PROJECT TITLE:

PROximal Fracture of the Humerus: Evaluation by Randomisation Trial no. 2 (PROFHER-2 Trial): A three-arm randomised controlled trial to assess the effectiveness and cost-effectiveness of reverse shoulder arthroplasty versus hemiarthroplasty versus non-surgical care for acute three and four-part fractures of the proximal humerus in older adults.

Short Title: PROFHER-2 Trial

PROximal Fracture of Humerus: Evaluation by Randomisation – 2

Funder: NIHR HTA; HTA Reference: 16/73/03

IRAS ID:

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Disclaimer: The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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PROximal Fracture of Humerus: Evaluation by Randomisation No. 2 – The PROFHER-2 Trial

This protocol describes a UK multi-centre three-arm randomised controlled trial to assess the effectiveness and cost-effectiveness of reverse shoulder arthroplasty versus hemiarthroplasty versus non-surgical care for acute three and four-part fractures of the proximal humerus in older adults.

This protocol is derived from the detailed project description of the HTA funding application entitled '*PROximal Fracture of the Humerus: Evaluation by Randomisation Trial no. 2 (PROFHER-2 Trial): A three-arm randomised controlled trial to assess the effectiveness and cost-effectiveness of reverse shoulder arthroplasty versus hemiarthroplasty versus non-surgical care for acute three and four-part fractures of the proximal humerus in older adults'* [HTA Reference: 16/73/03].

This trial has received endorsement by the British Elbow and Shoulder Society (BESS).

1. SUMMARY OF PLANNED INVESTIGATION

Proximal humeral fractures (PHFs) are painful and debilitating injuries, accounting for 5% to 6% of all adult fractures. They are two to three times more common in women and are mostly as a result of low energy trauma, typically a fall from a standing height (1,2) Similar to other fragility fractures, their incidence and age-specific incidence are increasing with time (3). Consequently, the health economic burden of PHFs is substantial and increasing (4, 5).

There are two types of shoulder arthroplasty currently used for treatment of complex [three and four part] displaced fractures. These are hemiarthroplasty (HA), which replaces the broken humeral head, and reverse total shoulder replacement (also known as reverse shoulder arthroplasty or RSA) which reverses normal geometry by replacing the humeral head with a socket and the glenoid (socket) with a hemisphere.

Shoulder function following surgery is ultimately reliant on the activity of the rotator cuff (muscles that stabilise and initiate shoulder movement). Clinicians believe that RSA has advantages, particularly in older patients who are at greater risk of rotator cuff dysfunction following a fracture (as their tuberosity attachments often can fail to heal) (6). In contrast to HA, RSA is not reliant on rotator cuff function by virtue of reversing the mechanical geometry of the joint. For this reason, clinicians are using RSA more often in older patients as they believe better function may be achieved with less need for physiotherapy and rehabilitation (7). RSA, however, is a more extensive and expensive procedure, with lack of good quality evidence to support its use (8). Both HA and RSA are associated with complications (6, 9, 10), which also underscores the importance of determining whether these interventions are superior to structured non-surgical treatment.

The recently reported PROximal Fracture of Humerus: Evaluation by Randomisation (PROFHER) Trial (ISRCTN: 50850043), which compared non-operative treatment with operative interventions, concluded that there was no significant difference between surgical treatments compared with non-surgical treatment in patient-reported clinical outcomes over two years following fracture occurrence (11). PROFHER offers valuable information regarding treatment of adults with displaced fractures involving the surgical neck of the humerus, but relatively little information on use of arthroplasty for more complex fractures. Following the publication of the PROFHER trial, a James Lind Alliance priority setting exercise was performed. This identified the need for research to establish the place of RSA in the management of shoulder problems, and specifically in the management of PHF (12). In addition, a recent study that compared the outcomes of HA with RSA, for complex PHF, found the mean Oxford Shoulder Score (OSS) following surgery to be similar to the OSS for patients with non-surgically treated fractures in PROFHER (13). Further assessment on whether either surgery (RSA or HA) is better than structured non-surgical treatment (NS) is therefore required.

The PROFHER-2 trial is a multi-centre, three-arm Randomised Controlled Trial (RCT) with internal pilot assessing the clinical and cost-effectiveness of RSA versus HA; and comparing the effectiveness of these surgical procedures with NS. The primary outcome is a validated patient-reported measure, the OSS assessed at two years post-randomisation (14). Secondary outcomes include the OSS at 6 and 12 months, quality of life as measured using the EQ5D-5L (15); pain as measured on a visual analogue scale; Patient Reported Outcomes Measurement Information System (PROMIS) pain interference tool (16); health care resource use collected from hospital data, and complications of surgery. Patients will complete follow up assessments at 6, 12 and 24 months post randomisation.

Based on a minimum clinically important difference of five points on the OSS for comparisons between surgical interventions (RSA vs. HA), and a six-point difference between surgical and non-surgical options (RSA vs NS, HA vs NS), with an associated standard deviation (SD) of 12, 380 patients (152 RSA, 152 HA, 76 NS) are required, allowing for up to 15% attrition at two years.

The internal pilot of 12 months will assess our assumptions about recruitment and provide guidance on optimising trial processes. We will aim to open at least half of the total target number of sites, and recruit an average of one patient per centre every two months, during the internal pilot.

2.0 BACKGROUND AND RATIONALE

2.1 THE IMPACT OF PROXIMAL HUMERUS FRACTURES (PHF)

Fractures of the proximal humerus are common and painful injuries. Their incidence rises markedly with age, being highest in those aged 70 years and over. A recent systematic

review found that the mean age of patients receiving RSA for acute fractures ranged from 74 years to 80 years (8).

Fractures of the proximal humerus are about three times more common in women than men and the majority (about 90%) result from falls from a standing height (17). Numbers of these fractures are predicted to increase due to the growing incidence of fragility fractures secondary to an aging population. PHFs are also known to be associated with disability, loss of independence and negative impact on health-related quality of life (Reference).

