Supplementary Online Content


Trial protocol

This supplementary material has been provided by the authors to give readers additional information about their work.
Appendix 3 ProFHER protocol version 7.0 (19/05/09)

PROximal Fractures of the Humerus: Evaluation by Randomisation
The PROFHER Trial

This protocol describes a UK multi-centre randomised controlled trial of surgical versus non-surgical treatment for the majority of displaced fractures of the proximal humerus in adults.

The NHS R&D Health Technology Assessment Programme (HTA) is the sole external funder of this trial. This protocol is derived from the detailed project description of the HTA funding application entitled "Pragmatic multi-centre randomised trial of surgical versus non-surgical treatment for proximal fracture of the humerus in adults" [HTA: 06/404/53].

The PROFHER trial is sponsored by the University of Teesside. Trial management is primarily by the York Trials Unit (YTU), University of York. This trial has received endorsement by the British Elbow and Shoulder Society.

SUMMARY OF PLANNED INVESTIGATION

Research objectives
Our primary aim is to obtain reliable evidence of effectiveness and cost-effectiveness of basic treatment strategies for the majority of displaced fractures of the proximal humerus in adults. Hence, we plan to undertake a pragmatic randomised clinical trial (RCT) of surgical versus non-surgical treatment of displaced proximal humeral fractures involving the surgical neck in adults.

Study population
After a period of preparation and upon MREC (Multicentre Research Ethics Committee) approval, recruitment into the RCT will be over an 18 month period from at least 18 NHS trauma centres; most of which are either already committed or have expressed keen interest in contributing to the trial, and thus identify with the study aims. We will promote a minimum recruitment rate of one patient per centre per month. Allowing for conservative estimate of recruitment success and for drop-outs we propose to recruit and randomise 250 patients over an 18 month period. We anticipate data from 200 patients followed up for 2 years. The HTA have accepted our proposal for an assessment point after 10 months of recruitment to determine if recruitment into the RCT is sufficient (set at 88 patients) to justify its continuation after 18 months.

Integral to the trial, and to inform on trial recruitment and applicability of trial results as well as to conform to trial-reporting standards, we plan a systematic prospective collection of key patient data for those meeting the main inclusion criteria (age 16 or over, presenting within 3 weeks of injury, with displaced fractures of the proximal humerus involving the surgical neck) for the RCT but who were not included. These will consist of three categories of patients: those that were excluded because they met one or more of the listed trial exclusion criteria, those who did not consent and those where there was a 'protocol violation' (reflecting lack of surgeon equipoise). The information collected for these patients will include data on patient preference, surgeon's advised treatment and the agreed treatment. In particular, we will stress the importance of the systematic prospective collection of key patient data and reasons for exclusion of otherwise eligible patients. At the end of the 10 month 'feasibility' study, we anticipate 1400 potentially eligible patients would not be included in the randomised trial; should recruitment continue, we anticipate 2150 such patients.

BACKGROUND

Proximal humeral fractures account for approximately 4-5% of all fractures. Their incidence rapidly increases with age, and women are affected over twice as often as men. Similar to other primarily osteoporotic fractures, the incidence of these fractures is increasing. Palvanen et al. 2006 found a three fold
increase over a 33 year period in the incidence of proximal humeral fractures resulting from low-energy trauma in people aged 60 and above.

A large prospective epidemiology study (Court-Brown et al. 2001) found that around half of these fractures (51%) are displaced, when assessed according to the criteria of Neer’s classification system (Neer 1970): one or more parts of the fractured bone are displaced by more than one centimetre, or angulated more than 45 degrees. Court-Brown et al. 2001 found that the largest groups of displaced fractures were 2 part surgical neck fractures (28% of the whole population), followed by 3 part greater tuberosity and surgical neck fractures (9%). Four part fractures without fracture dislocation were around 2% of the total. These figures are consistent with estimates from several members of the trial group.

Recent systematic reviews (Handoll et al. 2003; Misra et al. 2001), one of which was updated in 2007 (Handoll et al. 2003), have found a lack of evidence from randomised controlled trials (RCTs) to inform management decisions for proximal humeral fractures. In particular, there were only three completed RCTs comparing surgery with conservative treatment. All were small studies (numbers randomised: 30, 32, 40) with flawed methodology. Both reviews (Handoll et al. 2003; Misra et al. 2001) concluded that it was unclear whether operative intervention, even for specific fracture types, would produce consistently better long-term outcomes.

It is also clear from the literature, confirmed by an informal survey of the treatment provided by several UK centres, that there is great variation in the treatment of these fractures, both in basic (the use of surgery) and specific (type of implants and surgical technique; non-surgical management (Hodgson 2006) and rehabilitation packages) terms. Additionally, technology is changing all the time with various pressures towards early implementation.

The above findings point to a clear need to get reliable evidence to inform practice, and crucially to establish whether there is a role for operative intervention for the common types of acute displaced fractures of the proximal humerus. This is the focus of this trial.

RESEARCH METHODS

As indicated, we intend to undertake a pragmatic randomised clinical trial evaluating the effectiveness and cost-effectiveness of surgical intervention versus standard conservative therapy for the treatment of the majority of displaced (all involving the surgical neck) proximal humeral fractures in adults. This RCT includes the systematic collection of reasons for non-inclusion of eligible patients who were not recruited into the trial, and their baseline characteristics, treatment preferences and intended treatment.

Underpinning our approach are two key issues:

- There is a general dearth of reliable evidence to inform on the use of surgery (definitive treatment) for patients with these fractures.
- There are known difficulties in recruitment and particularly patient (and surgeon) preferences. Based on experience from previous studies, some abandoned, in this field it is anticipated that a large proportion of eligible individuals are likely to refuse to be randomised because they (or their surgeons) will have a strong preference for one of the study interventions; generally conservative in the case of patients. On discussions with orthopaedic surgeons, lack of clinical equipoise, which is another important barrier to performing surgical RCTs (Solomon et al. 1995), is anticipated to be less of an issue here. Because of these strong preferences it is likely that patients recruited into any RCT will be a highly selected group, which may threaten the external validity of our study. Thus, collecting key data for all patients eligible for the RCT will allow us to set our randomised results within the context of the whole patient population and give some pointers to the applicability of the results of the study.

How are the results of the trial to be used/interpreted?

