PROTOCOL

Sub-acromial spacer for Tears Affecting Rotator cuff Tendons: a Randomised, Efficient, Adaptive Clinical Trial in Surgery (START:REACTS).

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Contact NAMES and numbers

Role	Name, address, telephone
Sponsor:	University Hospital of Coventry and Warwickshire NHS Trust Clifford Bridge Rd, Coventry, West Midlands CV2 2DX Tel: 02476 965031 Email: R&DSponsorship@uhcw.nhs.uk
Chief Investigator:	Mr Andrew Metcalfe Warwick Clinical Trials Unit Tel: 02476 150925 Email: a.metcalfe@warwick.ac.uk
Trial Manager:	Elke Gemperle Mannion University of Warwick Clinical Sciences Research Laboratories Clifford Bridge Road Coventry, CV2 2DX Tel: 02476 968629 Fax: 02476 968653 Email: e.gemperle-mannion@warwick.ac.uk/ START@warwick.ac.uk

Co-investigators:

Mr Stephen Drew
Consultant Orthopaedic and Shoulder Surgeon, University Hospital of Coventry and Warwickshire NHS Trust
Email: steven.drew@uhcw.nhs.uk

Miss Josephine Fox
Email: josephine@bonesmart.org

Professor Lennard Funk
Consultant Orthopaedic and Shoulder Surgeon, Wrightington, Wigan & Leigh NHS Foundation Trust
Email: lenfunk@shoulderdoc.co.uk

Professor Simon Gates
Professor of Clinical Trials, Warwick Clinical Trials Unit
Email: s.gates@warwick.ac.uk

Professor Charles Hutchinson
Professor of Radiology, Warwick Medical School.
Email: C.E.Hutchinson@warwick.ac.uk

Dr Rebecca Kearney
Associate Professor of Rehabilitation, Warwick Clinical Trials Unit
Email: r.s.kearney@warwick.ac.uk

Mr Thomas Lawrence
Consultant Orthopaedic and Shoulder Surgeon, University Hospital of Coventry and Warwickshire NHS Trust
Email: Tom.Lawrence@uhcw.nhs.uk

Professor James Mason
Professor of Health Economics, Warwick Medical School.
Email: j.mason@warwick.ac.uk

Dr Helen Parsons
Senior Research Fellow, Warwick Clinical Trials Unit
Tel: 02476 572665
Email: H.Parsons@warwick.ac.uk

Dr Nicholas Parsons
Principal Research Fellow, Warwick Medical School
Email: nick.parsons@warwick.ac.uk

Professor Nigel Stallard
Professor of Medical Statistics & Epidemiology, Warwick Medical School
Email: N.Stallard@warwick.ac.uk

Professor Martin Underwood
Professor of Primary Care Research, Warwick Clinical Trials Unit
Email: m.underwood@warwick.ac.uk

Statistician:	Dr Helen Parsons (Trial statistician) Senior Research Fellow, Warwick Clinical Trials Unit Tel: 02476 572665 Email: H.Parsons@warwick.ac.uk Dr Nicholas Parsons (Adaptive methodology) Principal Research Fellow, Warwick Medical School Email: nick.parsons@warwick.ac.uk Professor Nigel Stallard (Adaptive methodology) Professor of Medical Statistics & Epidemiology, Warwick Medical School Email: N.Stallard@warwick.ac.uk
Health Economist:	Prof James Mason Professor of health economics, Warwick Medical School. Email: j.mason@warwick.ac.uk
Trial Steering Committee:	Chair: Rod Taylor Institute of Health Research, University of Exeter Medical School, South Cloisters, St Lukes Campus, Heavitree Road, Exeter EX1 2LU Email: R.Taylor@exeter.ac.uk Dr. Christopher Littlewood Research Institute for Primary Care & Health Sciences Primary Care Sciences Keele University Staffordshire ST5 5BG Email: c.littlewood@keele.ac.uk Prof. Angus Wallace Academic Orthopaedics, Trauma and Sports Medicine, The University of Nottingham, C Floor, West Block, Queens Medical Centre, Nottingham NG7 2UH Tel: Email: angus.wallace@rcsed.ac.uk Mr. Anthony Howard Academic Department of Trauma and Orthopaedics, Leeds Teaching Hospitals NHS Trust, School of Medicine, University of Leeds Email: ed06101ah@students.rcsed.ac.uk

Miss Julie McBirnie
Royal Edinburgh Hospital
Morningside Place
Edinburgh,
EH10 5HF
Email: julie.mcbirnie@gmail.com

Mr. Abel Geoffrey
26 Armorial Road
Coventry
CV3 6GJ
Email: patabel@talktalk.net

John Graham
50 Queen Isobel Avenue
Coventry
CV3 5GF
Email: Graham47@hotmail.co.uk

Prof. Martin Underwood
Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, CV4 7AL
Email: **M.Underwood@warwick.ac.uk**

Mr. Andrew Metcalfe
Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, CV4 7AL
Email: A.Metcalfe@warwick.ac.uk

Data Monitoring Committee:

Chair: Professor Thomas Jaki Medical and Pharmaceutical Statistics Research Unit, Department of Mathematics and Statistics, Lancaster University, Lancaster LA1 4YF
Email: t.jaki@lancaster.ac.uk

Miss Loretta Davies
Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, Windmill Road, Oxford, OX3 7LD
Email: loretta.davies@ndorms.ox.ac.uk

Mr. Stephen Gwilym
Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, Windmill Road, Oxford, OX3 7LD

steve.gwilym@ndorms.ox.ac.uk

For general queries and supply of trial materials please contact the coordinating centre:
Warwick Clinical Trials Unit (WCTU)
Clinical Sciences Research Laboratory
Clifford Bridge Road
Coventry
CV2 2DX
Tel: 02476 968629
Fax:02476 968 653
START@Warwick.ac.uk

Randomisation: INSERT RAND WEB LINK

Emergency Contact
Tel: 02476 150402 (Mon-Fri, 9am to 5pm)
Fax: 02476 151586

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TRIAL SUMMARY

Trial Title	Sub-acromial spacer for Tears Affecting Rotator cuff Tendons: a Randomised, Efficient, Adaptive Clinical Trial in Surgery (START:REACTS).
Internal ref. number (or short title)	Sub-acromial spacer for Tears Affecting Rotator cuff Tendons (START)
Trial Design	Adaptive multi-centre patient-assessor blinded randomised controlled trial using the REACTS model, with a 6-month internal pilot.
Trial Participants	People with symptomatic irreparable tears of the rotator cuff
Planned sample size	212
Treatment Duration	Surgical interventions in both trial arms, with standardised rehabilitation guidelines (duration not fixed).
Follow-up Duration	Clinical (i.e. face-to-face) follow up at 3, 6 and 12 months. Patient reported outcomes up to 24 months.
Planned Trial Period	01/02/2018-01/01/2022
Intervention treatment	Arthroscopic debridement of the subacromial space with insertion of the InSpace Balloon (Orthospace, Israel) performed by sub-speciality trained shoulder surgeons.
Control treatment	Arthroscopic debridement of the subacromial space performed by sub-speciality trained shoulder surgeons (patient and assessor blinded).
Rehabilitation	Post-operative rehabilitation for both groups will include standardised post-operative information, home exercises and a physiotherapy programme.
Aim of study	To implement an efficient adaptive clinical trial design for surgical interventions. We will assess the clinical effectiveness and safety of a sub-acromial spacer balloon for patients with symptomatic irreparable tears of the rotator cuff.
Primary clinical objective	To quantify and draw inferences on observed differences between arthroscopic debridement of the subacromial space and arthroscopic debridement with insertion of the InSpace balloon (Orthospace Ltd, Israel) 12 months after surgery, using the Constant-Murley shoulder score
Secondary objectives	1) To quantify and draw inferences on observed differences between arthroscopic debridement and arthroscopic debridement with insertion of the InSpace balloon (Orthospace, Israel) based on:

	- The Constant-Murley score at three and six months.(2, 3) - Shoulder pain-free range of motion at three, six and 12 months. - Strength of abduction and flexion measured using a hand-held dynamometer at 3, 6 and 12 months. - The Oxford Shoulder Score (OSS) (4) and the Western Ontario Rotator Cuff index(WORC) (5, 6) at three, six and 12 months. - The EQ-5D-5L at three, six and 12 months. (7, 8) - Patient global impression of change (PGIC) (9) - The incidence of adverse events. Patient Reported Outcome Measures (PROMs) and complications will be collected at 24 months. 2) To perform an economic analysis, assessing the comparative cost-effectiveness of the two treatments. 3) To develop appropriate statistical tools to allow efficient seamless adaptive phase II/III type clinical trial designs, with early futility stopping, to be implemented in the setting of three time-points (three, six and 12 months). (10) 4) To explore the challenges of supporting adaptive design decision-making with net benefit and expected value of information approaches to health economic analyses.
Radiology sub-study	To compare the acromio-humeral distance on MRI scans in a sample of participants with and without the balloon at six weeks and six months after treatment, to assess the proposed mechanism of action of the balloon when it is still inflated (at six weeks) and to determine if the effect persists when it has deflated (at six months).
Statistical sub-study	To compare the use of frequentist and Bayesian design and analysis on the conduct and interpretation of an adaptive clinical trial in surgery with particular reference to decision making by data management committees during the study and by clinicians, commissioners and other stakeholders at the conclusion of the trial.

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AD	Arthroscopic Debridement*
AE	Adverse Event
AHD	Acromio-humeral distance
ARUK	Arthritis Research UK
BOA	British Orthopaedic Association
BESS	British Elbow and Shoulder Society
CA	Coraco-Acromial (a small ligament in the shoulder)
CI	Chief Investigator
CM	Constant Murley score
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CRN	Clinical Research Network
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
ESSES	European Society for Shoulder and Elbow Surgery
FSE	Fast spin echo
GCP	Good Clinical Practice
HTA	Health Technology Assessment panel
ICF	Informed Consent Form
ICTMC	International Clinical Trials Methodology Conference
IP	Intellectual Property
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
KL	Kellgren-Lawrence grade

MCID	Minimal Clinically Important Difference
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NIHR	The National Institute for Health Research
OSS	Oxford Shoulder Score
PI	Principal Investigator
PIC	Participant Identification Centre
PPI	Patient & Public Involvement
PROMs	Patient Reported Outcome Measures
PROSPERO	International prospective register of systematic reviews
QoL	Quality of Life
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
RDS	Research Design Service
REACTS	Randomised, Efficient, Adaptive Clinical Trial in Surgery
REC	Research Ethics Committee
R&D	Research and Development
SAD	Sub-acromial decompression
SCT	Society for Clinical Trials
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SPM	Senior Project Manager
START	Subacromial spacer for Tears Affecting Rotator cuff Tendons (Study title)

TC	Trial Co-ordinator
TTC	Trainee Trial Co-ordinator
TMG	Trial Management Group
TSC	Trial Steering Committee
UNTRAP	University/User Teaching and Research Action Partnership
VAS	Visual Analogue Scale
WCTU	Warwick Clinical Trials Unit
WORC	Western Ontario Rotator Cuff

*[Arthroscopic Debridement (AD) refers to an arthroscopic debridement of the subacromial space with removal of inflamed tissue (bursectomy) and unstable remnants of the torn tendon, limited bone resection of the acromion, retention of the coraco-acromial ligament, and biceps tenotomy (if not already torn)].

1. BACKGROUND

1.1 Trial designs in new surgical procedures

The safe introduction of new surgical procedures is essential to the delivery of high quality surgical care for patients. New procedures can result in a step-change improvement in treatment, but also introduce new risks, and substantial costs. Major harm can be done when a misunderstood or well-intentioned intervention is used widely across the health service before it is formally evaluated. (11, 12)

While pharmaceuticals undergo rigorous clinical trials before introduction, this is not the case for surgical procedures, which are often introduced purely on basic science (such as cadaveric testing) or small case series data only.(13) There is a need to develop new processes and methodology to introduce surgical procedures safely, with early randomised controlled trials in specialist centres used to determine whether a treatment is likely to be safe, clinically effective and cost effective prior to widespread uptake.(13)

When surgical procedures are assessed rigorously, these currently tend to be large, costly and time consuming randomised trials focused on patient reported outcomes or health related quality of life scores. Large pragmatic surgical trials are expensive (typically NIHR HTA, £1-2M) and typically take five years from award to completion (e.g. FiXDT, WOLLF, AIM), even disregarding the time taken over feasibility and pilot studies.(14-16) Many of these trials produce reliable and statistically precise evidence, but need to recruit large numbers over extended time periods.(12, 14) Costly, ineffective or unsafe treatments may be used for many years before they are removed from practice. There is a need for an earlier, more efficient study design to assess efficacy and inform adoption decisions.

