way. Steroid abusers need them out the way as well.*
>
> *P203 – industry representative, company 2*

> *To me it's got to go on the size of the tear and how much discomfort they're getting because you can't treat everyone the same [each patient is different].*
>
> *P504 – patient, South Tees*

Patients' reactions to being hypothetically offered a patch were generally positive, as they focused on the idea that patches augment repairs and, therefore, 'can only be better' (P101 – patient, Thames Valley). Patients had a risk-seeking approach to manage their pain:

> *Can I go on your list first to have it done, please? (Addressing Investigator 3)*
>
> *P504 – patient, South Tees*

> *I mean it's not as if you're having a heart transplant or anything like that which you would discuss, or cancer, it's not is it, it's something which is just . . . you've got pain there and you know there's a relief, you can have an operation and the extra patches, yeah, let's go for it.*
>
> *P501 – patient, South Tees*

> *So something different [like patches] might just assist it.*
>
> *P103 – patient, Thames Valley*

However, there were also some cautious questions from the patient groups about what happens to the patch after the operation:

> *Does that stay in then, that patch, or not?*
>
> *P506 – patient, South Tees*

> *Are the patches likely to break down in compound over a period of time?*
>
> *P103 – carer, Thames Valley*

There were no apparent negative views towards using a patch in rotator cuff surgery. However, some patients expressed a preference for human-derived patches. One patient was concerned about the safety of animal-derived patches:

> *I would probably steer to one that comes from human beings . . . probably not cows and pig due to CJD [Creutzfeldt–Jakob disease] . . . foot and mouth because we don't really still understand those two diseases . . .*
>
> *P102 – patient, Thames Valley*

Views on potential interventions and controls in a trial assessing patches in rotator cuff repair surgery

Focus group participants had varying perspectives on what a trial intervention and control group should look like. The issue of randomisation was discussed, as were patch elements and types that may be used within a trial. These topics were then related to willingness, of both industry and patients, to participate in a trial.

Industry stakeholders had variable opinions on what a trial of patch use should look like. One recognised the need to provide an evidence base before progressing with patch development further:

> *I think [a patch A vs. patch B trial] is something a bit down the line isn't it, I think really we need to know that this [patch] works in the first place before you start enhancing it.*
>
> *P202 – industry representative, company 2*

Other industry representatives felt that current surgical practices had evolved further than this and that current trends needed to be represented in any study design involving the use of patches in rotator cuff surgery:

> *If clinical practice is moving onto augmentation already for these sorts of cuff tears, the question in the industry is who's got the best patch . . .*
>
> *P203 – industry representative, company 2*

> *I think [surgeons] would want to know which avenue to take as opposed to cuff versus patch as a broad thing, I think we'd want a little bit more than that, I think we're at that position now.*
>
> *P202 – industry representative, company 2*

There was also discussion among the patients about whether or not there was a need for a RCT at all, given the known failure rate of standard repair and widespread use of the patches in other parts of the body:

> *. . . why you're doing this research is basically because of the patches, so put the standard repair out of the window as far as I'm concerned and go right, we're doing nothing but patches here, that's all it's about.*
>
> *P501 – patient, South Tees*

> *If the normal process [standard repair] was only available and there was nothing else then I'd probably go down that [trial participation] route but because of listening to the percentages [40% failure rate for standard repairs] I still don't see the logic of having that [repair with no patch] as against the patch. Because you've moved on . . .*
>
> *P101 – patient, Thames Valley*

> *If you know the success rate of a patch on a certain [different] part of the body is 99% or whatever or 90% then you go, 'yeah, we can safely use that one as a guide'.*
>
> *P501 – patient, South Tees*

In line with their initial risk-seeking reaction to being hypothetically offered a patch, some patients said that they would seek to participate in a trial, regardless of what treatment they would potentially receive:

> *I'd go into trial to get rid of the pain, regardless of what they were going to do, I just have to have something done.*
>
> *P107 – patient, Thames Valley*

Excerpt from South Tees patient focus group:

> *If [it] was thought I'd have 50 : 50 chance of getting the patch or whatever even to have the normal surgery, I'd go for it.*
>
> *P506 – patient, South Tees*

> *Yeah, so would I.*
>
> *P504 – patient, South Tees*

> *Because it's something or nothing.*
>
> *P506 – patient, South Tees*

> *Yeah, yeah, you can't lose.*
>
> *P504 – patient, South Tees*

However, consistent with their positive reaction to the idea of being offered a patch, patients who had experienced numerous rounds of conservative treatment tended to dislike the concept of randomisation and the consequential risk that they may not receive a patch:

> *. . . [if] people decide to go for the trial they're not going to know which one they've had [patch or no patch]. I wouldn't even go down that route . . . If I had the patch I'm quite prepared to go down that route, but I'm not prepared to go down the route of I don't know what's happening.*
>
> *P101 – patient, Thames Valley*

The CRN discussions highlighted the importance of considering existing patch use at participating trusts when determining the content of the trial arms:

> *So if you standardise and say you have to use, say, these five [patches] and that's not what they're using then there could be a sourcing issue.*
>
> *P302 – regulatory representative, CRN*

> *Whatever they use as part of standard care if they're just using that and they're just taking another one [patch] off the shelf it'll go through [local trust approvals] a lot easier.*
>
> *P303 – regulatory representative, CRN*

The willingness of those in the industry to offer their products to a potential trial of patch augmentation was complex. Their involvement would depend on all the PICO elements that were proposed and what the definition of a patch was within the trial. The type of repair products used during the cuff repair was flagged up as an important element by one member of the industry focus group, in this case the anchors and tape (to anchor down the tendon) used in the operation:

> *There are just too many variables out of our control and potentially out of your control as in the ideal study, playing devil's advocate, so the ideal study would be [surgeons] all have to use [company Z] anchors with tape 'cause it's best [general laughter] with their [company Z] artificial patch or [company Z] dermal graft and that's the study, that's easy.*
>
> *P203 – industry representative, company 2*

Manufacturing processes, rehabilitation guidelines and the purpose of a patch would also need to be considered for industry representatives to participate and willingly put forward their product to be assessed:

> *The way [patches are] kind of weaved and that kind of thing all affects its strength and how it works, how it then heals in the patient that kind of thing . . . so we probably wouldn't want ours bunched in with [other patches in one treatment arm] . . .*
>
> *P202 – industry representative, company 2*

The industry group highlighted the importance of declaring conflicts of interest and of ensuring that there was transparency of involvement in any trial.

The regulatory body representatives also expressed some concerns about the components of a patch to be used within a trial and how these could exclude some communities within an otherwise eligible patient population.

Excerpt from regulatory representatives' discussion:

> *That's going to raise some practical difficulties though, because if you're at a centre and they are using patches that have got animal products in, and then they have a patient consent to take part in a study, but then they don't want one of those particular patches, will you, the study, then provide [non-animal derived] patches to that centre? . . . Or you exclude that patient.*
>
> *P401 – regulatory representative, ethics*

> *[Excluding those patients] can be difficult. For instance, we've had studies where they use a standardised fatty diet, which contains bacon, and they've actually excluded anyone who won't eat bacon. . . . Our [ethics] committee did actually have an issue with that, because, obviously, that excludes all Jewish people and Muslim people. So, then we were saying, 'Well, hang on, are you denying access to clinical trials for taking part in research to particular ethnic or religious groups?' It's just something that, if that's the direction you're going to go down, you just have to be prepared to have, to make, that argument.*
>
> *P402 – regulatory representative, ethics*

Views on the outcomes to explore in a trial assessing patches in rotator cuff repair surgery

Stakeholder opinions on outcomes of importance appeared to stem from their own experiences and knowledge about treatment and products. Patients highlighted that pain was the most important issue to address with treatment, regardless of what that treatment involved:

> *That's the bottom line . . . that pain is the bottom line and that's it.*
>
> *P501 – patient, South Tees*

If I didn't have the pain that I've got but I had the restricted movement I could probably live with that, it's living with the pain.

P506 – patient, South Tees

Certainly pain relief. I think that's the main issue with all these things because how much pain you can tolerate . . .

P101 – patient, Thames Valley

Other outcomes that were important to patients included sleep and being able to perform everyday activities.

. . . my pain was different actually because it manifested itself at night, I couldn't sleep.

P104 – patient, Thames Valley

No, I was the same, I didn't sleep for about 6 months.

P107 – patient, Thames Valley

During the day, for some reason, it didn't really irk me but at night it really was a problem.

P104 – patient, Thames Valley

Mine was . . . about 6 months I didn't sleep. Because the pain was so bad.

P107 – patient, Thames Valley

You might be doing things around the house like women do and I know men do as well, and you think 'oh, I'll just go and do that because it's all right' and you do it and you think, 'ooh, I shouldn't have done that', that sort of thing. It catches you off the cuff . . .

P102 – patient, Thames Valley

Patients, along with industry representatives, discussed the importance of preventing further surgery. With the current re-tear data in mind (40% re-tear rate following standard rotator cuff surgery), there was the feeling that treatment needed to be definitive and not used as a back-up if the initial repair failed:[2]

Safety seat belts, maybe it's overkill but the patient wants one procedure not two. [In discussion about why a patch would be used.]

P203 – industry representative, company 2

I think [patches] should be used from the start.

P506 – patient, South Tees

If it goes again how many times can you actually have that repaired the ordinary way before you end up with so much scar tissue that it's not going to happen at all? As against if you have the patch you've got a higher rate of success and you may not ever have to have it done again . . .

P101 – patient, Thames Valley

Outcome measurement was also discussed in some focus groups. Potential methods ranged from radiological imaging ('you're not going to get a second look' – P203 industry representative) to patient-reported questionnaires, safety measurements and reporting of failure (i.e. further surgery). Regulatory stakeholders highlighted the importance of product safety monitoring and minimising the burden of follow-up for patients:

Keep the study as simple as possible, so that the burden on the patient is as little as it can be. So, things like biopsies, if that's what you need to be able to answer your outcomes, then do the biopsies and explain it, but if you don't need to do the biopsies to answer your question, then I would say consider

them very carefully. Also, I don't know if we addressed how painful they are. If you can do something that's quick and painless, then that's not really a burden to the patient. If the biopsies are going to be as painful as, like, a lumbar puncture, then make sure you've got a really, really good reason for doing it.

P402 – regulatory representative, ethics

So, the key thing I've got is about safety and monitoring, because whatever patch you do, or whatever CE [Conformité Européene] mark, how do they currently monitor whether it's doing the job it's meant to be? Obviously, there's subjective [indicators], where you fill out questionnaires . . . but showing that the patch hasn't moved or slipped, do you do imaging?

P401 – regulatory representative, ethics

Practical considerations when designing a trial assessing patches in rotator cuff repair surgery

Practical elements of trial design and trial set-up were discussed within the PICO themes above. Participants also suggested other considerations in trial design and set-up, including what information about patches and treatment should be presented to patients when informing them about the trial.

The patient and the regulatory focus groups raised questions about the type of information patients may seek about patches, how the patch is physically inserted into the shoulder and what other research is being carried out:

Have you actually tested the patches on anybody else yet or . . . ?

P101 – patient, Thames Valley

Are the patches likely to break down in compound over a period of time?

P104 – patient, Thames Valley

Is your research part of a worldwide programme or is it just part of [named academic institution]?

P102 – patient, Thames Valley

I think you could say that there's different patches, and then tell them to speak to their doctor about which one they're likely to get at their centre.

P402 – regulatory representative, ethics

Patients also raised some questions about the safety that would need to be considered when developing patient information. This included the permanency and ease of removal of a patch:

Does that stay in then, that patch, or not?

P506 – patient, South Tees

If you have the patch done and it really gives you hell afterwards is it easy enough to get out again?

P105 – patient, Thames Valley

Discussion

The focus groups highlighted many elements to consider in the design of a trial assessing patches in rotator cuff tear surgery. Stakeholders held differing views as to the patient population that would be suitable for such a trial. Those patients who had undergone numerous rounds of treatment for their rotator cuff felt that the patch should be readily available to all patients having RCR surgery. Although a patch-augmented approach to repair was also advocated by industry, they would be more selective about the patients who would receive a patch to demonstrate efficacy. This is indicative of industry trends in clinical research.[134,135] However, a narrow selection of patients may also be needed to support

the use of a product for a particular patient population. This correlates with the claim from Suvarna[136] that industry need to not focus on which product is best, but more on which patients will benefit more from the product. Industry involvement in a trial would need further discussion when a trial design has been finalised.

Views on intervention and control arms in a proposed trial also varied within stakeholder groups. Some emphasised the need to provide evidence for best practice and felt that the trial question should be 'does a repair with a patch work better than a repair without a patch?'. Other stakeholders felt that a 'no patch' control arm was unnecessary and would not serve to advance treatment. However, this strategy would contradict the current drive to provide evidence for practice as early as possible.[128] Moving forward to compare a patch with another patch could be seen as unethical by stakeholders who believe that there first needs to be evidence of effectiveness of patch use in general. As evident in the systematic review conducted for this project (see *Chapter 2*), the evidence for any patch use in RCR surgery in itself is not yet sufficient to make clinical practice recommendations, even in fairly broad terms.

The chosen intervention and control arms, and the availability (or not) of a patch within usual care, would also seemingly affect patients' willingness to participate and be randomised. In general, patients appeared very keen to receive a patch, believing that this should enhance repair. A recent survey of surgical trials in head and neck oncology revealed that the top two barriers to participant recruitment were 'patients' consent refusal because of expressed treatment preference' and 'patients' consent refusal owing to aversion to randomisation'.[137] Our findings suggest that a RCT with a 'no patch' control, in a setting where patches are available as part of usual care, might struggle to recruit participants. This chimes with a qualitative study by Harrop *et al.*,[138] which found that patients primarily declined to participate in a surgical trial because they had preferences for a particular treatment arm (a new technology) and in usual practice could choose which surgical method they would be given. The authors concluded that for trials in which the 'new technology' is available to patients, there will probably be difficulties with recruitment. Research in this area by the QUINTET group suggests that patient preferences can be explored during recruitment, and need not always hinder recruitment.[139]

Randomisation is a well-documented contentious issue when recruiting patients to clinical research.[140] Patients often do not recognise the need for randomisation and, therefore, decline to participate in trials.[139] In any trial, details need to be presented to potential patient participants in an unbiased manner. Patient preferences also need to be explored to assess what these are based on and to ensure that patients entering a trial understand what will happen and why.[139]

Safety issues were discussed in all groups; however, these did not appear to be major concerns. The regulatory representatives advocated for the provision of full, appropriate patient information and safety monitoring. Patients, despite the recognition of recent media coverage on implants and an understanding of the risk involved in having a patch used in their shoulder, were overwhelmingly positive about patch use.[118,119] The basis of this preference seemed largely because of the severity of symptoms experienced and the hope that a patch would prevent the need for further treatment. Bower *et al.*[141] state that beliefs like this are based on 'personal subjective expectancies', when patients believe that they are particularly suited to an intervention that current evidence implies it may not be beneficial. Patients may also believe that procedures considered 'new' are more effective.[142]

Strengths and limitations

This qualitative study enabled us to elicit and understand the views of a broad range of stakeholders, including patients with experience of shoulder problems in northern and southern England. This would not have been possible through the use of crude surveys. The focus group participants included a balanced mix of men and women, and the patients had varied experiences of shoulder surgery (no surgery, surgery without a patch and surgery with a patch). The participation of industry representatives was a strength of this study, providing an insight into product development and use that is not often available to people outside the clinical setting.

However, because of the time-limited nature of the focus groups, we were unable to explore some complex issues in more depth. For example, the circumstances under which patients would or would not be willing to take part in a RCT of patch-augmented surgery were touched on but were not exhaustively investigated. The study team acknowledge that this could be an issue and will review it further during the design of recruitment and training processes in a definitive trial. Participation in the focus groups depended on patients' ability and willingness to travel to NHS sites outside routine appointments and on a weekday, potentially excluding those with daytime commitments or lacking transportation. It is possible that focus groups held at a community venue, at a weekend or in a different part of the UK may have resulted in a wider range of views being captured. The semistructured discussions with regulatory body representatives (CRN and ethics committee members) would have ideally included more participants. However, there were challenges in identifying appropriate people who were working in regulatory bodies, such as the Medicines and Healthcare products Regulatory Authority. The study team were also unable to organise a discussion with people who work in procurement in the NHS.