2.2 CURRENT TREATMENTS FOR PROXIMAL HUMERUS FRACTURES (PHF)

When a fracture of the proximal humerus occurs, the pattern of injury varies. The three key elements of the injury are the number of fractured parts (i.e. two, three or four parts); whether the shoulder joint is dislocated as well as fractured (found to be between 5% and 8.6% of PHF (2, 18) and whether the joint surface itself is fractured. Treatment of these fractures can be either non-surgical, or surgical. Surgical fracture fixation aims to recreate the normal shape of the proximal humerus and hold it in place with metal plates or rods. Alternatively a joint replacement (arthroplasty) may be performed.

Various factors influence clinical decision making on the management of these fractures. Some patients are too frail to undergo surgery, and are treated non-surgically. Conversely, some patients have fractures that are so complex (e.g. in many parts, includes dislocation or the joint surface is badly damaged) that they require surgical treatment. The majority of fractures however fall between these two extremes. Participant age may also affect treatment decisions.

2.3 RATIONALE FOR THE PROFHER-2 TRIAL

The optimal management of PHFs has remained controversial; hence, various non-surgical and surgical interventions have been used (19). The strength and quality of evidence to support the use of these interventions has mostly been poor (19).

The recently reported PROFHER trial, compared-surgery (fracture fixation using nails, plates and screws or ‘other’, and humeral head replacement) with non-surgical treatment (11) and concluded that there was no significant difference between surgical treatments compared with non-surgical treatments. The PROFHER trial aimed to recruit a population that reflected the normal spectrum of proximal humeral fracture epidemiology and only a quarter of the study population had displaced (three and four part) fractures. The findings of the PROFHER Trial provides unparalleled information regarding optimal treatment for the majority of displaced PHFs but relatively little information on the effectiveness of arthroplasty for the more complex fractures.

A number of case series reports have utilised RSA for PHFs (20, 21), in addition to observational studies comparing RSA against HA (22, 23). A recent systematic review suggests that using RSA for fracture results in reliable pain relief, functional range of

movement and acceptable levels of patient satisfaction (24). These effects seem to remain when compared with shoulder HA (23, 25). There is, however, an awareness of the potential complications of RSA, with up to a third of patients reported as having a minor or major complication following surgery. Given the lack of good quality evidence, there is clear clinical uncertainty regarding the use of arthroplasty as a treatment for the more complex PHFs.

Despite the risk profile, the significant cost associated with this form of surgery, and the presence of clinical uncertainty, the use of RSA is increasing over time (26, 27). Data from the latest National Joint Registry (NJR) report confirms this trend in the UK, with a 51% increase in the use of RSA from 2013 to 2015 (28). Considering the potential risks of surgery; costs associated with arthroplasty; and the increasing use of RSA, there is an urgent need for a definitive clinical trial to determine its effectiveness and cost-effectiveness in the treatment of complex PHFs. In addition, the recent James Lind Alliance priority setting partnership, identified the use of RSA for PHFs as a key research priority (12). Therefore, a sufficiently powered randomised controlled trial investigating RSA as a treatment for complex PHFs is required to fill this evidence gap.

The PROFHER-2 Trial is a pragmatic, multi-centre randomised controlled, cost effectiveness trial comparing RSA versus HA; and comparing the effectiveness of these surgical procedures with non-surgical treatment.

The design for the PROFHER-2 trial was informed by clinicians' feedback from two surveys; one exploring the impact of PROFHER trial and the second in preparation for application of funding for the PROFHER-2 trial. The post-publication survey of surgeons following PROFHER confirmed that surgeons felt empowered to guide their clinical practice based on the trial results and have consequently increased the utilisation of non-surgical treatment for displaced PHFs (unpublished data). A survey of BESS surgeons, including surgeons involved with PROFHER, about the clinical uncertainties in the use of RSA for PHFs, led to the following main conclusions: the effect of non-surgical treatment should be considered when comparing interventions for shoulder fractures; and a lower age limit of 65 years should be considered for RSA.

Qualitative research investigating key areas affecting disability and outcomes in patients with upper limb fractures (unpublished data), guided the patient derived outcome measures of morbidity and disability included in the PROFHER-2 trial.

3. AIMS AND OBJECTIVES

3.1 AIM

To investigate the clinical and cost-effectiveness of surgery compared to no surgery for patients presenting with three and four part PHFs. This will involve a comparison of RSA versus NS, and HA versus NS. Additionally, the effectiveness of RSA versus HA will also be compared.

3.2 OBJECTIVES

i. To undertake a 12-month internal pilot to obtain robust estimates of recruitment and confirm trial feasibility.

ii. To undertake a randomised parallel group comparison to determine if surgery is superior to no surgery in treating three and four part PHFs based on change in the OSS at 2 years.

iii. To undertake a randomised parallel group comparison to determine if RSA is superior to HA in treating three and four part PHFs based on change in the OSS at two years.

iv. To conduct a detailed economic evaluation to compare the cost-effectiveness of the comparisons described in Objectives ii and iii above at two years.

4. TRIAL DESIGN

4.1 DESIGN

PROFHER-2 is a pragmatic multi-centre, randomised controlled, three-arm superiority trial with parallel groups. The study includes an internal pilot phase to assess recruitment assumptions and optimise trial processes. The study has a 36-month recruitment period, including an internal pilot followed by the main recruitment period. Following randomisation, participants will be followed-up for two years, with visits conducted at 6 months, 12 months and 24 months post randomisation. A flow diagram demonstrating the patient pathway through the study is provided in Appendix 1

As the treatments cannot be adequately concealed, it is not possible to blind clinicians or participants to their treatment allocation.

The trial is pragmatic given that surgeons will perform the allocated surgical procedures as per their usual practice and peri-operative care, post-operative physiotherapy and post-intervention care will follow usual care pathways according to local guidelines.