If early trials are not performed, or are inadequate, then novel treatments may be restricted by NICE, which can delay the introduction of a beneficial technique; for example, this was the case for autologous chondrocyte implantation.(17) If a procedure is beneficial, good quality evidence is needed to ensure that patients across the NHS are able to receive the treatment. A trial design is required that can efficiently and rapidly determine if an intervention is ineffective or if there are major safety concerns, but can also adapt to demonstrate superiority if the intervention is a genuine improvement on standard care.

Adaptive trial designs are becoming increasing popular, and their use has been encouraged by major journals, the US Food and Drug Administration, and NIHR panels.(18-20) Adaptive trial designs allow prospectively planned modifications (such as stopping the study or dropping an intervention) based on emerging findings as the trial proceeds, while preserving the scientific validity and integrity of that trial. This more flexible strategy typically reduces costs and shortens time-scales, without compromising the integrity, statistical power or rigour of the study.(18, 21, 22) Adaptive designs have become well accepted in pharmaceutical and oncology trials but are rare in surgery.(23) This is despite the potential benefit of reducing the number of people exposed to a procedure that may be unnecessary, or even harmful.(18, 23, 24)

Efficiency savings in terms of cost and time can be substantial (a 40% reduction in sample size in one study) without a substantial loss in power or increase in false positive error rate. The use of adaptive designs which are flexible in their sample size may also avoid the delay associated with prolonged pilot or feasibility studies, as they can be incorporated into the trial without delaying the main study.(10, 25)

A novel approach to the assessment of new surgical procedures is proposed. When a new device is introduced, it should be assessed using a study designed specifically for that purpose. The aim of such

studies should be to provide evidence that a new procedure is able to achieve its stated clinical goals at a cost that is acceptable to the health service, with sufficient confidence that the technique could, if effective, be widely available in the NHS. Future pragmatic trials to assess the generalisability of a technique or its effects on health-related quality of life could be performed later, but this approach would prevent every new procedure from going through such costly and lengthy studies, whilst future large trials would be strengthened by data from this early, focused study design.

These interventions in these trials will initially be performed by established clinicians in high-volume centres who have both the technical skills and capability to take part in efficient trials and will be supported by a strong training programme. We propose an approach that utilises an adaptive study design, which is ideally suited to this setting, improving design efficiency and allowing ineffective techniques to be removed from practice more rapidly and at lower cost, minimising risk to patients both in the study and more widely across the NHS. Where there is good early evidence, the adaptive design would allow the study to progress seamlessly to a pre-defined maximum sample size to assess efficacy at the definitive study endpoint, allowing a new procedure to benefit patients (and inform both NICE and commissioners) with a strong evidence base established early.

We have termed this trial design REACTS (Randomised, Efficient, Adaptive Clinical Trials in Surgery). START will be the first study using this new approach, but further applications for REACTS studies are planned in a range of other specialities, with the aim of establishing this trial design as the future standard for assessing new surgical procedures. In the future, such an approach could be used before a new procedure is introduced into widespread clinical practice. Therefore, this study could potentially change how new surgical procedures are assessed both nationally and internationally.

1.2 Subacromial spacer balloons

Shoulder pain is a common and disabling problem. The population prevalence of shoulder pain is approximately 16% and rotator cuff disease accounts for 70% - 85% of this.(26-29) Surgery for rotator cuff disease has increased seven-fold in eight years, reaching approximately 28,685 cases in 2009/10, when this was last formally studied.(30) Patients with a symptomatic rotator cuff tear present with pain, restricted movement, loss of strength and disability, and the disease is associated with substantial expense to society through both costs of treatment and sick leave.(31-34)

The term ‘rotator cuff’ refers to the muscles and tendons that keep the ball of the humerus in the shoulder socket. The muscles of the rotator cuff include; subscapularis, supraspinatus, infraspinatus and teres minor. An intact rotator cuff functions to keep the humerus centred on the glenoid as the shoulder moves, providing a stable fulcrum for normal gleno-humeral (shoulder) joint motion (https://www.shoulderdoc.co.uk/education/rotator_cuff_mechanics.pdf)(35). A tear in the rotator cuff may result in loss of this stabilising function and lead to pain. The exact cause of pain is unknown but may be due to mechanical impingement between the humerus and the acromion, impingement of torn or loose tissue in the joint, or biological causes such as bursitis or synovitis.(35, 36)

Rotator cuff repair is a widely accepted treatment for symptomatic rotator cuff tears.(37, 38) Numerous factors influence whether a tear can be repaired, including the size of the tear, its chronicity, fatty infiltration of the muscle (atrophy) and the ability to bring the torn end back to its original site without excessive tension. Some tears cannot be repaired (in which case they are called irreparable tears), and the management of these patients can be very difficult.

Symptomatic irreparable rotator cuff tears are a challenging problem to treat, with treatment options including physiotherapy, injections, arthroscopic debridement, partial repair, muscle transfers,

interposition grafts and even shoulder replacements (hemiarthroplasty and reverse shoulder arthroplasty).(39-42) Arthroscopic debridement is commonly used and benefit has been demonstrated in case-series, but it remains a controversial option, with little or no benefit in randomised trials.(43-45)

In 2013**,** the InSpace subacromial balloon spacer (Orthospace, Israel) was introduced into UK orthopaedic practice as a potential treatment option people for people with irreparable tears of the rotator cuff. They were introduced underpinned by case series evidence and a cost of approximately £1250 for the implant.(46) In May 2016 an interventional procedure guidance document was published by NICE, five years following its use in clinical practice, demonstrating very limited evidence for its use at present and therefore it was limited to use in the context of research only; a research recommendation was made to assess its effectiveness.(1)

The InSpace device is a saline-filled, balloon made of biodegradable (dissolvable) synthetic material. It is inserted above the main joint of the shoulder at the end of an arthroscopic debridement after an irreparable tear has been identified. It is simple to deploy and adds less than 10 minutes to the operation.(46, 47) It cushions the humerus from pressing on the bone above it (the acromion) when the deltoid is active and during abduction of the arm, potentially reducing pain. It may also assist in the biomechanics of the shoulder, resisting proximal migration of the humerus under deltoid activity. The device is dissolvable and begins to degrade and deflate from three months. During this time, it is thought to improve rehabilitation of the remaining rotator cuff and deltoid, so that when the device deflates the biomechanics of the shoulder are better preserved.

The safety of the device in rodents has been established, with only one adverse event, a fibrosarcoma that was thought to be unique to rodents.(48) Proof of concept has been established in a series of 20 cases performed for irreparable cuff tears in Slovakia in 2012, and a 5-year follow up paper was published this year.(49, 50) The device has been used in a number of centres across the UK, with three recent conference abstracts from the UK totalling 61 cases.(51-53) These have demonstrated improvements in outcomes from baseline. Complications such as balloon displacement and non-cyst forming synovitis have been reported in a small number of cases (3 out of 61). One retrospective study of 23 patients (12 with the balloon) showed an improvement in outcomes compared to debridement alone(54). There have been no RCTs.

A systematic review of RCTs in rotator cuff tears found improvements in outcome with both conservative care and acromioplasty.(45) Therefore the benefits found in case series may not be unique to the InSpace balloon, although the relative effectiveness of the balloon in comparison to non-operative care or acromioplasty is not known and could still be a substantial improvement.

The device is costly (£1250 for the device alone) but there is no evidence that it is effective clinically. If the device is effective, then it would relieve pain and improve function for patients with a disabling condition that currently has few good alternative treatments and it should be recommended for widespread use. However, if the device is ineffective or harmful, alternative approaches should be sought.

There are two RCTs in progress for this device – a company funded study in the USA which will recruit 184, comparing partial cuff repair with balloon as a stand-alone intervention (clinicaltrials.gov NCT02493660). Partial cuff repair is not a technique that is often used in the UK and is not an appropriate comparator in a UK context. Another pilot study is underway using the device to protect rotator cuff repairs; a different population and indication (led by Prof L Funk, clinicaltrials.gov NCT02208440).

1.3 Aim

Our overarching **aim** is to implement a novel, efficient adaptive clinical trial design for new surgical interventions. Using a topic identified by NICE as a research priority we will assess the clinical effectiveness and safety of a sub-acromial spacer balloon for patients with symptomatic irreparable tears of the rotator cuff. (1)

1.4 Need for a trial

NICE in 2016 assessed this device (IPG558), limiting the procedure to use in the context of research only and have determined this as a research recommendation.(1)

Based on current knowledge and the recent NICE interventional procedures guidance, there is now an urgent need to assess the InSpace Balloon in UK practice to determine if it is effective and should be recommended for widespread use in the NHS, or should be withdrawn from practice.

1.5 Ethical considerations

All required ethical approval(s) for the trial will be sought using the Integrated Research Application System. The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to MRC Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation and University of Warwick Standard Operating Procedures (SOPs). All data will held in accordance with the General Data Protection Regulation 2018 and stored securely and only accessible by trial staff and authorised personnel. The participant data collected through CRFs will be identified only by year of birth and a participant's ID number on the CRF and any electronic database, this will ensure participants' anonymity is maintained.

For most shoulder surgeons in the UK, this patient population would normally undergo arthroscopic debridement (AD) and biceps tenotomy for this condition, and this will be the control arm for the study.(39) Arthroscopic debridement (AD) is considered by many to be the current best surgical practice for people who have failed non-operative care. It is a low risk procedure. There is controversy as to whether an AD provides benefit over non-operative care, although the current trials have been in different patient populations (most often patients with pain and with intact tendons).(45, 55) The recently published CSAW trial did not show benefit for arthroscopic decompression (a similar procedure to debridement) compared to placebo surgery, although this was for a different condition then the one that we are testing, and the comparison between decompression and physiotherapy did show benefit for surgery, with confidence intervals that included the minimally important difference of the Oxford Shoulder Score(55).

Because of its widespread clinical usage for patients with irreparable cuff tears, arthroscopic debridement remains a valid control to test the benefit of the InSpace device, whether as a placebo procedure or as an active control.(56, 57) A pragmatic trial comparing the balloon to physiotherapy would leave ongoing uncertainty if a positive result is demonstrated. If the control procedure is regarded as a placebo, then it is important to recognise that the use of placebo operations in research is justified by recent multiple calls and strong guidelines from the Royal College of Surgeons of England calling for their use.(56, 58) Given the widespread and persisting clinical use of the control operation, many patients would have undergone an arthroscopic debridement outside of the trial, and therefore we believe it remains appropriate to see this as the correct control procedure for this

trial. This issue, the use of blinding, and the need for patient follow-up to collect strength and range of motion for the Constant score, have been discussed with our patient representatives and co-applicants who remain fully supportive of the study.

Based on the early case series data, the balloon itself is a low risk addition to an arthroscopic debridement, with few risks identified at present. Safety data will be actively monitored throughout the study and if an important safety issue was identified the study would be terminated early. The use of an adaptive trial strengthens the safety of the trial design in this sense as the study would be designed to stop early if there is sufficient evidence of harm based on the outcome data, even if major safety issues have not been reported.

The MRI sub-study involves no ionising radiation and the activation of the deltoid muscle will be controlled so that it does not cause pain, so we do not anticipate this being an issue.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of capability is received by Warwick Clinical Trials Unit.

1.6 CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement (Lancet 2001, **357**: 1191-1194).

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

START is a participant and assessor blinded, adaptive, multi-centre RCT based in the UK comparing arthroscopic debridement using the InSpace balloon to arthroscopic debridement alone, performed using the REACTS framework.

