Study Title: HUSH – The HUmeral SHaft fracture trial: A multi-centre prospective randomised superiority trial of surgical versus non-surgical interventions for humeral shaft fractures in patients aged 18 years or older

Internal Reference Number / Short title: HUSH – The HUmeral SHaft fracture trial

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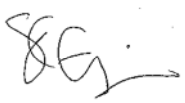
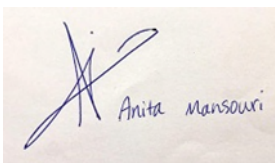
Chief Investigator:	Professor Steve Gwilym, University of Oxford
Co-Investigators:	Prof Matthew Costa, University of Oxford Prof Amar Rangan, University of York Prof James Mason, University of Warwick Associate Professor Susan Dutton, University of Oxford Dr Juul Achten, University of Oxford Dr Duncan Appelbe, University of Oxford Mr Harvinder Singh, University hospitals of Leicester NHS trust Mr Andrew Gray, South Tees Hospitals NHS Foundation Trust Mr Warren Sheehan, Oxford University Hospitals NHS foundation Trust Mrs Jennifer Gould, Oxford University Hospitals NHS Foundation Trust
Sponsor:	University of Oxford Joint Research Office, 1st floor, Boundary Brook House Churchill Drive, Headington, OX3 7GB; Email: ctrg@admin.ox.ac.uk
Funder:	National Institute for Health Research – Health Technology Assessment (NIHR 127817)
Chief Investigator Signature:	
Statistician Signature:	

No conflicts of interest to declare

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY CONTACTS

Chief Investigator	Professor Steve Gwilym Oxford Trauma University of Oxford John Radcliffe Hospital OX3 9DU Email: steve.gwilym@ndorms.ox.ac.uk Tel: 01865 227912
Sponsor	University of Oxford Research Governance, Ethics & Assurance Team (REGA) Research services, University of Oxford, Joint Research Office Boundary Brook House, Churchill Drive, Headington, Oxford OX3 7LE Email: ctrg@admin.ox.ac.uk Tel: 01865 616480
Funder(s)	National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme
Clinical Trials Unit	**Oxford Clinical Trials Research Unit: Oxford Trauma** Kadoorie Centre, NDORMS, University of Oxford, John Radcliffe Hospital, Headley Way, Oxford, OX3 9DU, hush@ndorms.ox.ac.uk
Statistician	Associate Professor Susan Dutton, susan.dutton@csm.ox.ac.uk Miss Anita Mansouri, anita.mansouri@csm.ox.ac.uk
Committees	**Data and Safety Monitoring Committee (DSMC)** Karen Thomas at the ICNARC CTU Email: Karen.Thomas@icnarc.org Tel: 020 7831 6878 David Woods Consultant Shoulder and Elbow Surgeon Email: david.woods7@nhs.net Mr Addie Majed BSc MBBS FRCS(T&O) MD (Res) E-mail: addie.majed@nhs.net Tel: 0208-909-5565 **Trial Steering Committee (TSC)** Prof Adam Watts MBBS, BSc, CRCS (Tr & Orth) Consultant Hand and Upper Limb Surgeon Email: Adam.C.Watts@wwl.nhs.uk Tel: 01257 256259

	Dr Shrouk Messahel Consultant in Paediatric Emergency Medicine Email: shrouk.messahel@alderhey.nhs.uk Tel: 0151 252 5052 Dr Joanna Thorn Research Fellow Email: Joanna.Thorn@bristol.ac.uk Tel: 0117 4283125 Miss Deb Smith Patient and Public Involvement Lay Member **Trial Meeting Group (TMG)** Prof Steve Gwilym (Chief Investigator) Dr Juul Achten (Operational Lead) Ms Amrita Athwal (Senior Trial Manager) Dr Marloes Franssen (Trial Manager) Ms Kylea Draper (Trial Coordinator) Ms Catherine Thompsett (Clinical Trial Administrator) Prof Matthew Costa (Professor of Orthopaedic Surgery) Dr Duncan Appelbe (Senior Research Information Specialist) Ms Anita Mansouri (Medical Statistician) Prof James Mason (Professor of Health Economics) Ass Prof Susan Dutton (Lead Statistician) Prof Amar Rangan (Professor of Orthopaedic Surgery) Mr Andrew Gray (Consultant Orthopaedic and Trauma Surgeon) Ass Prof Harvinder Singh (Consultant Orthopaedic Surgeon) Ms Jenny Gould (Participant and Patient involvement member)