Conclusion

Overall, there was general support for patch use in RCR surgery from all stakeholders who participated in the focus groups. There was acknowledgement of the risk involved in receiving an implant such as the patch, and advocacy for product safety monitoring during the trial. However, there was some discrepancy among stakeholders about what the patient population, intervention and control arms of the trial should be. Patients may be unwilling to participate in a trial with a 'no patch' control arm if access to a patch is available within routine care. Improvement in pain and function and preventing further treatment were important outcomes identified in the focus groups. How and when these would be measured in a trial needs further exploration. The uncertainties and further questions that emerged from the focus groups were used to inform the surgeon triallist survey (see *Chapter 3*) that followed. These included (1) who should have a patch, and how are patches used by surgeons? and (2) what could a patch be compared with within a trial?

Chapter 5 Consensus process

Introduction

This chapter reports the methods and findings of stages 5 (Delphi study) and 6 (consensus meeting and finalising) of the PARCS feasibility study. These two stages were intentionally designed to complement and link with each other, with the Delphi study leading into the consensus meeting (*Figure 9*).[1] Details on the methodology and implementation of the two stages are given below.

Methods

Stage 5: Delphi study

A Delphi study to develop a consensus on the best way to design a clinical trial of patch-augmented rotator cuff surgery was conducted. 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.[143] It is a well-known and increasingly common method used in the clinical setting to establish a consensus.[130,143,144] A multiple-stage online Delphi survey consisting of at least two but no more than three rounds was conducted. The surveys were developed and conducted online.

Participants involved in stages 2–4 of the PARCS study were invited to take part in stage 5, according to stakeholder group.

Given the nature of the study, there has been no formal sample size calculation, but around 50–80 responses were originally anticipated.[1] There are generally no accepted guidelines for the optimal sample size needed to achieve consensus in Delphi studies.[145] This sample size was based on previous experience of conducting this type of survey and anticipated attrition rates at each round. Substantial loss from the initial to the final round is not unusual.[144,146]

All participants invited into the Delphi survey had been involved in earlier stages of the project. The Delphi study proposed different options for elements of RCT design. The aim of this was to help reach a degree of agreement to take forward to the final consensus meeting. Findings from stages 1–4 were used to determine the trial design elements to be included in the first round of the Delphi study.

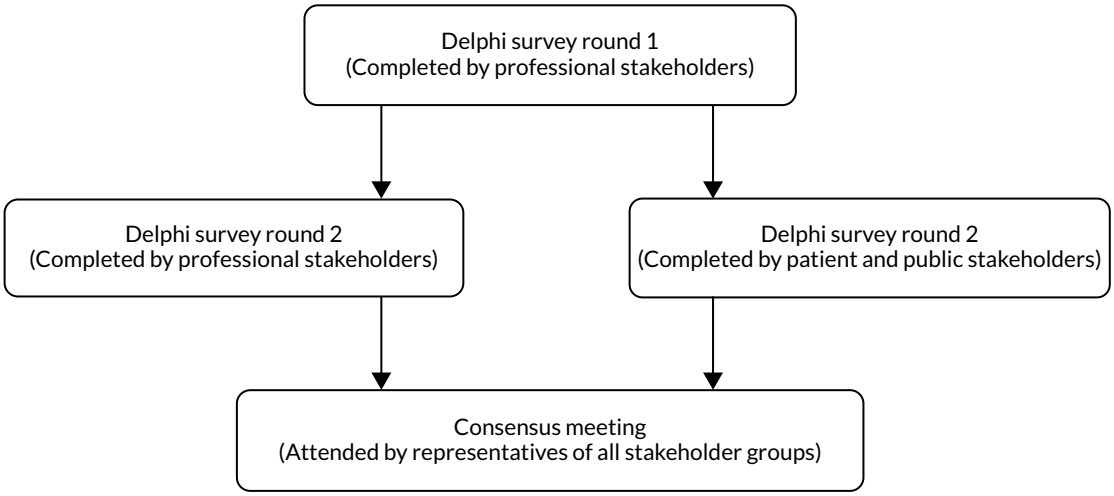


FIGURE 9 Interaction between the Delphi study and the consensus meeting.

Initially it was intended for all stakeholders to take part in both rounds. Based on feedback received from the patient representatives on the project team, the initial round was sent to the non-patient stakeholders only (i.e. surgeons, physiotherapists, industry and researchers). This was because of concern that the initial round would be too ambiguous and would be unfair to the individual to assess. Patients were involved in the second round only (a third round was not anticipated to be necessary once the initial round had been outlined). Two versions of the second-stage survey were used, one for patient and public stakeholders and one for professional stakeholders (e.g. surgeons and researchers). The patient and public version had a subset of the full set of questions that were most pertinent to this stakeholder group and were presented using more accessible language and avoiding, as far as possible, technical terminology.

An e-mail was sent to each participant containing a personalised link that enabled access for convenient survey completion. For a subset of potential participants' paper copies were sent as per the participants' preference, or a generic link was sent to a specific group of stakeholders.

During completion of the first round, survey participants were asked their stakeholder group and their place of work (professional stakeholders only). Data were extracted to Microsoft Excel and summarised for data analysis.

Participants were presented in the survey with proposed trial design elements (e.g. choice of two- or three-arm trial design, eligibility criteria for participation and information on the timing of the outcome data collection) and asked to score agreement with each using a 1–5 scale, where 1 represents complete disagreement and 5 represents complete agreement. A 'do not know/not relevant' option was provided as applicable. Participants were given the opportunity to comment further in free-text boxes. The aim was to allow the justification of any answers and the communication of new or proposed adjustments to the design elements. No new elements were suggested by participants in round 1 of the Delphi survey, although a number of the existing ones were revised.

For each section on the second round Delphi study, a summary of the findings from the previous round was offered. Participants then scored their agreement on each design element. The final set of proposals, areas of provisional consensus and remaining disagreement and uncertainty were then taken forward to the consensus meeting in stage 6 and used as the basis for discussion.

Where necessary, in both rounds of the Delphi survey non-responders received a maximum of two reminder messages. The final reminders contained a specific deadline for survey closure.[147] Each survey took approximately 15 minutes to complete. Scores (range 1–5) from each round were calculated as a percentage of the total responses. Consensus for a proposed design element was defined as > 70% of responses scoring the element 4 or 5, and no more than 15% of responses scoring the element one. Median and ranges were also produced for the scores. We explored similarities and differences across stakeholder groups. Textual responses were summarised narratively.

Stage 6: consensus meeting

Findings from stages 1–5 were fed into, and informed the structure of, a 2-day face-to-face consensus meeting. This meeting sought to agree on an acceptable and feasible trial design for a definitive RCT to assess the clinical effectiveness and cost-effectiveness of a patch to augment surgical RCR. A range of stakeholders were involved, including surgeons, triallists and patient and public representatives, who took part in stages 2–5 of the study. An independent academic surgeon was invited to chairperson the meeting. Participants were selected for invite based on their perspectives and experience to ensure that there was a variety or representation. For example, surgeons who do currently use patches to augment RCR were invited along with those who would be potentially willing to do so for a trial. To ensure that a robust decision was made, approximately 30 stakeholders were invited to participate.[1]

Ahead of the consensus meeting, participants were sent a proposal of a trial scenario for consideration, based on the results from the Delphi study. Patient and public representatives were reimbursed for

expenses and compensated for their time.[148] The meeting was structured to ensure that key areas of uncertainty and disagreement were reviewed and discussed. Consensus on key elements of the trial design was sought, namely patient eligibility, intervention and control definitions, surgeon requirements, outcomes and target difference. Previous stages informed draft guidance, options and recommendations for a RCT assessing patch-augmented rotator cuff surgery. A post-meeting report was drafted and circulated to participants for their review and comments. The report included details of the key design decisions made at the meeting with points for clarification.

Results

Stage 5: Delphi study

Twenty-nine out of the 43 (67%) individuals who were invited to take part in the Delphi study took part: 18 surgeons, two industry representatives, four physiotherapists, two medical researchers and three patient representatives. *Table 14* gives a breakdown of the groups and the location of work for the participants. Round 1 had 23 responses and round 2 had 24, including three patient participants. Findings from the two rounds are presented in turn below.

Round 1

In the first round of the Delphi survey, non-patient stakeholders completed questions that covered their stakeholder group and place of work, in addition to asking about agreement related to patient eligibility, surgical approach, patch use, trial design and follow-up. Patient participants did not take part in this round. Findings from round 1 are summarised in *Table 15*, in which the nature of question is also given along with a breakdown by response.

TABLE 14 Delphi study participant characteristics

Category	*n* (%)
Stakeholder type	
Surgeons	18 (62)
Physiotherapists	4 (14)
Project team	2 (7)
Industry	2 (7)
Patients	3 (10)
Place of work	
District general hospital	5 (17)
Teaching hospital	9 (31)
Other	2 (7)
University	1 (3)
Private hospital	1 (3)
Commercial company	2 (7)
District general hospital, private hospital	2 (7)
District general hospital, teaching hospital, private hospital	1 (3)
Teaching hospital, private hospital	2 (7)
Teaching hospital, university	1 (3)
N/A	3 (10)

N/A, not applicable.

TABLE 15 Delphi study round 1 responses

Proposal	Responses, *n* (%)					
	Completely agree	Somewhat agree	Neutral	Somewhat disagree	Completely disagree	Do not know/not relevant to me
Patient eligibility						
No clinically significant OA present (e.g. patients with Kellgren–Lawrence Classifications grades 3 and 4 will be excluded)	16 (70)	4 (17)	1 (4)	0 (0)	0 (0)	2 (9)
< 50% muscle atrophy present (patients with ≥ 50% will be excluded)	2 (9)	9 (39)	3 (13)	5 (22)	2 (9)	2 (9)
Medium, large and massive tears (patients with small tears will be excluded)	13 (57)	8 (35)	0 (0)	1 (4)	0 (0)	1 (4)
Primary repairs only (patients with re-tears/revisions will be excluded)	9 (39)	6 (26)	2 (9)	3 (13)	1 (4)	2 (9)
Patients aged < 50 years	8 (35)	5 (22)	3 (13)	1 (4)	5 (22)	1 (4)
Patients aged 50–70 years	16 (70)	5 (22)	1 (4)	0 (0)	1 (4)	0 (0)
Patients aged > 70 years	5 (22)	3 (13)	6 (26)	5 (22)	4 (17)	0 (0)
Patients with other shoulder conditions, not just rotator cuff problems, that affect their muscles, joints, bones, tendons, etc. (e.g. OA)	0 (0)	2 (9)	4 (17)	3 (13)	13 (57)	1 (4)
Surgical approach						
Use on-lay approach only, in which a patch overlies a successful primary repair	5 (22)	4 (17)	4 (17)	2 (9)	2 (9)	6 (26)
Use bridge approach only, used to fill a residual defect for tears that cannot be repaired at or near their anatomical insertion site	5 (22)	2 (9)	1 (4)	5 (22)	4 (17)	6 (26)
Depends on patient characteristics, allow the operating surgeon to vary the approach depending on the patient in front of them	9 (39)	1 (4)	3 (13)	3 (13)	2 (9)	5 (22)
Patch use						
Patches made from animal products	6 (26)	3 (13)	2 (9)	5 (22)	3 (13)	4 (17)
Synthetic patches (e.g. made from plastic type of material)	8 (35)	3 (13)	2 (9)	2 (9)	4 (17)	4 (17)
Allograft patches (made from another human's tissue)	11 (48)	6 (26)	2 (9)	0 (0)	1 (4)	3 (3)
Autograft patches (made from the patient's own tissue)	10 (43)	2 (9)	2 (9)	1 (4)	4 (17)	4 (17)
Trial design						
Randomised trial of standard repair with a patch vs. standard repair with no patch	11 (48)	6 (26)	3 (13)	2 (9)	1 (4)	N/A
Randomised trial of standard repair with patch A vs. standard repair with patch B vs. standard repair alone	7 (30)	6 (26)	4 (17)	2 (9)	4 (17)	N/A

The level of agreement with the proposed eligibility criteria varied substantially. For example, the number in either complete or somewhat agreement ranged from 20 (87%) to 11 (48%) for the OA and the muscle atrophy criterion, respectively. Thirteen comments were made, all of which suggested possible modifications (some mutually exclusive of others). Neither the exclusion of OA nor the exclusion of other shoulder conditions was raised in these comments, suggesting that these were not the likely source of disagreement. Specific comments addressed age, although four of the five commenting on this noted uncertainty about the specific age limit that might be used. One respondent commented that they would not repair a 'massive tear in over 70s'. Two commented on muscle atrophy, questioning its value as an eligibility criterion, and one surgeon noted that they always used a patch in a revision RCR operation.

When asked about the surgical approach when using a patch, there was general approval for on-lay use once the primary repair had been successfully completed (39% agreed vs. 18% disagreed). Use of bridging was supported less, with more disagreement than agreement (31% agreed vs. 39% disagreed). A substantial number stated that this topic was not relevant to them, of whom all except one were not surgeons (26%). Varying the approach in accordance with patient characteristics was mostly agreed with (43%), although there was still sizeable disagreement. Four additional comments addressed the different use of patches for on-lay versus bridging with reference to a completed repair. Three of these comments queried whether or not two separate studies would be needed or if stratification was necessary.

Participants were asked for their opinions patches of different types. There was 39% agreement for using animal products versus 35% disagreement. Synthetic, allograft and autograft patches had more support, with approximately $\geq$ 50% agreement and 26% less disagreement. Regarding the use of patches in a trial, there was similar level of agreement between using what was readily available in the NHS (10, 43%) and using only one specific type of patch (9, 39%). There was much less support for using only a specific patch within a trial (3, 9%). Three additional comments were received. Two of these noted concern about specific patch types (namely the safety of animal product-based patches and the practical challenge of autograft use). One comment noted a desire for consistency in patch use within a trial or a larger study for all issues to be explored. Another noted a desire for surgeons to use their usual patch.

Participants responded with a good level of agreement for a comparison of repair with a patch with standard repair with no patch (74%) and less, although reasonable, agreement for a three-arm trial that compared two types of patch with no patch (56% agreement). One respondent noted the potential value of a 'no surgery' group. When asked about the best time to measure outcomes, there was equal support for 12 and 24 months (10, 43%) as the primary assessment time point. There was much less support for 18 months (3, 9%). One participant noted a desire for MRI-based assessment to be the primary outcome.

Round 2

In the second round of the Delphi survey, 21 non-patient stakeholder participants completed questions related to patient eligibility, timing of randomisation, patch use and trial design. Three patient participants completed a tailored survey that covered patch types to be used, trial design, timing of randomisation, blinding of participants and follow-up regimes. Findings from the combined second round are summarised in *Table 16*, in which each question is given, along with a breakdown by response.

Just over 50% of the respondents agreed either completely or somewhat with the proposal for patient eligibility based on the responses from round 1. There was substantial disagreement from 38% of respondents. Thirteen provided specific comments related to their response, raising one or more specific topics. Six disagreed on the muscle atrophy criterion and five commented on the presence of OA. They were generally in favour of the presence of either as an exclusion criterion but suggested that a fuller definition was needed. Three participants noted that revision operations should be included; all three commented on how the size of tears would alter who would be operated on, and one noted concern about 'too many confounding factors'.