The trial aims to establish whether surgery yields superior results to non-surgical treatment. As detailed below, our protocol emphasizes standardised protocols and care pathways throughout, comparable and sufficient expertise of care providers and that the surgeon uses established techniques with which they are already familiar. Any questions over whether the use of other surgical methods, perhaps new methods,
would give different results are countered by two considerations. Firstly, there is an absence of robust evidence to inform best surgical methods. Secondly, and arguably, the avoidance of 'learning curves' and the reliance on surgeon's competence is more representative of best surgical treatment.

**Brief details of the proposed practical arrangements for trial recruitment and allocating participants to trial groups**

A detailed generic scheme of the recruitment process will be devised for adoption according to local circumstances in the participating centres. At radiological review by the surgeon or their nominated deputy, a trial eligibility form (see Appendix 1) will be completed for any patient who meets the trial inclusion criteria. For ineligible patients, the surgeon is asked to indicate what treatment they would advise for the patient before the form is sent to the York Trials Unit. Those patients who the surgeon indicates as eligible for the trial will be invited to take part in the trial and the site-specific patient consent process is initiated. For non-consenting patients, this fact will be indicated on the Consent status form (see Appendix 2), where the surgeon or their deputy is asked to indicate their advised treatment, the patient’s preferred treatment (if any) is completed.

Once patients have given consent (see Appendix 3), the recruiting clinician will complete the baseline data form (see Appendix 4) and then contact the York Trials Unit, either by telephone or via the internet, to access a secure randomisation service. This will ensure immediate and unbiased allocation of treatment.

**Proposed methods for avoidance of bias and to ensure validity**

Randomisation eliminates selection bias: there are, however, other forms of bias we will guard against. We will also take measures to ensure the external validity of trial results. We will undertake the following:

- Adherence to local guidelines for radiographic assessment will be actively promoted. If not stipulated already, we will encourage the use of the full shoulder trauma series (Neer 2002). Documentation including a power point presentation illustrating the full trauma series will be made available as part of the trial materials. A minimum of two x-ray views/projections is required for the assessment of study eligibility.

- At the end of the recruitment period, there will be scrutiny and categorization based on the Neer classification system, using pre-prepared forms, of the baseline X-rays of all randomised patients. This will be done by an independent panel of musculoskeletal radiologists or orthopaedic surgeons who have experience with the Neer classification (Neer 1970). Copies of X-rays will be prepared beforehand to ensure they are anonymised. On an on-going basis during trial recruitment there will also be a review of the quality of the copies of X-ray images for each trial participant provided by trial centres. This is to ensure that at the end of trial recruitment the images are of sufficient quality for the independent panel to assess and classify the fractures. For the X-rays of the first five participants at each centre, independent assessment of the quality of images will be done by three orthopaedic surgeons, one of whom will be the Chief Investigator. Assessment of the X-rays of subsequent participants of each centre will be done by one orthopaedic surgeon (the Chief Investigator), who if he has concerns will ask the two other independent surgeons for their comments.

- Clear entry criteria, including checks at randomisation, will reduce inappropriate entry into the RCT.

- We will endeavour to provide a consistent approach to recruitment and obtaining informed consent by providing an unbiased account of the study to eligible participants using a specially produced information sheet. These materials will be produced in collaboration with service users.

- Concealment of treatment allocation prior to trial entry will be ensured by use of an independent telephone randomisation service, as provided by the University of York's Trials Unit. After an initial, prespecified, period of randomisation, stratified by the presence or not of a tuberosity fracture and with a prespecified block size, randomisation will then be performed using a computer generated minimisation programme. The minimisation factors will be fractures involving either tuberosity and centre.
• We will emphasize good practice and standardised protocols and care pathways throughout, and comparable and sufficient expertise of care providers. Surgery for these types of fractures are usually carried out by consultants; this has been confirmed by an informal survey of the centres initially included in our study. We will attempt to minimise 'learning curve' issues for the surgical interventions by allowing the surgeon to use techniques with which they are familiar, but prohibiting the introduction of radically new or experimental methods during the recruitment period.

• We will encourage the prescription of comparable care, including rehabilitation programmes, such that any substantive departures from the norm would reflect the special requirements of a specific intervention. Consensus guidelines for non-surgical treatment and rehabilitation for both groups are being prepared by rehabilitation specialists and will be circulated for comment and input. These will form part of the trial materials and we will request details of where the prescribed treatment differs substantively from the standardised protocols. (See Notes added in clarification below.)

Notes added for clarification
1. Upon discussion, the proposed consensus guidelines for non-surgical treatment were considered inappropriate in the context of a pragmatic trial and the lack of evidence to inform practice. It was decided that the onus should be on the provision of good standard care and that our approach would be to indicate both verbally and in the site manual that we would anticipate initial care to comprise sling immobilisation for about 3 weeks or for as long as the treating clinician deemed necessary and active early rehabilitation. We considered that written information to advise patients during sling immobilisation was needed and should be provided to all eligible patients for the trial. We provide a generic document to be adopted by the hospital should a suitable document not already be available locally.

2. We stipulate that physiotherapy should be provided equally to both treatment groups. A consensus protocol giving basic treatment guidelines has been devised. Although, deviation from the protocol is allowed and expected, we stipulate that electrotherapy (except TENS) is not used, and point to an absence of evidence for these modalities as well as endorsement via a consultation process with specialist shoulder physiotherapists. We will promote the need to encourage home exercises, but decided not to provide generic information leaflets illustrating exercises for home use by patients. Instead we will check that physiotherapists either provide these already or access a standard web-based facilities to generate 'bespoke' exercise sheets.

3. We are prospectively collecting details of rehabilitation treatment which will also allow the detection of substantial differences from the physiotherapy protocol.

• We shall follow the CONSORT guidelines for considering and reporting RCTs (Moher et al. 2001). For instance, if eligible patients decline to be randomised, then this is refusal to consent (as per CONSORT); if surgeons choose not to randomise an eligible patient then this is a break in protocol (protocol violation) which must be recorded along with a reason.

• Intention to treat analyses will be undertaken as the primary analysis in the RCT.

• Active and systematic follow-up of all randomised participants at 3, 6, 12 and 24 months is planned. This will include pre-notification letters as well as the use of reminders after 2 and 4 weeks. For 6, 12 and 24 month follow-ups, there will be an option for completion of an abridged questionnaire via telephone after 6 weeks. We will also include an unconditional incentive payment of £5 to maximize the 12 and 24 month follow-up.