4.2 SETTING

The study will use approximately 35 centres (NHS hospitals) that regularly treat PHFs, to recruit on average 127 participants per year, over the three-year recruitment period. The recruitment estimates for the PROFHER-2 study are based on experience with the PROFHER Trial (11) and indicative numbers of eligible patients on the NJR (28), where 305 RSA and 216 HA were recorded for acute trauma between 1/4/15 and 31/03/16 based on data from the 2015 and 2016 annual reports.

All consultant surgeons recruiting to this trial will have expertise in all three management arms (conservative, HA and RSA) as part of their routine NHS work. The recruitment of surgeons to the PROFHER-2 trial will be primarily through the National Specialist Society of British Shoulder and Elbow Surgeons (BESS).

In order to ensure the specific skills required to perform RSA we will ask potential surgeon-researchers to confirm they perform RSA replacement as part of their pre-trial clinical practice. We do not propose to implement a threshold number or experience level as this detracts from the pragmatic nature of the trial.

4.3 OUTCOMES

4.3.1 PRIMARY OUTCOME

The primary outcome is the OSS at 24 months.

The OSS is a 12-item condition-specific questionnaire providing a total score based on the person's subjective assessment of pain and activities of daily living impairment (29).

This patient reported outcome has established content-validity in post-operative patients, and has been used successfully in large surgical trials and cohort studies (13). This outcome measure has been chosen, not only because of its reported construct and face validity, but also to allow comparison with the data obtained from the PROFHER trial.

4.3.2 SECONDARY OUTCOMES

Secondary Outcomes will include:

1. Quality of life using EQ-5D-5L: a validated, generic health status measure asking 5 questions on mobility, self-care, usual activities, pain and discomfort, and anxiety and depression, accompanied by a health status thermometer visual analogue scale (VAS) (15)

2. Pain using PROMIS (Patient-Reported Outcomes Measurement Information System) pain interference (16) questionnaire that assesses the effect pain has on the individual. This will supplement the shoulder function assessment by the OSS.

PROMIS is designed to reduce responder burden and is increasingly used in healthcare trials. A visual analogue pain scale will also be used.

3. Physiotherapy requirements and use (including time to start of physiotherapy; number of sessions; modalities used; and duration of rehabilitation)

4. Range of shoulder motion (recorded at discharge from physiotherapy)

5. Healing and implant position using AP, Axial and lateral Y view X-rays taken at 6 months post-surgery

6. Further procedures and complications

7. Grip strength at baseline will be used to assess frailty and as a predictor of morbidity and mortality.

5. TARGET POPULATION

We will include all patients who meet the "Inclusion/Exclusion Criteria" below:

5.1 INCLUSION CRITERIA

- Adult patients aged 65 years or over
- Presenting to a participating centre within three weeks of injury
- Radiographically confirmed three-part (including surgical neck) or four-part displaced fracture of the proximal humerus (Neer Classification) including a head-splitting fracture of the humeral head, or fractures with associated dislocation where closed reduction of dislocation can be achieved
- Patient is deemed medically fit for surgery by the clinical care team.

5.2 EXCLUSION CRITERIA

- Patients who are unable to adhere to trial procedures or complete questionnaires
- Poly-trauma – where one or more additional fractures are present or other body-systems are affected
- Fractures with associated dislocation where closed reduction of the dislocation cannot be achieved
- Patients who cannot receive assigned treatment within five weeks of injury
- Open fractures or fractures where there is severe soft tissue compromise requiring urgent surgery

- Pathological (other than osteoporotic) fractures

6. TRIAL PROCEDURES

6.1 PARTICIPANT IDENTIFICATION AND RANDOMISATION

Screening to identify patients eligible for the trial will occur in the orthopaedic trauma / fracture clinics, emergency departments and orthopaedic / trauma wards of participating NHS hospitals. The research teams will work closely with the treating clinicians at each participating centre to optimise the local screening and recruitment processes.

Potential participants will be provided with information about the study including a patient information sheet. Patients will have the opportunity to ask questions of the surgeon and the local research team before consent for the study is obtained. Consent will be sought for follow-up beyond the duration of the trial to allow the possibility of future long-term follow-up, which may include accessing relevant data on the NJR.

Once patients have consented to participate in the trial, baseline data will be collected which includes:

- OSS (assessing pre-fracture function)
- PROMIS Pain Interference Scale
- Pain VAS
- EQ5D-5L
- Shoulder X ray
- Grip strength in unaffected arm

The research team at site will then contact York Trials Unit (YTU), either by telephone or via the internet, to access a secure central randomisation service. The randomisation service will record information and check patient eligibility to avoid inappropriate entry of patients into the trial. YTU will then perform independent random allocation 2:2:1 to RSA:HA:NS, in blocks stratified by centre (see study flowchart in Appendix 1).

Patients and treating clinicians will be informed of the allocation. Patients, surgeons or outcome assessors will not be blinded as the surgical site on post-operative X-rays will be visible.

6.2 PARTICIPANT FOLLOW-UP

Participants will be followed up for the purposes of the study at 6, 12 and 24 months. The primary follow-up time point is 24 months post-randomisation (see Appendix 1 and 2).

Visits will be completed as close to the due date as possible (+/- four weeks at six months, 12 months and 24 months)

Details of assessments are summarised below and in the study procedure summary (Appendix 2).

6 month Follow Up (Clinic Visit)

- OSS
- PROMIS Pain Interference Scale
- Pain VAS
- EQ5D-5L
- Resource Use
- Further procedures and complications
- Shoulder X ray
- Range of Movement

12 month Follow Up (Postal Follow Up)

- OSS
- EQ5D-5L
- Resource Use
- Further procedures and complications

24 month Follow Up (Postal Follow Up)

- OSS
- PROMIS Pain Interference Scale
- Pain VAS
- EQ5D-5L
- Resource Use
- Further procedures and complications

All data will be collected on paper Case Report Forms, which will be completed at recruiting sites or by participants in their homes and returned to YTU for scanning and processing.