2. LAY SUMMARY

A humeral shaft fracture is a break in the long bone of the upper arm. It occurs mainly in two groups of individuals; older women, as their bones are more fragile, and young men.

Currently, the most common treatment for these fractures is non-operative. Approximately 70% of cases are treated using a cast for two weeks and then a brace until the bone begins to heal properly – although there is large variation in treatments between and in hospitals. The risk of complications is low and the cost is also relatively low at £1,100. The disadvantages are that the patient is immobilised for a prolonged period and the cumbersome cast can lead to significant pain and discomfort in some patients. There is also a 20% chance that the break will not heal. This then requires surgery and involves additional costs of approximately £15,500.

There appears to be a worldwide trend towards treating these fractures with surgery (rather than a cast and a brace), however there is no high quality evidence that this is indeed a better option. Various reviews of the current evidence have recognised the need for further trials. Surgery is the more expensive route, and has a higher risk of complication e.g. infection and nerve damage. However, there is a better chance of the bone healing successfully and the patient is likely to recover more quickly allowing them to regain their independence sooner.

Our aim is to directly compare these two methods of treating fractures of the humeral shaft. We want to find out whether arm function and quality of life in patients with this fracture is better with the more conservative cast-and-brace treatment, or with surgery. We also need to compare the cost effectiveness of both approaches. We want to produce sound evidence to establish if the drawbacks of surgery are balanced by improved results and acceptable costs.

The technique of surgery used for those patients allocated to the surgery group will be chosen by the surgeon. Surgery will typically be followed by two weeks in a sling. Patients treated non-surgically will have a cast applied in the Emergency Department which they will use for two weeks. They will then change to a brace which is usually worn for a further 8-10 weeks. Both groups will be given a structured rehabilitation programme.

The trial will last for 12 months. Patients will be followed up weekly for the first 8 weeks, and at 3 months, 6 months and 12 months after their injury. They will be asked about their quality of life, daily activities, pain, physiotherapy treatment and any complications. We will also look at resources and services they have used to determine the costs involved in both treatments.

The Chief Investigator and members of the research team have been heavily involved in research which identifies what these patients say is important to them. A patient representative will be part of the trial management team and will also be involved in communicating the final results of the trial to all groups involved in caring for these patients, as well as the patients themselves.

3. SYNOPSIS

Study Title	**The HUmeral SHaft fracture trial:** A multi-centre prospective randomised superiority trial of surgical versus non-surgical interventions for humeral shaft fractures in patients aged 18 years or older
Internal ref. no. / short title	HUSH
Study registration	The study has been registered with the current controlled trials database under reference number ISRCTN: 17108318
Sponsor	University of Oxford
Funder	National Institute for Health Research
Study Design	Multi-centre randomised superiority trial
Study Participants	Adult patients aged 18 years and older with a fracture of the humeral shaft (diaphysis).