• As far as possible, all participants will be followed-up for any unplanned events. Their hospital notes will include a reminder to notify of relevant subsequent treatment / events and they will be flagged for mortality. With the participant’s permission, letters will be sent to their General Practitioners to inform of participation (see Appendix 6). Participant’s permission will also be sought to allow us to ask their GP to provide the participant’s contact details should there be problems contacting them directly.
• There will be independent data entry, processing and analysis. Aside from accrual and whole populations baseline statistics, interim results will not be made available to the trial investigators or associates in the participant centres.

**Data collection on all potentially eligible patients**

In addition to the systematic collection of basic baseline data for those eligible for the RCTs but who did not consent or where there was a protocol violation (reflecting lack of surgeon equipoise) to satisfy the requirements of CONSORT, we will collect data on patient-preferred and intended management. To complete the CONSORT flow diagram, we will collect the baseline data and reasons for ineligibility for ineligible adults presenting in the recruiting centres with the study fractures: see inclusion criteria.

**Pilot study**

The study will initially be set up in Teesside for training, and piloting materials and procedures.

**ETHICAL ARRANGEMENTS**

MREC (Multicentre Research Ethics Committee) approval has been obtained from York Research Ethics Committee (reference number 08/H1311/12). Consequently, separate submissions of the protocol are being submitted to the ethical committee of each centre. The approval of the HTA funding and MREC is being raised in support of applications to preclude unsatisfactory local variation.

**Risks and anticipated benefits for trial participants and society, including how benefits justify risks**

In the context of the lack of robust evidence to determine the best treatment for patients with these fractures, the risks are not increased through trial and/or study participation. Measures, such as our emphasis on good practice and standardised protocols / care pathways throughout, taken by us are indeed likely to reduce risk and could bring additional benefits. We will emphasise the importance of surgeons performing operations with which they are familiar and undertake on a regular basis. We will also stress the importance of competence in conservative methods, principally rehabilitation. We will stipulate that radically different novel devices or methods are not introduced at each centre for the duration of the trial; any necessary training will focus on already established methods. We will adhere to the good clinical research practice guidelines (MRC and Research Governance Framework). Though we will perform active and systematic follow-up, the timing of early follow-up parallels usual clinical practice and we will not place an undue burden on participants. Our adoption of the Oxford Shoulder Score, Euroqol (EQ-5D) and SF12, all of which are self completion questionnaires, avoids the need for participants to specially return for clinical follow-up assessments at 6, 12 and 24 months.

Ultimately, the RCT will provide evidence that should make a major contribution to the future management of these fractures. It is conceivable that the heightened awareness of and focus on these fractures in each centre could directly benefit study and trial participants: for instance, there is some evidence of improved outcomes of participants participating in RCTs.

**Informing potential trial participants of possible benefits and known risks**

A participant information sheet for the study has been compiled, with involvement of service users (see Appendix 5). This aims to give a balanced account of the possible benefits and known risks of the interventions under test. It states explicitly that quality of care will not be compromised if the participant decides to a) not enter the trial or b) withdraw their consent. We believe that the information provided is clear and easily understandable to the reader. Surgery is often performed the following day and therefore the information leaflet will be made available for the potential participant to allow them time to make an informed decision. Where possible, translations of the participant information sheet will be provided for non-English speakers.

**Obtaining informed consent from participants whenever possible or proposed action where fully informed consent is not possible**

Written informed consent will be obtained from all participants. Where possible, provision of interpreters will be made on a local basis for non-English speaking participants. Where local interpreters are...
unavailable, we will consider using the National Interpreting Service. No participant will be entered into the RCT without informed consent.

Proposed time period for retention of relevant trial documentation
Minimum 20 years.

PARTICIPANTS: PLANNED INCLUSION/EXCLUSION CRITERIA

Inclusion criteria
Adults (aged 16 or above) presenting to the participating trauma centre within 3 weeks of their injury with a radiologically confirmed displaced fracture of the proximal humerus involving the surgical neck. This should include all 2 part surgical neck fractures; 3 part (including surgical neck) and 4 part fractures of proximal humerus (Neer Classification). It may also include displaced surgical neck fractures that do not meet the exact displacement criteria of the Neer classification (1 cm or/and $45^\circ$ angulation of displaced parts) where this reflects an individual surgeon's equipoise (e.g., whether the surgical neck fracture should be treated surgically).

Exclusion criteria
- Associated dislocation of the injured shoulder joint
- Open fracture
- Mentally incompetent patient: unable to understand trial procedure or instructions for rehabilitation; significant mental impairment that would preclude compliance with rehabilitation and treatment advice
- Co-morbidities precluding surgery / anaesthesia
- A clear indication for surgery such as severe soft-tissue compromise requiring surgery / emergency treatment (nerve injury / dysfunction)
- Multiple injuries: same limb fractures; other upper limb fractures
- Pathological fractures (other than osteoporotic) & terminal illness
- Participant not resident in trauma-centre catchment area

Sample population
This will be all adults (aged 16 or above) presenting within 3 weeks of injury with fracture types listed in the inclusion criteria. Ineligible patients will be defined as those who are excluded for reasons given in the exclusion criteria. All those who meet the above criteria will be termed eligible patients. Some patients still may not be not included in the RCT, for instance due to lack of patient consent (patient has strong preference for specific treatment option or refuses randomisation) or because the surgeon considers one of the treatment options is strongly indicated for reasons other than above.

INTERVENTIONS

Each centre participating in this trial has to agree to forgo the introduction of radically novel and experimental interventions for these fractures during the recruitment period.

Central to the obtaining of reliable evidence is that good standard care, both surgical and non-surgical, is provided throughout the trial. Where possible, the decisions on the actual method of surgery, when allocated, and non-surgical treatment is left to the clinical judgement of the participating surgeon. Participating surgeons will be advised that they should, however, use surgical interventions and procedures with which they are familiar. This is to avoid learning curve problems. Similarly, physiotherapists are advised that they should use procedures with which they are familiar. The essential components of physiotherapy at each session will be recorded prospectively.