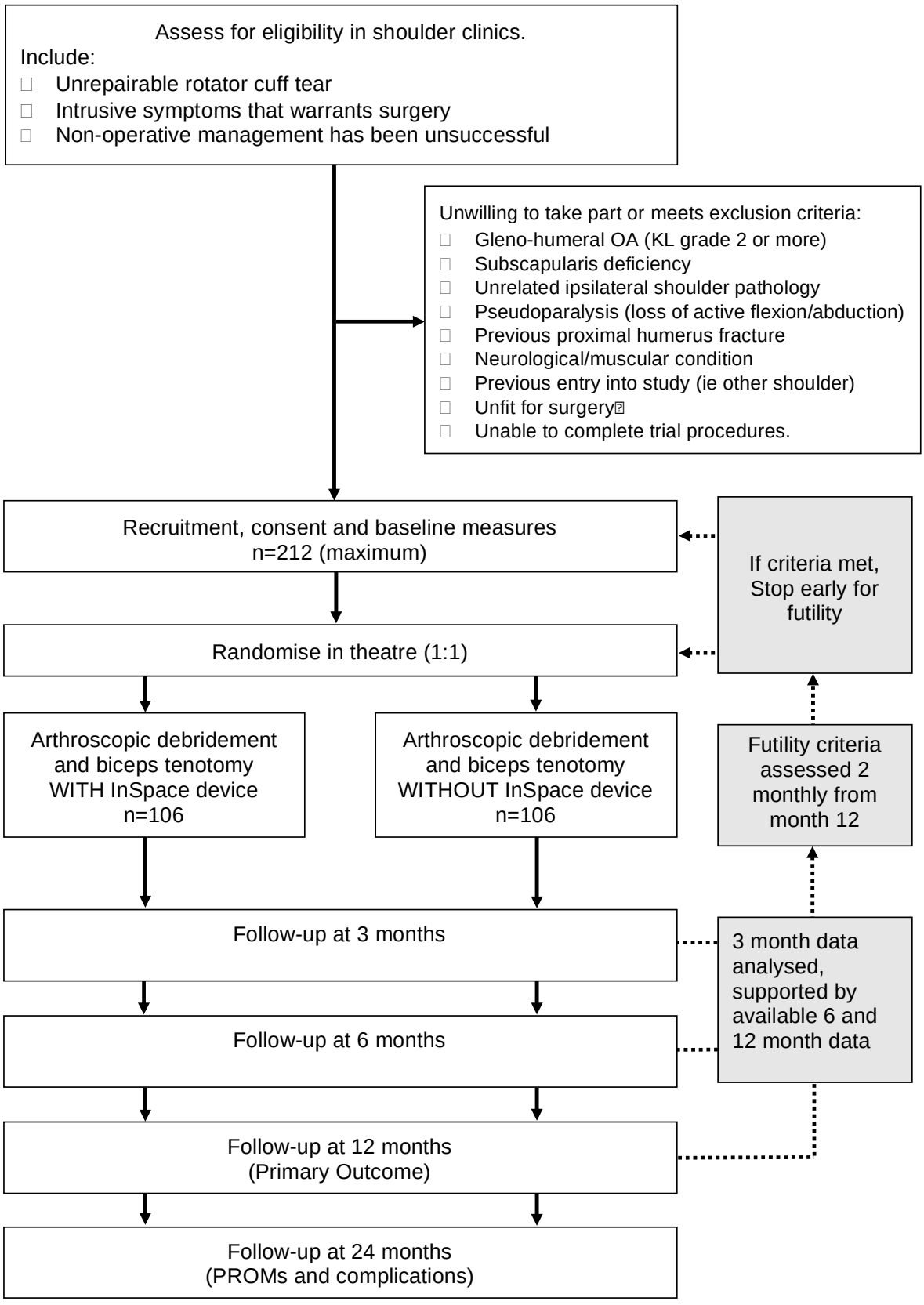

Figure 1 Trial flow diagram

2.2 Aims and objectives

2.2.1 Primary objective

Our **primary clinical objective** to quantify and draw inferences on observed differences between arthroscopic debridement of the subacromial space and arthroscopic debridement with insertion of the InSpace balloon (Orthospace Ltd, Israel) 12 months after surgery, using the Constant-Murley shoulder score(2, 3).

2.2.2 Secondary objective

Secondary clinical objectives are:

1) To quantify and draw inferences on observed differences between arthroscopic debridement and arthroscopic debridement with insertion of the InSpace balloon (Orthospace, Israel) based on:

- The Constant-Murley score at baseline, 3 and 6 months.(2, 3)
- Shoulder pain-free range of motion at baseline, 3, 6, and 12 months.
- Strength of abduction and flexion measured using a hand-held dynamometer/isometer at baseline, three, six, and 12 months.
- The Oxford Shoulder Score (OSS) (4) and the Western Ontario Rotator Cuff index (WORC) (5, 6) at baseline, 3, 6, 12 months and 24 months.
- The EQ-5D-5L at baseline, 3, 6, and 12 months and 24 months. (7, 8)
- Patient global impression of change (PGIC) at, 3, 6, 12 months and 24 months (9)
- Adverse Events up to 12 months and complications at 24 months

2) To perform an economic analysis, assessing the comparative cost-effectiveness of the two treatments.

3) To compare the acromio-humeral distance on MRI scans in a sample of participants with and without the balloon at six weeks and six months after treatment, to assess the proposed mechanism of action of the balloon when it is still inflated (at six weeks) and to determine if the effect persists when it has deflated (at six months).

Methodological objectives are:

4) To develop appropriate statistical tools to allow efficient seamless adaptive phase II/III type clinical trial designs, with early futility stopping, to be implemented in the setting of three time-points (3, 6 and 12 months). (10)

5) To compare the use of frequentist and Bayesian design and analysis on the conduct and interpretation of an adaptive clinical trial in surgery with particular reference to decision making by data management committees during the study and by clinicians, commissioners and other stakeholders at the conclusion of the trial.

6) To explore the challenges of supporting adaptive design decision-making with net benefit and expected value of information approaches to health economic analyses.

2.3 Outcome measures

2.3.1 Efficacy

Primary outcome: The **Constant-Murley score at twelve months**(2, 3). The score is widely used in shoulder trials, is well accepted by surgeons, has good reliability and responsiveness, and has been improved by published standardised protocols. (2, 3, 45, 49, 59-62) This scoring system has been adopted by The European Society for Shoulder and Elbow Surgery (ESSES). Based on our meta-analysis the Constant-Murley typically reaches a plateau by 12 months after any intervention for a rotator cuff tear, whilst the 24-month Constant score does not give sufficient additional value to justify increase in the cost of the research (note that PROMs will be collected at 24 months).

This scoring system consists of four variables that are used to assess the function of the shoulder. The subjective variables are pain and activities of daily living (ADL) (sleep, work, recreation / sport) which give a total of 35 points and the objective variables are range of motion and strength which give a total of 65 points. Each component can be reported separately or can be combined to give a score out of 100. A standardised protocol will be adopted and used in the study to ensure consistency across sites and therapists, with training provided (typically at at the SIV). The strength measurements will be collected using the supplied ISO Isometer (IDO Isometers, Innovative Design Orthopaedics Limited, Reading, UK) and the range of motion will be collected using a long-handled goniometer.

Secondary outcomes (baseline, three, six, & 12 months):

- The **Constant-Murley score** at baseline, 3, and 6 months: as outlined above. (2, 3)
- **Range of pain-free movement of the shoulder** at baseline, 3, 6 and 12 months measured using a long-handled goniometer.
- **Strength of shoulder abduction and flexion** at baseline, 3, 6, and 12 months measured by a handheld dynamometer/isometer (the readings taken using the standardised protocol for the Constant score).
- **The Oxford Shoulder Score (OSS)** at baseline, 3, 6 and 12 months. The OSS is a validated scoring system used to assess the degree of pain and disability caused by shoulder pathology.(4) It is a PROM with 12 questions sensitive to clinical change, is simple to complete and has proved to be consistently reliable in determining the outcome from shoulder surgery. A higher score corresponds with a better outcome.
- **Western Ontario Rotator Cuff index** (5, 6) at baseline, 3, 6 and 12 months: The Western Ontario Rotator Cuff Index (WORC) is a condition-specific self-reported instrument to assess 'quality of life' (QoL). It consists of 21 visual analogue scale (VAS) items organised as five subscales: physical symptoms, sports/recreation, work, lifestyle, and emotions. Each item in WORC has a possible score from 0–100 (100 mm VAS). Scores can be computed for individual subscales and summated for a total score, which can range from 0–2100, with a higher score representing lower quality of life. To present this in a more clinically meaningful format, the distance from the left side of the line is measured and recorded to the nearest 0.5 mm, calculated for a score of out of 100, and summed for each subscale (physical symptoms/600, sports and recreation/400, work/400, lifestyle/400, and emotions/400). The subscale scores are summed and reported as a percentage of normal.
- **EQ-5D-5L** at baseline, 3, 6 and 12 months: Is a validated, generic health-related quality of life measure consisting of five dimensions each with a 5-level answer possibility. Each combination of answers can be converted into a health utility score. It has good test-retest

reliability, is simple for participants to use, and gives a single preference-based index value for health status that can be used for broader cost-effectiveness comparative purposes.(7, 8)

- **Resource use** at, 3, 6 and 12 months: The primary analysis will concentrate on direct intervention and healthcare/personal social services costs, while wider impact (societal) costs will be included within the sensitivity analyses. Relevant resource use questionnaires will be administered to participants at baseline and all follow-up points, to collect resource use data associated with the interventions under examination.

- **Patient global assessment of change** (PGIC) score, taken at3, 6, and 12 months. A simple 7-point scale assessing perception of improvement.(9)

- **Analgesia use** will be recored as current analgesia taken (drug, and approximate frequency).

- **MRI Scans** (sub-study of 56 patients, six-weeks & six-months post-surgery): see 'additional mechanistic study' below

We will also collect patient reported outcome measures (OSS, WORC, EQ-5D-5L, PGIC) at 24 months and adverse events up to 12 months.

2.3.2 Safety

- Adverse event data (see section 5).

- Participants will be asked in the3, 6 and 12 months questionnaire if they have had any adverse events. The PIs will be asked to comply with the procedure to report SAEs within 24 hours of becoming aware of the event to the START trial office.

2.4 Eligibility criteria

Patients are eligible to be included in the trial if they meet the following criteria:

2.4.1 Inclusion criteria

1. **Rotator cuff tear deemed by the treating clinician to be technically irreparable (to be confirmed intra-operatively)*.** This pragmatic definition has been chosen to reflect current practice and allow results to be generalised. Rotator cuff tears are often classified by their size (and this will be accounted for in the final analysis as a covariate) but large or massive tears may be repairable, and many factors other than size influence whether a tear can be repaired (such as chronicity, retraction of the tendon ends, fat infiltration in muscle). A 'size' based definition would exclude potentially participants who would be suitable for this trial, and ineligible potential participants can be excluded at arthroscopy. However, a potential participant who has a tear that is technically repairable, such as a small tear, but is unsuitable for repair due to age or co-morbidities, is not eligible for this study.

2. **Intrusive symptoms (pain and loss of function) which in the opinion of the treating clinician warrants surgery.**

3. **Non-operative management has been unsuccessful.** The exact nature of non-operative management will be left pragmatically to the treating clinician, although commissioning

guidelines indicate that a period of physiotherapy is recommended. Steroid injection has not been considered a necessary part of non-operative management, as whilst it is an option, there is little evidence for lasting benefit in irreparable cuff tears. (63)

2.4.2 Exclusion criteria

4. **Advanced gleno-humeral osteoarthritis on pre-operative imaging (in the opinion of the treating clinician).** Advanced gleno-humeral OA may be interpreted as Kellgren Lawrence grade 3 or 4 changes on routine pre-operative radiographs(64), or the MRI equivalent if radiographs have not been taken.

5. **Subscapularis deficiency*, defined as a tear involving more than the superior 1cm (approximately) of the subscapularis if repaired, or any tear that is not repaired.** Minor, repairable, upper border tears are common and a repairable upper-border tear is not considered a contra-indication by the manufacturer.

6. **The treating clinician determines that interposition grafting or tendon transfers are indicated.** Some surgeons prefer to treat younger, more active patients with operations designed to restore or replace rotator cuff function. There is no established age criterion for this, however and the decision is based on multiple factors including age, co-morbidities, occupation, level of activity, and surgeon preference.

7. **Pseudoparalysis (an inability to actively abduct or forward flex up to 20°), as determined by the treating clinician.**

8. **Unrelated, symptomatic ipsilateral shoulder disorder that would interfere with strength measurement or ability to perform rehabilitation**

9. **Other neurological or muscular condition that would interfere with strength measurement or ability to perform rehabilitation, in the opinion of the treating clinician.**

10. **Previous proximal humerus fracture that could influence shoulder function, as determined by the treating clinician.**

11. **Previous entry into the present trial (i.e. other shoulder).**

12. **Unable to complete trial procedures.**

13. **Age under 18**

14. **Unable to consent to the trial.**

15. **Unfit for surgery as defined by the treating clinician.**

[*criteria regarding whether the tear is technically repairable, and the integrity of the subscapularis are unreliably assessed by pre-operative imaging and will be reassessed in theatre, prior to randomisation. If the patient is not eligible they will be treated according to the best judgement of the surgeon at the time.]