Sample Size	334		
Planned Study Period	Jan 2020 – Oct 2023 (46 months)		
Planned Recruitment period	August 2020 – May 2022		
	Objectives	Outcome Measures	Timepoint(s)
Primary	Function	DASH	12 months
Secondary	Function	DASH	Baseline, 8 weeks, 3, 6 months
	Early pain recovery	Pain VAS	Weekly until week 8
	Sports/Art	DASH sports/performing arts	Baseline, 8 weeks, 3, 6 and 12 months
	Function/Pain	PROMIS Upper Extremity PROMIS pain interference	Baseline, 4, 8 weeks, 3, 6 and 12 months
	Quality of Life	EQ-5D-5L	Baseline, 8 weeks, 3, 6 and 12 months
	Complications	Complications Case Report Form	8 weeks, 3, 6 and 12 months
	Cost effectiveness	Health economics questionnaire	8 weeks, 3, 6 and 12 months
Intervention	Surgical fixation		
Comparator	Functional Brace		

4. ABBREVIATIONS

AE	Adverse Event
BNF	British National Formulary
CAT	Computer Adaptive Test
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DASH	The Disabilities of the Arm, Shoulder and Hand Outcome Measure
DSMC	Data Safety & Monitoring Committee
EQ-5D-5L	EuroQol 5 Dimensions – quality of life questionnaire
GCP	Good Clinical Practice
HRA	Health Research Authority
HTA	Health Technology Assessment
HUSH	HUmeral SHaft Fracture Trial
IRT	Item Response Theory
NHS	National Health Service
NIHR	National Institute for Health Research
OCTRU	Oxford Clinical Trials Research Unit
PI	Principal Investigator
PIS	Participant Information Sheet
PP	Per Protocol
PPI	Patient and Public Involvement
PROM	Patient Reported Outcome Measure
PROMIS	Patient-Reported Outcomes Measurement Information System
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
REGA	Research Governance, Ethics & Assurance Team

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFQ	Site Feasibility Questionnaire
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
US	United States
VAS	Visual Analogue Scale

5. BACKGROUND AND RATIONALE

Fractures of the humeral shaft represent 3-5% of all fractures. They occur in a bimodal distribution, typically affecting younger men and older women (1). Overall, the incidence is highest in older women due to the process of osteoporosis (bone fragility) associated with age. The vast majority of humeral shaft fractures occur in patients over 50 years (2).

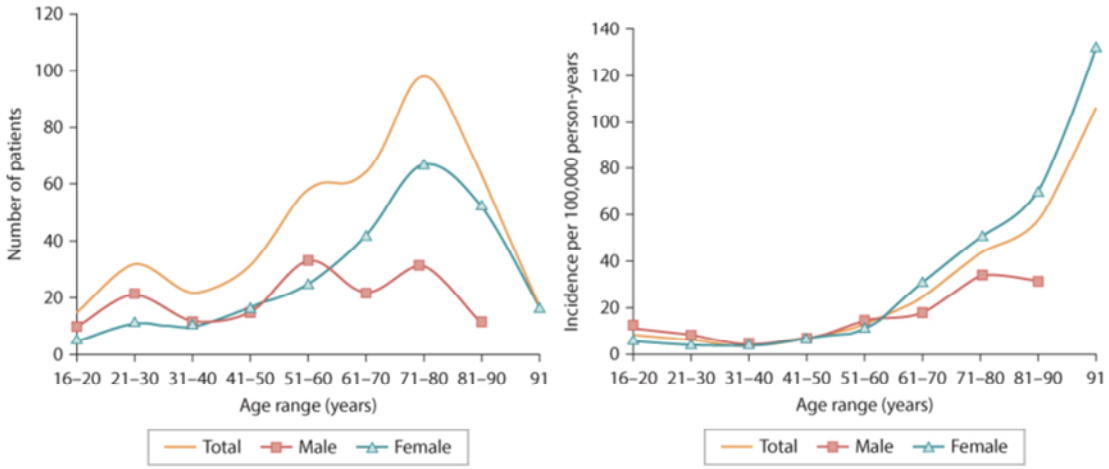

Figure 1: Overview of number of patients with a humeral shaft fracture (left) and the incidence per 100,000 persons (3).

Fractures of the humeral shaft are associated with pain, prolonged impairment of arm function, and a reduced quality of life for the duration of treatment (4). Treatment goals are directed towards pain relief, the early restoration of function, and minimisation of associated disability. It is recognised that providing stability at the fracture site, as well as an environment conducive to fracture-healing, is a key aim of treatment in order to achieve these goals.