Surgery
For displaced (2 part) surgical neck fractures: surgical interventions with which the surgeon is familiar. These are likely to be plate fixation or intramedullary nailing.
For 3 part (including displaced surgical neck) or 4 part fractures: surgical interventions with which the
surgeon is familiar. These are likely to include internal fixation such as nail, plate or other method which
preserves the humeral head; or humeral head replacement (hemi-arthroplasty).

_Peri- and post-operative management_

Peri-operative management including anaesthesia and analgesia, and antibiotic and thromboembolism
prophylaxis, dressing policies will follow local guidelines. It is envisaged that similar rehabilitation
packages, including mobilisation protocols, should be provided for all interventions. Specifically
developed guidelines will be included in the materials for each centre.

_Non-surgical intervention (the control group)_

Brief recommendations for conservative treatment for trial participants will be included in the materials for
each centre. Essentially, these advise that conservatively treated patients will be given sling immobilisation
for about 3 weeks or for as long as the treating clinician deems necessary and active early rehabilitation.
We will stress the need for competence in conservative methods, including rehabilitation.

_Rehabilitation_

As far as practical, centres are required to provide written advice on personal care during sling
immobilisation to all eligible patients. A generic document has been devised that can be adopted by the
centre if required. We will stress that similar access to physiotherapy should be provided for surgical and
non-surgical participants. A basic treatment protocol for physiotherapy will be provided. This will
emphasise that while the protocol acts as a guide, variation in practice is accepted and anticipated.
Electrotherapy other than TENS will be disallowed. We will promote strongly the need to encourage
patients to perform home exercises and that they receive information sheets illustrating how to do the
exercises.

_OUTCOME MEASURES_

The primary outcome measure is the Oxford Shoulder Score (OSS) assessed at 6, 12 and 24 months
(Dawson et al. 1996). The Oxford Shoulder Score is a condition-specific questionnaire providing a total
score based on the patient's subjective assessment of pain and activities of daily living (ADL) impairment.
Consistent with recent developments, the range of available scores is 0 (worst) to 48 (best) (Dawson et al.
2008). The OSS contains 12 items, each with five categories of response. It has been shown to correlate
well with both the professionally-endorsed Constant Score (Constant et al. 1987) and the SF36 assessment
and to be sensitive to clinical change at six months after surgical intervention (Dawson et al. 2001). It has
been demonstrated to be consistent, reproducible and valid in a UK population (Dawson et al. 1996). This
questionnaire will be administered by post for self completion by the trial participant without need for an
examination and thus avoids the requirement for follow-up visits to the clinic for assessment. To improve
compliance, reminders will be sent and patients will be offered the option of completing the questionnaire
via a telephone call. We will also send pre-notification letters and use unconditional incentives; both have
been shown to be effective at improving response rates (Edwards et al. 2002)

Secondary outcomes are:
- Surgical complications; including shoulder dislocation, failure of implant, proven wound infection
  (purulent discharge plus positive bacteriology or need for revision due to infection), sepsicaemia
  (clinical evidence of systemic infection plus positive blood cultures).
- Early medical complications, i.e. chest infection, confirmed MI or stroke (confirmed by senior
  clinician), treated DVT, treated pulmonary embolism and other serious event.
- Mortality, subsequent referral for operation or substantive treatment.
- The SF12 and Euroqol (EQ-5D) to collect general health status data (at 6, 12 and 24 months).

_Data for economic evaluation_

Prospective cost data on trial participants include costs incurred in hospital and subsequently. Thus, time
spent in theatre and hospital consumables will be collected. Health utility data will also be obtained from
the EQ-5D collected at 3, 6, 12 and 24 months (EuroQol Group 1990). Information for estimating NHS and
societal costs will be collected from the trial participants at each follow-up.
We will collect data on the actual procedures done, including anaesthesia, and interventions provided and the experience of operators / care providers (according to grade). We will collect these data for all trial participants.

**DATA COLLECTION**

We shall aim to make the trial processes as simple as possible in order to minimise the work entailed at the participating centres. As far as possible, we hope to achieve complete follow-up of all randomised patients.

**Baseline data**

Basic information including key baseline characteristics will be collected for all potentially eligible patients (i.e. those meeting the trial inclusion criteria) who are found not to be eligible (see Study eligibility form: Appendix 1).

Additional data on patient preferences, surgeon’s advised treatment and the agreed treatment will be obtained for patients who do not consent to trial participation (see Consent status form: Appendix 2).

For consenting patients, we will collect data on ethnicity, education, employment, previous fractures, shoulder dominance, injury mechanism, smoking, diabetes, treatment preference, current health status (EQ-5D), GP name and surgery and the patient’s contact details (see Baseline form: Appendix 4).

**Description of treatment**

**Surgical methods**

Brief details of the actual surgery and procedures used will be recorded by the surgeon, or assigned deputy, following the operation. Also prescribed rehabilitation.

**Non-surgical methods**

Brief details of the prescribed non-surgical treatment will be recorded by surgeon, or assigned deputy. Also prescribed rehabilitation.

**Collection of hospital outcome data - before hospital discharge**

Centres will be required to complete data forms detailing:

- Clinical outcomes including surgical complications and early medical complications
- Resource use: the data on hospital costs will be collected using a cost proforma designed for the trial.
- Substantive deviations from prescribed treatment and rehabilitation
- Patient destination after hospital discharge

**Long term follow-up**

*One and two year follow up forms from centres*

Forms to notify mortality or subsequent surgery for completion and return at any time will be made available for the completion by centre staff.

Forms for completion will be sent at 1 and 2 year follow-up - it is likely that all the data for these can be gleaned from the hospital records for these patients.

*Follow-up patient questionnaires: 3, 6, 12 and 24 months post trial recruitment*

A short questionnaire including the EQ-5D and brief questions on the number of consultations of NHS care providers (GPs, physiotherapists, district nurses etc), hospitals attendances, use of private healthcare and days lost from work or other normal activities will be sent by the YTU to all participants at three months. See Appendix 7 for a copy of the 3 month form and covering letter. Reply paid envelopes will be included. Reminders will be sent after 2 and 4 weeks.