2.5 Site Staff Training

The Trial Manager will provide training prior to recruitment to the local Principal Investigator (PI) and all research team members who will be responsible for conducting trial related procedures including confirming eligibility, obtaining consent, collecting baseline data and subsequent SAE reporting. The trial team will perform site initiation visits and will provide training tips via a presentation outlining the overview of the trial (key personnel, protocol, management and oversight) case report form completion, trial specific training (surgical plan, rehabilitation package and outcome assessment training), SAE reporting, withdrawals, screening log and data clarifications. A training log will be used to document who has received training and this log will be held in the ISF, research staff taking part in the study will sign the site delegation log and update the trial team when a new member joins the research team or the local PI changes.

Participating surgeons will have the opportunity to attend one of two training events, one in spring 2018 (a cadaveric surgical workshop) and another to coincide with the British Elbow and Shoulder Society (BESS) annual meeting – the latter meeting will not include cadaveric training. During these events, the surgical technique for the arthroscopic debridement and the InSpace balloon will be reviewed for the study and advice about rehabilitation plans and trial processes will also be given. In addition to this, ad-hoc training sessions will also be provided for site staff as required. A surgical training manual and/or video will be produced to educate surgeons (using the UHCW standard consent form for capturing surgical videos for educational & public use) and it will be recorded whether surgeons have read/watched this. A representative of Orthospace may be present during each case to offer technical advice in the use of the balloon to ensure that it is correctly deployed according to manufacturer's instructions. This will be co-ordinated by the site staff in communication with Orthospace.

2.6 Participant identification / Screening

Potential participants will be identified by the attending clinical team by clinicians in intermediate or secondary care clinics, or from the surgical waiting list. Where a persons first contact with intermediate or secondary care is not in a specialist shoulder clinic, Patient Identification Centre (PIC) sites will be considered based on the processes in local sites. Initial identification will be performed by the normal clinical team, if this is not a shoulder surgeon or a suitably trained member of staff, a referral will be made to the appropriate clinic to assess eligibility.

The attending clinician will confirm appropriateness for study eligibility on a CRF based on clinical assessment and standard care pre-operative imaging for that site (this is typically MRI or ultrasound depending on local protocols). Potential participants suitable for inclusion will be given information about the study and invited to discuss the study further with a member of the research team. A member of the local research team will carry out the informed consent process (see 2.7), enrolment and baseline data collection. This process will be detailed further in the quality assurance monitoring plan held at WCTU.

Participants will be placed on the waiting list with a typical wait of up to twelve weeks following entry into the study. The eligibility will also be confirmed by the operating surgeon intra-operatively and patients may be excluded at this stage if there is a discrepancy between the imaging findings and the operative findings; although this is likely to be infrequent. This allows a participant who has been recruited to the study to be withdrawn if they are not found to be eligible intra-operatively (such as finding that a rotator cuff tear can be repaired). The participant will be informed by letter that they are no longer taking part in the study.

All people who meet the study entry criteria will be checked for eligibility and recorded on the monthly screening log. Eligible potential participants who are willing to be approached by a suitably trained member of the research team will be provided with verbal and written information about the study, and will have the opportunity to discuss and ask questions in regards to the study.

2.7 Informed consent

The investigator or their nominee, e.g. from the research team (research associate or research nurse) will provide both written and verbal information to inform the patient of all aspects pertaining to participation in the study. The PI retains overall responsibility for informed consent at their site and must ensure that any person listed on the site delegation log with the delegated responsibility to participate in the informed consent process is duly authorised, trained and competent. The Investigator or their nominee will provide the potential participant with verbal and written information regarding the study and also answer any questions that the patient may have concerning study participation. The potential participant will be provided with a study information sheet.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the study, the participant information sheets, and consent form. For sites in Wales, to comply with the Welsh Language Act 1993, the Participant Information Sheets and Consent forms will be translated into Welsh or provided bilingually where this is requested by a potential participant.

Potential participants will be given adequate time to consider the information and will be invited to give their consent to become participants in the trial. People who wish to take more time to consider participation will be given the opportunity to do so, and will be offered the option of a further visit, or they will be provided with a consent form to take away, sites will follow up with a telephone call for further clarification and ask if the they agree to participate. If the potential participant agrees they will be requested to return the signed consent form by post in a pre-paid envelope or alternatively a follow up visit will be arranged. As there is a delay of a number of weeks before randomisation (the waiting list for surgery), people who have entered the study will still have the option to withdraw before treatment starts if for any reason they change their mind.

All participants will provide written, signed and dated, informed consent. Trial procedures including baseline assessments will not be undertaken until the informed consent form has been signed and dated by the participant.

Sites which agree to take part in the additional MRI substudy as well as the main study will be provided with a combined main and sub-study patient information sheet and consent form (see section 4).

The investigator or their nominee and the participant must both sign and date the consent form. One copy of this will be kept by the participant, one will be kept by the investigator, and a third will be retained in the patient's hospital record.

Any new information that arises during the trial that may affect the participant's participation in the trial will be discussed with the participant and, if applicable, continuing consent will be obtained using an amended consent form.

Participants' GPs may be informed by letter that they are taking part in this clinical trial (but will not be told the allocation). Participants may decline for their GP being informed of their participation in the trial involvement by not initialling the appropriate box on the consent form.

It will be explained that entry into the study is entirely voluntary and the right of a patient to refuse participation without giving reasons will be respected and recorded on the screening log. They may be provided with a contact point where he/she may obtain further information about the trial if requested. The participant will remain free to withdraw from the study at any time without giving reasons and without prejudice to any further treatment (see 2.8.2).

2.8 Randomisation

2.8.1 Randomisation

Participants will be randomly allocated (1:1) to the two treatment groups via a central computer-based randomisation system provided by the Warwick Clinical Trials Unit (WCTU, independent of the study team). This will be performed by minimisation with a random factor, with a 70% weighting towards balance across the whole study, using site, gender and age group (<70 years and ≥70 years, based on age distribution of previous studies) and cuff tear size (as assessed by the operating surgeon, ≥3cm or <3cm, commonly used as the definition between small/medium and large/massive cuff tears) as strata.

Randomisation will be performed, by theatre staff, using an online system in a separate room to maintain blinding, after the intra-operative findings have been confirmed and will be communicated to the surgeon after the debridement has been performed. A back-up automated telephone system will be available 24 hours.

Warwick Clinical Trials Unit

Online Randomisation Weblink:

First back-up: Automated telephone randomisation (24 hours): +44 (0) 24 7693 7487

Second back-up: Manned telephone randomisation service (Mon-Fri 9am-5pm):
+44 (0) 24 7615 0402, Fax +44 (0)24 7615 1586
.

Participants will be randomised strictly sequentially at site level, as participants are eligible for randomisation. Allocation concealment will be maintained by an independent randomisation team who will be responsible for the generation of the sequence and will have no role in the allocation of participants. Blinding and emergency unblinding procedures are documented in section 2.10.

Stickers may be used to on the participant's clinical notes to flag their inclusion in the trial (without recording allocation), depending on local site arrangements for flagging inclusion in trials.

2.8.2 Withdrawals, exclusions and moves out of region

Participants may be discontinued from the trial treatment and/or the trial at any time without prejudice. Unless a participant explicitly withdraws their consent, they will be followed-up wherever possible and data collected as per the protocol until the end of the trial. Should a participant withdraw from the trial they will continue to be treated as per normal routine postoperative management, follow-up and clinical practice. Data collected up to the point of withdrawal will be retained.

Unless a participant explicitly withdraws their consent, they will be followed-up wherever possible and data collected as per the protocol until the end of the trial. Multiple contact details will be recorded such as collection of addresses and telephone numbers, mobile telephone numbers and email addresses and contact details of next of kin to prevent loss to follow up. This information will be held separately from the trial data to uphold anonymisation. If the participant is lost to follow up at a certain time point, reasonable efforts will be used to acquire outcome data at each time point. Where they cannot attend for their primary outcome measure, and alternative arrangements cannot be made for the measure to be taken at another time or place, then secondary outcome measures will still be collected as per protocol, unless they explicitly withdraw.

Particpants who are registered, but not randomised, may also withdraw at any time without predjudice. In this situation, they will not be considered to have entered the study and will continue to be treated as per normal routine postoperative management, follow-up and clinical practice. Data collected up to the point of withdrawal will be retained but they will not be followed up.

Participants may be withdrawn from the trial at the discretion of the investigator and/or TSC due to safety concerns.

Criteria for prematurely stopping the trial will be determined as part of the initial statistical work package and in discussion with the trial steering committee, and are described in more detail later in the protocol. The Chief Investigator or sponsor may prematurely stop the study, outside of the processes determined by the adaptive design on the advice of the TSC and DMC or on safety grounds.

2.9 Trial treatments / intervention

2.9.1 Trial treatment(s) / intervention

Group 1 – Standard Arthroscopic debridement (control): The control intervention will be an arthroscopic debridement of the subacromial space with removal of inflamed tissue (bursectomy) and unstable remnants of the torn tendon, limited bone resection of the acromion, retention of the coraco-acromial (CA) ligament and biceps tenotomy (if not already torn). The anaesthetic (general+/-regional block) will be left to the choice of the anaesthetist but will be recorded. Within the confines described in a trial specific surgical guideline (to be produced by the trial team in conjunction with an expert surgical group), surgeons may use their normal surgical technique.

Group 2 – Standard Arthroscopic debridement plus insertion of InSpace balloon (Intervention): Arthroscopic debridement, as described above, with insertion of the InSpace Balloon performed by sub-speciality trained shoulder surgeons. The same arthroscopic debridement will be performed as described in group 1 and the allocation will be confirmed intra-operatively. If allocated to the balloon procedure, the companies recommended surgical technique will be followed for sizing, insertion and deployment of the balloon. This is a short procedure that does not add greatly to the surgical time.

For both groups, fidelity will be assessed with an operative record form and an arthroscopic photograph (posterior and lateral portal photographs after debridement for both groups, and a photograph from the posterior portal just before balloon inflation in the balloon group to demonstrate balloon position).

2.9.2 Rehabilitation

Post-operative rehabilitation for both groups will include standardised post-operative information, home exercises and a physiotherapy programme developed by an expert panel during the set-up phase of the trial.

The rehabilitation programme will be developed by:

- Collection of rehabilitation protocols from participating sites
- Assimilation of these protocols by the trial team and presentation of this and the findings of a literature scoping exercise to a group of expert physiotherapists (this may be performed online or in person depending on the complexity of the proposed protocol and the consistency of protocols used in partipating sites).
- An expert consensus will be achieved amongst the group of physiotherapists and a physiotherapy protocol and home exercise package will be produced by the trial team and ratified by the expert group.

2.9.3 Deviations

The delivery of the trial interventions will be recorded on a surgical CRF which will be used in the fidelity assessment along with an arthroscopic photograph (at the end of the debridement for both groups and once the balloon has been inflated for group 2, see 3.9.1) which will be assessed by an expert member of the trial team to determine if the appearance at the end of the procedure is acceptable, with reliability of the rater assessed in a sub-group of the images.

Completion of the post-operative rehabilitation package will be assessed by self-report on the three month CRF, with the opportunity on the six and twelve month CRFs to record ongoing rehabilitation if this has persisted beyond three months. Whilst all patients should be offered rehabilitation according to the protocol, failure to comply with rehabilitation will not constitute failure or lack of compliance with the treatment, as it is the surgical intervention which is primarily being tested and the rehabilitation is being delivered using a pragmatic approach.

2.10 Blinding

2.10.1 Methods for ensuring blinding

Randomisation will be performed by theatre staff, using an online system, after the intra-operative findings have been confirmed. Theatre staff will be asked not to discuss the balloon and to communicate the allocation by using methods such as holding up a piece of paper with the allocation clearly written on. Drapes will be used to obscure the participant's view – this is normal practice for the procedure. If the participant is awake, the arthroscopic screens will be positioned in such a way that the patient is unable to see the screens.

The incisions required for the two operations are similar and there is no external way in which the patients will be able to detect the presence or absence of the balloon. One of the incisions (the 'lateral portal') will need to be slightly larger to insert the balloon – 1.5cm as opposed to 1cm. This size of incision will be used for all participants, which is a very small change from standard care and is very unlikely to have a negative effect on any participant. There is no increase in risk due to the size of the portal.