The most common treatment for isolated humeral diaphysis fractures in the UK is non-operative, using casts, splints, braces, and slings. These are collectively referred to as ‘functional bracing’. This treatment physically supports the fractured humeral shaft through external pressure. This prevents the fractures from moving during activities of daily living, and this in turn reduces pain.

After a number of weeks, the bones will typically begin to unite, with callous formation at the fracture site. As the callous forms, the need for bracing becomes less and eventually the bracing is discarded.

Functional bracing carries a low risk of medical complications. It does however require a prolonged period of immobilisation in a brace which is often painful in the early stages of healing. Importantly, functional bracing also has a recognised rate of non-union (failure of the bone to heal) of approximately 20% (5). Non-union of a humeral shaft fracture is associated with prolonged pain, impaired function and disability.

Surgical fixation of the humeral shaft is most commonly performed with either a plate and screws, or an intramedullary nail. Plate and screw fixations tend to be used more frequently in younger patients, whilst nail fixation is often used in older patients as it relies less on the strength of the bone, which is often reduced due to age-related osteopenia and osteoporosis.

It is claimed that surgical intervention may lead to quicker functional recovery and lower rates of fracture non-union than functional bracing (6). There are however risks associated with this treatment not seen with functional bracing. These include: wound infections, nerve injuries, shoulder pain associated with the surgical approach and the metalwork being palpable or prominent (7).

We propose to directly compare a non-surgical (functional bracing) intervention with surgical intervention in the treatment of patients aged 18 years or older with a fracture of the humerus. We will focus on the effectiveness of both treatments in reducing pain, improving the functionality of the arm and improvements in the patients' quality of life. In addition, we will also make a comparison of cost effectiveness.

5.1. Why is this important?

There is both an increasing incidence of this fracture type as the population ages, and an increasing trend towards surgical fixation of humeral shaft fractures (8, 9).

However, there is a lack of high quality evidence to support this change in practice in this population. This has been highlighted in a number of publications including a Cochrane review (10), a meta-analysis (11) and systematic review (12). These conclude that there is no definitive answer to the questions of whether patients should undergo functional bracing or surgical fixation for humeral shaft fractures. The decision between surgical and non-surgical treatment is essentially arbitrary, based on surgeon preference.

In addition to the questions relating to effectiveness and safety, there is also a current lack of information on cost-effectiveness for these two treatment strategies. Functional bracing initially appears to be the less expensive treatment option. It has a relatively low immediate treatment cost (estimated at £1100 per patient (13)). However, functional bracing does have a recognised non-union rate of approximately 20% (5). If a non-union occurs, secondary surgical intervention is indicated, with a prolonged treatment period and costs estimated at £15.5k per case, considering direct medical costs only (14).

Surgical fixation is initially more expensive than functional bracing. Surgery is also associated with an increased rate of complications, which themselves incur a cost to treat. However surgical

fixation may lead to quicker functional recovery and lower rates of fracture non-union (6), therefore requiring less additional surgery.

6. OBJECTIVES AND OUTCOME MEASURES

The aim of this pragmatic randomised controlled trial is to evaluate the clinical and cost-effectiveness of functional bracing, compared to surgical fixation for the treatment of humeral shaft fractures in patients over the age of 18.

The primary objective is:
To quantify and draw inferences on observed differences in function using the Disabilities of Arms Shoulders and Hand patient reported outcome questionnaire (DASH) between functional bracing and surgical fixation at 12 months.

The secondary objectives are:

1. To quantify and draw inferences on observed differences in patient reported outcomes between the trial treatment groups in the first 12 months.
2. To quantify and draw inferences on observed differences in the pain experienced by patients who have sustained a humeral shaft fracture during the first 12 months, and compare the recovery profile between the trial treatment groups.
3. To investigate the risk of complications between the trial treatment groups in the first 12 months.
4. To investigate the resource use, costs and comparative cost effectiveness between the trial treatment groups at 12 months.
5. To record and compare the duration of time off work, for participants of working age, between the intervention groups.