Full questionnaires will be sent by the YTU to all participants at six, 12 and 24 months after recruitment. These include the Oxford Shoulder Score, EQ-5D and SF12, all of which are self completion questionnaires. As at 3 months, brief questions on the number of consultations of NHS care providers (GPs, physiotherapists, district nurses etc), hospitals attendances, use of private healthcare and days lost from work or other normal activities will also be requested. See Appendix 8 for a copy of the 6 month follow up...
form and covering letter. Reply paid envelopes will be included. Reminders will be sent after 2 and 4 weeks and options for completion of the questionnaires via telephone after 6 weeks. If completed over the telephone, only the Oxford Shoulder Score, EQ-5D and information on hospital readmissions will be requested. An unconditional incentive payment of £5 will be sent for the 12 and 24 month follow-ups (Edwards et al. 2002).

X-rays
Copies of all baseline X-rays for all randomised patients will be requested for independent and blinded assessment at the end of study recruitment. X-rays will also be reviewed by local experts on an on-going basis during trial recruitment to ensure the images are of sufficient quality for scrutiny and classification based on the Neer classification system by an independent panel of experts at the end of recruitment.

PROPOSED SAMPLE SIZE

The primary outcome for the trial is differences in patients’ subjective assessments of pain and activities of daily living (ADL) as measured by the Oxford Shoulder Score (OSS). For surgery to be worthwhile, it needs to demonstrate greater improvements in patient’s subjective assessments of pain and ADL than those for conservative treatment to justify both its increased costs and the exposure to the hazards of surgery. In an observational study conducted by one of us (AR) it was found that those patients who had surgery had a 5 point differential improvement in the OSS compared with those patients treated conservatively. Given a standard deviation of 12 this equates to an effect size of 0.42. We propose, therefore, to design the study to observe an effect size of 0.4 at 80% power using 5% significance level, which would require approximately 200 participants. After allowing for drop-outs of 20%, we propose to recruit and randomise 250 patients (125 surgery and 125 controls). Our estimate of 20% loss from the RCT is purposefully pessimistic for sample size calculations.

Recruitment rate
We anticipate that recruitment for this trial will be potentially challenging. Therefore, we have set very conservative recruitment targets. Our recruitment period is 18 months. We aim to recruit between 18-20 centres. Each centre will be expected to recruit only one participant per month, though encouraged to aim higher than this. We estimate across 18 centres there will be 6066 patients (6000 is used as a working figure here) with a proximal humeral fracture over the 18 months of recruitment. Of these, 2391 (thus, 2400 is used as a working figure below) will have the fracture types suitable for inclusion into the RCT. To achieve our sample size we need to recruit only 11% of these patients.

Loss to follow-up
We anticipate that the main reason for loss to follow-up will be mortality. We will follow up patients assiduously using postal questionnaires and in the event of non-response we will contact their GP to ascertain whether it is appropriate to contact the patient and, if so, their address.

STATISTICAL ANALYSIS

All of the analyses will use the intention to treat principle. Consequently, any patients who cross over from either study arm will be analysed as per their randomisation status. The primary outcome is the Oxford Shoulder Score (OSS). The difference between the two treatment groups will be compared over all follow-up assessments (i.e. 6, 12 and 24 months) using a repeated measures model. The model will include terms for treatment, follow-up time, and also adjust for type of fracture, age and gender (as older people and women are more likely to sustain these fractures). Because participants are clustered by surgical centre there is a theoretical possibility that there may be a ‘surgeon’ effect. We will therefore repeat the primary analysis using appropriate statistical techniques (robust standard errors) to account for the clustering of patients within surgeon. The anonymity of individual surgeons and centres will be preserved for all analyses and there will be no presentation or comparisons of the treatment results from individual centres or surgeons. Subgroup analyses based on the Neer classification system are planned to assess the effectiveness of treatment for the different fracture groups (2 part surgical neck; 3 part including surgical neck and 4 part fractures; fractures not meeting the Neer classification displacement criteria). The secondary outcomes will be summarised for each treatment group.
Frequency of analyses
We anticipate that there will be a single analysis at the end of the study. However, before the study starts we will establish an independent Trial Steering Committee (TSC) and a Data Monitoring and Ethics Committee (DMEC). The chair of the TSC will make the decision in conjunction with the chair of the DMEC about the need and the number of interim analysis.

Assessment of study recruitment and applicability
We will report the numbers of and reasons for ineligible adults (aged 16 or above) with the study fractures, we will also report the numbers of and reasons for the non-inclusion of potentially eligible patients. We will compare the baseline characteristics, patient preferences with those of randomised patients.

ECONOMIC EVALUATION
An economic analysis will be taken from the perspective of the UK National Health Service and Social Services. The horizon for the baseline analysis will be two years. However, we will model any potential benefits forward to 5 years and an average lifetime in a sensitivity analysis.

Health benefits for the economic analysis will be measured in terms of quality adjusted life years (QALYs). Health utility values for individuals with displaced proximal humeral fractures will be estimated using the Euroqol (EQ-5D) questionnaire. QALYs will be calculated for each patient using the area under the curve defined by her / his EQ-5D scores over the two-year follow-up period and adjusted by the Kaplan Meier estimates of patients’ survival over the same period of time. Given the horizon for the analysis is longer than a year a discount rate of 1.5% will be applied to health benefits (NICE 2001).

Resource use, and clinical data will be collected for all trial participants. Information regarding total volume of resources used in the treatment (conservative / surgical) and rehabilitation procedures will be recorded for each patient. Unit cost will then be applied to estimate the total cost per patient. To account for the censored nature of cost data, the Lin method will be used to estimate the mean average total cost per treatment arm (Lin et al. 1997). Non parametric bootstrapping techniques will be used to estimate 95% confidence intervals for the mean differential cost between conservative and surgical treatment (Efron et al. 1993). Total cost will be discounted using a 6% annual discount rate (NICE 2001).

Health benefits and mean average total costs associated with each of the trial arms will be combined in a cost-utility analysis, incremental costs per quality ratios will be computed comparing the conservative and surgical treatment interventions for adult patients with a displaced proximal humeral fracture. Multilevel modelling will be used to explore potential variations in treatment effect and costs between health professionals (Roberts 1999).

PROJECT TIMETABLE AND MILESTONES
Currently (December 2007), the anticipated start for full-trial trial recruitment is 1st October 2008. As well as MREC approval, all trial materials and processes will have been established and piloted where practical and appropriate at Middlesbrough, the lead centre. Applications for LREC approval will also have been submitted, and may have been approved, for several centres. Staff training for these centres will also have been initiated. The 10 months target date after recruitment for the feasibility study means that a robust approach is needed for getting centres started and recruiting as soon as possible.