TABLE 16 Delphi study round 2 responses

Proposal	Responses, *n* (%)					
	Completely agree	Somewhat agree	Neutral	Somewhat disagree	Completely disagree	No opinion[a]
Non-PPI participants						
Patient eligibility						
Adults with a rotator cuff tear suitable for primary repair with or without a patch should be included in the RCT. Within this population it was indicated the following should be excluded: small or partial tears, patients unfit for surgery, patients with clinically significant OA, patients with > 50% muscle atrophy and patients needing revision surgery	7 (33)	4 (19)	2 (10)	5 (24)	3 (14)	0 (0)
Timing of randomisation						
Randomisation will take place in theatre after the primary repair has taken place. At this point the surgeon will know which technique is needed for the repair and this can be used to stratify the patients	11 (52)	7 (33)	2 (10)	1 (5)	0 (0)	0 (0)
Patch use						
Using an 'off-the-shelf' patch as part of the RCT. The patches used must fall into the subtypes synthetic, animal product, allograft or autograft. A non-animal patch should be available in case of surgeon or patient preference	9 (43)	8 (38)	2 (10)	0 (0)	1 (5)	1 (5)
Trial design						
What do you think about a two-arm RCT comparing RCR augmented with an 'off-the-shelf' patch with repair without a patch?	13 (62)	5 (24)	0 (0)	2 (10)	1 (5)	0 (0)
Answers from the first round of the survey suggested that both 12 months and 24 months are appropriate time points to measure key outcomes. It was also indicated that both imaging and PROMs would be valuable. Therefore, the project team propose for imaging (specifically MRI) and PROMs to be collected at 12 and 24 months post randomisation as key outcomes for the study	17 (81)	2 (10)	0 (0)	1 (5)	1 (5)	0 (0)
PPI participants						
Patches						
Work for PARCS so far suggests that four types of patches are used in the NHS and there is not an overall preference for one type of patch compared with another. These types are synthetic patches, patches made from animal products, patches made from human (donor) tissue	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

TABLE 16 Delphi study round 2 responses (*continued*)

Proposal	Responses, *n* (%)					
	Completely agree	Somewhat agree	Neutral	Somewhat disagree	Completely disagree	No opinion[a]
and patches made from your own tissue. All these patches are already used clinically in the NHS and have been approved as a safe implant to insert into the human body. Given that there is no clear evidence to support one type of patch over another, we would like to allow the different types of patches to be used in the study. This would reflect current practice in the NHS. In the study, a participant could then receive any of the different types. There would be an alternative to patches made from animal products (e.g. synthetic) for participants who do not want them. What do you think of all of the different types of patches being available for use in a study? The option of a non-animal-based patch would be available to all participants						
Trial design						
Findings from the PARCS study so far suggest that a reasonable way to look at the use of patches in RCR surgery within a study is to compare the following two groups of patients: group 1 – this group would have their rotator cuff tear repaired without a patch; group 2 – this group would have their rotator cuff tear repaired with a patch. What do you think about comparing these two groups?	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Blinding						
Often in studies, patients are 'blinded' to their randomised group. This term means that they do not know which group they are in when the study is running. This is done to get a more scientifically reliable result from the study. For PARCS, this means a participant would not know whether or not their shoulder was repaired with a patch, unless there was a significant safety issue that meant that they needed to know	2 (67)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)
Timing of randomisation						
As was explained at the focus group, patients in a study are given a treatment at random from those available. This is undertaken because it is the best way to fairly compare different treatments. All patients in the study will be allocated a treatment in this way. Whatever	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

continued

TABLE 16 Delphi study round 2 responses (*continued*)

Proposal	Responses, *n* (%)					
	Completely agree	Somewhat agree	Neutral	Somewhat disagree	Completely disagree	No opinion[a]
group participants are in, they will still be under the care of their doctor and followed up regularly. Randomisation can happen at any point between entering the study and receiving the treatment. Findings from the PARCS study so far suggest that the best time to randomise participants may be in the operating theatre. This would mean that, going into the operation, the participant would not know whether or not a patch would be used. The participant could expect to have their rotator cuff repaired, although this would depend on the nature of the shoulder problem, which can be more easily assessed during the operation. We would like to know whether or not patients would be comfortable with this idea. What do you think about participants being randomised in the operating theatre as described above?						
Follow-up						
To find out whether or not using a patch helps to repair the rotator cuff tear, it would be useful to follow up participants for 24 months after entering the study. For example, they might be asked to complete a questionnaire at 6, 12 and 24 months about their shoulder symptoms and related care	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
What do you think about participants coming to hospital 24 months after joining the study for a study-specific visit?	1 (33)	0 (0)	1 (33)	0 (0)	0 (0)	1 (33)

a For PPI participants the response was 'don't know'.

There was very good agreement about randomising in theatre after the initial repair had taken place (86% agreement). Only one (5%) somewhat disagreed and commented with the justification that they would like to know before they start the repair whether or not a patch would be used. Two respondents noted that the randomisation process would need to be straightforward for in-theatre randomisation to work. All three PPI participants agreed with the proposal regarding patches.

Non-PPI participants agreed (81%) with using the patch that is available locally, with the caveat of making sure that a non-animal product patch was available. Only two were neutral (10%) and only one completely disagreed (5%). Five specifically confirmed this by noting a desire not to use an animal product patch. Four comments expressed a preference, to varying degrees, for more consistency in the patch type used or for this to be addressed in the design and analysis. All three PPI participants agreed with the proposal regarding patches.

Non-PPI respondents agreed (86%) with the proposed two-arm design. Only one (5%) completely disagreed and two somewhat disagreed (10%). One respondent queried whether or not a placebo comparison might be useful and another whether or not the proposal would give the required answer. One comment noted that a specific patch would be desirable in the trial design. All three patient respondents agreed with this proposal. Two out of three agreed that participants should be blinded whether or not they have received a patch, with the third being unsure. The non-PPI participants agreed (90%) with the proposed outcome follow-up strategy, with PROMs and imaging collected at 12 and 24 months. One respondent commented that imaging was less important to them. One respondent thought that 3 months would be a useful time point to collect some data and another indicated that imaging at only one time point would be sufficient. All three patient respondents were happy with the proposed questionnaire follow-up strategy and timing. There were mixed views among these respondents on a hospital visit at 24 months for the study (one agreed, one neutral and one unsure).

Stage 6: consensus meeting

The consensus meeting was held on 29 and 30 January 2019 in Oxford. A total of 22 individuals attended the meeting: representatives from industry (2), patients (2), surgeons (8), researchers (4), project team members (5), and an independent chairperson. Prior to the meeting, the agenda and a summary of a trial proposal using the round 2 Delphi survey were circulated. The proposal had only minor adjustments from the round 2 Delphi survey, with the explicit age restriction removed and imaging clarified to take place only at 12 months. In addition, a number of issues related to each component raised in the Delphi study were included in the proposal, highlighted for discussion in the meeting. Towards the end of the first day it became clear that the proposal trial design needed revision to address the varied use of patches and a revised proposal was presented at the beginning of the second day. The overall decision of the meeting was that a RCT of RCR with a patch was both acceptable and feasible. However, it was agreed that a single study or randomised comparison would not be able address all the key questions. The outline of two RCTs was agreed in principle at the meeting, as was the desire for a study to capture safety data for patch use irrespective of involvement in a trial (e.g. registry study). Following the meeting a summary of the proposal was circulated and agreed.

Study proposal

An outline of the agreed study proposal is given in *Tables 17* and *18*. Two areas for a RCT assessing the use of patches in rotator cuff surgery were identified. The first one assesses the use of a patch for patients with a completed RCR and the second relates patients with a partial RCR. *Figure 10* illustrates the patient flow, along with patients who potentially could contribute data to a registry to inform on the safety of specific patches. The two randomised comparisons could potentially be within one more comprehensive trial or conducted separately.

Discussion

Together, there was agreement from the Delphi study and the face-to-face consensus meeting about the acceptability and feasibility of a RCT for evaluating the use of a patch when carrying out RCR. Findings from the previous stages of the PARCS feasibility study were built on in the two rounds of the Delphi survey with the rough outline of a potential trial. During the consensus meeting, it was clear that, although a trial could be conducted, it would need to respect two distinct uses of patches (on-lay and bridging). Accordingly, two separate trials could be envisaged; alternatively, one overall study that accounts for both uses and has two distinct random allocations could be developed.

Using differing methods and multiple rounds of approaches to build consensus is a key strength of this work. The consensus was also strengthened at the attempt to involve all stakeholder groups as much as possible in the consensus-building process. It was also informed by and built on the previous stages of the PARCS feasibility study. Although not without its limitations, this was a much more structured and systematic approach to considering the feasibility and design of a future study than is typically the case.

TABLE 17 A RCT proposal using on-lay patch technique

Element	Details
Patients	Include adults with full-thickness rotator cuff tears involving supraspinatus, with or without infraspinatus involvement, confirmed intraoperatively (no restriction on size)
	Exclude no rotator cuff tear present, full-thickness tear involving subscapularis only and patients with glenohumeral OA
	Note: patients are consented prior to operation and are randomised only after eligibility confirmed
Surgeon eligibility	Consultant shoulder surgeon
Surgical approach	RCR with double row, no restrictions on the use of anchors or suture material
	Randomise patch use once RCR has been completed
	Bicep tenodesis or tenotomy at surgeon's discretion
Suitable patch	Types: allograft, synthetic or xenograft suitable for on-lay use
	Note: need to be available within NHS and have no evidence of safety concerns
Intervention and comparison groups	Intervention: RCR with on-lay use of patch
	Control: RCR with no use of patch (standard RCR)
Outcome/time frame	Key outcomes: patient-reported pain and function, MRI assessment of full-thickness tear
	Follow-up time frame: 12 and 24 months

TABLE 18 A RCT proposal using bridging patch technique

Element	Details
Patients	Include adults with full-thickness rotator cuff tears involving supraspinatus, with or without infraspinatus involvement, confirmed intraoperatively (no restriction on size)
	Exclude no rotator cuff tear present, partial-thickness tears, full-thickness tears involving subscapularis only, and patients with glenohumeral OA
	Note: patients are consented prior to operation and are randomised only after eligibility confirmed
Surgeon eligibility	Consultant shoulder surgeon
Surgical approach	RCR with double row, no restrictions on the use of anchors or suture material
	Randomise patch use once RCR has been attempted but cannot be completed
	Bicep tenodesis or tenotomy at surgeon's discretion
Suitable patch	Types: allograft, synthetic or xenograft suitable for bridging use
	Note: need to be available within NHS and have no evidence of safety concerns
Intervention and comparison groups	Intervention: RCR with bridging of patch
	Control: RCR with no use of patch (standard RCR)
Outcome/time frame	Key outcomes: patient-reported pain and function, MRI assessment of full-thickness tear
	Follow-up time frame: 12 and 24 months

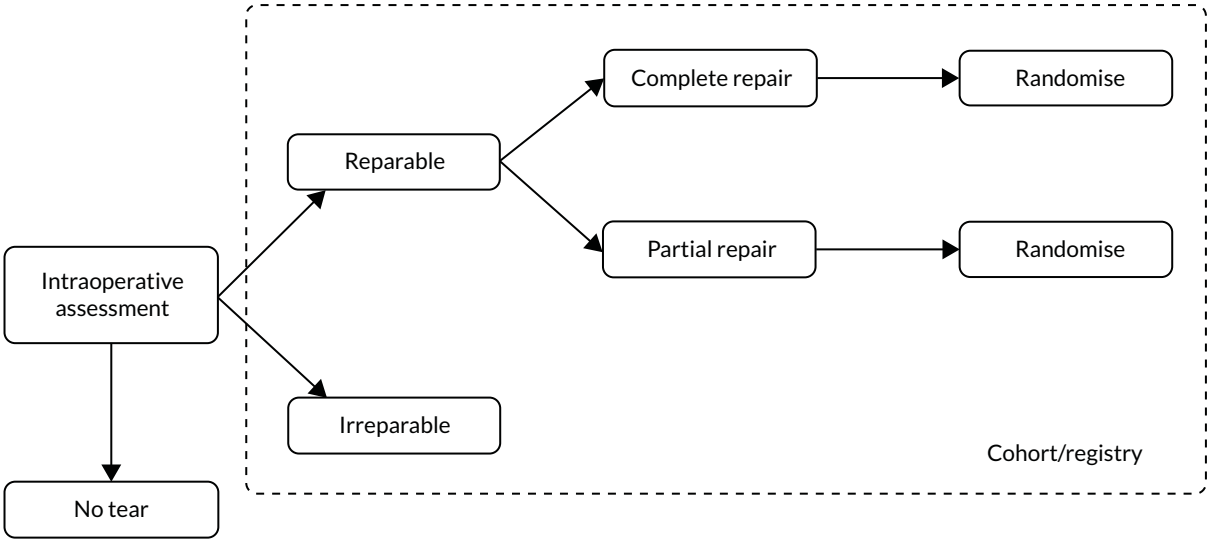


FIGURE 10 Proposed study patient eligibility pathway.

Limitations of the work include the self-selecting nature of the participants that may make them, particularly in terms of surgical practice, somewhat atypical. For example, the sample is likely to include more who use a patch than may be typical across surgical practice in the NHS. However, to an extent this is not concerning if they reflect more closely the pool of surgeons who would likely participate in a RCT. Indeed, it was a conscious aim to include these surgeons from the point of the triallist survey through to the consensus meeting. A number of surgeons participated following this structure. The Delphi study had fewer participants than initially had been hoped, which is a limitation as it increases the potential for unrepresentative findings or an absence of less common, but relevant, viewpoints. In particular, the number of patient participants was disappointing, despite the effort made to produce a specific questionnaire for them, and also despite approaching individuals who had shown interest in the study to date. We had only two rounds of the Delphi process, which would be considered a minimum by many, and the study did not reach agreement on one of the key (patient eligibility) design features at this point. More generally, our Delphi approach varied somewhat from the approach used in previous studies, given the more fluid nature of the study and the varied topics on which consensus was being sought. Other Delphi studies[53] have tended to use very specific questions about inclusion of provided items or domains in all rounds.

Although the desire and feasibility of a trial were generally agreed, the specifics within the trial were debated. Of all the topics, patient eligibility was the most contentious, reflected as being the only component that did not meet the a priori criteria for 'consensus'. The challenge is to maintain sufficiently broad inclusion criteria to allow as many as surgeons to participate as possible, without undermining the validity and relevance of the findings. However, it is worth noting that the eligibility criteria designate who can be included and, within that pool, the surgeon's clinical decision-making (and both surgeon and patient equipoise) is still key to recruiting patients. The disagreement, although exhibited in the response to patient eligibility, seems to relate to the surgical approach as well. The consensus meeting proposal sought to deal with the most problematic aspects of this.

As with other areas where a medical device is used for a surgical operation (e.g. hip and knee replacement surgery) and where there are important variations in both the device's use and the design, there is a tension between proposing a deliverable trial and carrying out the perfect study that addresses all key research questions. This was reflected in some of the responses to the Delphi survey where concern about the value of a study that allowed different types of patches when the main comparison was against no patch. Although focusing on the use of a specific patch in a specific way has a number of benefits, it runs great risk of not being generalisable. It also risks providing a potentially redundant finding, because

of changes in the design of patches. For example, GRAFTJACKET is probably the current market leader in the UK for rotator cuff tear repairs, and has been available for 12-plus years, yet is purported to be about to undergo a revision of its design.

In summary, the findings of the PARCS feasibility study are that a RCT evaluating the use of a patch for rotator cuff surgery is both acceptable to stakeholders and feasible. An outline of the design (see *Figure 10* and *Tables 17* and *18*) that such a study can take has been produced.

Chapter 6 Discussion

Summary of findings

This feasibility study has confirmed the need for a RCT of the clinical effectiveness and cost-effectiveness of patch-augmented RCR. It has demonstrated that this trial would be both acceptable to key stakeholders and feasible. Across the five stages of the feasibility study with stakeholder engagement, these groups demonstrated general support for further research on the use of patches, including the willingness to participate in a RCT. There were key challenges related to the implementation of such a trial, and decisions related to its conduct were identified and tackled. Given the variations in the patches and their current use, it is unlikely that a single study would be able to address all of the key research questions.

Strengths and limitations of the work

The main strength of the PARCS feasibility study was the use of multiple methods to engage with all potential stakeholders to address the aim and objectives of the study. The objectives were addressed as intended. However, there were a number of limitations to the work. Inevitably the success of engagement with the stakeholder groups varied, with the most limited input from industry representatives. The response rate of the BESS membership survey was low, even if consistent with other surveys sent to the society. Participation in the Delphi study was lower than originally hoped. It is difficult, therefore, to know how representative the findings are of each stakeholder groups' views. However, there is confidence that those who participated, particularly the surgeons, would want to be involved in a trial.

Three studies that would progress the field were identified, including two RCTs. Ultimately, the value of the PARCS study will be confirmed only if a RCT assessing the use of a patch in the UK NHS setting is attempted and, if successful, how influential the study is for clinical practice.