For patients randomised to either surgical treatment, clinical follow up will follow usual care pathways at participating centres, which is typically at around six and 12 weeks post-surgery. Any other additional clinical follow up will be at the discretion of the treating surgeon, guided by clinical need. For patients randomised to receive non-surgical treatment, follow up will be guided by clinical need, and we estimate a median of 12 physiotherapy sessions being required (compared to eight required for the non-surgical arm in PROFHER) (11). Clinical need and usual local care pathways will guide any further follow up or treatment after completion of these sessions.

Details on the surgical procedure, including type of anaesthesia and analgesia used will be collected.

X-rays:

Pre-intervention x-rays (taken at baseline) will be used to assess osteopenia, which has been shown to be a predictor of fracture healing / outcome or complications (30).

6.3 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS

Each participant has the right to withdraw from the study at any time without prejudice. In addition, the investigator may advise that a participant be discontinued from the study at any time if the investigator considers it necessary for any reason, however the decision on full withdrawal will remain with the participant at all times.

The reason for withdrawal will be recorded in the case report form (CRF). If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

Participants who request to fully withdraw during a study visit will be asked if they would be willing to complete the questionnaires prior to withdrawal. Where a participant fully withdraws outside of a scheduled study visit, completion of further follow up questionnaires will not be requested.

Unless the participant specifically withdraws consent for their data to be stored, all data collected from them will continue to be stored as per the original patient consent. At a participant's request, their data collected up to the point of withdrawal can however be withdrawn from the trial and will not be used in the final analysis.

7. STUDY TREATMENTS

7.1 REVERSE SHOULDER ARTHROPLASTY (RSA)

RSA will be performed under general anaesthesia and anterior (delto-pectoral) or superior (McKenzie type) surgical approaches may be used as per the treating surgeon's usual practice.

During RSA surgery, the fractured anatomical articular head fragment of the humerus is removed. The glenoid (socket) on the scapula is prepared to receive a metal backed base plate, fixed with screws, which is designed to accept the implantation of a prosthetic hemi-sphere on the glenoid surface. The humerus is prepared to receive the implantation of a humeral prosthetic stem component that has a socket-like design that articulates with the glenoid sphere. The stem of the humeral component may be cemented in place or inserted without cement as a 'press-fit', as per the treating surgeon's usual practice. The remaining tuberosity fragments and associated rotator cuff attachments are repaired around the humeral component, to help with stability of the joint replacement and with rotational control of the shoulder following healing.

The implant design aims to alter the biomechanics of the deltoid muscle, making it more efficient at moving the shoulder in the absence of the rotator cuff muscles. With RSA, function of the rotator cuff is less critical, which is relevant as many older patients have dysfunction of the rotator cuff muscles.

Along with the risks of general anaesthesia, RSA has significant potential risks and complications, which include deep prosthetic infection, prosthetic instability and dislocation, neurological injury and loosening of the components with time all of which may require revision surgery.

7.2 HEMIARTHROPLASTY (HA):

HA will be performed under general anaesthesia and anterior (delto-pectoral) or superior (McKenzie type) surgical approaches may be used as per the treating surgeon's usual practice.

During HA surgery the fractured, anatomical, articular head fragment of the humerus is removed. The humerus is then prepared to accept a humeral stem implant that replaces the spherical head fragment. The stem of the humeral component may be cemented in place or inserted without cement as a 'press-fit', as per the treating surgeon's usual practice. The remaining tuberosity fragments and associated rotator cuff are repaired to the proximal humerus and prosthesis, thus effectively reconstructing "normal" anatomy around the prosthesis. The native glenoid is not instrumented and articulates with the replaced humeral component, thus only half the joint is replaced in this procedure.

Along with the risks of general anaesthesia, HA has significant potential risks and complications, which include deep prosthetic infection, prosthetic instability and dislocation, neurological injury and loosening of the components with time all of which may require revision surgery. As normal joint geometry is preserved, the function of the rotator cuff remains very important to maintain shoulder function. As such, there is risk of non-union or mal-union of the tuberosities resulting in rotator cuff dysfunction that would have an adverse effect on shoulder function.

7.3 POST OPERATIVE CARE FOR RSA AND HA

Following surgery (RSA and HA) the shoulder will be immobilised in a supportive arm sling and a graduated rehabilitation program followed, as per usual care in the treating hospital. This typically involves supervised physiotherapy with the aim of gradually increasing range of motion and function. Internal rotation (i.e. hand behind back movement) will be avoided following RSA to protect the joint until clinician review (at around 6 weeks). This is due to the biomechanics of RSA and the increased risk of dislocation with such movements (31).

Perioperative care provided to participants will be recorded; however there will be no standardisation of perioperative care, in line with the pragmatic nature of the PROFHER-2

Trial. For the PROFHER-2 study, perioperative care will be defined as the period from start of anaesthesia to the discharge of the patient from the ward following surgery.

Intravenous antibiotics may be given prophylactically to minimise the risk of subsequent prosthetic infection. The type of analgesia (regional or intravenous) and antibiotic use will be recorded within the case report form.

7.4 NON-SURGICAL CARE (NS):

Non-surgical management will involve supporting the injured arm in a sling for a period of three weeks for comfort as in the PROFHER trial (11). The arm and shoulder will then be gently mobilised under supervision of a physiotherapist with the aim of increasing range of motion and performing active exercises beyond six weeks. Physiotherapy sessions will be tailored but include advice and education on a home exercise programme predominantly based on daily functional tasks. The physiotherapy sessions will include a combination of exercise, soft tissue techniques, joint mobilisations, stretching and relaxation techniques. As severe fractures will be included in this trial, we have allowed for a median of 12 physiotherapy sessions being required (compared to eight required in PROFHER). The exact treatments will be individualised on a per patient basis to ensure that rehabilitation is tailored to individual needs in line with routine conservative care.