Trial timeline from start of full-trial recruitment
0 months
Start of recruitment for RCT: duration 18 months (assuming satisfactory outcome of the 10 month feasibility study)
Start of data collection for baseline, treatment, early complications and economic outcomes
3 months
Start of 3 month follow-up for RCT participants (reminders 2 & 4 weeks)

6 months
Start of 6 month follow-up for RCT participants (reminders 2 & 4 weeks)

10 months
Cut-off for analysis of feasibility study after 10 months of recruitment.
Analysis and presentation of feasibility study

12 months
End of recruitment of feasibility study
Start of 12 month follow-up for RCT (reminders 2 & 4 weeks)

18 months
End of all recruitment (RCT)

21 months
End of 3 months RCT follow-up (reminders 2 & 4 weeks)

24 months
End of 6 months RCT follow-up (reminders 2 & 4 weeks)
Start 24 months RCT follow-up (reminders 2 & 4 weeks)

30 months
End of 12 months RCT follow-up (reminders 2 & 4 weeks)

42 months
End 24 months RCT follow-up (reminders 2 & 4 weeks)
Analyses
Preparation of HTA report
Preparation of study publications

Complete project: 48 months inclusive

If recruitment is stopped at the conclusion of the 12 months feasibility study, the study will complete at 42 months.

DISSEMINATION OF TRIAL FINDINGS

We shall disseminate our findings through relevant local, national and international conferences and peer-reviewed publications. Reflecting the collaborative basis of this research, all active contributors will be named and credited in the main report.

TRIAL MANAGEMENT

The day to day management of the project is the responsibility of the Trial Management Group.

Clinical co-ordination: Amar Rangan (Chief Investigator)
Trial management: Stephen Brealey (Trial Manager, University of York) and Laura Dennis (Trial Co-ordinator, University of Teesside)

Methodological support: Helen Handoll (University of Teesside), David Torgerson (University of York)

Clinical queries should be directed to any of the listed clinical co-ordinators, and any other issues may be discussed with any member of the Trial Management Group.
The trial co-ordinating centre is York Trials Unit. Specifically assigned to the ProFHER trial are a Statistician (Mrs Gill Worthy, replaced by Dr Catherine Hewitt (April 2009)), a Health Economist (Dr Jo Dumville, replaced by Miss Ling-Hsiang Chuang (May 2009)), Data Managers (Mr Ben Cross and Mrs Valerie Wadsworth), and a Trial Secretary (Mrs Sarah Gardner).

**RESEARCH GOVERNANCE**

The University of Teesside, of which the Chief Investigator holds an honorary lecturership position, is the sponsor.

*Independent supervision*

A Trial Steering Committee (TSC) will be established upon acceptance by the HTA of our nominees for an independent chair and two other independent members. Other members will be those key to trial management and function. Accrual, whole population and ‘housekeeping’ statistics will be calculated and disseminated to members on a monthly basis to monitor the progress of the RCT. The TSC will meet at the discretion of the independent chair, however, we anticipate that it will meet approximately a total of nine times throughout the study.

A separate Data Monitoring and Ethics Committee (DMEC) will be established that is independent of the applicants and the TSC. The names of three nominees, a trial statistician, a shoulder specialist and a consultant rheumatologist, who have accepted our invitation to fulfil this role have been submitted to the HTA. We anticipate that the DMEC will meet a total of six times, approximately every 6 months, or at any other time if any issues were to arise that required urgent attention. An analysis of major complications will be provided for the DMEC every three months following the commencement of the recruitment phase of the trial.

**TRIAL FUNDING**

The PROFHER trial is funded by the NHS R&D Health Technology Assessment Programme (HTA).

**Reimbursement for centres**

Centres will be advised to consider employing dedicated clinical staff, such as a research nurse, to act as the contact person for recruitment and data collection for each centre. This could involve increasing someone’s hours.

The HTA has agreed to a reimbursement scheme that recognises the additional efforts and resources required for recruitment into this trial. The following payments have been proposed:

a) Receipt of eligibility form for non-eligible patients (see Appendix 1): £10  
b) Receipt of eligibility and consent status forms where patient consent has been sought: £30  
c) For each randomised patient. Provisional scheme: upon receipt of baseline materials and description of treatment received (£500); receipt of pre-discharge information and copies of X-rays (£250); all remaining information at 1 and 2 year follow-up (£250).

The following activities are covered by these reimbursement payments:

- Distribution of trial materials in appropriate locations  
- Setting up the trial processes  
- Screening of patients’ notes for eligibility  
- Contacting patients or alerting appropriate clinicians for this activity  
- Discussing the trial with patients and providing documentation for consideration  
- Completion of trial eligibility and consent status forms  
- Obtaining consent  
- Randomisation of individual patients and completion of baseline form
Completion of forms for treatment, costs and in-hospital outcome and complications for randomised patients.
Completion of forms for randomised patients at one and two years.
Copying and carriage of baseline X-rays for independent review.

Health service costs

We anticipate that there will be no excess treatment costs overall. Whilst this is likely to be the case in the majority of centres, this may not necessarily apply to certain hospitals, even in the context of a potentially low recruitment rate, that have a below average rate of surgery. It will be up to the individual providers to consider this aspect in giving their approval for the trial. Some check at randomisation to prevent excess surgery (especially in small centres) is being considered at present.

REFERENCES


APPENDICES
1. Study eligibility form
2. Consent status form
3. Consent form
4. Baseline data and randomisation form
5. Patient information sheet
6. GP letter
7. 3 month patient follow up form, including covering letter
8. 6 month patient follow up form, including covering letter
1. Primary trial objective

To compare surgical and non-surgical treatment (conservative treatment) of displaced proximal humeral fractures involving the surgical neck. This analysis plan deals only with the statistical analysis, the cost-effectiveness analysis will be detailed in a separate plan.

2. Sample size

Observational data collected by the Chief Investigator found that patients undergoing surgery had a 5 point difference on the primary outcome (the Oxford Shoulder Score) compared with conservative treatment, with a corresponding standard deviation of 12. This translates into a standardised effect size of 0.42 (difference in means/standard deviation). To detect a minimum effect size of 0.4, with 80% power and a two-sided 5% significance level would require 100 patients in each treatment group. Allowing for a potential loss to follow-up of 20% the final sample size needed is 250 patients (125 in each group).