Table 1: Assessments performed to enable delivery of objectives:

Outcomes	Objectives	Instruments	Timepoints
Primary	Function	DASH	12 months
Secondary	Function	DASH	Pre-injury at baseline, 8 weeks, 3, 6 months
	Early pain recovery	Pain VAS	Weekly until week 8
	Sports/Art	DASH sports/performing arts	Pre-injury at baseline, 8 weeks, 3, 6 and 12 months

	Function/Pain	PROMIS Upper Extremity PROMIS pain interference	Pre-injury at baseline, 4 weeks, 8 weeks, 3, 6 and 12 months
	Quality of Life	EQ-5D-5L	Pre-injury at baseline, 8 weeks, 3, 6 and 12 months
	Complications	Complications Case Report Form	8 weeks, 3, 6 and 12 months
	Cost effectiveness	Health economics questionnaire	8 weeks, 3, 6 and 12 months
	Time off work and driving	Case Report Form question	Weekly until week 8

6.1. Outcome measures

The primary outcome measure for this study is the DASH patient reported outcome measure.

The DASH Outcome Measure is a 30-item, self-reported questionnaire designed to measure physical function and symptoms in patients with musculoskeletal disorders of the upper limb. The items enquire about the degree of difficulty in performing different physical activities because of arm, shoulder and hand problems (21 items), the severity of each of the symptoms of pain, activity-related pain, tingling, weakness and stiffness (five items) and the impact of the problem on social functioning, work, sleep and self-image (four items). Each item has five response options. The scores are then used to calculate a scale score ranging from 0 (no disability) to 100 (most severe disability)—this is called the DASH score (15). The questionnaire was designed to help describe the disability experienced by people with upper-limb disorders and also to monitor changes in symptoms and function over time. Testing has shown that the DASH performs well in both these roles. DASH has been the most consistently reported Patient Reported Outcome Measure (PROM) in studies investigating humeral fractures and as such, its use will allow contextual comparison with previous and future work.

Previous work has highlighted the reliability and validity of the DASH score in the study of humeral fractures (16, 17).

The selected secondary outcome measures aim to further explore the domains of pain, function and quality of life. The latter will contribute to an associated cost-effectiveness analysis.

Pain VAS

To assess pain recovery in the immediate post-injury period (up to week 8), a visual analogue scale (VAS) on a scale of 0-100, where 0 is no pain at all and 100 is the worst pain imaginable, will be used (18). This will be administered through SMS/text message or email.

DASH Sports/Performing arts module

This additional sub section of the DASH questionnaire investigates the effect of upper limb injury on a patient's participation in sports or playing instruments. The measure consists of 4 questions which will be completed if the participant indicates usual participation in sports or musical activities. The questions are each scored on a 5 point Likert scale. This module ranges from 0 (not disabled) to 100 (most severe disability)(19).

PROMIS Physical Function (upper extremity) and PROMIS Pain Interference

Patient Reported Outcome Measurement Information System (PROMIS) questionnaires are patient reported outcome measures which are administered electronically. They represent a form of Computer Adaptive Test (CAT). CATs are dynamic tests based on Item Response Theory (IRT), a mathematical model that adapts the sequential questions based on a participant's previous response, enabling the successive administration of a tailored set of questions from a large item pool. CATs have been validated in a variety of chronic health conditions. Multiple instruments have been designed including the United States (US) National Institute of Health, PROMIS. PROMIS instruments cover a variety of domains, and are scored from 0 to 100 with 50 points representing the mean score for the US general population and higher scores indicate better function. These instruments address the demand for shorter, more practical measurement of patient-focused outcomes with increased efficiency and precision. This study will utilise the Physical Function (upper extremity) which focusses on function and disability and the pain-interference PROMIS questionnaires which investigates pain intensity and impact. Both of these questionnaires have been found to be valid in the context of upper limb fractures (4, 20). If internet access is not available to the participant, paper-based (short-form) versions of the PROMIS questionnaires will be sent to the participants for completion.