Key issues related to conducting a randomised controlled trial

Patient eligibility

Patient eligibility provided the most disagreement in the study. A number of aspects were agreed on, such as the exclusion of patients with other shoulder problems and with clinically significant OA. There was a variety of specific exclusion criteria proposed by individual respondents, with a range of views on age, muscle atrophy, tear size and having a previous RCR. The relationship between patient eligibility and patch technique was noted by a number of participants. The final proposal reflects an inclusive approach whenever possible. The broad criteria were accepted, although the details were not fully resolved.

Types of patches

A variety of patches are available for clinical use, reflecting different materials, processes and designs. The systematic review (see *Chapter 2*) identified 28 different patches, defined as an implantable human, synthetic or animal material that is used with the aim of improving tissue healing and/or patient outcome via some form of mechanical support. Of these, 22 could be classed as a product, and six were a tissue graft from either the patient or (in one case) a cadaver. There was comparative evidence for only 12 different patches. The survey of the surgical BESS membership identified 13 different patches currently in use in

the UK. Most are produced from decellularised human dermis, with the rest being made form porcine or synthetic materials. It is concerning that these two groups did not overlap fully, with at least two patches (dCELL and Leeds–Kuff) in current clinical use that have no clinical evidence identified. No single type of patch could be considered either to be dominant in terms of use or to have compelling evidence in its favour. There was some evidence for the support of allograft and synthetic patches to improve the re-tear rate and for synthetic patches to reduce pain. Mostly the evidence is non-existent, or too weak to draw even tentative conclusions.

With regard to running a large definitive trial, it was clear that the use of a specific patch would be unwarranted but a decision about which types of patch to allow within the study would be important. Any secondary evaluation of evidence, such as safety of the included patches, would be advantageous. Uncovering the need for preliminary safety evaluation of patches was unexpected in this study. The requirement for a non-animal patch in the trial design, particularly an alternative to a porcine based patch, was noted.

Surgical use of a patch

The surgical use of patches in rotator cuff surgery falls broadly into two groups. In an on-lay technique the patch is sutured on top of the tendon-to-bone repair, whereas in a bridging technique the patch is sutured into the exposed area following a partial repair. Although to some degree a partial repair can be anticipated in advance, this is not always the case, as the quality of the tissue is not entirely clear until the repair has been attempted.

The distinction between the two techniques was clear in some of the studies in the systematic review. This became increasingly apparent as surgeon stakeholders were engaged through stages 2–6. To reconcile the two techniques, two RCTs for patch use were proposed: one for on-lay use and one for bridging. Different patch types and designs may be thought to be better suited to each approach.

Beyond this, there was overall support for flexibility for surgeons to conduct patch-augmented RCR according to their personal practice. A standardised postoperative regime was supported by the surgeon triallists in stage 4.

Conducting a randomised controlled trial

Specific information related to how a RCT might be conducted was gained from the surgeon triallist survey, the Delphi study and the consensus meeting. The Delphi study and the consensus meeting showed most support for a two-arm trial of RCR with and without patch use. Although differences between patch types were noted by a number of participants as being of interest, the difference in how patches are used appeared to be a higher priority for evaluation. This is reflected in the research recommendations of the study.

Randomisation during the operation was most supported, once the RCR had been attempted. This has the benefit of confirming the presence and nature of a tear and knowing whether or not the repair could be completed.

Participants in the surgeon triallist survey, Delphi study and consensus meeting supported use of both a patient-reported pain and function measure and imaging as trial outcomes. There was support for a 24-month follow-up. The timing of assessments within this period indicate support for an ‘early’ assessment around 4 months, followed by further assessments at 12 and 24 months. It would not be necessary to have the same outcomes at every time point.

Economic evaluation considerations

A future definitive RCT of patch use should consider embedding an economic evaluation of the patches under investigation to assess their cost to the NHS as well as their benefits to patient HRQoL.

Little evidence was available to shape a RCT economic-based evaluation. Considerations about the types of data (e.g. inpatient/outpatient visits, medication), frequency and intensity of patient data collection (e.g. 1 and 4 months post surgery) as well as the means of data collection (e.g. paper/electronic forms) have to be made when designing a prospective RCT. Resource utilisation not related to the surgery, such as use of non-NHS care to deal with daily activities, as well as loss of income caused by surgery, are also recommended to be included in the patient data collection process. Although SF-36 was the only HRQoL measure to be captured in the current literature, a future economic evaluation should also administer the EQ-5D measure, which is recommended by NICE.

Further research priorities

As outlined in *Chapter 5*, there were four clear research questions that require evaluation. Proposed research studies to address these are as follows:

1. a RCT to assess the on-lay use of a patch in rotator cuff surgery once the surgical repair of the rotator cuff has been completed
2. a RCT to assess the bridging use of a patch where the surgical repair of the rotator cuff is partial
3. a registry or observational study to assess the safety of all patches available for clinical use
4. an economic evaluation of the use of patches in RCR preferably embedded within a RCT or as a standalone evaluation.

An outline of the proposed studies is given in *Tables 17* and *18* and in *Figure 10*.

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Contributions of authors

Professor Jonathan A Cook (https://orcid.org/0000-0002-4156-6989) (Associate Professor, Chief Investigator) led the study design and funding application, provided overall oversight of the project, contributed to conduct of all stages and approved the report.

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Dr Joanna C Crocker (https://orcid.org/0000-0002-8223-0349) (Research Fellow) contributed to the design and conduct the focus groups and reviewed the report.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

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Appendix 1 The EMBASE search strategy

	Searches	Results
1	exp rotator cuff rupture/	5732
2	exp rotator cuff injury/	8726
3	exp tendon injury/	20,086
4	(rotator cuff tear or rotator cuff rupture or rotator cuff injur* or supraspinatus tear or supraspinatus rupture or supraspinatus injur* or infraspinatus tear or infraspinatus rupture or infraspinatus injur* or subscapularis tear or subscapularis rupture or subscapularis injur* or tendon tear or tendon rupture or tendon injur* or shoulder pain or shoulder injur*).mp.	38,603
5	or/1-4	39,799
6	exp tissue repair/	17,952
7	exp shoulder surgery/	4863
8	(tissue repair or shoulder surgery or augment*).mp.	212,917
9	exp tissue scaffold/	11,559
10	exp extracellular matrix/	99,144
11	exp bioprosthesis/	7140
12	exp allograft/	40,591
13	exp autograft/	13,831
14	exp surgical mesh/	12,582
15	exp acellular dermal matrix/	1282
16	(tissue scaffold or extracellular matrix or bioprosthesis or allograft or autograft or surgical mesh or acellular dermal matrix or “GraftJacket” or “Zimmer Collagen Repair Patch” or “Permacol” or “TissueMend” or “BioBlanket” or “Conexa” or “AlloPatch” or “Shelhigh Encuff Patch” or “OrthADAPT” or “Restore” or “CuffPatch” or “Polytape” or “SportMesh” or “Arthelon” or “Gore-tex” or “BioFiber” or “STR Grafts” or “Lars Ligament” or “X-repair”).mp.	321,825
17	or/6-16	533,208
18	5 and 17	3914
19	Clinical trial/	1,042,043
20	Randomized controlled trial/	481,803
21	Randomization/	84,993
22	Single blind procedure/	29,844
23	Double blind procedure/	141,452
24	Crossover procedure/	55,396
25	Placebo/	333,461
26	Randomi?ed controlled trial$.tw.	155,939
27	Rct.tw.	23,487
28	Random allocation.tw.	1668
29	Randomly allocated.tw.	27,352
30	Allocated randomly.tw.	2233
31	(allocated adj2 random).tw.	860
32	Single blind$.tw.	19,262

	Searches	Results
33	Double blind$.tw.	178,171
34	((treble or triple) adj blind$).tw.	698
35	Placebo$.tw.	254,195
36	Prospective study/	401,796
37	Retrospective study/	538,437
38	Longitudinal study/	109,396
39	(Case control adj (study or studies)).tw.	103,770
40	(Cohort adj (study or studies)).tw.	187,964
41	or/19-40	2,619,904
42	18 and 41	794
43	limit 42 to dd = 20060401-20170228	370

Note
The results do not reflect the actual numbers for the systematic review, but are illustrative of an early run of the search strategy.

Appendix 2 Systematic review supplementary tables

TABLE 19 Summary of study designs

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Randomised comparative studies								
Barber 2012;[26] USA	RCT	GRAFTJACKET-augmented repair vs. no augmentation	Aged 18–75 years Large (> 3-cm wide and two tendon involvement) RC tears Primary RC repair Amenable to arthroscopic repair Good preoperative movement of contralateral arm Ability to perform postoperative exercises Ability to read and understand English for PROMs Willingness to participate in postoperative follow-up No massive (> 5 cm) or subscapularis tears No inflammatory disease, autoimmune disease, cancer, highly communicable disease or active infection Non-smokers only	NR	42	MRA at 12 or 24 months Clinical evaluation at 6 and 12 months; annually thereafter	Repair failure	Constant, UCLA, ASES

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Bryant 2016;[65] Canada	RCT	Restore-augmented repair vs. no augmentation	All patients scheduled for RC repair Able to repair defect with a residual defect of ≤ 1 cm or < 1 cm of medialisation No other shoulder disease; grades II–IV SLAP lesion, Bankart lesion, Hill–Sachs lesion, ≥ grade 3 OA[b] No significant shoulder girdle paralysis No systemic or active joint infection No major medical or psychiatric illness or developmental handicap No previous shoulder surgery (except acromioplasty or diagnostic arthroscopy) Ability to read and understand English Willingness to be assessed for 1 year after surgery	62	62	MRA at 12 months Clinic evaluation at 1.5, 3, 6, 12, 18 and 24 months	Repair failure	WORC, ASES, Constant, SST, SF-36

continued

TABLE 19 Summary of study designs (*continued*)

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Iannotti 2006;[35] USA	RCT	Restore-augmented repair vs. no augmentation	Large or massive tears of supraspinatus and infraspinatus tendons on preoperative MRI	32	30	MRA at 12 months	Repair failure	PENN, SF-36
			Aged > 18 years					
			Tear of ≥ 3 months' duration					
			Fully repairable tear – determined intraoperatively			Clinical scores, mean 14 months (range 12–26.5 months)		
			No prior shoulder surgery					
			No glenohumeral arthritis, frozen shoulder or cervical spine disease					
Leuzinger 2016;[63] Switzerland	RCT	GRAFTJACKET vs. Artelon vs. Restore	Primary or revision RC repair	92	89	MRI at 6 months	Repair failure, Constant, SSV	–
			Stage > 2 fatty degeneration of supraspinatus according to Goutallier *et al.*[115,125]			Clinical evaluation at 6 and 36 months		
			No history of glenohumeral OA					
			Repairable tear not requiring bridging with a patch					
			At least 3 years' follow-up					

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Non-randomised comparative studies								
Ciampi 2014;[40] Italy	Comparative observational study	Repol Angimesh-augmented repair vs. TUTOPATCH-augmented repair vs. no augmentation	Preoperative MRI evidence of a full-thickness tear involving two tendons Postoperative residual retraction of 2 cm Stage 1 or 2 fatty degeneration according to Goutallier *et al.*[115,125] Failure of 6-month non-operative management consisting of physical therapy and anti-inflammatory medications Duration of symptoms for at least 3 months No other shoulder pathology requiring additional procedures; grades II–IV SLAP lesion, Bankart lesion, biceps tenodesis No glenohumeral OA, inflammatory arthritis or any rheumatic condition No cortisone injections within 12 weeks of surgery No contralateral shoulder injuries	N/A	152	US at 12 months Clinical scores at 2 and 35 months	UCLA	VAS, repair failure

continued

TABLE 19 Summary of study designs (*continued*)

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Gilot 2015;[42] USA	Comparative observational study	Arthroflex-augmented repair vs. no augmentation	Patient is scheduled for primary RC repair Large to massive rotator cuff tear on MRI Aged 18–85 years Patient is willing and able to provide scores for the study No known allergy to the augmentation material No drug, solvent or alcohol addiction No bacteraemia, systemic or surgical site infection No pregnant or nursing patients No history of autoimmune disease No personal beliefs prohibiting use of grafts	40	35	US and clinical score at 1.5, 3, 6, 12 and 24 months	Repair failure	SF-12, ASES, VAS, WORC, shoulder activity-level survey
Ito 2003;[66] Japan	Comparative observational study	Fascia lata allograft vs. no augmentation	Large or massive cuff tears on MRI or pneumoarthrography Pain and loss of function despite conservative therapy	28	21	Final follow-up (range 2–8 years)	Japanese Orthopaedic Association shoulder surgery score, ROM (degrees)	–

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Jeon 2017;[67] Republic of Korea	Comparative observational study	Long head of biceps vs. no augmentation	L-shaped rotator cuff tears Minimum follow-up period of 2 years No revision surgery No subscapularis tendon tears No glenohumeral OA or instability	N/A	64	MRI at 6 months US at 12 months Clinical evaluation at 3, 6 and 12 months and final follow-up (range 24–40 months)	ASES, Constant, VAS, strength (NR)	–
Maillot 2018;[64] France	Comparative observational study	Conexa vs. standard repair vs. debridement only	Large to massive RC tear on MRI or CTA Failure of non-operative management consisting of a period of relative rest, non-steroidal anti-inflammatory medication, physiotherapy > 3 months and > 2 corticosteroids Functional impairment or unacceptable pain for a minimum of 3 months Stage 2 or 3 fatty degeneration according to Goutallier *et al.*[115,125] No glenohumeral OA or prior ipsilateral shoulder surgery	32	32	Clinical evaluation at 3, 6, 12 and 24 months	Constant	VAS, ROM (degrees)

continued

TABLE 19 Summary of study designs (*continued*)

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Mori 2013;[33] Japan	Comparative observational study	Tensor fascia lata vs. no augmentation	Irreparable large or massive RC tear with pain and functional disability refractory to conservative treatment Stage 3–4 fatty degeneration of supraspinatus and stage 1–2 degeneration of infraspinatus according to Goutallier *et al.*[115,125] Intact teres minor tendon Availability of MRI to evaluate the integrity of the rotator cuff tendons and/or autografts preoperatively and postoperatively Minimum follow-up period of 24 months Absence of the drop-arm sign Absence of stage 3 or 4 fatty degeneration of infraspinatus Stage 1 or fatty degeneration of supraspinatus were excluded Absence of full-thickness subscapularis tendons No history of surgery, nerve palsy, glenohumeral OA, diabetes or symptom onset following motor vehicle accident	N/A	48	MRI, NR Clinical evaluation at 6, 12 and 24 months	Repair failure	Constant, ASES, UCLA, VAS

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Mori 2015;[68] Japan	Comparative observational study	Tensor fascia lata and grade 1–2[115,125] infraspinatus fatty atrophy vs. tensor fascia lata and grade 3–4[115,125] infraspinatus fatty atrophy	Irreparable large to massive RC tear Pain and disability refractory to non-surgical treatment (oral anti-inflammatory medications, corticosteroid injections and physical therapy) Stage 3–4 fatty degeneration of supraspinatus according to Goutallier *et al.*[115,125] Intact teres minor tendon < 75% fatty degeneration of infraspinatus Availability of MRI to evaluate the integrity of the rotator cuff tendons and/or autografts preoperatively and postoperatively Minimum follow-up period of 24 months Absence of the drop-arm sign No history of surgery, nerve palsy, glenohumeral OA, diabetes or symptom onset following motor vehicle accident No full subscapularis tears	N/A	45	MRI, NR Clinical evaluation at 6, 12 and 24 months	Repair failure	Constant, ASES, ROM

continued

TABLE 19 Summary of study designs (*continued*)

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Tempelaere 2017;[69] France	Comparative observational study	Quadriceps tendon vs. no augmentation	Massive RC tears Patients aged < 70 years Pain and loss of strength refractory to medical treatment (≥ 1 injection, rehabilitation session) No stage 3–4 fatty degeneration of supraspinatus or infraspinatus according to Goutallier *et al.*[115,125] No history of ipsilateral shoulder surgery, dislocation, fracture, glenohumeral OA, diabetes or symptom onset following motor vehicle accident	80	50	Final follow-up (range 12–116 months)	Constant, SSV, strength (kg)	–
Vitali 2015;[43] Italy	Comparative observational study	Repol Angimesh and long head of biceps-augmented repair vs. no augmentation	MRI evidence of a full-thickness tear involving two tendons Stage 1 or 2 fatty degeneration according to Goutallier *et al.*[115,125] Patients with pain and a deficit in elevation, not responding to physiotherapy Intraoperative evidence of irreparable rotator cuff lesion Minimum follow-up of 3 years after surgery	N/A	120	MRI at 12 months Clinical evaluation at 3 and 36 months	UCLA	Repair failure, VAS, range of motion (degrees), strength (kg)