3. Randomisation

Patients will be randomised to surgery or non-surgical treatment by the remote randomisation service (telephone or web based) provided by the York Trials Unit, this ensures allocation concealment. An initial period of randomisation will use stratification by tuberosity involvement (yes or no) with allocation using random block sizes. After this a computer-generated minimisation program will be used and the minimisation factors will be tuberosity involvement (yes or no) and study centre. However, minimisation was not implemented as planned. It was agreed that with fewer patients being recruited at centres than originally anticipated, the rationale for minimisation by centre was questionable. There was a potential for predictability of the sequence, and the low recruitment and lower rate of recruitment at individual centres meant that there was not the anticipated logistical problem of an imbalance in the number of patients needing an operation at individual centres.

4. Outcomes

Primary outcome

The primary outcome measure is the Oxford Shoulder Score (1), a patient-reported assessment of pain, function and activities of daily living. This will be completed by patients at 6, 12 and 24 months. This measurement has not been collected at baseline as it asks about problems caused by the shoulder injury in the previous four weeks and patients will be recruited into the trial as soon as they seek medical advice for their shoulder fracture.
Secondary outcomes

- Health status data measured by
  - SF-12 at 6, 12 and 24 months
  - EQ-5D at baseline, 3, 6, 12 and 24 months
- Surgical and other shoulder fracture related complications
- Medical complications during inpatient stay
- Secondary surgery to shoulder or increased/new shoulder related therapy
- Mortality

5. Analysis

All analyses will be conducted on an intention to treat basis, including all randomised patients in the groups to which they were randomised. Analyses will be conducted in Stata, using 2-sided significance tests at the 5% significance level. To enable appropriate data checking, the trial statistician conducting the analyses will be unblinded to treatment group. However, all data summaries and results will be checked and repeated by a second blinded statistician.

Baseline data

All patient baseline data will be summarised by treatment group. No formal statistical comparisons will be undertaken.

Trial completion

The flow of patients through the trial will be presented in a CONSORT diagram (see Appendix). Summaries of the numbers of patients screened for trial entry; those who are ineligible and the reasons why; numbers of eligible patients not providing consent; and the numbers of eligible patients subsequently randomised will be presented. The characteristics of the screened population, the ineligible participants and eligible participants who consent and do not consent will be summarised.

Information regarding the number of physiotherapists, surgeons and centres (median, interquartile range, minimum and maximum) will be presented. The number of patients treated by each surgeon and centre and the number of sessions for each physiotherapist in both hospital and the community will also be presented. Data for the above summaries will be collated from the group allocation at randomisation, surgery form and the physiotherapy treatment log. In the non-surgical arm, surgical data will only be used for patients who are considered crossovers rather than those who had surgery following failed conservative treatment.

All data on patient eligibility will be summarised in a table (using information from the patient eligibility form). Reasons for withdrawal from treatment and/or the trial will also be summarised in a table, by treatment group where data are available (using information recorded on the trial management database).
Primary outcome

*Oxford Shoulder Score (OSS)*

The OSS will be summarised descriptively (n, mean, sd, median, minimum and maximum) at each time-point by treatment group and overall. Plots of the mean and 95% CI by time and treatment group will also be presented.

As no specific assessment time is of primary interest the primary analysis will compare the surgical and non-surgical treatment groups over all follow-up assessments. A multilevel model will be fitted to the data from all time-points where patients will be treated as random effects (to allow for the clustering of data within each patient). This model will adjust for time (6, 12 or 24 months), tuberosity involvement at baseline (yes or no), age (less than 65 years, 65 years or older), gender, health status at baseline (EQ-5D index), treatment group and the interaction between treatment and time (to assess whether any difference between treatment groups changes over time). Different covariance patterns for the repeated measurements will be explored and the most appropriate pattern will be used for the final model.

Model assumptions will be checked and if they are in doubt the data will be transformed prior to analysis or alternative non-parametric analysis methods will be used. The difference between treatment groups in the mean overall OSS and corresponding 95% confidence interval (CI) will be presented as well as the estimated difference in means between groups at each time-point (6, 12, and 24 months). Although centre was planned as a minimisation factor, we will not include centre as a fixed effect as we expect some centres to only recruit a small number of patients (2). We have dropped our plan for a secondary model which included fitting the surgeon as a random effect, to allow for the clustering of patients who are operated on by the same surgeon (see Sensitivity analyses).

This analysis will be conducted on all patients with follow-up data following the intention to treat principle as closely as possible. Use of a repeated measures multilevel regression model assumes that any missing data is missing at random (3). We will summarise the numbers of patients with missing OSS data by treatment group and time-point, together with the reason for missing data (if available). The baseline characteristics of patients who were lost to follow-up or withdrew from the trial and do not provide sufficient data for an estimate of the primary outcome (non-response) will be compared to those who have complete data at all follow-up points using descriptive statistics. Separate logistic regression models will be used to identify predictors of non-response, which will include all baseline data and OSS at assessments prior to any missing values. If any variables are found to be predictive of non-response (p<0.10), they will be included in the model specified previously for the primary analysis.
Subgroup analyses

Two subgroup analyses will be performed. These will be for the primary outcome only (OSS), and the interaction term between the baseline factor and treatment group will be fitted in the primary analysis model as described in the previous section. The change in the -2 log likelihood will be compared between the models with and without the interaction term, using a chi-squared distribution with the change in corresponding degrees of freedom. As this study has not been powered to detect interactions, a statistical significance level of 10% (p<0.10) will be used.

The two subgroup analyses are:
- Age (65 years or older versus under 65) (4)
- Surgical neck fractures involving one or both tuberosities (no versus yes) as per initial surgeon classification. Neer 1 and 2 part fractures versus Neer 3 and 4 part fractures based on classification by two independent experts from x-rays will be used as sensitivity analysis.

A priori specification of subgroup direction (5):
- The benefit of surgery over conservative treatment will be larger in patients under 65.
- The benefit of surgery over conservative treatment will be larger in patients with surgical neck fractures with displacement of one or both tuberosities (Neer 3 and 4 part).

Secondary outcomes

SF-12

The SF-12 scores for the physical component scores (PCS) and mental component scores (MCS) will be summarised at each time-point by treatment group and overall. Each component score will be compared between treatment groups using the same analysis methods (multilevel regression model) as for the OSS. Plots of the mean and 95% CI for the PCS and MCS by time and treatment group will also be presented.