Non-surgical treatment has the advantage of avoiding the risks of anaesthesia and surgery described. If pain or function remains poor after non-surgical treatment, delayed surgery may be performed at clinical discretion, although we anticipate RSA would be the main treatment choice in this situation. This would not usually be considered before 6 months to allow an adequate period of rehabilitation to be pursued.

8. ADVERSE EVENT MANAGEMENT

8.1 ADVERSE EVENTS

Adverse events (AE) are defined as any untoward medical occurrence in a clinical trial participant and which do not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease which is temporally associated with the study medication or procedure (intervention or control), whether or not considered related to the study medication or procedure (intervention or control). Adverse events, which might be expected with this condition and treatments, include infection, dislocation/instability, haematoma, neurovascular injury including ulnar nerve neuropathy and axillary nerve palsy, pain including complex regional pain syndrome, delayed wound healing and/or wound dehiscence, septic arthritis and intraoperative fracture (23, 32). Additionally, adverse events associated with anaesthetic such as DVT, pulmonary embolism and respiratory tract infection are also expected in this patient group.

8.2 SERIOUS ADVERSE EVENTS

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining reporting obligations.

Serious adverse events are defined as any untoward and unexpected medical occurrence that:

1) Results in death

2) Is life threatening

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

3) Requires hospitalisation or prolongation of existing inpatients' hospitalisation

4) Results in persistent or significant disability or incapacity

5) Is a congenital anomaly or birth defect

6) Any other important medical condition that, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed.

For the purposes of the PROFHER-2 Trial, the following are **not** considered a SAE but will be reported using the PROFHER-2 Adverse Event Form:

- Complications of anaesthesia or surgery (e.g. wound complications, infection, damage to a nerve or blood vessel and thromboembolic events)
- Secondary operations for or to prevent infection, malunion, non-union or for symptoms related to the metalwork.

8.3 REPORTING PROCEDURES FOR ADVERSE AND SERIOUS ADVERSE EVENTS

Adverse events (AE) will be entered onto the Adverse Event reporting form and reported to York Trials Unit within 5 days of discovery or notification of the event.

Serious adverse events (SAE) will be entered onto the Serious Adverse Event reporting form and reported to York Trials Unit within 24 hours of discovery or notification of the event. Once received, causality and expectedness will be confirmed by the Chief Investigator.

SAEs that are deemed to be unexpected and related to the trial will be notified to the Research Ethics Committee (REC) and Sponsor within 15 days. All such events will be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings.

All participants experiencing SAEs will be followed-up as per protocol until the end of the trial.

Where repeated adverse events (Serious Adverse or Adverse) of similar type are observed, these will be discussed with the Data Monitoring Committee (DMC) and will be onward reported should concerns be raised in relation to the type of event and/or frequency observed.

9. STATISTICS

9.1 SAMPLE SIZE ESTIMATION

A mean difference of five OSS points (11, 29, 33) will be sought between the two surgical arms and six OSS points between each surgical arm and non-surgical care (34).

Assuming a standard deviation (SD) of 12, 90% power and 5% two-sided statistical significance, 320 participants are required to power all three-group comparisons. Assuming 15% attrition over 2 years, the total recruitment target is 380 (152 RSA, 152 HA, 76 NS).

9.2 INTERNAL PILOT ANALYSIS

The internal pilot phase includes predefined criteria to ascertain our ability to recruit and randomise. The success of the pilot study is based on the following objectives:

1) To setup at least half of the total target number of sites
2) To randomise, on average, one patient per centre every two months
3) To ensure the feasibility of follow up during the pilot to help inform progression
4) To inform the feasibility of continuing with the non-surgical arm of the trial

9.3 STATISTICAL ANALYSIS

A statistical analysis plan will be written, and agreed with the oversight committees, before any analyses are undertaken. Any subsequent amendments to the plan will be clearly documented. Analysis will be carried out on a locked dataset. All analysis will be conducted taking into consideration the reporting requirements of the Consolidated Standards of Reporting Trials (CONSORT)(35) .

All analyses will be conducted on intention-to-treat (ITT) basis, except for a pre-specified CACE analysis of the primary outcome. Statistical significance will be at the two-sided 5% level. Analyses will be conducted using the latest available version of Stata.

The primary analysis will assess OSS scores up to 2 years follow-up using a mixed effects model, adjusting for relevant baseline characteristics, such as pre-fracture OSS estimates. OSS outcome data in the model will be included from all interim follow-up points, and the correlation of outcomes within each patient over time will be modelled by an appropriate covariance structure. Surgeons will be added as a random effect to account for individual clinician differences; if clusters by surgeon are too small, then centre effect will be used instead. Adjusted mean OSS estimates from the analysis model for each follow-up time point and differences between treatment arms will be reported with 95% confidence intervals and a p-value for each of the three mean group differences using pairwise comparisons.

Secondary analyses of the OSS data will include an appropriate model to account for missing data (e.g. using multiple imputation) and an analysis adjusting for treatment compliance (CACE analysis). Surgeon expertise in terms of years of experience in each technique, number of procedures performed and number of cases seen per year will be compared between the surgical trial arms. As the number of randomised patients is expected to be small for most surgeons, learning curve effects will be based on existing surgeon expertise in each technique at the start of the trial. In a sensitivity analysis of the OSS and safety data for the RSA vs HA comparison, surgeon expertise will additionally be adjusted for, and the relationship between expertise and outcome will be illustrated graphically. A treatment by experience interaction will be used to explore differential treatment effects between more and less experienced surgeons.

Secondary outcomes (including pain, range of motion and estimates of OSS at 6 and 12 months) will be analysed similarly to the primary analysis, using analytic models that are appropriate for each type of secondary outcome variable. Safety data, including complications and adverse events will be described and compared between trial arms if event numbers are sufficient. Site specific post-treatment practices will be reported descriptively.