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
			Active and motivated patients					
			No other shoulder pathology requiring additional procedures: grades II–IV SLAP lesion, Bankart lesion, biceps tenodesis					
			No glenohumeral OA, inflammatory arthritis or any rheumatic condition					
			No cortisone injections within 12 weeks of surgery					
			No contralateral shoulder injuries					
Walton 2007;[41] Australia	Comparative observational study	Restore-augmented repair vs. no augmentation	Poor-quality tendon or a large to massive full-thickness tear of a tendon that could be attached to the greater tuberosity after appropriate mobilisation techniques	NR	31	MRI at 24 months	Repair failure, pain and function questionnaire,[150] systematic shoulder examination,[151] strength (N)	–
			Intact subscapularis tendon			Clinical evaluation at 3, 6 and 24 months		

continued

TABLE 19 Summary of study designs (*continued*)

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Yoon 2016;[71] Republic of Korea	Comparative observational study	Bone marrow stimulation and allocover-augmented repair vs. no augmentation	Massive RC tears Persistent severe pain and disability Unresponsive to ≥ 6 months of non-operative treatment Repairable RC tears Minimum follow-up of 1 year after surgery No advanced glenohumeral OA (≥ stage 4, Hamada *et al.*[152]) No prior surgery to affect shoulder No contralateral shoulder lesions	87	75	MRI at 12 months Clinical evaluation at 12 months and at the final follow-up (range 14–43 months)	VAS, UCLA, Constant, ASES, SST, repair failure	–
Non-comparative studies								
Agrawal 2012;[72] USA	Non-comparative observational study	Allopatch HD	Primary RC tears ≥ 3 cm Recurrent RC tears of any size Arthroscopic repair undertaken	N/A	14	MRI at 1–2 years Clinical evaluation at 12 months	Repair failure, Constant Flex SF	–

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Audenaert 2006;[73] Belgium	Non-comparative observational study	MERSILENE	Primary massive full-thickness tears of two or more tendons, measuring > 4 cm in maximal diameter Irreparable by simple suture Open repair undertaken Inability to elevate arm beyond 90° after 3 months, despite maximal conservative treatment	41	41	US and clinical evaluation, mean 43 months (range 24–86 months)	Repair failure, Constant	–
Badhe 2008;[74] UK	Non-comparative observational study	Zimmer collagen repair patch	MRI or US evidence of RC tears ≥ 5 cm involving both the supraspinatus and the infraspinatus tendons Refractory to a trial of non-operative management, including physiotherapy and steroid injections	10	10	MRI and US at 'final follow-up', mean 54 months (range 36–60 months) Clinical evaluation at 12 months and 'final follow-up'	Constant, repair failure	–
Bektaser 2010;[75] Turkey	Non-comparative observational study	Coracoacromial ligament	(Eligibility criteria not explicitly stated) Treated for a rotator cuff tear between 2003 and 2009	N/A	46	Clinical evaluation at 1, 3 and 12 months (range NR)	Constant, acromiohumeral distance	–
Bond 2008;[76] USA	Non-comparative observational study	GRAFTJACKET	MRI evidence RC tears ≥ 5 cm and/or two tendon tears Irreparable tears – determined at prior arthroscopy	N/A	16	MRI at 3 and 12 months Clinical evaluation at 3, 6 and 12 months and at the 'final follow-up', mean 26.7 months (range 12–38 months)	UCLA, Constant, SST, pain score, repair failure	–

continued

TABLE 19 Summary of study designs (*continued*)

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Burkhead 2007;[77] USA	Non-comparative observational study	GRAFTJACKET	Massive (two or more tendons plus ≥ 5 cm) or recurrent RC tears Repairable tears only No active infection	N/A	17	MRI/CTA and clinical evaluation, mean 14.4 months (range NR)	UCLA, pain, repair failure	–
Cho 2014;[78] Republic of Korea	Non-comparative observational study	Permacol	Posterosuperior massive RC tear (≥ 5 cm or two or more tendons), confirmed by MRI and arthroscopy Inability to reduce the residual cuff to the anatomic Active individuals aged ≤ 60 years Unresponsive to > 3 months of non-operative treatment No prior shoulder surgery Able to comply with the postoperative rehabilitation programme Anterosuperior massive RC tears were excluded No irreparable RC tears – could be only partially repaired despite full mobilisation No superior humeral head migration No stage 3–4 fatty degeneration according to Goutallier *et al.*[115,125]	5	5	MRI at 6 months Clinical evaluation at the 'final follow-up', mean 20.6 months (range 14–27 months)	VAS, UCLA, ASES, repair failure	–

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Consigliere 2017;[79] UK	Non-comparative observational study	DX reinforcement matrix	Large (> 3 cm) and massive (more than two tendons) RC tears Repairable RC tears only Poor tissue quality only Patients will achievable objectives (pain relief and improved function) No evidence of cuff arthropathy No signs of glenohumeral OA No stage 4 fatty degeneration according to Goutallier *et al.*[115,125] No active infections	10	10	Clinical evaluation at 3, 6 and 12 months	Constant, OSS, VAS	–
Encalada-Diaz 2011;[80] Mexico	Non-comparative observational study	Polycarbonate polyurethane patch	Full-thickness tear of supraspinatus or infraspinatus tendon and intact subscapularis	10	10	MRI and US at 6 and 12 months Clinical evaluation at 0.5, 1, 3, 6 and 12 months	SST, VAS, ASES, UCLA, SF-12, repair failure	–
Flury 2012;[81] Germany	Non-comparative observational study	GRAFTJACKET or Arthroflex	Symptomatic revision RC tear with poor-quality tendon (degeneration or delamination) Aged > 60 years with unfavourable comorbidities (massive rupture, diabetes, steroid therapy) No irreparable RC tear	N/A	8	US or MRI at 6 months Clinical evaluation at 6 or 9 months	Constant, OSS, SSV	–

continued

TABLE 19 Summary of study designs (*continued*)

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Giannotti 2014;[82] Italy	Non-comparative observational study	Zimmer collagen repair patch	(Eligibility criteria not explicitly stated) Massive RC tear with minimum follow-up of 30 months	N/A	9	US, MRI and clinical evaluation, mean 36 months (range 30–45 months)	Repair failure, ASES, Constant, strength (BMRC), electromyography	–
Gupta 2012;[83] USA	Non-comparative observational study	GRAFTJACKET	Full-thickness RC tear with > 5-cm retraction on preoperative MRI Unresponsive to > 6 months of non-operative treatment, including physiotherapy and non-steroidal anti-inflammatories Inability to reduce the residual cuff to the anatomic Ability to fully participate in the postoperative rehabilitation No glenohumeral OA and/or cuff tear arthropathy No stage 3–4 fatty degeneration according to Goutallier *et al.*[115,125] No prior RCR	24	24	US, mean 36 months (range NR) Clinical evaluation, mean 36 months (range 29–42 months)	VAS, ASES, SF-12, ROM (degrees), strength (BMRC), repair failure	–

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Gupta 2013;[84] USA	Non-comparative observational study	Conexa	Full-thickness RC tear with > 5-cm retraction and/or more than two tendons full-thickness RC tear visualised during arthroscopy Unresponsive to > 6 months of non-operative treatment, including physiotherapy and non-steroidal anti-inflammatories Inability to reduce the residual cuff to the anatomic Ability to fully participate in the postoperative rehabilitation No glenohumeral OA and/or cuff tear arthropathy No stage 3–4 fatty degeneration according to Goutallier *et al.*[115,125]	26 patients, 27 shoulders	26 patients, 27 shoulders	US and clinical evaluation, mean 32 months (range 24–40 months)	VAS, ASES, SF-12, ROM (degrees), strength (BMRC), repair failure	–
Hirooka 2002;[85] Japan	Non-comparative observational study	GORE-TEX-expanded PTFE patch	NR	27 patients, 28 shoulders	27 patients, 28 shoulders	Clinical evaluation, mean 44 months (range 24–72 months)	Japanese Orthopaedic Association shoulder surgery score, strength (kg)	–

continued

TABLE 19 Summary of study designs (*continued*)

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Lederman 2016;[86] USA	Non-comparative observational study	Conexa	Aged 40–70 years Repairable primary large (3–5 cm) RC tears ≥ 90° movement of the non-operative arm Able to perform postoperative exercises Able to return for all scheduled and required study visits No irreparable tears – inability to approximate the tendon to the tuberosity without tension No subscapularis tears No stage 3–4 fatty degeneration[c] No prior RC repair on the affected shoulder No patients with inflammatory disease, autoimmune disease, cancer, insulin-dependent diabetes, chronic steroid use, malnourishment, active infection, history of alcohol or drug abuse, significant mental illness, tobacco user within last 6 months or ASA class 4 or 5 Can walk without aids No known allergy to the augmentation material	68	61	MRI at 6 and 12 months Clinical evaluation at 6, 12 and 24 months	ASES, Constant, SST, repair failure	–

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Lenart 2015;[87] USA	Non-comparative observational study	X-repair	Massive RC tears (two or more tendons) repaired with X-repair patch Primary or revision RC surgery No history of instability, moderate to severe glenohumeral OA or shoulder surgery within the follow-up period	N/A	13	Clinical evaluation, mean 18 months (range 14.4–20.4 months)	ASES, PENN, SANE, repair failure	–
Malcarney 2005;[54] Australia	Non-comparative observational study	Restore	A poor quality of deficient tendon Five patients also met the criteria for a concurrent comparative trial (i.e. Walton *et al.*, 2007[41])	N/A	25	NR	Early complications	–
Marberry 2013;[88] USA	Non-comparative observational study	Artelon	Large or massive RC tear diagnosed on MRI Pain and insufficient muscle function for ≥ 3 months Reparable tendon of poor quality, determined at the time of surgery No evidence of active infection, significant OA in the shoulder, chronic dislocation or glenohumeral OA No systemic corticosteroids, chemotherapeutics or major medical conditions	17	16	MRI, NR Clinical evaluation at 3, 6 and 12 months	Constant, WORC, SF36, repair failure	–

continued

TABLE 19 Summary of study designs (*continued*)

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Metcalf 2002;[89] USA	Non-comparative observational study	Restore	(Eligibility criteria not explicitly stated) Massive RC tears (> 5 cm^2) with retraction medial to glenoid Significant atrophy of supraspinatus and infraspinatus on preoperative MRI	N/A	12	Clinical evaluation at 2 years	UCLA, SST, SF-36. ROM (degrees), strength (BMRC)	–
Modi 2013;[90] UK	Non-comparative observational study	GRAFTJACKET	Irreparable large or massive RC tears (≥ 3 cm) No history of inflammatory or autoimmune disease Patients undergoing RC repair after arthroplasty were excluded	61	61	Clinical evaluation at 3, 6 and 12 months and yearly thereafter	OSS, VAS, ROM (degrees), strength (BMRC)	–
Moore 2006;[91] USA	Non-comparative observational study	Cadaveric allograft	Irreparable, massive RC tears (two or more tendons)	N/A	32	MRI, mean 33.7 months (range 3–124 months) Clinical evaluation, mean 31.3 months (range 1–123 months)	Repair failure, UCLA	–

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Nada 2010;[92] UK	Non-comparative observational study	Dacron	Full-thickness massive RC tear (> 5 cm plus two or more tendons) on MRI Pain and disability despite conservative treatment A functional deltoid muscle Primary or revision (three cases) RC repairs Compliance with postoperative rehabilitation No history of cuff tear arthropathy with stiffness or infection, or any neurological condition effecting the shoulder girdle	21	21	MRI and clinical evaluation, mean 36 months (range 30–46 months)	Constant, VAS, ROM(degrees), strength (BMRC), satisfaction	–
Neumann 2017;[93] USA	Non-comparative observational study	Conexa	Irreparable massive RC tear (> 5 cm) on MRI Primary or revisions (eight cases) RC repairs Failure of 6 months non-operative management (non-steroidal anti-inflammatories and/or physical therapy) Able to participate in post-operative physical therapy No glenohumeral OA, cuff arthropathy, > 50% fatty infiltration of supraspinatus on MRI	85 shoulders, 84 patients	61 shoulders, 60 patients	US and clinical evaluation, mean 50.3 months (range 24–63 months)	Modified ASES, VAS, ROM (degrees), strength (BMRC)	–

continued

TABLE 19 Summary of study designs (*continued*)

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Petrie 2013;[94] UK	Non-comparative observational study	LARS	Symptomatic massive RC clinically and radiologically Stage 3–4 fatty degeneration according to Goutallier *et al.*[115,125] Not amenable to primary arthroscopic repair No patients aged > 75 years with arthritis	53 shoulders, 50 patients	31 shoulders, 28 patients	Clinical evaluation at 4 and 24 months	OSS	–
Petri 2016;[95] USA	Non-comparative observational study	Arthroflex	Open revision of large to massive posterosuperior RC tears with biological augmentation Patients with concomitant SLAP tears, OA, biceps pathology or subscapularis tears were included No stage 3–4 fatty degeneration according to Goutallier *et al.*[115,125] Patient who underwent primary-augmented repair, arthroscopic-augmented repair or revision of a prior augmented repair were excluded	N/A	13	MRI, mean 9.9 months (range 0.3–26.3 months) Clinical evaluation, mean 30 months (range 24–48 months)	ASES, QuickDASH, SANE, SF-12, repair failure	–

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Petriccioli 2013;[96] Italy	Non-comparative observational study	SportMesh™	(Eligibility criteria not explicitly stated) Open repair of subscapularis tendon	N/A	10	US and clinical evaluation, mean 23 months (range 12–34 months)	Constant, DASH, VAS, repair failure	–
Phipatanakul 2009;[97] USA	Non-comparative observational study	Restore	Rotator cuff tears that could not be advanced to the native footprint or to reinforce thin attritional tissues	11	11	MRA, mean 25 months (range 14–38 months) Clinical evaluation, mean 26 months (range 14–38 months)	UCLA, ASES, repair failure	–
Proctor 2014;[98] USA	Non-comparative observational study	X-repair	Massive RC tears (two or more tendon tears) Failure of non-operative treatment No evidence of adhesive capsulitis	18	18	US or MRI, NR Clinical evaluation at 3, 6 and 12 months and at the 'final follow-up', mean 42 months (range 35–47 months)	ASES, repair failure	–
Rhee 2008;[99] Republic of Korea	Non-comparative observational study	Long head of biceps	Massive (> 5 cm) RC tears at arthroscopy No history of SLAP lesion, acromioclavicular arthritis requiring distal clavicle resection, glenohumeral OA or neural damage prior shoulder surgery	N/A	31	MRI, NR Clinical evaluation at 1.5, 3, 6 and 12 months and at the 'final follow-up', mean 32 months (range 24–67 months)	Constant, UCLA, SST, VAS, ROM (degrees), strength (kg)	–

continued

TABLE 19 Summary of study designs (*continued*)

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Rotini 2011;[100] Italy	Non-comparative observational study	Acellular human dermal matrix	Aged < 55 years Healthy with high functional demands Large to massive tears[61] Tendon retraction of < 3 according to Thomazeau *et al.*[153] No stage 3–4 fatty degeneration according to Goutallier *et al.*[115,125] ≥ 1-year follow-up No OA degeneration (even mild), frozen shoulder, symptomatic acromioclavicular arthritis, autoimmune connective tissue disease or allergy to penicillin or pork Able to engage with rehabilitation regimen	N/A	5	MRI, NR Clinical evaluation, mean NR (range 12–18 months)	Repair failure, Constant	–
Sano 2010;[101] Japan	Non-comparative observational study	Long head of biceps	(Eligibility criteria not explicitly stated) Irreparable massive RC tears (two or more tendons) with concomitant long head of biceps pathology > 12 months' follow-up available	N/A	14	MRI and clinical evaluation, mean 28 months (range 48–79 months)	Repair failure, Japanese Orthopaedic Association shoulder surgery score	–