Apart from the surgical team, no other individual involved in the care of the patient will be able to know which operation has been delivered, unless by contacting the trial team. Therefore nurses, physiotherapists and the person performing the outcome assessment will all be blinded to treatment allocation.

The operation note will be blinded to prevent contamination, or accidental unblinding of the patient (for example, in the discharge information, or during post-operative physiotherapy). A standard recommended operation note template (with space to amend or add free text as required) will be given to all sites adjusted to fit their local operation note systems. In this trial, this will specifically include details of the study, the participants trial number and a website link for emergency unblinding.

The freehand details of the operation which would normally be put into the operation note will be recorded in an online form easily accessible to the surgeon. This will include a tick-box to confirm if the allocated treatment was delivered and a space to document the clinical details of the specific case. An unblinding plan has been developed to ensure that appropriate staff can access this at any time of day or night in case of clinical need, such as an infection (see section 2.10.2).

Any post-operative imaging, whether as part of the sub-study or for clinical reasons (there are no requirements for post-operative imaging in the protocol, outside of the sub-study) will be reviewed by the surgical team but will not be seen by the participant, this will be achieved by the surgical team turning screens away from the patient in clinic or viewing the images on alternative screens if this is not possible. Participants will be asked at the12 month time point if they were aware of their allocation.

2.10.2 Methods for unblinding the trial

Unblinding may very rarely be required in an emergency situation, such as an overnight admission for suspected post-operative infection. Such an event is thought to be unlikely in this trial. Unblinding will be performed only by staff at the trial site in an emergency situation, by using a pre-defined web-based system, from a link inserted in the operation note. It is recognised that in an emergency situation (for example, an A&E admission overnight), the participant might be seen and treated by any member of staff and therefore access needs to be available at any time.

START trial cards will be given to participants, clearly stating the process for unblinding. Participants are not obliged to carry them, and the unblinding process is not dependant upon the cards being available, but they will serve as an additional reminder or source of information for participants.

As the operation note would only be held in the treating centre, unblinding will only be performed from the treating centre. In the case that a participant presented to a different hospital, site staff would need to contact the treating hospital for the operation note details. This would be the case in normal clinical practice and so we are not deviating from normal practice in this regard.

The web-link recorded in the operation note will connect to the trial database. A two-way secure verification process will be performed using email, and an access code will be emailed only to an email address whose domain corresponds to the hospital site in which a patient has been treated (for example XXX@uhcw.nhs.uk for the lead site). The person entering the site details will be asked for the patients trial number (recorded in the operation note) to gain access to the record, although for identification purposes, and to ensure that the correct clinical detail was being given about the correct patient, the patients name and date of birth would be accessed when unblinding the record.

All access given for emergency unblinding will be logged by the database and a full explanation of the clinical circumstances and the need for access to clinical data will be requested by the trial team for audit and monitoring purposes from the person who performed the unblinding, and the PI for the site will be informed.

The system will be designed by the WCTU programming team to ensure that it is both secure and fully functional.

The treatment code must not be broken except in clinical emergencies when the appropriate management of the participant necessitates knowledge of the treatment randomisation. The database will also directly flag up the unblinding to the Chief Investigator.

Treatment codes will not be broken for the planned analyses of data until all decisions on the data from each individual participant have been made and documented.

2.11 Co-enrolment

Co-enrolment will not normally be recommended, but individual requests can be discussed with the TMG to determine if these will affect the delivery or conduct of the trial.

2.12 End of trial

The trial will end when all participants have completed their 24 month follow-up.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- There is an unexpected major safety concern
- Following recommendations from the Data Monitoring Committee (DMC) or Trial Steering Committee (TSC)
- Funding for the trial ceases

Given that the trial intervention has been delivered in many thousands of patients over nearly a decade, and the control procedure has been in standard clinical practice for decades, it is highly unlikely that a safety concern would emerge that would result in early termination of the trial.

The sponsor and Research Ethics Committee will be notified in writing within 90 days when the trial has been concluded or within 15 days if terminated early.

3. METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection

Visit		**1**	**2**	**substudy**	**3**	**4**	**5**	**6**
Visit Window (No. Weeks ± No. Days)	**Screening**	**Baseline**	**Surgery**	**6 weeks (±2 weeks) after V2**	**3m (± 6 weeks) After V2**	**6 m (±6 weeks) After V2**	**12 m (± 3m) After V2**	**24m (±3m) After V2**
Check eligibility and provide PIS	✓							
Confirm Inclusion/ exclusion criteria		✓						
Consent		✓						
Consent for sub-study (in participating centres)		✓						
Baseline assessments		✓						
Randomisation			✓					
Intervention			✓					
Constant-Murley Score		✓			✓	✓	✓	
PROMs		✓			✓	✓	✓	✓
Resource use					✓	✓	✓	✓
Adverse Events					✓	✓	✓	✓
Sub-study MRI (in participating centres)				✓		✓		
End of trial								✓

Table 1 Trial assessments

4. MRI SUB-STUDY (OPTIONAL FOR SITES/PATIENTS)

4.1 Pilot work to support the main sub-study

MRI pilot

The plan for the sub-study MRI has already been piloted at UHCW, but further piloting of the technique in this patient population is planned to refine and optimise the method. To do this, four people with a symptomatic rotator cuff tear (meeting similar criteria for the main trial, except that patients awaiting rotator cuff repair may also be invited to avoid a conflict between potential trial participants and those for the sub-study pilot work) will be recruited using a specific patient information sheet and consent form and undergo the scan protocol described below. They will fill in the same baseline assessment questionnaire as in the main trial, but no other outcome assessments will be completed, and age, gender and findings of previous imaging will be recorded to document the details of their shoulder pathology. Participants in this developmental study will be recompensed for their time and travel with a £10 shopping voucher.

EMG pilot

In addition to testing our MRI proptocol we wish to confirm that we are satisfactorily activating the deltoid muscle when people are postioned for the MRI scan. The best way of doing this is using electro-myograpy (EMG), a painless test using skin sensors that can detect muscle activation when postioned as planned for the MRI sub-study (but not in an MRI scanner). Therefore we will do an additional pilot with up to ten people with a symptomatic rotator cuff tear (also meeting similar criteria for the main trial, except that patients awaiting rotator cuff repair may also be invited to avoid a conflict between potential trial participants and those for the sub-study pilot work) to test the methods used in the proposed MRI sub-study. If the deltoid is not activated with this protocol, a further 10 people will be recruited and the same test will be performed with a stronger theraband (ie providing more resistance). Participants in this developmental study will be recompensed for their time and travel with a £10 shopping voucher.

This will be performed in a clinical space at UHCW but outside of the MRI suite. Informed consent will be obtained prior to the study using specific patient information sheets and consent forms and Warwick CTU SOPs will apply throughout, using the same processes described elsewhere in the protocol. They will fill in the same baseline assessment questionnaire as in the main trial, but no other outcome assessments will be completed, and age, gender and findings of previous imaging will be recorded to document the details of their shoulder pathology. EMG measurements will be performed or supervised by Dr Mark Elliot, associate professor in the institute of digital healthcare at the University of Warwick, who has prior experience of EMG measurement in clinical studies.

It will take approximately 20 minutes to perform for each participant. Skin surface EMG sensors will be placed over the deltoid muscle in regions corresponding to the maximal muscle mass of the anterior and posterior deltoid muscle. These will have a wireless link to a computer which will record data. The participant will lie down on a couch on the plastic arm rest, placed 10cm from the side of the body, and the protocol described in section 4.2 for activating deltoid by using a Theraband to provide gentle resistence to 10cm of movement at the elbow will be followed. Measurements will be taken at rest and then with gentle deltoid activity with the arm abducted up to 10cm or within the confines of comfort if this is less then 10cm. The measurements will take just a few seconds and will be perfomed twice, and the test will finish. The measurements are painless and are not invasive. Once finished, the participant will be free to go and will not require any further follow-up.

The data will be analysed at the University of Warwick. The results will be included in a publication which describes the MRI methodology, this will either be a separate paper or the main results for the sub-study, this will be reviewed by the trial management group after the intial methodology work for the MRI sub-study has been completed.

4.2 Main Sub-study

Fifty-six participants spread across both treatment groups will undergo two research MRI scans at six weeks and six months post intervention. All participants at centres who are recruiting to the sub-study will be invited to take part in this additional piece of research at entry into the trial, using the combined patient information sheet and consent form, until the sub-study has completed recruitment.

The aim of the sub-study is to assess the mechanism of action of the balloon in comparison to no balloon, when the balloons are likely to be still inflated (but when acute post-operative pain has subsided), and when they are likely to have fully deflated, to see if the proposed mechanism for ongoing improvement is maintained.

We have discussed the proposed mechanism of the balloon with its inventor (Dr Assaf Dekel), who has explained that it is not designed to depress the humeral head passively, but to cushion the humeral head from impinging on the acromion during activity. Therefore, passive imaging alone will not be adequate to demonstrate the function of the balloon and imaging will also need to be performed when the deltoid muscle is active, producing a proximally directed force on the humerus.(35, 36)

The subacromial space cannot be imaged reliably using radiographs or fluoroscopy, and whilst ultrasound imaging might allow an analysis during multiple activities, it has poor inter-rater reliability and scanning procedures will be very difficult to standardise across multiple sites and sonographers.(65) Therefore, MRI scans will be used. Whilst range of shoulder motion in an MRI scan is limited due to the size of the bore, the image resolution of open MRI is too poor to demonstrate shoulder anatomy adequately. A recent study has demonstrated it is still possible to abduct the arm to 40 degrees in an MRI scanner. This is sufficient to demonstrate proximal migration of the humerus in rotator cuff tears that is not present when the cuff is intact.(66) For this study we have developed (and piloted) a novel dynamic approach to assessing the function of the rotator cuff using MRI imaging under a mild deltoid load, to specifically assess the mechanism of the balloon.

We will use conventional MRI with images in the oblique coronal and oblique sagittal planes as the preferred technique for imaging the rotator cuff. Evidence shows that fat-suppressed, fast spin-echo (FSE), T2-weighted images are the most accurate for the assessment of rotator cuff tears and a variation of this sequence will be used that can be applied on the range of MRI machines across the different sites in this sub-study (67, 68). Patients will lie with arm abducted and a small plastic 'L-shaped' board (with a vertical side support) will be placed under their lumbar spine, level with the elbow. The side support will be placed 10cm lateral to the neutral (ie adducted to 0°) resting position of the arm. A loop of light (yellow) 'Theraband' will loosely hold the arm just above the elbow and wrap around the trunk. When taking the image, participants will be asked to push their arm outwards by 10cm, initially with the elastic released (ie providing no resistence) and their elbow resting against the side support , whilst a fast coronal sequence is taken. They will then be asked to hold the the band so it provides resistance to movement but is not tight with the arm by their side, and move their arm to again rest against the side support in the same position (this 10cm movement against resistance is a very low force for the patient, but enough to recruit the deltoid), and the scan will be repeated. If

the movement is painful, the same movement will be performed but within the confines of comfort. We have piloted this technique and produced good quality images under deltoid activity with short, fast sequences (approx. three mins) and this will be performed against minimal resistance to prevent discomfort for patients.

Staff carrying out the scans and trial staff assessing images will be blinded to participant allocation. The primary outcome will be the minimum acromio-humeral distance (AHD, as defined by Gumina et al) on the 'deltoid-active' coronal sequences at six months, a reliable and proven measure (65, 66, 69) Secondary measures will be AHD on passive and sagittal images, and the change in AHD between active and passive images. The position of the balloon will be assessed on both sequences (with particular focus on the sagittal images) to check for migration and consistency of placement relative to the acromion.

Based on Gumina's study, the minimum AHD has standard deviation of 1.72mm, so to observe a minimum important difference of 1.5mm (above the minimum detectable change of 1.3mm established elsewhere(70)) with an alpha of 0.05 at 80% power, assuming a loss to follow-up at 6 months of 20%, **56 participants** are required for this sub-study. It is estimated that five centres will be used to recruit patients for this sub-study based on an assumption that only 50% of participants decide to join the sub-study.

Recruitment to the sub-study will finish when the sample size is reached. The primary end-point will be the between group difference on the six-month MRI, as that is the better indicator of long-term function and will determine whether the early effect of the balloon is likely to be maintained. The between-group differences on the six-week scan will be a secondary outcome. The primary analysis will compare the 'deltoid active' AHD on coronal images between intervention and control groups using a linear regression model adjusting for age, sex, recruitment site and tear size. For the purpose of this study, the research sites standard MR exclusion criteria will apply and an MR safety questionnaire will be administered prior to inclusion in this part of the study as is standard for MRI imaging at each site.