9.4 HEALTH ECONOMIC ANALYSIS

The economic evaluation will assess the cost-effectiveness of the three competing interventions for treatment of acute three and four part fractures of the proximal humerus in older adults. The analysis will be conducted from the perspective of the UK National Health Services (NHS) and Personal Social Services (PSS) in accordance with NICE (National Institute for Health and Care Excellence) reference case standards. All analyses will be conducted using the latest available version of Stata and a health economics analysis plan

(HEAP) will be written, and agreed with the oversight committees, before any analyses are undertaken. Any subsequent amendments to the plan will be clearly documented.

Self-reported questionnaires and hospital forms will be used to evaluate resource use and associated costs over the follow-up of the trial. Cost components will compromise hospital stay (initial and subsequent inpatient episodes, outpatient hospital visits and A&E hospital admissions) and primary care consultations (e.g. GP, nurse and physiotherapy). An accurate record of procedures at hospital level (e.g. centres in the trial) will be put in place in order to record per patient information (e.g. surgical procedures, complications related to the surgical intervention, other medical complications). Costs relating to surgical procedures will be based on time in theatre, staff time, consumables and devices, and nights in hospital after the procedure. These data will be collected via a form that will be specifically designed for this trial. Similarly, physiotherapy treatment logs will be completed by physiotherapists providing patient care. These will record prospectively the essential components of physiotherapy at each session for each participant (as described in Section 9 above). Cost components for health resource use will be derived from established national costing sources such as NHS Reference Costs, PSSRU Unit costs of health and social care, and the British National Formulary. Unit costs will be multiplied by resource use to obtain a total cost for each patient.

The primary outcome for the economic analysis will be the additional cost per quality-adjusted life year gained (QALY). Value for money will therefore be estimated in terms of cost per QALY following an intention-to-treat approach using EQ-5D-5L data (15). The EQ-5D-5L will be collected at Baseline, 6 months, 12 months and 24 months follow-up. Descriptive statistics of the utility scores for both trial arms at each data collection point and raw EQ-5D scores according to domain will be presented. The overall difference in EQ-5D index scores between the two arms will be examined through regression methods, consistent with the model selected in the statistical analysis. The EQ-5D health states will be valued using the mapping function developed by van Hout et al (2012) and following the NICE position statement (36). QALYs will be calculated by plotting the utility scores at each of the three time points and estimating the area under the curve (37). A discount rate will be applied to all costs and QALYs accrued after 12 months at a rate of 3.5% per annum in line with NICE guidance (38).

For the analysis, regression methods will be used to allow for differences in prognostic variables. Incremental cost-effectiveness ratios and net-benefit statistics will be calculated. The pattern of missing data will be analysed and handled by means of multiple imputation (MI) (39). A range of sensitivity analyses will be conducted to test the robustness of the results under different scenarios, including probabilistic sensitivity analysis. In case of positive results of the trial, we will recommend that costs and outcomes will be extrapolated and modelled over a longer time horizon than captured by the trial (e.g. lifetime of the patient).

10. ETHICAL ARRANGEMENTS

10.1 ETHICAL APPROVAL

The PROFHER-2 trial will be conducted in accordance with the Clinical Trials Regulations (2004/1031) and will be subject to approval from the Research Ethics Committee and the Health Research Authority prior to study activity commencing. The study will be conducted in accordance with the Research Governance Framework and MRC Good Clinical Practice Guidance (40, 41).

Before being enrolled in the PROFHER-2 study, participants must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them. The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

A Patient Information Sheet (PIS) that includes information about the study and a consent form will be given to the participant. These documents will contain all the elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. Patients will be given the opportunity to ask questions and the nature and objectives of the study will be explained. At the time of consent, consent must be confirmed by the personally dated signature of the participant and the person conducting the informed consent discussions.

The original signed consent form will be retained in the study files. Other copies of the consent form are required:

- One copy of the informed consent form will be faxed to YTU and filed in the TMF
- One copy of the informed consent form will be kept in the patient's clinical notes where applicable. If a patient does not have clinical notes at the trial site, the informed consent document will be filed in a separate folder.
- One copy will be given to the patient.

Consent is an ongoing process and will be reassessed at each study visit.

10.2 RISKS AND ANTICIPATED BENEFITS

Risks to participants because of any of the treatments are not increased through trial participation. Risks associated with each intervention and anticipated benefits with each procedure are detailed under Section 7. Measures taken by us, such as our emphasis on good practice and standardised protocols/care pathways throughout, are likely to reduce risk and could bring additional benefits. In this trial, surgeons will perform interventions, which they undertake on a regular basis and with which they are familiar. We will also stress the importance of competence in non-surgical methods, and support site investigators to this end.

10.3 INFORMING POTENTIAL TRIAL PARTICIPANTS OF POSSIBLE BENEFITS AND KNOWN RISKS

Informed consent will be obtained by the trained local research nurse or clinician using a detailed patient information sheet developed with the help of service users, which will explain the risks and benefits clearly. In the unlikely event that new information arises during the trial that may affect participants' willingness to take part, this will be reviewed by the Trial Steering Committee for addition to the patient information sheet. A revised consent form will also be completed if necessary.

10.4 END OF TRIAL

The end of the PROFHER-2 Trial will be the Last Patient Last Visit (LPLV), defined as:

- Completion of 2 years follow up assessments in the study
- Withdrawal from follow up due to any reason

10.5 RETENTION OF RELEVANT TRIAL DOCUMENTATION

In line with the principles of Good Clinical Practice/UK Clinical Trials Regulations, essential Trial documentation will be kept with the Trial Master File and Investigator Site Files. This documentation will be retained for a minimum of five years after the conclusion of the trial to comply with standards of Good Clinical Practice.