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Schlegel 2018;[103] USA	Non-comparative observational study	Collagen sheet	Chronic, degenerative partial (≥ 25%) thickness tear of supraspinatus tendon Aged ≥ 21 years Unresponsive to conservative therapy (analgesia, physiotherapy or injections) for > 3 months No patients with full-thickness tears, acute injuries, previous surgery on same shoulder, shoulder instability, chondromalacia (> grade 3), > grade 2 cuff muscle fatty infiltration, severe calcification, IDDM, Workers' Compensation, smokers, hypersensitivity to bovine collagen, genetic collagen disease, autoimmune disease, immunodeficiency or chronic inflammatory disorders No oral steroid use for 2 months (or i.m. steroid use for 1 month)	33	33	MRI and clinical evaluation at 3 months and 1 year	Repair failure, Constant, ASES	–

continued

TABLE 19 Summary of study designs (*continued*)

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Scheibel 2007;[102] Germany	Non-comparative observational study	Humeral periosteum	Degenerative symptomatic full-thickness supraspinatus tears High functional demand Tendon retraction of < 3 according to Thomazeau *et al.*[153] No stage 3–4 fatty degeneration according to Goutallier *et al.*[115,125] No partial RC tears, traumatic history, prior surgery to affected shoulder or cuff tear arthropathy (acromiohumeral distance < 6 mm)	20	20	MRI at 12 months Clinical evaluation, mean 14.4 months (range 12–21 months)	Repair failure, Constant, SST	–
Sclamberg 2004;[104] USA	Non-comparative observational study	Restore	Symptomatic, atrophic, retracted large and massive (two or more tendon) RC tears on MRI and confirmed at surgery	N/A	11	MRI and clinical evaluation, mean, NR (range 6–10 months)	ASES, repair failure	–
Sears 2015;[105] USA	Non-comparative observational study	GRAFTJACKET or Tissuemend or Conexa	(Eligibility criteria not explicitly stated) Full-thickness RCRs Revision surgery	31	24	MRI or US, mean 4.2 years (range, NR) Clinical evaluation, mean 4.2 years (range 30–112 months)	Repair failure, ASES, SANE	–

Study (first author and year of publication; location)	Design	Intervention	Stated eligibility criteria	Size		Follow-up	Outcomes	
				Recruited[a]	Analysed		Primary	Secondary
Venouziou 2013;[106] USA	Non-comparative observational study	GRAFTJACKET	Massive (> 5 cm) RC tear Not capable of mobilisation ≥ 18 months' follow-up was available	N/A	14	Clinical evaluation at 1.5, 3, 6 and 12 months and at the 'final follow-up', mean 30.2 months (range 18–52 months)	VAS, ASES, ROM (degrees), strength (BMRC)	–
Wong 2010;[32] USA	Non-comparative observational study	GRAFTJACKET	(Eligibility criteria not explicitly stated) Large and massive RC tears Motivated, intelligent, younger patients with disabling pain but intact biceps tendons Functioning subscapularis muscle No glenohumeral OA, immunocompromised or heavy smokers	N/A	45	Clinical evaluation, mean, NR (range 24–68 months)	UCLA, WORC, ASES	–

ASA, American Society of Anesthesiologists; BMRC, British Medical Research Council Scale; CTA, computed tomography arthrogram; DASH, Disabilities of the Arm, Shoulder and Hand; Flex SF, Flexilevel Scale of Shoulder Function; i.m., intramuscularly; IDDM, insulin-dependent diabetes mellitus; MRA, magnetic resonance arthrogram; N/A, not applicable; NR, not reported; OSS, Oxford Shoulder Score; PTFE, polytetrafluoroethylene; QuickDASH, Quick Disabilities of the Arm, Shoulder and Hand; RC, rotator cuff; ROM, range of motion; SANE, Single Assessment Numerical Evaluation; SLAP, superior labrum from anterior to posterior; SST, Simple Shoulder Test; SSV, subjective shoulder value; US, ultrasonography; WORC, Western Ontario Rotator Cuff.

a Recruited number of patients only refers to studies reporting a prospective design.

b OA defined according to Kellgren *et al.*[149]

TABLE 20 Functional outcome scores

Study (first author and year of publication)	Intervention	Shoulder-specific functional scores, mean (± SD or range)								
		ASES			Constant			OSS		
		Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]
Randomised comparative studies										
Barber 2012[26]	GRAFTJACKET	48.5 (± NR)		2 years: 98.9 (± 4.2)	41.0 (± NR)		2 years: 91.9 (± 9.2)			
	Control	46.0 (± NR)		2 years: 94.8 (± 14.2)	45.8 (± NR)		2 years: 85.3 (± 11)			
				$p = 0.035$			$p = 0.008$			
Bryant 2016[65]	Restore	52.2 (± 3.3)	1 year: 83.3 (± 2.6)	2 years: 84.6 (± 2.9)	58.4 (± 3.9)	1 year: 72.8 (± 3.0)	2 years: 79.3 (± 3.5)			
	Control	54.6 (± 3.7)	1 year: 84.8 (± 2.9)	2 years: 87.9 (± 3.1)	46.8 (± 4.2)	1 year: 79.5 (± 3.1)	2 years: 87.5 (± 3.7)			
			$p = 0.69$	$p = 0.44$		$p = 0.14$	$p = 0.13$			
Iannotti 2006[35]	Restore									
	Control									
Leuzinger 2016[63]	GRAFTJACKET				47.3 (± 7.3)		6 months: 81.4 (± 11.4)			
	Artelon				46.2 (± 9.6)		6 months: 81.3 (± 11.1)			
	Restore				41.0 (± 9.6)		6 months: 78.5 (± 12.3)			
							$p =$ NR			
Non-randomised comparative studies										
Ciampi 2014[40]	Repol Angimesh									
	TUTOPATCH									
	Control									

PENN			SST			UCLA			WORC		
Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]
						13.3 (± NR)		2 years: 28.2 (± 2.1)			
						15.9 (± NR)		2 years: 28.3 (± 3.0)			
						$p = 0.43$					
			47.2 (± 4.3)	1 year: 78.5 (± 3.2)	2 years: 78.5 (± 3.6)				40.2 (± NR)	1 year: 78.6 (± NR)	2 years: 78.8 (± NR)
			40.7 (± 4.8)	1 year: 82.1 (± 3.6)	2 years: 85.4 (± 4.0)				40.1 (± NR)	1 year: 79.8 (± NR)	2 years: 82.2 (± NR)
				$p = 0.48$	$p = 0.21$					$p = 0.73$	$p = 0.46$
42 (± NR)		14 months: 83 (IQR 70–92)									
34 (± NR)		14 months: 91 (IQR 81–99)									
		$p = 0.07$									
						10.9 (± 1.5)	2 months: 19.1 (± 2.0)	36 months: 24.6 (± 3.2)			
						10.4 (± 1.2)	2 months: 11.4 (± 1.5)	36 months: 14.7 (± 2.0)			
						10.7 (± 1.1)	2 months: 11.3 (± 1.5)	36 months: 14.9 (± 2.0)			
								$p < 0.001$[b]			

TABLE 20 Functional outcome scores (*continued*)

Study (first author and year of publication)	Intervention	Shoulder-specific functional scores, mean (± SD or range)								
		ASES			Constant			OSS		
		Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]
Gilot 2015[42]	Arthroflex	63.8 (± 13.8)	12 weeks: 60.6 (± 8.3) 24 weeks: 64.3 (± 7.8)	96 weeks: 88.9 (± 4.8)						
	Control	60.3 (± 9.5)	12 weeks: 57.6 (± 8.8) 24 weeks: 60.4 (± 10.1) $p = 0.59$; $p = 0.08$	96 weeks: 72.6 (± 11.9) $p = 0.048$						
Ito 2003[66]	Fascia lata									
	Control									
Jeon 2017[67]	Biceps tendon	52.8 (± 10.6)	12 weeks: 60.1 (± 15.8) 24 weeks: 76.3 (± 10.6)	29 months: 88.2 (± 6.9)	43.2 (± 9.9)	12 weeks: 54.9 (± 12.8) 24 weeks: 72.2 (± 12.8)	29 months: 86.8 (± 6.2)			
	Control	53.0 (± 11.8)	12 weeks: 63.0 (± 10.2) 24 weeks: 75.7 (± 11.5)	29 months: 87.4 (± 7.2) $p = 0.901$	44.3 (± 11.3)	12 weeks: 56.1 (± 10.8) 24 weeks: 71.6 (± 9.7)	29 months: 84.0 (± 7.9) $p = 0.742$			
Maillot 2018[64]	Conexa				43.6 (± 11.0)	12 weeks: 49.4 (± 14.1) 24 weeks: 59.0 (± 18.8)	24 months: 75.8 (± 8.6)			
	Repair only				45.7 (± 11.6)	12 weeks: 52.4 (± 10.2) 24 weeks: 64.1 (± 8.5)	24 months: 74.7 (± 4.3)			
	Debridement				44.1 (± 11.6)	12 weeks: 54.9 (± 10.0) 24 weeks: 62.2 (± 5.9)	24 months: 64.2 (± 5.0) $p = 1.0$[c]; $p = 0.002$[d]			
Mori 2013[33]	Fascia lata	40.8 (± 13.0)	12 months: 84.9 (± 8.1)	35 months: 94.1 (± 5.4)	37.4 (± 8.1)	12 months: 73.6 (± 6.6)	35 months: 81.1 (± 5.7)			
	Control	41.8 (± 11.3)	12 months: 84.2 (± 19.7)	35 months: 85.7 (± 14.1) $p = 0.021$	36.3 (± 9.9)	12 months: 72.9 (± 16.8)	35 months: 69.9 (± 10.3) $p = 0.001$			

PENN			SST			UCLA			WORC		
Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]
									54 (± 8)	12 weeks: 52 (± 6) 24 weeks: 81 (± 12)	96 weeks: 84 (± 4)
									58 (± 5)	12 weeks: 59 (± 8) 24 weeks: 64 (± 6)	96 weeks: 66 (± 5)
										$p = 0.36$; $p = 0.05$	$p = 0.04$
						14.3 (± 2.9)	12 months: 28.6 (± 4.3)	35 months: 32.6 (± 3.4)			
						13.7 (± 3.1)	12 months: 27.3 (± 6.1)	35 months: 29.8 (± 5.3) $p = 0.094$			

TABLE 20 Functional outcome scores (*continued*)

Study (first author and year of publication)	Intervention	Shoulder-specific functional scores, mean (± SD or range)								
		ASES			Constant			OSS		
		Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]
Mori 2015[68]	Fascia lata and grade 1–2 infraspinatus atrophy	41.6 (± 13.0)		41 months: 91.3 (± 6.7)	38.7 (± 9.1)		41 months: 78.4 (± 5.7)			
	Fascia lata and grade 3–4 infraspinatus atrophy	39.9 (± 9.9)		67 months: 73.6 (± 10.1)	40.7 (± 0.7)		67 months: 63.9 (± 8.0)			
				$p < 0.001$			$p < 0.0001$			
Tempelaere 2017[69]	Quadriceps tendon				42.9 (17–72)		58 months: 67.5 (41–87)			
	Control				45.7 (22–63)		55 months: 72.1 (21–90)			
							$p =$ NS			
Vitali 2015[43]	Repol Angimesh									
	Control									
Walton 2007[41]	Restore									
	Control									
Yoon 2016[71]	Allocover	50.4 (± 15.3)	1 year: 84.5 (± 12.2)	2 years: 82.5 (± 11.2)	56.3 (± 9.4)	1 year: 79.0 (± 9.5)	2 years: 78.3 (± 12.8)			
	Control	48.9 (± 16.0)	1 year: 84.2 (± 13.1)	2 years: 82.0 (± 15.3)	53.6 (± 13.2)	1 year: 80.0 (± 11.6)	2 years: 75.7 (± 15.7)			
			$p = 0.92$	$p = 0.88$		$p = 0.72$	$p = 0.47$			
Non-comparative studies										
Agrawal 2012[72]	Allopatch				49.7 (13–74)		1 year: 81.1 (45–92)			
							$p = 0.009$			
Audenaert 2006[73]	MERSILENE				25.7 (20–39)		43 months: 72.1 (34–89)			
							$p < 0.001$			
Badhe 2008[74]	Zimmer collagen repair patch				41.5 (13–78)	1 year: 62.5 (50–97)	4.5 years: 62.2 (50–80)			
						$p = 0.0003$	$p =$ NR			
Bektaser 2010[75]	Coracohumeral ligament				45 (± NR)		1 year: 80 (± NR)			
							$p =$ NR			
Bond 2008[76]	GRAFTJACKET	53.8 (39–70)		27 months: 84 (69–100)						
				$p = 0.0001$						

PENN			SST			UCLA			WORC		
Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]
						10.8 (± 1.4)	3 months: 20.9 (± 1.3)	36 months: 24.6 (± 3.3)			
						10.9 (± 1.2)	3 months 11.3 (± 1.4)	36 months: 14.7 (± 2.0) *p* = unclear			
			4.1 (± 2.3)	1 year: 8.8 (± 2.9)	2 years: 8.8 (± 2.9)	23.0 (± 5.5)	1 year: 29.5 (± 4.1)	2 years: 29.5 (± 4.1)			
			4.1 (± 2.6)	1 year: 10.0 (± 2.7) *p* = 0.09	2 years: 10.0 (± 2.7) *p* = 0.60	23.7 (± 5.6)	1 year: 29.8 (± 4.5) *p* = 0.79	2 years: 29.8 (± 4.5) *p* = 0.10			
						18.4 (11–25)		27 months: 30.4 (22–35) *p* = 0.0001			

continued

TABLE 20 Functional outcome scores (*continued*)

Study (first author and year of publication)	Intervention	Shoulder-specific functional scores, mean (± SD or range)								
		ASES			Constant			OSS		
		Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]
Burkhead 2007[77]	GRAFTJACKET									
Cho 2014[78]	Permacol	39.4 (± NR)		21 months: 86.4 (± NR) $p = 0.04$						
Consigliere 2017[79]	DX reinforcement matrix				54 (± 4)	3 months: 65 (± 12) $p < 0.05$	7 months: 75 (± 11) $p < 0.05$	30 (± 8)	3 months: 38.7 (± 12.7) $p > 0.05$	7 months: 47 (± 10) $p < 0.05$
Encalada-Diaz 2011[80]	Polycarbonate polyurethane patch	44 (± NR)	6 months: 61.3 (± NR) $p = 0.008$	12 months: 73.3 (± NR) $p < 0.001$						
Flury 2012[81]	GRAFTJACKET or Artelon				51 (29–74)		6 months: 57 (43–71) $p > 0.05$	21 (7–38)		6 months: 38 (19–45) $p < 0.05$
Giannotti 2014[82]	Zimmer collagen repair patch	38 (± NR)		34 months: 79 (± NR) $p =$ NR	42 (± NR)		34 months: 73 (± NR) $p =$ NR			
Gupta 2012[83]	GRAFTJACKET	66.6 (± NR)		3 years: 88.7 (± NR) $p = 0.0003$						
Gupta 2013[84]	Conexa	62.7		32 months: 91.8 (± 13.3) $p = 0.0007$						
Hirooka 2002[85]	GORE-TEX PTFE									
Lederman 2016[86]	Conexa	48.7 (± 20.2)	1 year: 85.4 (± 18.4) $p < 0.0001$	2 years: 90.4 (± 15.3) $p < 0.0001$	45.4 (± 15.2)	1 year: 68.7 (± 11.3) $p < 0.0001$	2 years: 71.7 (± 9.6) $p < 0.0001$			
Lenart 2015[87]	X-repair	32.8 (± 9.5)		18 months: 74.2 (± 5.0) $p = 0.0001$						
Malcarney 2005[54]	Restore									
Marberry 2013[88]	Artelon				17.1 (± 6.4)		1 year: 67.1 (± 11.6) $p = 0.002$			
Metcalf 2002[89]	Restore									

PENN			SST			UCLA			WORC		
Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]
						9.06 (± NR)		1.2 years: 26.12 (± NR) $p < 0.001$			
						15.4 (± NR)		21 months: 31.2 (± NR) $p = 0.04$			
			3.6 (± NR)	6 months: 6.5 (± NR) $p = 0.02$	12 months: 7.7 (± NR) $p = 0.004$						
			5.0 (± 2.6)	1 year: 9.9 (± 2.7) $p < 0.0001$	2 years: 10.6 (± 2.2) $p < 0.0001$						
50.9 (± 4.2)		18 months: 77.6 (± 5.3) $p < 0.005$									
									34 (± 18)		1 year: 86 (± 12) $p = 0.002$
			NR		NR	9.3 (± NR)		24 months: 19.9 (± NR) $p = 0.01$			

continued

TABLE 20 Functional outcome scores (*continued*)