5. ADVERSE EVENT MANAGEMENT

5.1 Definitions

5.1.1 Adverse Events (AE) and Adverse Device Effect (ADE)

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation participant taking part in health care research which does not necessarily have a causal relationship with the research. An adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding or ECG result), symptom, or disease that occurs during the time a participant is involved in the trial whether or not it is considered to be related to the intervention.

An adverse device event (ADE) is and adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the installation, the operation, or any malfunction of the investigational medical device. This also includes any event that is a result of a user error or intentional misuse.

For the purposes of this trial AEs should be recorded for any participant where it is thought there may be a relationship between the trial interventions or the condition being studied (in this case, any shoulder condition).

Some events will be considered expected AEs (or SAEs, if they meet the criteria). In certain cases, the diagnoses will be confirmed, where there is uncertainty, by the treating clinician. These include the following.

Those related in general to surgery and anaesthetic:

- Injury to teeth, mouth or throat during anaesthetic.
- Chest infection.
- Myocardial infarction.
- Death.
- Nerve or vessel injury due to local anaesthetic (ie local blocks).

Those related to the operation itself:

- Exacerbation/persistence of shoulder pain or restriction of range of motion.
- Adhesive capsulitis (frozen shoulder).
- Mis-placement of the balloon or its subsequent migration.
- Infection.
- Wound healing problems.
- Thrombosis.
- Damage to nerves or vessels in the surgical area.

Those related to physiotherapy:

- Persistent muscle soreness or muscle injury.
- Bruising.

Where participants are lost to follow up, a system of recording AEs and SAEs from their GP records has been developed. This is documented in section 7.3.5 ‘procedure to account for missing data’.

5.1.2 Device deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.

5.1.3 Investigational medical device

Medical device being assessed for safety or performance in a clinical investigation.

5.1.4 Serious Adverse Events (SAEs)

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical condition.

5.1.5 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

5.1.1 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

5.2 Reporting SAEs , SADEs and USADEs

All **SAEs SADEs and USADEs** occurring from the time of randomisation until 12 months post-randomisation must be recorded on the SAE Form in the participant's CRF and faxed (or emailed to a NHS email account) to the Sponsor, WCTU for this purpose, **within 24 hours** of the research staff becoming aware of the event.

For each **SAE** the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to intervention), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the Sponsor as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached. An outcome of 'unknown' is not considered to be an acceptable final outcome. An outcome of 'not yet resolved' is an acceptable final outcome for non-serious AEs at the end of a patient's participation in a trial, and for SAEs at database lock.

SAEs will be reported using the SAE form in the participant's CRF. The Principal Investigator in each centre must report any SAEs to the trial coordinating centre within 24 hours of them becoming aware of the event. The SAE form should be completed and faxed to the dedicated fax at Warwick CTU: 02476 150549. The trial manager will liaise with the investigator to compile all the necessary information. The trial coordinating centre is responsible for reporting any related and unexpected SAEs to the sponsor and REC within required timelines. Events which are possibly, probably or definitely related to the trial intervention and are unexpected will be reported to the REC within 15 days.

The EC Medical Devices Directive (93/42/EEC) requires a manufacturer to fully record all adverse incidents that occur during a clinical investigation and include them in the annual reports to the main REC (and MHRA if appropriate). The legal responsibility for reporting SAEs/SADEs lies with the manufacturer or their authorised representative. However, the MHRA also has a voluntary reporting requirement for 'users' of devices i.e. where a device is being used in a trial in which the manufacturer has no involvement, and in this case, the coordinating centre would submit the appropriate reports and also inform the manufacturer of the event.

The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the investigator(s) on the SAE form.

Relationship to trial medication	Description
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention or device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

All SAEs will be recorded for inclusion in annual reports to the research ethics committee.

The following process will be used to review individual SAEs

- Clinical review of a line listing of all life-threatening SAEs or SAEs resulting in death within 1 week of their occurrence.

- Clinical review of a line listing of all other SAEs on a monthly basis at TMG meetings

The following process will be used to independently monitor trends in SAEs in addition to usual trial safety monitoring procedures.

- Cumulative review of all safety information by the DMC on a 6-monthly basis.

All others AEs conveyed are recorded and reported annually

A member of the Principal Investigator's trial team will be instructed to closely monitor each participant who experiences an AE until the outcome of the AE has been determined.

5.3 Responsibilities

Principal Investigator (PI):

- Checking for AEs when participants attend for treatment / follow-up.

- Using medical judgement in assigning seriousness, causality and expectedness

- Ensuring that all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.

- Ensuring that AEs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Sponsor (University of Warwick under co-sponsorship agreement):

- All AEs will be reported to the trial team

- Central data collection and verification of AEs, and SAEs, according to the trial protocol.

- Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.

- Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.

- Expedited reporting of related and unexpected SAEs to the REC within required timelines.

- Notifying Investigators of related and unexpected SAEs that occur within the trial.

- The unblinding of a participant for the purpose of expedited reporting.

6. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act.

Personal identifying information will be brought to WCTU for follow up purposes. Handling of personal data will be clearly documented in the patient information sheet and consent obtained.

Disclosure of confidential information will only be considered if there is an issue which may jeopardise the safety of the participant or another person, according to Warwick Standard Operating Procedures (WCTU SOP 15 part 1) and the UK regulatory framework. There is no reason to expect this situation to occur in this trial more than any other.

6.1 Data collection and management

The CRFs will be developed by the trial manager in consultation with chief investigator, trial statistician, health economist and other relevant members of the trial team to collect all required trial data. A suitably trained member of the research team will complete and return the CRFs to the START:REACTS trial office. The coordinating team will check and enter the data on to a secure trial database held at WCTU as outlined in the data management plan and in accordance with the WCTU SOPs.

Various methods will be used to chase missing data/ unreturned questionnaires including post, phone, text and email (see 2.8.2), the procedures for managing this will be outlined in the data management plan and appropriate consent will be sought to contact participants if required. To maximise follow-up, appropriatly trained staff members may follow up participants at home to collect the primary outcome measure.Data will still be collected for participants who discontinue or deviate from the intervention protocol, unless they withdraw their consent (see section 2.8.2).

6.2 Database

The database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmers and trial staff.

6.3 Data storage

All essential documentation and trial records will be stored at Warwick Clinical Trials Unit in conformance with the applicable regulatory requirements and access to stored information (paper and electronic) will be restricted to authorised personnel. All data will be stored in a designated storage facility within the University Hospitals Coventry and Warwickshire and/or Warwick Clinical Trials Unit. Electronic data will be stored on password protected university computers in a restricted access building.

6.4 Data access and quality assurance

All data collected will be anonymised after the collection of the baseline demographic data for each participant. Confidentiality will be strictly maintained and names or addresses will not be disclosed to anyone other than the staff involved in running the trial. Participants will be identified by ID number initials and date of birth only where necessary. Identifiable participant data will be held in a locked filing cabinet and coded with the trial number to tag identifiable data to the outcome data.

Direct access to source data/documents will be available for trial-related monitoring or audit by UHCW or Warwick CTU for internal audit, regulatory authorities or ethics committees.

The principle investigator must arrange for retention of trial records on site in accordance with GCP and local Trust's policies.

A statement may be required to detail who will have access to the final trial data set, and disclosure of contractual agreements that limit access for investigators.

6.5 Data Shared with Third Parties

Requests for data sharing will be managed in accordance with University of Warwick/WCTU policy on data sharing.

6.6 Archiving

Trial documentation and data will be archived for at least ten years after completion of the trial.

7. STATISTICAL ANALYSIS

7.1 Power and sample size

The clinically important difference that has been chosen for the Constant score is 10 units, this has been widely used for other trials.(45, 71, 72) Typically in other studies of this population the standard deviation is 20 giving a moderate standardised mean difference of 0.5.(45, 49) For a costly invasive procedure of this nature a smaller effect size is unlikely to be considered worthwhile. For a power of 90% and alpha of 5% a study without early stopping would require 170 participants. Allowing 20% for loss to follow-up, whilst striving to keep this below 10%, gives a **maximum sample size of 212**.

7.2 Development of the adaptive design (Statistical work package 1)

A three-month work package will commence at the start of study to develop appropriate methodological tools, implement a series of simulation studies using synthetic data to understand the properties of the selected design and its sensitivities to model assumptions and, in collaboration with the study DMC, agree futility and efficacy stopping boundaries. A full understanding of the operating characteristics of the design will be required before strict (pre-set) stop/go rules can sensibly be determined.

Study endpoints for the primary outcome (Constant-Murley shoulder score) are at three, six and twelve months. For the adaptive design, the twelve-month primary outcome would be too late to be

used for determining futility before the study has finished recruiting, and therefore the available early and late outcome data needs to be used to determine early stopping.

A proxy outcome of three months will be primarily used as the balloon degrades after this time and therefore if there is no benefit at three months then there is unlikely to be benefit at later time points. This proxy outcome will be strengthened further in this study, by accounting for the available six-month and twelve-month data to improve the predictive strength of the model. Therefore, a decision to stop for futility will be made only when there is sufficient confidence in the decision (based on this comprehensive simulation work) using all available three, six and twelve-month data. A decision to stop because of clear evidence of efficacy will be considered in the modelling but especially strong evidence of efficacy (and the relationship to later outcomes) will be required for early stopping, as there is a risk that early benefit when the balloon is in inflated will not necessarily translate to late efficacy.

Futility stopping boundaries based on early and late observations of a single study endpoint with a final analysis adjusted for futility stopping have been suggested previously by Stallard.(10) In the first stage of the work package, methodology developed previously by the group for two time points will be extended to three time points (and also made more general) to allow the totality of observed data at planned interim analyses to be used to inform study progress (e.g. stopping).

Results from our systematic review suggest there is a strong association between early and late outcomes based on data from trials of interventions for rotator cuff tears. A strong positive correlation between three and six month outcomes and twelve month outcomes indicates that information on the former early outcomes will be strongly indicative of later outcomes, and consequently intervention efficacy or futility. The correlation between data at three and six months was estimated as 0.75, between six and twelve months as 0.78 and between three and twelve months as 0.39. This suggests that a first order autoregressive correlation structure may be appropriate; this will form the basis of our initial development work to modify the previous approach.

Sequential stopping boundaries will be constructed that allow stopping for futility or stopping to reject the null hypothesis (efficacy), with interim analyses determined by the results of the simulations and agreed with the TSC and DMC (73). Stopping boundaries for safety will also be agreed and will be set as a separate criterion for early stopping.

In the second stage of the methodological development work, simulated data that replicate the metric properties of the primary outcome will be used to explore the characteristics of the design and sensitivities to likely treatment effect sizes and correlations between early and late outcomes. The focus of this work will be to understand changes in study power and rates of early stopping for a range of likely treatment effect sizes. The results of these simulation studies will be presented to the TSC and DMC at the second meeting (end of the internal pilot and the first interim analysis), and rules agreed such that it is clearly defined as to when interim analyses will happen, what the thresholds will be for early stopping, and how decisions will be communicated within the study team.

Preliminary simulations indicate that a single interim analysis using three-month data on 53 patients per arm with the probability of early stopping under the null hypothesis set to 50% would result in only a small reduction in power to 88% for modest correlations between three and twelve-month data. Given the findings of our systematic review of a good relationship between early and late outcomes in trials of interventions for rotator cuff tears, and the fact that correlations will be improved by considering all of the available time-points, there is likely to be little loss of power.