Case Report Forms will be used to record all the information required from the protocol and will be stored for a minimum of 10 years after the conclusion of the trial as paper records (stored in a secure storage facility or off-site) and a minimum of 20 years in electronic format (on a password protected server) in accordance with guidelines on Good Research Practice (40).

10.6 COMPLIANCE WITH THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS

The techniques under investigation are in routine use within the NHS and are internationally accepted surgical procedures using CE-marked implants and medical devices. We do not therefore require prior authorisation by the UK Competent Authority, the MHRA, under the Medical Devices Regulations (2002).

11. TRIAL FINANCE AND INSURANCE

11.1 TRIAL FUNDING

The PROFHER-2 trial is funded by the NIHR Health Technology Assessment Programme (HTA). HTA Reference: 16/73/03.

The Schedule of Events and Statement of Activity approved by the Health Regulatory Authority details all related costings for the PROFHER-2 Trial.

All interventions are standard treatment options currently available in NHS hospitals. We anticipate therefore that there will be no excess treatment costs for these interventions.

11.2 TRIAL INSURANCE

The Clinical Negligence Scheme for Trusts is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent harm. In certain circumstances, we provide insurance cover for claims arising from non-negligent harm. Clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

12. PROJECT MANAGEMENT

12.1 TRIAL SPONSOR

The trial will be sponsored by South Tees Hospitals NHS Foundation Trust.

12.2 TRIAL MANAGEMENT

York Trials Unit (YTU) at the University of York will manage the study and provide quality assurance for trial processes.

Each site will have a site Principal Investigator (PI) who will be responsible locally for the study. All trial staff will have current GCP certification and will be trained in the trial procedures by YTU during site set up, thereby meeting the Sponsors (and NIHR) standards. Annual investigator meetings will be arranged to ensure the continued development of networks for UK-wide orthopaedic surgical trials.

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

Regular progress reports will be submitted as required to the Funding Body.

12.3 TRIAL MANAGEMENT GROUP

A Trial Management Group (TMG) will monitor the day-to-day management of the trial including the detailed design, set up, initiation and supervision of the study. This will comprise the Chief Investigator (CI), all co-applicants, trial team at YTU, trial statistician, and trial health economist. A representative of the Sponsor will also be invited to attend. The group will meet monthly from the start of the study to the end of the pilot phase and quarterly thereafter to manage the detailed design, set up, initiation and supervision of the study.

12.4 TRIAL STEERING AND DATA MONITORING COMMITTEES

Independent oversight of the study will be conducted by the Trial Steering Committee (TSC), who will monitor the progress of the trial and provide independent advice. The TSC will

comprise of independent clinicians and health service researchers with appropriate expertise and an independent patient representative. The TSC meetings will also be attended by the trial statistician and the study Sponsor will be invited to attend.

The study will be regularly reviewed by the Data Monitoring Committee (DMC), comprising of independent clinicians and health service researchers with appropriate expertise. The DMC will monitor the data arising from the study and recommend whether there are any ethical or safety reasons why the trial should not continue.

Both the TSC and DMC will meet at regular intervals to provide project oversight to the trial.

12.5 PATIENT AND PUBLIC INVOLVEMENT (PPI)

Patients and public have been involved in the development of this study in a number of ways:

- Through the James Lind Alliance Priority Setting, patients and the public have identified that the effectiveness and long-term outcomes of reverse shoulder replacement in treatment of older patients with three and four part PHFs in comparison to HA required further future research (12).
- Input from patient and public representatives to inform the trial design, including questionnaire acceptability and frequency of follow up.
- Inclusion of a patient representative experienced in supporting other orthopaedic trials (e.g. PROFHER)

We plan to have continued PPI involvement throughout the conduct and dissemination of the study as outlined below:

- A Public Advisory Group (PAG) comprising patients with experience of all trial interventions, including non-surgical treatment, and members of the public interested in research. The group will have opportunity to review all participant-facing documentation, promotional materials and case report forms for the study. They will also provide feedback on study procedures specifically in relation to recruitment, consent and retention.
- Involvement in study committees; two patient representatives will attend the TMG meetings, and one representative will attend the TSC.
- Involvement in generating patient friendly summaries of the study results, including assisting with updating entries on Wikipedia and Map of Medicine.

Financial support for PPI including TMG attendance and PAG sessions will be provided through reimbursement of time and travel at recommended rates in conjunction with the budget for involvement calculator from Involve.

13. DISSEMINATION AND PROJECTED OUTPUTS:

Results from this study will be written up and submitted to peer-reviewed journals, irrespective of the magnitude or direction of effect. A publications policy will be generated in advance to detail authorship, acknowledgements and review processes for any publications arising from the PROFHER-2 Trial.

The executive summary and copy of the trial report will be sent to the National Institute for Health and Care Excellence (NICE) and other relevant bodies, including Clinical Commissioning Groups, so that study findings can be translated into clinical practice. We will also work with the relevant National Clinical Director in the Department of Health to help ensure the findings of the trial are considered when implementing policy and will work with the Speciality Advisory Committees (SAC) to incorporate the findings into the training curriculum for clinicians who will undertake treatment for three and four part fractures.

A summary of the study report will be produced and made available to participants, members of our user group and relevant patient-focused websites. Patient information will also be generated for “Shared Decision Making”, the entry on Wikipedia and the Map of Medicine entry. Service users involved in the PROFHER-2 will be asked to actively participate in dissemination of the conclusions of this study to ensure these are easily accessible to patients.

All publications, presentations, correspondence and advertisements arising or related to the grant must acknowledge the funder using the National Institute of Health Research (NIHR) approved disclaimer. The NIHR Programme Manager must be notified of intention to publish peer-reviewed journals at least 28 days in advance of publication. Public oral or poster presentations should be notified to the NIHR Programme Manager 28 days prior to submission of an abstract. A draft copy of the proposed publication should also be provided as part of this notification.