Quality of life

EQ-5D-5L: The EuroQol 5 Dimensions (EQ-5D-5L) is a validated, generalised and standardised instrument comprising a VAS measuring self-rated health and a health status instrument, consisting of a five-level response (no problems, some problems, moderate problems, severe problems and unable) for five domains related to daily activities; (i) mobility, (ii) self-care, (iii) usual activities, (iv) pain and discomfort and (v) anxiety and depression. Responses to the health status classification system are converted into an overall score using a published utility algorithm for the UK population. A respondent's EQ-VAS gives self-rated health on a scale where the endpoints are labelled 'best imaginable health state' (100) and 'worst imaginable health state' (0).(21) We will follow the most up-to-date position statement from NICE when processing the data. Utility scores for the UK population will be used to derive 12 months quality-adjusted life years (QALYs) using the area under the curve method.

Resource Use

Patient and hospital reported resource use we will be recorded including hospital admissions, outpatient appointments and personal social services use in relation to injury.

Return to work

As the time to return to work is such an important aspect of patient management, this specific element of cost effectiveness will be explored by weekly SMS/email.

Complications

All complications will be recorded, but particular note will be made of complications related to the surgical procedure (wound infection, nerve injury, injury to a blood vessel, non-union, shoulder stiffness, elbow stiffness), and problems identified during the Patient and Public Involvement (PPI) process by those having undergone functional bracing (pressure sores, elbow stiffness).

Radiographic images obtained as part of routine practice will also be collected. In particular, we will seek images pre-operatively, post-treatment, and as close as possible to 12 months (the primary outcome) following randomisation.

Table 2: Expected complications assessment methods

Potential complication	**How assessed?**
Wound infection	Patient self-report at each time point and then explored / reported in detail by RA
Radial Nerve injury (following surgery or application of cast/brace)	1. Radial Nerve injury requiring further surgery (release, transfer, repair, tendon transfer) 2. Radial Nerve injury identified by the clinician but managed expectantly
Pressure sores	Clinical reporting: “Partial thickness” (Grades 1 & 2) “Full thickness” (Grades 3 & 4) Reference: https://nhs.stopthepressure.co.uk/docs/PU-Grading-Chart.pdf
Treatment for delayed / Non-union	Surgery required to treat delayed / non-union If performed, how long after fracture? • before 6 weeks after treatment will be described as cross-over; • after 6 weeks after treatment will be described as surgery for non-union Functional bracing extended beyond 12 weeks to treat delayed/non-union • If brace worn for more than 12 weeks, how long worn for?
Clinically suspected fungal infection of the skin	Clinical reporting

Cost effectiveness

Resource use will be monitored for the economic analysis. Unit cost data will be obtained from national databases such as the British National Formulary (BNF) and Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care. Where these are not available the unit cost will be estimated in consultation with the Oxford University Hospitals finance department.

Resource use following discharge, including National Health Service (NHS) and Personal Social Services (PSS) costs will be recorded via a short questionnaire which will be administered at 3, 6 and 12 months post-treatment. Patient self-reported information on service use has been shown to be accurate in terms of the intensity of use of different services.

We will also record information about participants usual and current work status. Where participants are signed-off work, due to their humeral fracture, the duration of this work absence will be recorded.

7. STUDY DESIGN

This trial is a pragmatic, multi-centre, two-arm, parallel group, randomised controlled superiority clinical trial with parallel economic analysis and direct patient follow-up to 1-year. The trial will employ 1:1 treatment allocation, stratified by centre, age, and nerve injury with patients randomised to either functional bracing or surgical fixation, based on the surgeons' usual surgical practice.