7.3 Statistical monitoring and analysis (statistical work package 2)

7.3.1 Planned recruitment rate

A typical shoulder unit sees around 40 patients per year who meet the eligibility criteria. Using a conservative estimate of a 30% conversion rate from eligible patients to recruited participants; 12 recruited per year per site is anticipated. Recruitment rates in multi-centre trials run by our unit have previously been high (FASHIoN: 54%, DRAFFT: 72%) and so this is likely to be an underestimate. Based on opening two centres a month, we estimate at least 10 but more likely 16-20 centres will be required to recruit 212 participants over 24 months. We have a large network of sites used for previous studies in our unit, a number of sites have been approached prior to the funding application, and we have close collaboration with the shoulder community through the chair of the BESS research committee (Mr Drew) and our co-investigators, and would open additional sites if required.(12)

7.3.2 Internal pilot

The first six months after the first randomisation will be used as an internal pilot to assess the feasibility of recruitment. This will be assessed after six months of recruitment, with a target of one recruited participant per centre per month (for example: 35 patients at end of month 6 with a staggered start of sites) expected to be recruited. A traffic-light system has been used successfully in another trial currently running in our unit (PROSPER, NIHR HTA, ref 13/84/10) and the same process will be used for this study. If recruitment is within 75% of target, or more, the study will proceed as planned, with processes reviewed in the TSC. If the study is between 50% and 75% of target, processes and screening logs will be reviewed in all sites, the paperwork will be re-reviewed by the lay members and the TSC, a recommendation as to whether to proceed or not will be made, and a further review after 3 months will be planned to assess change. If recruitment is less then 50% of target, the study will be deemed not feasible, with no expectation of likely rapid improvement in rate, then the TSC will consider terminating the trial.

7.3.3 Statistical analysis plan

All data will be analysed and reported in accordance with the CONSORT statement. Treatment effects will be presented with appropriate 95% confidence intervals. Tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05 (5% significance level). All analyses will be conducted as intention to treat unless otherwise specified.

Analyses will predominately carried out using R (www.r-project.org).

7.3.3.1 Summary of baseline data and flow of patients

Baseline data will be summarised to check comparability between treatment arms, and to highlight any characteristic differences between those individuals in the study, those ineligible, and those eligible but withholding consent. Standard statistical summaries (e.g. means and standard deviations, dependent on data type) will be presented for the primary outcome measure, the Constant-Murley score and all secondary outcome measures.

A CONSORT flow diagram will be produced and will be updated for TMGs, TSCs and DMCs at the study progresses (http://www.consort-statement.org/).

7.3.3.2 Primary outcome analysis

Standard statistical summaries (e.g. medians and ranges or means and variances, dependent on the distribution of the outcome) and graphical plots showing correlations will be presented for the primary outcome measure and all secondary outcome measures.

The main analysis will investigate differences in the primary outcome measure, the Constant-Murley shoulder score 12 months after surgery, between the two treatment groups on an intention-to-treat basis. In addition, early functional status will also be assessed and reported at three and six months. Differences between groups will be assessed, based on a normal approximation for the Constant-Murley score at twelve months post-surgery, and at interim occasions. Tests will be two-sided and considered to provide evidence for a statistically significant difference if P-values are less than 0.05 (5% significance level).

The definitive analysis will provide adjusted estimates of treatment group differences (with 95% confidence intervals) for the Constant-Murley score using a mixed-effects model, including a random effect for the recruitment centre, and fixed effects for patient age, gender and size of tear. In addition to the primary intention-to-treat analyses, a per-protocol analyses will also be undertaken.

A full and detailed statistical analysis plan will be agreed with the Trial Steering Committee and DMC prior to commencing the study.

7.3.3.3 Secondary outcome analysis

Descriptive statistics of patient reported outcome measure (PROM) data (i.e. the OSS, WORC, EQ-5D-5L, PGIC) at each time point will be constructed with between groups analyses following the method set out for the primary analysis above.

7.3.4 Subgroup analyses

A pre-specified sub-group analysis will be undertaken to assess whether there is evidence that the intervention effect differs between:

- The size of the rotator cuff tear as measured at the start of surgery, defined as large or massive cuff tear (≥3cm) or moderate to small (<3cm).
- Gender
- Age (>70 or <70)

The subgroup analyses will follow the methods described for the primary analysis, with additional interaction terms incorporated into the mixed-effects regression model to assess the level of support for these hypotheses.

The study is not powered to formally test these hypotheses, so they will be reported as exploratory analyses only, and as subsidiary to the analysis reporting the main effects of the intervention in the full study population.

7.3.5 Procedure to account for missing data

It seems likely that some data may not be available due to voluntary withdrawal of participants, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for data 'missingness' will be ascertained and reported. The nature and pattern of the missingness will be carefully considered, including whether data can be treated as missing completely at random. If judged appropriate, missing data will be imputed using the multiple imputation facilities available in the statistical analysis software.

If imputation is undertaken, the resulting imputed datasets will be analysed, together with appropriate sensitivity analyses. Any imputation methods used for scores and other derived variables will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated and any patterns summarised. More formal analysis, for example using logistic regression with 'protocol violation' as a response, may also be appropriate and aid interpretation.

Where participants have been lost to follow up at or beyond the 12 month time point, and data on adverse events can therefore not be recorded, the participants General Practitioner (GP) will be contacted and a short form requesting any information or health record that could be an adverse event will be requested from the GP, as well as confirmation of the current contact details of the participant. This will be associated with a small fee for the GP. These records will be examined and AEs and SAEs will be recorded, and when this process is complete the data will be destroyed. Sites will be informed of SAEs identified in this manner and will be given the opportunity to pass on any more information that may help ascertain the nature and severity of the adverse event.

7.4 Interim analysis and criteria for the premature termination of the trial

The assessment of early recruitment and rules for the internal pilot are described in 7.3.2 (statistical work package 1). These will be reviewed at the scheduled TSC meeting to be held at the end of the internal pilot phase.

Both the primary and interim analyses will be performed using a frequentist approach although a Bayesian analysis will be explored as a sub-study (statistical sub-study, section 8).

The timing of interim analyses will be determined following the simulation package described in 7.2 and agreed with the DMC and TSC, although a final decision on timing will only be made after six months of recruitment when the early rate of recruitment to the study is known, as this determines the availability of data in the later phases of recruitment. Interim analyses will not start until at least 12 months of recruitment has passed. The interim analyses will be analysed using the methods developed in statistical work package 1 (section 7.2), and pre-arranged 'stop/go' criteria will be applied. These will be agreed with the DMC and TSC prior to their application.

The trial statistician will prepare the interim analyses but will not be blind to the trial results, we have concluded that blinding of the trial statisitician would not be feasible and is of little value to the study. The incidence of AEs and SAEs in each group will also be collated for the interim analyses and will be presented to the DMC at 6 monthly intervals but will not be summarised statistically unless at the request of the DMC.

For each interim analysis, the DMC will be sent 'virtual DMC' report via email. When the pre-determined stop/go criteria have been met, this will be highlighted to the DMC and the trial team will be informed that a teleconference DMC and subsequent TSC is required. The contents of the report,

or the criteria which have been met, will not be communicated outside of the DMC until they have reported to the TSC, and it will not be communicated beyond the TSC until the end of the study.

7.5 Subject population

The primary analysis and any applicable secondary analyses will be applied to an all-randomised population on an intention-to-treat basis, that is any subject randomised into the study, regardless of whether they received study intervention and regardless of protocol deviations, unless specified above.

7.6 Health Economic Evaluation

The economic component will include a standard health policy-relevant economic analysis and an exploration of how economic analyses might support the adaptive design.

Set out within a health economic analysis plan, a prospective economic evaluation will be integrated into the trial and adhere to the recommendations of the NICE Reference Case.(74) Mechanisms of missingness of data will be explored and multiple imputation methods will be applied to impute missing data. Imputation sets will be used in bivariate analysis of costs and QALYs to generate incremental cost per QALY estimates and credible intervals.(75-78) It is anticipated that incremental costs and benefits will be captured within the trial and that extrapolated modelling will not be required.

Relatively little research has been conducted prospectively on how interim economic analysis might inform an adaptive design. Approaches generally include a net-benefit regression approach and value of information analysis (79, 80) and have considered the problem of right-censored cost and quality-of-life data. A six-month work package will commence at the start of study to develop appropriate analytic tools. We will use the trial to evaluate putative analytic methods, as set out within a health economic analysis plan; as with the Bayesian sub-study we will carry out parallel interim analyses, separate from the real trial analyses, exploring how interim decisions might have been influenced.

8. STATISTICAL SUB-STUDY: COMPARISON OF FREQUENTIST AND BAYESIAN ADAPTIVE DESIGNS

A methodological sub-study will be performed that complements a current MRC methodology grant held by Prof Gates (Evaluation of Bayesian Adaptive Designs for Phase 3 Effectiveness Trials; grant number MR/N028287/1, starting date July 2017).

One of the key uncertainties when designing an adaptive trial is whether adaptive trials are better designed, monitored and analysed using a Bayesian or frequentist approach. Decision making in the monitoring of a phase II/III adaptive trial can be difficult and frequentist analyses of trials may be misinterpreted by clinicians and stakeholders. It may also be argued that Bayesian analyses are more intuitive for clinicians and stakeholders to interpret at the end of a trial.

One of the components of this project is to produce, using Bayesian adaptive methodology, alternative designs for ongoing trials that are in progress, and to evaluate the effects that this would have on decision-making during the trial. As the trial progresses, we will carry out parallel interim

analyses, separate from the real trial analyses, and we will determine whether different interim decisions would have been made using the alternative design and analyses. These parallel analyses will be known only to the statisticians performing them, and will not be revealed to the trial investigators, DMC or published until the trial has finished. This avoids the problem in retrospective analyses that the results of the trial could be known, and could influence the design. We propose that START:REACTS should be one of the trials that we include in this project. As the MRC project is already funded this can be done at minimal additional cost.

We will also perform a small sub-study, once the main trial has finished recruitment, to investigate the effects of Bayesian and frequentist design and information on decision making by Data Monitoring Committees. We will set up multiple mock DMCs, each of which will consist of three people, and each will receive a sequence of short reports, containing the results of a set of interim analyses. Each mock DMC will be randomised to receive either (a) traditional frequentist information, in which the mock DMC will receive information from the interim analyses specified in the frequentist design (i.e. the design it is proposed to use) or (b) Bayesian information in which the DMC will receive information resulting from the sequence of interim analyses in the Bayesian design, analysed using Bayesian methodology.

We will use four scenarios of treatment effectiveness; 1. The real trial data; 2. The treatment has no effect; 3. Treatment is moderately harmful; 4. Treatment is beneficial. We will request volunteers to play the role of members of DMCs. We plan to build this experiment into a clinical trials conference (SCT or ICTMC) soon after completion of the study, and will contact conference organisers to do this. We will also seek volunteers by internet contacts (such as the NIHR statistics group), and conduct mock DMC meetings by web conference. The questions of interest are whether there is concordance of stopping decisions and conclusions between the information modes, the number of patients and time for the trial to be completed, and mock DMC members' views. We will aim for at least 20 replicates of each information mode, each of which will consider all four treatment effectiveness scenarios in a random order.

9. TRIAL ORGANISATION AND OVERSIGHT

9.1 Sponsor and governance arrangements

University Hospitals of Coventry and Warwickshire and University of Warwick co-sponsor the trial, although the lead contracting organisation is UHCW. The day-to-day running of the trial will be managed according to WCTU SOPs, with UHCW SOPs used for contracting and oversight issues.

9.2 Ethical approval

All ethical approvals for the trial will be sought using the Integrated Research Application System. The trial will be conducted in accordance with all relevant regulations and guidelines.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of R&D agreement is received by the co-ordinating team.

Substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, analyses) will be communicated by the trial team to relevant parties i.e. investigators, RECs, participants, NHS Trusts, trial registries, journals, as appropriate.

Annual reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The REC and sponsors will be notified of the end of the trial (whether the study ends at the planned time or prematurely).

The CI will submit a final report to the required authorities with the results, including any publications within one year of the end of the trial.

9.3 Trial Registration

The trial will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Register. A protocol paper will be published prior to completing recruitment.

The statistical and health economic sub-studies will be pre-registered on the Studies within a Trial registry (go.qub.ac.uk/SWAT-SWAR).

9.4 Notification of serious breaches to GCP and/or trial protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

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

If a serious breach occurs:

- the sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase
- the sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

9.5 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol.

9.6 Trial timetable and milestones

A three-month period is planned to prepare the Health Research Authority (HRA) application. This will be performed prior to the study to ensure the trial is set-up efficiently at minimal cost. We plan a 5-month set-up period (preparing case report forms, setting-up sites) to start recruitment and we have estimated a time of 3 months between recruitment and surgery as being typical in the NHS,

where there is an 18-week referral to treatment target. Reasonable effort will be made to prevent waiting times longer then 3 months between recruitment and surgery. If the trial runs its full length, recruitment will be for 24 months followed by 12 months for collection of outcomes. 4 months will be allowed for analysis and completion of the report. Therefore, the maximum study length is 48 months.