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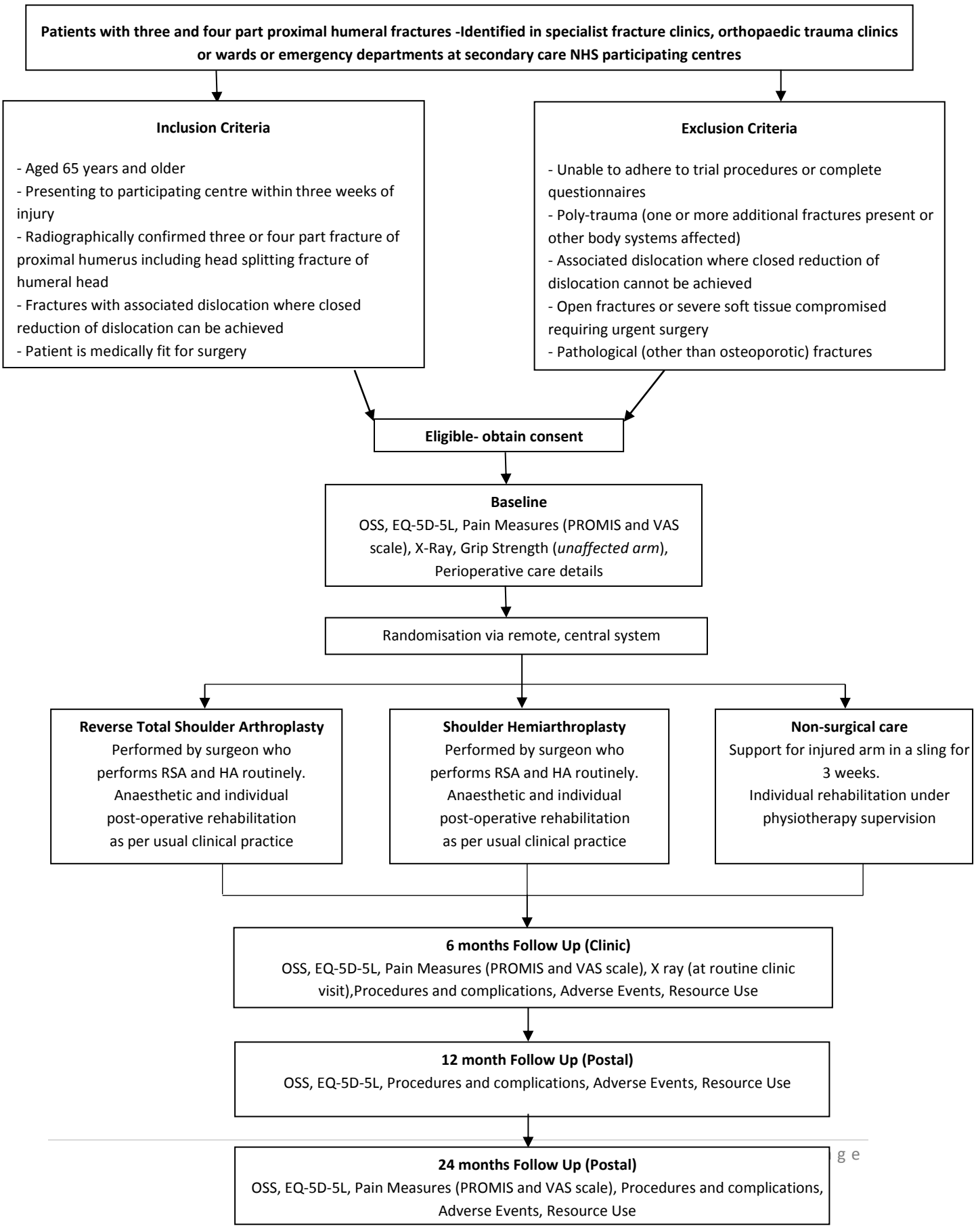
42. ACRONYMS

AE	Adverse Event
BESS	British Elbow and Shoulder Society
CACE	Complier Average Causal Effect
CE	European Conformity
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DMC	Data Monitoring Committee
EQ5D-5L	European Quality of Life-5 Dimensions – 5 level scale
GCP	Good Clinical Practice
HA	Hemiarthroplasty
HTA	Health Technology Assessment
IRAS	Integrated Research Approval System

ITT	Intention-to-treat
LPLV	Last Participant Last Visit
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Multiple Imputation
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NJR	National Joint Registry
NS	No-surgery
OSS	Oxford Shoulder Score
PAG	Public Advisory Group
PHFs	Proximal humerus fractures
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patient and Public Involvement
PROFHER	PROximal Fracture of the Humerus: Evaluation by Randomisation
PROFHER 2	PROximal Fracture of the Humerus: Evaluation by Randomisation Trial no. 2
PROMIS	Patient Reported Outcomes Measurement Information System
PSS	Personal Social Services
QALY	Quality-adjusted Life Year
RCT	Randomised controlled trial
REC	Research Ethics Committee
RSA	Reverse Shoulder Arthroplasty
SAC	Speciality Advisory Committees
SAE	Serious Adverse Event
SD	Standard Deviation
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	Visual Analogue Scale
YTU	York Trials Unit

43. APPENDICES

APPENDIX 1: STUDY FLOW DIAGRAM



APPENDIX 2: STUDY PROCEDURE SUMMARY

	Enrolment	**Allocation**			
TIMEPOINT	**Pre-randomisation/ baseline**	**Randomisation**	**6 month post-treatment**	**12 month post-treatment**	**24 month post-treatment**
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Baseline questionnaire	X				
Allocation		X			
ASSESSMENTS					
OSS	X		X	X	X
EQ-5D-5L	X		X	X	X
X-ray	X		X		
Visual analogue scale	X		X		X
PROMIS			X		X
Grip Strength unaffected arm	X				
Range of movement			X		
Complications			X	X	X
Further procedures			X	X	X
Resource use			X	X	X
Adverse events			X	X	X