The trial is split into two phases – a pilot phase and a main phase. Study procedures during both phases will be identical as per this protocol. During the initial pilot phase of 6 months, 8 centres will be opened to recruitment. Strict stop-go criteria based on recruitment rates have been outlined elsewhere. The Trial Steering Committee (TSC) will, with support from the Data and Safety Monitoring Committee (DSMC), advise the funder during the decision making process.

Screening and subsequent recruitment for the main phase will occur at a minimum of 16 NHS hospitals over a 21 month period. All treatments are standard NHS treatments and will be conducted at the recruiting centres. Participants will be followed up clinically as per standard hospital policy. They will be followed-up via postal or electronic questionnaires by the central trial team for a period of 12 months.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Adult patients aged 18 years and older with a fracture of the humeral shaft (diaphysis).

8.2. Inclusion Criteria

- Fracture of the humeral diaphysis which the surgeon believes may benefit from surgical fixation

- ‘Diaphysis’ defined as the section of bone outside 1 Muller-square of the proximal and distal ends of the Humerus (23).

- Participant is willing and able to give informed consent for participation in the study.
- Adults, aged 18 years or above.

8.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- The fracture is open
- The fracture is complicated by local tumour deposits
- Bilateral fractures
- The index injury occurred more than 16 days prior to recruitment
- The patient is unable to adhere to trial procedures
- Other upper limb injuries which may reasonably be expected to affect responses to outcome PROMs

Inclusion criteria encompasses all adult patients. The exclusion criteria reflect current clinical practice. Open fractures and fractures complicated by local tumour deposits are almost universally treated with surgical intervention. In this situation, allocation to functional bracing would be inappropriate.

9. PROTOCOL PROCEDURES

9.1. Recruitment

A total of 334 participants will be recruited across a minimum of 24 sites.

The trial will be advertised to sites and potential Principal Investigators (PIs) through professional conferences and networks, with the help of the regional Clinical Research Network and through word of mouth. Our unit has a network of over 50 sites that have previously worked with us on multicentre randomised trials.

Sites will be selected based on suitability. An invitation pack which includes a Site Feasibility Questionnaire (SFQ) will be provided to potential sites. The SFQ may be completed by an individual with adequate, authoritative knowledge of the site (where a site is known to the study office through previous research enterprises the SFQ may be part-completed in advance). The PI

or an appropriate deputy must confirm participation and the accuracy of any SFQ submitted to the study coordinating office in Oxford.

The coordinating team will evaluate returned SFQs to ensure a site is equipped with appropriate resources to deliver the project and meet recruitment targets. Confirmation of collaboration will be provided in writing to the PI.

9.2. Screening and Eligibility Assessment

Potentially eligible patients will be identified after referral to orthopaedic services from local emergency departments, Minor Injury Units or primary care and highlighted to the research team at the daily trauma meeting or fracture clinics. After radiographic confirmation of a fracture the local clinical team will confirm the eligibility of the individual patient to participate.

Screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for exclusion. In addition, the number of eligible and recruited patients, and the number of patients who decline consent or withdraw will be recorded. The DSMC and TSC will closely monitor recruitment during the pilot phase and make a decision regarding continued progress of the trial against the specified stop/go criteria. These criteria will be agreed by the committees at their initial meeting, in line with the metrics outlined in section 11.5. If the trial is stopped after the pilot phase, then all trial participants will be followed up as per protocol. If the trial continues into the main phase, participants from the internal pilot will be included in the final analysis.

9.3. Informed Consent

A member of the responsible clinical team will briefly highlight the study to the patient and introduce a member of the local research team. They will approach the patient, or contact them via telephone if they are unable to meet the patient face-to-face, and explain the trial. In order to standardise the information provided to the patients, online and written recruitment materials will be made available to local research teams, including a short video detailing the study. The local research team will also be able to answer any additional questions that the patient might have.