Study (first author and year of publication)	Intervention	Shoulder-specific functional scores, mean (± SD or range)								
		ASES			Constant			OSS		
		Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]
Modi 2013[90]	GRAFTJACKET							26 (8–40)		1 year: 42 (21–48) $p = 0.001$
Moore 2006[91]	Cadaveric allograft									
Nada 2010[92]	Dacron				46.7 (39–61)		36 months: 84.5 (52–96) $p < 0.001$			
Neumann 2017[93]	Conexa	NR		50 months: 87.8 $p =$ NR						
Petrie 2013[94]	LARS							46.7 (± NR)		3.3 years: 30.6 (± NR) $p < 0.0001$
Petri 2016[95]	Arthroflex	64.5 (± 10.0)		2.5 years: 86.0 (± 12.3) $p = 0.005$						
Petriccioli 2013[96]	SportMesh				47.0 (± NR)		23 months: 69.0 (± NR) $p =$ NR			
Phipatanakul 2009[97]	Restore	36.3 (± NR)		26 months: 71.8 (± NR) $p < 0.01$						
Proctor 2014[98]	X-Repair	26 (± NR)	3 months: 57 6 months: 68 12 months: 71 months $p < 0.05$[e]	42 months: 70 (± NR) $p < 0.05$[e]						
Rhee 2008[99]	Biceps tendon				48.4 (8–70)		32 months: 81.8 (37–96) $p < 0.001$			
Rotini 2011[100]	Acellular human dermal matrix				64 (55–75)		> 1 year: 88 (77–95) $p =$ NR			
Sano 2010[101]	Biceps tendon									
Scheibel 2007[102]	Periosteum				51.8 (25–68)		14 months: 80.9 (73–89) $p < 0.001$			

PENN			SST			UCLA			WORC		
Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]
						12.1 (± NR)		31 months: 26.1 (± NR) $p < 0.001$			
						13.9 (± NR)		26 months: 25.7 (± NR) $p < 0.01$			
			4.2 (1–8)		32 months: 10.2 (8–12)	12.5 (6–19)		32 months: 31.1 (9–35) $p < 0.001$			
			4.5 (1–8)		14 months: 10.7 (8–12) $p < 0.001$						

continued

TABLE 20 Functional outcome scores (*continued*)

Study (first author and year of publication)	Intervention	Shoulder-specific functional scores, mean (± SD or range)								
		ASES			Constant			OSS		
		Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]
Schlegel 2018[103]	Collagen sheet	57.0 (± 3.2)[f]	3 months: 73.9 (± 3.2)[f] $p = 0.0001$	1 year: 89.1 (± 2.8)[f] $p < 0.0001$	57.1 (± 2.8)[f]	3 months: 62.3 (± 5.2)[f] $p = 0.122$	1 year: 81.4 (± 2.2)[f] $p < 0.0001$			
Sclamberg 2004[104]	Restore	60.3 (40–75)		> 6 months: 58.4 (30–95) $p = 0.70$						
Sears 2015[105]	GRAFTJACKET or Tissuemend or Conexa			4.2 years: 67.2 (± 27.9) $p =$ NR						
Venouziou 2013[106]	GRAFTJACKET	23.8 (15–34)		30 months: 72.3 (52–94) $p = 0.001$						
Wong 2010[32]	GRAFTJACKET	NR		> 2 years: 84.1 (± NR) $p =$ NR						

NR, not reported; NS, not significant; PTFE, polytetrafluoroethylene; SD, standard deviation; SEM, standard error of mean; SST, Simple Shoulder Test; WORC, Western Ontario Rotator Cuff.

a Follow-up time typically varied between participants.
b *p*-value refers to the polypropylene group (Repol Angimesh) compared with all other groups.
c *p*-value refers to the Conexa group compared with standard repair only.
d *p*-value refers to debridement compared with standard repair only.
e *p*-value refers to all time points compared with preoperative scores.
f Standard error of mean reported.

PENN			SST			UCLA			WORC		
Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]	Baseline	Intermediate	Final[a]
						18.4 (± NR)	> 2 years: 27.5 (± NR) $p < 0.001$	NR			> 2 years: 75.2 (± NR) $p =$ NR

TABLE 21 Risk of re-tear and complications

Study (first author and year of publication)	Intervention	Safety population (*n*)	Recurrence of rotator cuff tears					Reported? (yes/no)	Complications			
			Definition	Imaging	Time of imaging, months (range)	Absolute risk of re-tear, %	*p*-value		Superficial infection, *n* (%)	Deep infection, *n* (%)	Inflammatory response, *n* (%)	Other, *n* (%)
Randomised comparative studies												
Barber 2012[26]	GRAFTJACKET	22	Incomplete excursion of the repaired tendon to the greater tuberosity with gadolinium leakage	MRA	14.5 (12–14)	15	< 0.01	Yes	0 (0)	0 (0)	0 (0)	Shoulder bursitis, 1 (5)
	Control	20				60			2 (10)	0 (0)	0 (0)	Biceps rupture, 1 (5) Post-traumatic fibrosis, 1 (5)
Bryant 2016[65]	Restore	34	A > 5-mm increase in size of any immediate postoperative defect	MRA	12 (NR)	53	0.33	Yes	0 (0)	1 (3)	0 (0)	Biceps rupture, 1 (3) Unexplained fever, 2 (6)
	Control	28				65			1 (4)	0 (0)	0 (0)	Shoulder manipulation, 1 (4)
Ianotti 2006[35]	Restore	15	Not healed: tear size ≥ size on preoperative MRI Partially healed: smaller tear than preoperative MRI	MRA	12 (NR)	73	0.11	Yes	0 (0)	0 (0)	2 (13)	Wound erythema, 1 (8)
	Control	15				40			0 (0)	0 (0)	0 (0)	0 (0)
Leuzinger 2016[63]	GRAFTJACKET	29	Complete integrity of the repair with no tendon retraction	MRI	6 (NR)	23	0.08	Yes	0 (0)	0 (0)	1 (3)	0 (0)
	Artelon	33				27			0 (0)	0 (0)	1 (3)	0 (0)
	Restore	30				39			0 (0)	0 (0)	1 (3)	0 (0)

Study (first author and year of publication)	Intervention	Safety population (*n*)	Recurrence of rotator cuff tears					Complications				
			Definition	Imaging	Time of imaging, months (range)	Absolute risk of re-tear, %	*p*-value	Reported? (yes/no)	Superficial infection, *n* (%)	Deep infection, *n* (%)	Inflammatory response, *n* (%)	Other, *n* (%)
Non-randomised comparative studies												
Ciampi 2014[40]	Repol Angimesh	52	NR	US	12 (NR)	17	0.001[a]	Yes	0 (0)	0 (0)	0 (0)	0 (0)
	TUTOPATCH	49				51			0 (0)	0 (0)	0 (0)	0 (0)
	Control	51				41			0 (0)	0 (0)	0 (0)	0 (0)
Gilot 2015[42]	Arthroflex	20	NR	US	24 (NR)	10	0.048	Yes	1 (5)	0 (0)	0 (0)	0 (0)
	Control	15				26			0 (0)	0 (0)	0 (0)	0 (0)
Ito 2003[66]	Fascia lata	30	NR	MRI	NR	0	NR	Yes	0 (0)	0 (0)	0 (0)	0 (0)
	Control	17				18			0 (0)	0 (0)	0 (0)	0 (0)
Jeon 2017[67]	Biceps tendon	31	Complete tendon detachment from the footprint of the greater tuberosity or loss of continuity in the midsubstance portion	MRI	6 (NR)	32	0.55	No	–	–	–	–
	Control	33				39			–	–	–	–
Maillot 2018[64]	Conexa	11	N/A	N/A	N/A	N/A	N/A	Yes	0 (0)	1 (9)	0 (0)	Shoulder stiffness, 4 (4)
	Repair alone	12							1 (8)	0 (0)	0 (0)	0 (0)
	Debridement	9							0 (0)	0 (0)	0 (0)	0 (0)
Mori 2013[33]	Fascia lata	24	High signal intensity or tendon discontinuity on one or more T2-weighted images	MRI	NR	21	0.015	Yes	0 (0)	0 (0)	0 (0)	0 (0)
	Control	24				42			0 (0)	0 (0)	0 (0)	0 (0)

continued

TABLE 21 Risk of re-tear and complications (*continued*)

Study (first author and year of publication)	Intervention	Safety population (*n*)	Recurrence of rotator cuff tears					Reported? (yes/no)	Complications			
			Definition	Imaging	Time of imaging, months (range)	Absolute risk of re-tear, %	*p*-value		Superficial infection, *n* (%)	Deep infection, *n* (%)	Inflammatory response, *n* (%)	Other, *n* (%)
Mori 2015[68]	Fascia lata and grade 1–2 infraspinatus atrophy	26	High signal intensity or tendon discontinuity on one or more T2-weighted images (complete defect) or insufficient thickness (partial defect)	MRI	NR	27	< 0.001	Yes	0 (0)	0 (0)	0 (0)	0 (0)
	Fascia lata and grade 3–4 infraspinatus atrophy	19				89			0 (0)	0 (0)	0 (0)	0 (0)
Tempelaere 2017[69]	Quadriceps tendon	23	N/A	N/A	N/A	N/A	N/A	Yes	0 (0)	0 (0)	0 (0)	Knee pain, 12 (52) Patellar fracture, 2 (8) Quads tendon tear, 1 (4) Nerve injury, 1 (4) Knee stiffness, 1 (4)
	Control	27							0 (0)	0 (0)	0 (0)	0 (0)
Vitali 2015[43]	Repol Angimesh	60	NR	MRI	12 (NR)	15	NR	Yes	0 (0)	0 (0)	0 (0)	0 (0)
	Control	60				40			0 (0)	0 (0)	0 (0)	0 (0)
Walton 2007[41]	Restore	16	Thickness of supraspinatus immediately medial to insertion. 0 mm if re-torn	MRI	24 (NR)	60	NR	Yes	0 (0)	0 (0)	4 (21)	0 (0)
	Control	16				58			0 (0)	0 (0)	0 (0)	0 (0)
Yoon 2016[71]	Allocover	21	Sugaya classification grades 4 and 5 were considered re-tears[154]	MRI	12 (NR)	19	0.036	Yes	0 (0)	0 (0)	0 (0)	0 (0)
	Control	54				46			0 (0)	0 (0)	0 (0)	0 (0)

Study (first author and year of publication)	Intervention	Safety population (*n*)	Recurrence of rotator cuff tears					Reported? (yes/no)	Complications			
			Definition	Imaging	Time of imaging, months (range)	Absolute risk of re-tear, %	*p*-value		Superficial infection, *n* (%)	Deep infection, *n* (%)	Inflammatory response, *n* (%)	Other, *n* (%)
Non-comparative studies												
Agrawal 2012[72]	Allopatch	14	Sugaya classification grades 4 and 5[154]	MRI	16.8 (12–24)	14	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)
Audenaert 2006[73]	MERSILENE	41	NR	US	NR	7	N/A	No	–	–	–	–
Badhe 2008[74]	Zimmer collagen repair patch	10	An identifiable gap between the greater tuberosity and the graft	US/MRI	54 (36–60)	20	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)
Bektaser 2010[75]	Coracoacromial ligament	46	N/A	N/A	N/A	N/A	N/A	No	–	–	–	–
Bond 2008[76]	GRAFTJACKET	16	NR	MRI	12 (NR)	19	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)
Burkhead 2007[77]	GRAFTJACKET	17	NR	MRI/CTA	14 (NR)	25	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)
Cho 2014[78]	Permacol	5	Fluid-equivalent signal or discontinuity of the rotator cuff in ≥ 1 T2-weighted images	MRI	8 (6–12)	20	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)
Consigliere 2017[79]	DX reinforcement matrix	10	N/A	N/A	N/A	N/A	N/A	No	–	–	–	–
Encalada-Diaz 2011[80]	Polycarbonate polyurethane patch	10	NR	MRI	12 (NR)	10	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)
Flury 2012[81]	GRAFTJACKET or Arthroflex	8	NR	US/MRI	6 (NR)	Full: 13 Partial: 25	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)

continued

TABLE 21 Risk of re-tear and complications (*continued*)

Study (first author and year of publication)	Intervention	Safety population (*n*)	Recurrence of rotator cuff tears					Reported? (yes/no)	Complications			
			Definition	Imaging	Time of imaging, months (range)	Absolute risk of re-tear, %	*p*-value		Superficial infection, *n* (%)	Deep infection, *n* (%)	Inflammatory response, *n* (%)	Other, *n* (%)
Giannotti 2014[82]	Zimmer collagen repair patch	9	NR	US/MRI	34 (30–45)	0	N/A	No	–	–	–	–
Gupta 2012[83]	GRAFTJACKET	24	Not intact: a full-thickness defect at the graft–tendon or graft–humerus interface	US	36 (NR)	Full: 0	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)
			Partially intact: a partial-thickness defect at the graft–tendon or graft–humerus interface			Partial: 26						
Gupta 2013[84]	Conexa	26	As above (Gupta 2012[83])	US	32 (24–40)	Full: 5	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)
						Partial: 22						
Hirooka 2002[85]	GORE-TEX PTFE	27	NR	Arthrography	NR	11	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)
Lederman 2016[86]	Conexa	61	Complete: ≥ 80% of the size of the original tear in the sagittal plane	MRI	12 (NR)	Full: 15	N/A	Yes	1 (2)	0 (0)	0 (0)	Superficial haematoma, 1 (2)
			Partial: tears between 1 cm and 80% of original size			Partial: 34						
Lenart 2015[87]	X-Repair	13	NR	MRI	18 (14–20)	62	N/A	No	–	–	–	–
Malcarney 2005[54]	Restore	25	NR	Arthroscopy	NR	16	N/A	Yes	0 (0)	0 (0)	4 (16)	0 (0)
Marberry 2013[88]	Artelon	17	NR	MRI	NR	18	N/A	Yes	1 (6)	1 (6)	0 (0)	0 (0)

Study (first author and year of publication)	Intervention	Safety population (*n*)	Recurrence of rotator cuff tears					Reported? (yes/no)	Complications			
			Definition	Imaging	Time of imaging, months (range)	Absolute risk of re-tear, %	*p*-value		Superficial infection, *n* (%)	Deep infection, *n* (%)	Inflammatory response, *n* (%)	Other, *n* (%)
Metcalf 2002[89]	Restore	12	NR	MRI	NR	8	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)
Moore 2006[91]	Cadaveric allograft	32	NR	MRI	34 (3–124)	100	N/A	Yes	0 (0)	1 (3)	1 (3)	0 (0)
Modi 2013[90]	GRAFTJACKET	61	NR	MRI	12	Full: 0 Partial: 17	N/A	Yes	0 (0)	1 (2)	0 (0)	Persistent pain, 1 (2)
Nada 2010[92]	Dacron	21	NR	MRI	36 (30–46)	19	N/A	Yes	0 (0)	1 (5)	0 (0)	0 (0)
Neumann 2017[93]	Conexa	60	Not intact: full-thickness defect at graft–tendon or graft–humerus interface Partial: less than full-thickness defect at graft–tendon or graft–humerus interface	US	50 (24–63)	Full: 5 Partial: 3	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)
Petrie 2013[94]	LARS	31	N/A	N/A	N/A	N/A	N/A	Yes	0 (0)	0 (0)	0 (0)	Persistent pain, 1 (3) Shoulder stiffness, 1 (3)
Petri 2016[95]	Arthroflex	12	NR	MRI	9.9 (0.3–26.3)	17	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)
Petriccioli 2013[96]	SportMesh	10	Bare area between the edge of subscapularis and the bicipital groove Coexistence of fluid in the subacromial subdeltoid bursa and/or fluid in the long head of biceps sheath	US	23 (12–34)	10	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)

continued

TABLE 21 Risk of re-tear and complications (*continued*)