9.6.1 Gantt Chart

		Pre-work			Year 1											Year 2												Year 3												Year 4											
Tasks		-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	##	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
Ethics, HRA and R&D approval																																																				
Trial oversight	TMG meetings	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	DMC meetings		x						x						x						x						x						x					x										x			
	DMC On-line reports for adaptive design*																																																			
	TSC meetings		x							x						x						x						x						x**						x										x			
Set-up																																																			
Open site 1																																																			
Open additional sites																																																			
Recruitment period																																																			
Surgery and randomisation																																																			
Milestone to assess feasibility (stop-go)																																																			
Follow-up visits																																																			
Potential early stop to recruitment																																																			
Analysis																																																			
Prepare final report																																																			
Final report submssion																																																			
Potential early finish (funding staged for final year)**																																																			
	*includes potential teleconference DMC or TSC to consider early stop if futility boundaries crossed																																																		
	**decision on staged funding for final year to be made at end of recruitment TSC month 30																																																		

9.7 Administration

The trial coordination will be based primarily at UHCW in the Clinical Sciences Research Laboratories, but staff will, on occasion, work at WCTU, University of Warwick.

9.8 Trial Management Group (TMG)

The Trial Management Group, will consist of an operational group where the procedural side of the trial will be discussed and the methodological group will focus on the methodology aspect of the trial. The latter group will feed into the operational group TMGs. The operational TMG will consist of the project staff and co-investigators who are involved in the day-to-day running of the trial. Both groups will meet on a 4 weekly basis. Smaller team meetings consisting of the CI, TM, TC, SPM and any other invited member will meet between these times when required. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

9.9 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but approximately every 6 months. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

The membership of the TSC is shown on page ***5-7***.

9.10 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant clinical research, and statistical experience. The DMC and TSC (held separately to ensure quorate numbers from both committees could attend) will meet at the start of the trial, and then at 6 monthly intervals, and more frequently during the

interim analysis period (exact details of timings to be discussed with the DMC at their first meeting, based on the simulation data) and regularly thereafter. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated.

The membership of the DMC is shown on page 7-8.

DMC meetings will also be attended by the CI, TM and TC (for non-confidential parts of the meeting) and the trial statistician.

9.11 Essential Documentation

A Trial Master File will be set up according to WMS SOP and held securely at the coordinating centre.

The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

9.12 Financial Support

The trial has been funded by a research grant from the National Institute for Health Research, Efficacy and Mechanism Evaluation programme, following their commissioned call for 'Novel trial designs in new surgical procedures'.

10. MONITORING, AUDIT AND INSPECTION

The study will be monitored by the Research and Development Department at UHCW as representatives of the lead Sponsor and by the Quality Assurance team at WCTU as representatives of the co-sponsor, to ensure that the study is being conducted as per protocol, adhering to Research Governance and GCP. The approach to, and extent of, monitoring will be specified in a trial monitoring plan determined by the risk assessment undertaken prior to the start of the study. A trial monitoring plan will be developed and agreed by the TMG and TSC based on the trial risk assessment, including on site monitoring. Processes to be considered in the monitoring plan will include participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection. This plan will be available from the trial coordination centre and will also be lodged with the sponsors. Whilst the monitors work in the same institution as the CI and trial team (WCTU), they will act independently of the trial team in this role. Sites persistently late in reporting SAEs, receipt of multiple late/poorly completed CRFs, or evidence from CRFs that the trial protocols and procedures are not being adhered to (as assessed by the CI or the TMG) will may be considered triggers for on-site monitoring visits. The co-sponsors will ensure investigator(s) and/or institutions will permit trial-related monitoring, audits and REC review, providing direct access to source

data/documents as required. Monitoring will be performed by exploring the trial dataset or performing site visits, as defined in the trial monitoring plan.

Recruitment sites are obliged to assist the sponsor in monitoring the study. These may include hosting site visits, providing information for remote monitoring, or putting procedures in place to monitor the study internally.

The level of on-site monitoring might be initially conducted across all sites, and subsequently will be conducted determined using a risk based approach that focuses, for example, on sites that have the highest enrolment rates, large numbers of withdrawals, or atypical (low or high) numbers of reported adverse events.

11. PATIENT AND PUBLIC INVOLVEMENT (PPI)

The views of patients and public have been key in informing this trial. One of the co-investigators is a lay member and is a patient liaison representative for the British Orthopaedic Association. She is also active in advising patients online about recovery after surgery and has recently had arthroscopic shoulder surgery. She agrees with the study question and the design of the trial and will be actively engaged in the conduct of the trial.

Two further patients who have previously undergone surgery with the InSpace balloon have agreed to contribute to the study as lay representatives. They both agree with the need for the research, will assist the study as members of the TSCand would have joined the trial had it been open when they were considering surgery. Prior to surgery they both suffered from pain, weakness and specifically restricted motion due to pain, which was functionally very limiting. This has strongly affected the choice of primary and secondary outcome measures. The timing of recovery has also influenced the plan for the adaptive design, confirming that most of the recovery was in the first few months after surgery.

Miss J Fox, has agreed to act as a lay representative on the Trial Management Team. She will attend TMGs at regular intervals throughout the trial and will contribute to trial process and paperwork, such as patient information leaflets and will take a lead in the development of any material (for example leaflets, website information) to be used for dissemination regarding the trial to a wider audience. Two other patients have also agreed to take part and will attend trial steering committee and assist with the preparation of trial paperwork and processes.

The lay representatives will be supported by the Chief Investigator and the trial coordination team. They will have access to training and advice through the UNTRAP network (University/User Teaching and Research Action Partnership), an organisation which promotes the engagement and involvement of service users and carers from the local community in research and teaching in Health and Social Care at the University of Warwick.

12. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of doctors, nurses and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

The trial management team and other collaborators will prepare the study monograph within the agreed timetable, which will start to be prepared at the end of recruitment, ensuring that the results of the analysis can be inserted into a well prepared document and reducing the time to prepare the final report after the analysis.

The results will be submitted to a high impact peer-reviewed journal, which will allow for the results to be disseminated across the orthopaedic and rehabilitation communities, the wider medical community, NICE and hence policy makers. In addition, the findings of the study will be presented at national and international meetings such as the British Elbow and Shoulder Society, the British Orthopaedic Association, and the American Academy of Orthopaedic Surgeons.

The lay co-applicant will lead on the dissemination of the trial results to patients and the wider public. To inform patients and the public, we intend to produce a lay summary, which will be made available in the trial hospitals and to patients involved in the trial. In addition, we will publicise the work through social media outlets (e.g. Facebook and twitter) as well as websites such as Patient.co.uk.

HRA guidance on information for participants at the end of a trial will be followed: *http://www.hra.nhs.uk/research-community/end-of-study-and-beyond/participants-at-the-end-of-study/*

The REACTS methodology, the sub-studies to assess differences in Bayesian and frequentist approaches to adaptive designs and the health economic approaches will be disseminated in trials methodology conferences (such as the International Clinical Trials Methodology Conference and the Society for Clinical Trials) and relevant journal articles will be submitted to appropriate journals (eg Statistics in Medicine, Trials). The statistical and health economic sub-studies will be pre-registered on the Studies Within a Trial registry (go.qub.ac.uk/SWAT-SWAR) and the results will be posted to ensure that the outcomes are easily available to trials methodologists.

The REACTS approach will be disseminated to the surgical community via direct communication with the royal colleges and the research leads of the specialist societies. A description of the trial methodology appropriate to the wider surgical community will be prepared as letters or short articles and submitted to the college or orthopaedic publications (such as the Bulletin of the Royal College of Surgeons of England).

Prior to submission and according to legal contracts between parties, the draft manuscript of each paper will be reviewed by Orthospace solely to check for misuse of their intellectual property, this

will be agreed formally in a legal contract between UHCW and Orthospace and timescales will reflect this. All contracts will be in line with the NIHR standard agreement.

The datasets generated during and/or analysed during the current study are/will be available upon request. The publication of a trial protocol, methodology papers, trial results and trial data will be in line with the NIHR standard terms and will follow WCTU SOP 22: Publication & Dissemination.

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14. APPENDICES

Summary of Changes to Protocol v1.0 07 Feb 2018		
Page	**Section**	**Change**
4-5		TSC members added
5-6		DMC members added
18	1.5	Only year of birth will be used and TNO will be used to identify CRFs instead of "date of birth" and "initials" and TNO.
23	2.3.1	Only drug and frequency will be collected for current analgesic use.
25	2.5	A training manual or video will be produced to educate surgeons and it will be recorded whether surgeons have read/watched this. Clarification that the BESS training event will not contain cadaveric training in comparison to the training day in spring.
26	2.6	Participants will be informed by letter that they are no longer taking part in the study if they are deemed ineligible intra-operatively.
27	2.8	On the basis of a simulation exercise, demonstrating a high risk of major imbalance in the study arms with random permutated blocks, the randomisation process has been changed to minimisation with a random factor, with a 70% weighting towards balance across the whole study. As this is a multi-site study, with treatments happening at multiple sites at unpredictable

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Page	**Section**	**Change**
		times, the next randomisation is highly unlikely to be predictable using this method.
27	2.8	Information deleted regarding registration on to the trial database. Details of online randomisation and telephone randomisation contact information has been included.
28	2.8.2	Clarification that registered patients are free to withdraw at any time without prejudice. Clarification regarding what will happen to the data and that these patients will not be followed up.
29	2.10.1	Size of the incision at the lateral portal will be 1.5cm as opposed to 1cm and will be used for all participants it's a small change from standard care and is unlikely to have a negative effect on the participant. And there is no increase in risk to the patient.
34-35	4.1	Inclusion of an MRI Pilot to support the main sub-study. 4 people with symptomatic rotator cuff tear will be recruited using a PIS and CF and will undergo the scan protocol proposed in section 4.2. They will be asked to complete the baseline questionnaire that will be used for the main trial but no other outcome assessments will be completed, age, gender and findings of pervious imaging will be recorded to document details of their shoulder pathology. Addition of EMG pilot to confirm satisfactory activation of the deltoid muscle when positioned in the MRI scanner, the EMG will detect muscle activation using painless skin sensors. Up to 10 people with symptomatic rotator cuff tear will be be invited to take part. This will be the method that wil be used in the main substudy. These pilots will be carried out to confirm that the design of the sub study is robust enough to achieve the objectives set out.
35	4.2	Changes to main sub study – a small L shaped plastic board will be used. The particiant will be expected to press their arm gently against this.

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Page	**Section**	**Change**
		Therefore reducing movement of the arm caused by fatigue during the duration of the scan and will ensure consistency of movements.
37	5.1.1	For participants who are lost to follow up, a system of recording AEs and SAEs from their GP records has been developed. This is documented in section 7.3.5 'procedure to account for missing data'.
41	6.1	To maximise follow up, appropriately trained staff members may follow up participants at home to collect the primary outcome measure.
43	7.2	The results of these simulation studies will be presented to the TSC and DMC at the second meeting (end of the internal pilot and the first interim analysis)
44	7.3.1	we estimate at least 10 centres but more likely 16-20.
44	7.3.2	(for example: 35 patients at end of month 6 with a staggered start of sites)
46	7.3.5	Where participants have been lost to follow up at or beyond the 12 month time point, and data on adverse events can therefore not be recorded, the participants General Practitioner (GP) will be contacted and a short form requesting any information or health record that could be an adverse event will be requested from the GP, as well as confirmation of the current contact details of the participant. This will be associated with a small fee for the GP. These records will be examined and AEs and SAEs will be recorded, and when this process is complete the data will be destroyed. Sites will be informed of SAEs identified in this manner and will be given the opportunity to pass on any more information that may help ascertain the nature and severity of the adverse event.
47	7.6	Relatively little research has been conducted prospectively on how interim economic analysis might inform an adaptive design. Approaches generally include a net-benefit regression

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Page	**Section**	**Change**
		approach and value of information analysis and have considered the problem of right-censored cost and quality-of-life data. A six-month work package will commence at the start of study to develop appropriate analytic tools.
52	9.8	The Trial Management Group, will consist of an operational group where the procedural side of the trial will be discussed and the methodological group will focus on the methodology aspect of the trial. The latter group will feed into the operational group TMGs. The operational TMG will consist of the project staff and co-investigators who are involved in the day-to-day running of the trial. Both groups will meet on a 4 weekly basis.
52	9.10	The DMC and TSC (held separately to ensure quorate numbers from both committees could attend).
26	12	The datasets generated during and/or analysed during the current study are/will be available upon request.
Other		ISRCTN Minor typos and corrections. Additions and deletions of text for further clarification. Update of footer