EQ-5D

The EQ-5D data will be fully reported and analysed as part of the economic evaluation, which is detailed in a separate plan.

Surgical and other shoulder fracture related complications

Shoulder fracture related complications such as site infection or nerve injury were recorded at the end of patients’ orthopaedic inpatient episodes where applicable and again at one- and two-year follow-up. The number of patients experiencing each complication and the mean number of complications per patient will be summarised descriptively at each time point by treatment group and overall. Any complications for which information was provided under ‘Other’ sections of these forms will be grouped by two expert raters. Patient baseline characteristics (age, gender, injury to the dominant arm, baseline tuberosity, previous history of fractures, EQ-5D health status index, smoking status, diabetes and steroid
medication) will be summarised descriptively for patients who did and did not experience at least one complication over the total follow-up period. If comments provided as part of the physiotherapy treatment logs refer to any complications as judged by two experts, these will be reported descriptively if they were not picked up by the inpatient or follow-up forms.

**Medical complications during inpatient stay**
Medical complications, such as chest infection or stroke, were recorded during inpatient stay. These complications will be reported in the same way as shoulder fracture related complications.

**Secondary surgery to shoulder or increased/new shoulder related therapy**
The need for subsequent shoulder surgery or increased/new therapy for shoulder related complications was recorded at the end of patients’ orthopaedic inpatient episodes and at one- and two- year follow-up. The number of recorded planned or actual treatments will be summarised descriptively at each time point by treatment group, for those patients for whom a shoulder related complication was reported and overall. Chi-square test will be used to compare proportions between treatment groups if more than five participants experience the above events in each arm. The number of patients for whom secondary surgery/further treatment was reported in response to a recorded shoulder related complication will also be presented.

**Mortality**
The numbers of deaths occurring during the trial period will be summarised by treatment group and overall. Chi-square test will be used to compare proportions between treatment groups if more than five participants died in each arm.

**Other treatments and patient admissions**
Any treatments for serious newly diagnosed medical complications were reported at the end of patients’ orthopaedic inpatient stay and at one- and two- year follow-up. Further patient admissions (patient visits to the orthopaedic/fracture clinic following discharge as well as patient admissions to hospital for other fractures) were reported at one- and two- year follow-up. Details provided for these events were categorised by two expert raters. The number of reported treatments and admissions as well as the mean number of these events per patient will be presented by time point for each treatment arm and overall, broken down by category. The total number of further fractures mentioned as part of the inpatient episode form or follow-up forms will be summarised by treatment arm and overall, broken down by type. The frequencies of multiple further fractures where patients had had at least one further fracture will also be summarised by treatment arm and overall.

**Adverse Events**
Frequencies of any reported adverse events will be summarised by treatment group and overall. Figures will include a breakdown by type of event (serious or non-serious), expectedness and estimated relatedness to treatment. The nature of adverse events will be grouped by two expert raters and presented descriptively.
Patient and surgeon preferences
Eligible patients were asked at baseline if they had any treatment preference, recorded on the baseline form for consenting patients and the consent status form for non-consenting patients. Patient preferred treatment will be summarised overall and by whether the patient consented to trial participation or not. For consenting patients, preferences will also be summarised by randomised treatment. To investigate whether patient preference has any effect on treatment outcomes, patient preference will be included in the model for the primary outcome (the OSS). An interaction term will also be included between randomised treatment and preferred treatment in the model to assess if the effect of treatment is different depending on a patient’s prior preference, using a p-value of 0.10.

Surgeon treatment preferences were recorded for ineligible patients on the eligibility form and for eligible patients who did not consent to trial participation on the consent status form. Details of the preferred treatment will be summarised for these two groups.

Sensitivity analyses
After recruitment to the trial had finished, an imbalance in smoking status was observed. Baseline imbalance in itself is not considered an appropriate reason to include a baseline measure as a covariate. However, smoking is associated with a number of complications including fracture and wound healing (including surgical site infection), impaired new bone formation and development of osteoporosis (6-8). Hence, a sensitivity analysis will be undertaken including smoking status in the primary outcome model to explore whether the conclusions drawn from the primary analysis are robust.

Exploration of centre variability
The number of participants excluded due to lack of equipoise (as estimated by independent assessment by two raters of other reasons for non-eligibility (option j of the eligibility form)) will be summarised by centre and surgeon. The impact of lack of surgeon equipoise on study generalisability will be explored by comparing participants’ age, gender, time since injury and tuberosity involvement between those ineligible due to lack of equipoise and all eligible participants (irrespective of their consent status) using a t-test or chi-squared test depending on the type of outcome.

The relationship between age and fracture type (the pre-specified subgroup analyses) and surgeon treatment preference will be explored for those participants excluded due to lack of equipoise. Age and fracture type will be compared between the surgeon treatment preference groups using a chi-squared test.

As surgeons at some hospitals will operate on very few patients the analysis will be performed at a centre level and thus quantify the performance of the surgical team(s) rather than an individual surgeon. The OSS will be summarised descriptively (n, mean, 95% CI) at each time-point by centre and overall. Plots of the mean and 95% CI by centre at each time point will also be presented.
Neer’s Classification Agreement
Participants’ shoulder fractures using baseline radiographs were categorised at two time points. First, the recruiting orthopaedic surgeon assessed x-rays and recorded on the study eligibility form whether there was involvement of greater and/or lesser tuberosity in addition to the surgical neck. Later, two shoulder surgeons independently reviewed the x-rays and assigned fractures to one of 16 categories using Neer’s classification and then reached a consensus when there was discordance in their classification. Frequencies for both classifications will be presented in total and by trial arm.

Assessed tuberosity involvement at baseline (No, Yes) will be cross-tabulated against Neer’s classification (1 and 2 part, 3 and 4 part). The Kappa statistic will be used to measure agreement in the classification of the fractures for the two assessments. These will be compared in further detail by cross-tabulating frequencies of all possible classifications (Baseline assessment: 1-4 categories, Neer: 1-16 categories).
Appendix: CONSORT Diagram
References

4. The care of patients with fragility fracture - the 'blue book' published by British Orthopaedic Association; September 2007 (page 56, figure 4)
Signatures of Approval

Date: 27 August 2013
Version: 19

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