Study (first author and year of publication)	Intervention	Safety population (*n*)	Recurrence of rotator cuff tears					Reported? (yes/no)	Complications			
			Definition	Imaging	Time of imaging, months (range)	Absolute risk of re-tear, %	*p*-value		Superficial infection, *n* (%)	Deep infection, *n* (%)	Inflammatory response, *n* (%)	Other, *n* (%)
Phipatanakul 2009[97]	Restore	11	Partially intact: smaller tear than preoperative imaging. Otherwise not stated	MRA	25 (14–38)	50	N/A	Yes	1 (9)	0 (0)	0 (0)	Skin reaction, 3 (27)
Proctor 2014[98]	X-Repair	18	NR	US/MRI	12	17	N/A	No	–	–	–	–
Rhee 2008[99]	Biceps tendon	31	Fluid-equivalent signal or non-visualisation of supra-, infra- or subscapularis tendon in one or more T2-weighted images	MRI	NR	Full: 21 Partial: 14	N/A	Yes	0 (0)	0 (0)	0 (0)	'Popeye' biceps deformity, 2 (7)
Rotini 2011[100]	Acellular human dermal matrix	5	NR	MRI	12	20	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)
Sano 2010[101]	Biceps tendon	14	Sugaya classification > grade 4 were considered re-tears[154]	MRI	28 (12–51)	7	N/A	Yes	0 (0)	0 (0)	0 (0)	'Popeye' biceps deformity, 1 (7)
Scheibel 2007[102]	Periosteum	20	Fluid equivalent signal in the way of a tendon, discontinuity or retraction	MRI	12	20	N/A	Yes	0 (0)	1 (5)	0 (0)	Ectopic ossification, 4 (20)

Study (first author and year of publication)	Intervention	Safety population (*n*)	Recurrence of rotator cuff tears					Reported? (yes/no)	Complications			
			Definition	Imaging	Time of imaging, months (range)	Absolute risk of re-tear, %	*p*-value		Superficial infection, *n* (%)	Deep infection, *n* (%)	Inflammatory response, *n* (%)	Other, *n* (%)
Schlegel 2018[103]	Collagen sheet	33	NR	MRI	3 + 12 (NR)	N/A	N/A	Yes	1 (3)	0 (0)	0 (0)	Persistent pain, 1 (3) Cardiac event, 1 (3) Possible inflammatory response, 1 (3)
Sclamberg 2004[104]	Restore	11	NR	MRI	(6–12)	90	N/A	No	–	–	–	–
Sears 2015[105]	ECM	16	NR	US/MRI	50 (NR)	63	N/A	No	–	–	–	–
Venouziou 2013[106]	GRAFTJACKET	14	N/A	N/A	N/A	N/A	N/A	Yes	0 (0)	0 (0)	0 (0)	0 (0)
Wong 2010[32]	GRAFTJACKET	45	N/A	N/A	N/A	N/A	N/A	Yes	0 (0)	1 (2)	0 (0)	0 (0)

CTA, computed tomography arthrography; ECM, extracellular matrix; MRA, magnetic resonance arthrography; N/A, not applicable; NR, not reported; PTFE, polytetrafluoroethylene; US, ultrasonography.
a Values refers to polyprophylene patch (Repol Angimesh) vs. control (standard repair). No *p*-value was reported for TUTOPATCH vs. control.

TABLE 22 Pain scores

Study (first author and year of publication)	Intervention	Pain scores, mean (SD or range)									
		VAS					Other pain scales				
		Baseline	Intermediate	*p*-value	Final[a]	*p*-value	Baseline	Intermediate	*p*-value	Final[a]	*p*-value
Randomised comparative studies											
Iannotti 2006[35]	Restore						12.5[b] (± NR)			14 months: 25[b] (± NR)	0.18
	Control						12.0[b] (± NR)			14 months: 29[b] (± NR)	
Non-randomised comparative studies											
Ciampi 2014[40]	Repol Angimesh	8.3 (± 1.0)	2 months: 4.9 (± 0.9)	< 0.001[c]	36 months: 3.3 (± 1.1)	< 0.001[c]					
	TUTOPATCH	8.3 (± 1.1)	2 months: 6.5 (± 1.0)	0.01[c]	36 months: 4.1 (± 1.0)	< 0.001[c]					
	Control	8.2 (± 1.1)	2 months: 7.0 (± 1.1)	< 0.001[c]	36 months: 3.7 (± 1.1)	< 0.001[c]					
Gilot 2015[42]	Arthroflex	6.8 (± 1.6)	12 weeks: 5.3 (± 1.6)	12 weeks: 0.52	96 weeks: 1.3 (± 1.2)	0.013					
			24 weeks: 3.9 (± 1.6)	24 weeks: 0.04							
	Control	6.9 (± 1.1)	12 weeks: 5.8 (± 1.1)		96 weeks: 4.1 (± 1.1)						
			24 weeks: 6.8 (± 1.1)								
Ito 2003[66]	Fascia lata						10.0[d] (± 5.6)			2.9 years: 27.8[d] (± 3.6)	< 0.01[c]
	Control						9.2[d] (± 2.9)			4.2 years: 28.3[d] (± 3.3)	< 0.005[c]

Study (first author and year of publication)	Intervention	Pain scores, mean (SD or range)									
		VAS					Other pain scales				
		Baseline	Intermediate	*p*-value	Final[a]	*p*-value	Baseline	Intermediate	*p*-value	Final[a]	*p*-value
Jeon 2017[67]	Biceps tendon	5.1 (± 1.4)	12 weeks: 3.7 (± 1.5) 24 weeks: 2.2 (± 1.4)	NR	29 months: 1.0 (± 0.8)	0.892					
	Control	5.2 (± 1.4)	12 weeks: 3.9 (± 1.6) 24 weeks: 2.1 (± 1.2)	NR	29 months: 0.9 (± 0.8)						
Maillot 2018[64]	Conexa	7.1 (± 1.2)	12 weeks: 3.5 (± 1.3) 24 weeks: 1.9 (± 1.3)	12 weeks: 1.0 24 weeks: 1.0	24 months: 0.6 (± 0.7)	1.0[e]					
	Repair only	6.9 (± 1.2)	12 weeks: 3.0 (± 1.9) 24 weeks: 1.6 (± 1.3)		24 months: 0.7 (± 0.8)						
	Debridement	7.2 (± 0.8)	12 weeks: 3.2 (± 1.2) 24 weeks: 1.4 (± 1.2)	12 weeks: 1.0 24 weeks: 1.0	24 months: 1.0 (± 0.8)	0.501[e]					
Mori 2013[33]	Fascia lata	7.0 (± 0.9)	12 months: 1.2 (± 0.8)	NR	35 months: 0.3 (± 0.6)	0.028					
	Control	7.0 (± 1.0)	12 months: 1.8 (± 1.7)		35 months: 1.2 (± 1.5)						

continued

TABLE 22 Pain scores (*continued*)

Study (first author and year of publication)	Intervention	Pain scores, mean (SD or range)									
		VAS					Other pain scales				
		Baseline	Intermediate	*p*-value	Final[a]	*p*-value	Baseline	Intermediate	*p*-value	Final[a]	*p*-value
Tempelaere 2017[69]	Quadriceps tendon						5.5[f] (0–14)			58 months: 11.9[f] (3–15)	NS
	Control						7.6[f] (5–13)			55 months: 12.6[f] (5–15)	
Vitali 2015[43]	Repol Angimesh	8.2 (± 1.1)	3 months: 4.9 (± 0.9)	NR	36 months: 3.2 (± 1.1)	Unclear[d]					
	Control	8.4 (± 1.0)	3 months: 6.9 (± 1.1)		36 months: 3.7 (± 1.0)						
Walton 2007[41]	Restore						NR	3 months:[g] 9.9 (± 1.6)	< 0.01	NR	NR
	Control						NR	3 months:[g] 4.0 (± 1.3)		NR	
Yoon 2016[71]	Allocover	6.0 (± 1.9)	1 year: 1.5 (± 2.1)	0.95	2 years: 1.6 (± 1.7)	0.68					
	Control	6.1 (± 1.5)	1 year: 1.6 (± 1.8)		2 years: 1.8 (± 1.9)						
Non-comparative studies											
Agrawal 2012[72]	Allopatch						7.7[f] (± NR)			1 year: 13.6 (± NR)	0.008
Audenaert 2006[73]	MERSILENE						1.3[f] (± NR)			43 months: 13.1[f] (± NR)	< 0.001
Badhe 2008[74]	Zimmer collagen repair patch						6.8[f] (± NR)			4.5 years: 14 (± NR)	0.00003
Bond 2008[76]	GRAFTJACKET						4.6[b] (± NR)			26 months: 9.8 (± NR)	0.0001
Cho 2014[78]	Permacol	6.8 (± NR)			21 months: 0.8 (± NR)	0.041					

Study (first author and year of publication)	Intervention	Pain scores, mean (SD or range)									
		VAS					Other pain scales				
		Baseline	Intermediate	*p*-value	Final[a]	*p*-value	Baseline	Intermediate	*p*-value	Final[a]	*p*-value
Consigliere 2017[79]	DX reinforcement matrix	7.0 (± 2)	3 months: 0.8 (± 0.8)	< 0.05	6 months: 0.6 (± 0.8)	< 0.05					
Encalada-Diaz 2011[80]	Polycarbonate polyurethane patch	5.7 (2–8)	6 months: 3.8 (NR)	0.009	12 months: 2.6 (0–4)	< 0.001					
Gupta 2012[83]	GRAFTJACKET	5.4 (± NR)			3 years: 0.9 (± NR)	0.0002					
Gupta 2013[84]	Conexa	5.1 (± NR)			32 months: 0.4 (± 1.0)	0.002					
Hirooka 2002[85]	GORE-TEX PTFE						9.1[d] (± NR)			44 months: 27.7[d] (± NR)	< 0.0001
Marberry 2013[88]	Artelon						4.5[f] (± 2.9)			1 year: 11.6[f] (± 3.3)	0.002
Modi 2013[90]	GRAFTJACKET	7.0 (4–10)			3.6 years: 0.8 (0–5)	0.001					
Moore 2006[91]	Cadaveric allograft						2.5[h] (± NR)			31 months: 7.9[h] (± NR)	< 0.001
Nada 2010[92]	Dacron	7.0 (5–8)			36 months: 1.0 (0–2)	< 0.001					
Neumann 2017[93]	Conexa	4.0 (± 2.5)			50 months: 1.0 (± 1.6)	< 0.001					
Petrie 2013[94]	LARS	7.7 (± NR)			3.3 years: 4.4 (± NR)	< 0.0001					
Petri 2016[95]	Arthroflex						38.6[i] (± 8.6)			2.5 years: 44.6[i] (± 10.6)	0.506
Petriccioli 2013[96]	SportMesh	7.9 (± 1.1)			23 months: 2.0 (± 1.9)	NR					

continued

TABLE 22 Pain scores (*continued*)

Study (first author and year of publication)	Intervention	Pain scores, mean (SD or range)									
		VAS					Other pain scales				
		Baseline	Intermediate	*p*-value	Final[a]	*p*-value	Baseline	Intermediate	*p*-value	Final[a]	*p*-value
Phipatanakul 2009[97]	Restore	6.6 (± NR)			26 months: 2.2 (± NR)	< 0.01					
Rhee 2008[99]	Biceps tendon	At rest: 2.0 (0–7)			32 months: 0.3 (0–5)	< 0.001					
		On exercise: 6.6 (3–10)			32 months: 1.4 (0–10)	< 0.001					
Sano 2010[101]	Biceps tendon						13.1[d] (± 2.5)			28 months: 22.9[d] (± 5.1)	0.002
Scheibel 2007[102]	Periosteum						7.9[f] (6–12.5)			14 months: 14.0[f] (12–15)	< 0.001
Schlegel 2018[103]	Collagen sheet	4.2[i] (± 0.4)[j]	3 months: 1.5[i] (± 0.3)[j]	< 0.001	12 months: 0.6[f] (± 0.2)[j]	< 0.0001					
Venouziou 2013[106]	GRAFTJACKET	7.4 (4–9)			30 months: 1.7 (0–5)	0.001					

NR, not reported; NS, not significant; SD, standard deviation; SEM, standard error of mean.
a Follow-up time typically varied between participants.
b Pain subcomponent of PENN score reported.
c Comparison is between pre- and post-treatment values and does not refer to statistical differences between groups.
d Pain subcomponent of Japanese orthopaedic association shoulder score reported.
e *p*-value refers to comparison of Conexa or debridement to standard repair.
f Pain subcomponent of the Constant score reported.
g Pain and function questionnaire developed by L'Insalata *et al.*[150]
h Pain subcomponent of the UCLA score reported.
i Pain subcomponent of the ASES score reported.
j Standard error of mean reported.

TABLE 23 Quality-of-life scores

Study (first author and year of publication)	Intervention	Quality-of-life outcome score, mean (SD or range)										
		SF-12					SF-36					
		Baseline	Intermediate	*p*-value	Final[a]	*p*-value	Baseline		Intermediate	*p*-value	Final[a]	*p*-value
Randomised comparative studies												
Bryant 2016[65]	Restore						PCS	40.1 (± 1.3)	1 year: 46.6 (± 1.4)	PCS: 0.50	1 year: 47.3 (± 1.6)	PCS: 0.56
							MCS	48.8 (± 2.2)	1 year: 55.7 (± 1.4)	MCS: 0.52	1 year: 55.0 (± 1.2)	MCS: 0.83
	Control						PCS	40.5 (± 1.5)	1 year: 48.1 (± 1.7)		1 year: 48.7 (± 1.7)	
							MCS	52.8 (± 2.4)	1 year: 54.3 (± 1.6)		1 year: 55.0 (± 1.2)	
Iannotti 2006[35]	Restore						PCS	50.3 (± NR)			14 months: NR	NS
							MCS	56.3 (± NR)			14 months: NR	
	Control						PCS	51.8 (± NR)			14 months: NR	
							MCS	51.9 (± NR)			14 months: NR	
Non-randomised comparative studies												
Gilot 2015[42]	Arthroflex	PCS	29.2 (± 6.4)	12 weeks: 29.2 (± 5.1) 24 weeks: 36.2 (± 4.4)	12 weeks: 0.68 24 weeks: 0.05	96 weeks: 42.6 (± 10.8)	PCS: 0.05 MCS: 0.04					
		MCS	42.2 (± 12.1)	12 weeks: 45.7 (± 10.8) 24 weeks: 47.3 (± 6.5)	12 weeks: 0.71 24 weeks: 0.06	96 weeks: 64.1 (± 9.3)						
	Control	PCS	30.7 (± 6.0)	12 weeks: 30.3 (± 5.7)		96 weeks: 31.7 (± 9.5)						

continued

TABLE 23 Quality-of-life scores (*continued*)

Study (first author and year of publication)	Intervention	Quality-of-life outcome score, mean (SD or range)									
		SF-12					SF-36				
		Baseline		Intermediate	*p*-value	Final[a]	*p*-value	Baseline	Intermediate	*p*-value	Final[a]	*p*-value
				24 weeks: 30.4 (± 5.0)								
		MCS	43.1 (± 8.2)	12 weeks: 47.1 (± 11.8)		96 weeks: 42.9 (± 10.8)						
				24 weeks: 41.1 (± 8.2)								
Non-comparative studies												
Encalada-Diaz 2011[80]	Polycarbonate polyurethane patch	PCS	35.6 (± NR)	6 months: 42.5 (±NR)	0.03	12 months: 40.4 (± NR)	0.13					
		MCS	45.4 (± NR)	6 months: 53.1 (±NR)	0.10	12 months: 51.1 (± NR)	0.32					
Gupta 2012[83]	GRAFTJACKET	48.8 (± NR)				3 years: 56.8 (± NR)	0.03					
Gupta 2013[84]	Conexa	48.4 (± NR)				32 months: 56.6 (± 6.1)	0.04					
Marberry 2013[88]	Artelon	NR				1 year: 'positive change for physical component'	NR					
Petri 2016[95]	Arthroflex	PCS	44.5 (± 8.9)			2.8 years: 52.9 (± 5.7)	0.005					
		MCS	NR			NR	NR					

MCS, Mental Component Score; NR, not reported; NS, not significant; PCS, Physical Component Score; SD, standard deviation.
a Follow-up time typically varied between participants.

EME
HS&DR
HTA
PGfAR
PHR

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