This will then lead on to an informed consent discussion, which may place take in person or remotely if the research team is unable to meet the patient face-to-face, and if happy to proceed the patient will provide written electronic consent. Patients will be given as much time as possible to consider the information and discuss it with relatives/carers. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

Prior to any study related procedures or data being collected participants will complete the latest approved version of the consent form and provide their contact details if they are willing to consent in order for an electronic copy of the form to be sent to them immediately. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Principal Investigator. Once completed, an electronic version of the signed consent form will be automatically emailed to the participant. The local research team will be able to download a copy

to place in the participant's medical notes. If the participant does not have access to email then a paper copy of their consent form will be provided by the local research team instead.

The consent form will include the link to the trial website so that participants will have access to all the trial information. If a participant does not have internet access a paper information sheet will be provided. The trial website will be maintained until the study archive period has reached completion.

9.4. Randomisation

Once informed consent has been given, the participant will be randomised by the local research team using a web-based service.

Allocations will be implemented as close as possible to the time of randomisation, whether this be in outpatient clinics or daily trauma meetings. Such a design most faithfully replicates real clinical practice so that the results of the trial will be as generalisable as possible to the wider NHS. This trial will test the two interventions as treatment pathways and hence be as pragmatic as possible.

The randomisation will be on a 1:1 basis, using a validated computer randomisation program managed through a secure (encrypted) web-based service by the Oxford Clinical Trials Research Unit (OCTRU), with a minimisation algorithm to ensure balanced allocation across the treatment groups, stratified by centre and age (<50 vs ≥50) and nerve injury at presentation (Yes/No). The minimisation algorithm will include a probabilistic element and a small number of participants randomised by simple randomisation at the start of the trial to seed the algorithm in order to ensure the unpredictability of treatment allocation. (24)

Stratification by centre will help to ensure that any outcome effect of the treatment centre- will be equally distributed in the trial arms. While it is possible that the surgeons at one centre may be more expert in one or the other treatment than those at another centre, all of the recruiting hospitals have been/will be chosen on the basis that both techniques are currently routinely available at the centre i.e. theatre staff and surgeons will already be equally familiar with both forms of intervention. Similar to the findings from other trauma trials (25), we anticipate that each individual surgeon will only treat 2-3 participants enrolled in the trial, greatly reducing the risk of a surgeon-specific effect upon the outcome in any one centre. We will also incorporate centre as a random effect in the mixed effect primary analysis which takes into account any heterogeneity between centres.

Stratification by age has been adopted as previous work has shown that age is a reliable surrogate for bone density and this in turn influences the surgeon's decision when choosing between different surgical implants. Age stratification (<50/≥50) was successfully applied in previous, successfully delivered HTA funded trials (25) and is felt to be relevant to this fracture population and the way they are currently treated.

Stratification by 'Nerve injury at presentation' will account for the recognised effect that nerve injury may have on the early, and possibly late, patient reported outcome measures. Radial nerve injury (the most common nerve injury with this sort of fracture) will, for example, affect the ability

to use the arm and hand for functional activities enquired about in the primary and secondary outcome measures.

On randomisation of a participant the central trial office, main site contact and local study team will be notified. This will take place via an automated email as part of the randomisation process.

A paper-based randomisation system will be in place for use in emergencies, e.g. if the web-based randomisation service is not functioning, an event that is rare with this service.

9.5. Blinding and code-breaking

The primary outcome data will be collected from participants and entered directly onto the trial central database. It will not be possible to blind participants or those delivering the interventions.

The local research team reviewing hospital records will also not be blind to the treatment allocation. Any radiographs collected will be reviewed by an independent adjudication committee who, due to the presence of metalwork, will also not be able to perform their assessments blinded.

9.6. Description of study intervention, comparators and study procedures (clinical)

Participants will be randomised to receive either surgical or non-surgical treatment. All treatments will be delivered under the supervision of a consultant trauma and orthopaedic surgeon.

9.6.1. Surgical intervention

General or regional anaesthesia will be used for surgery, as per routine practice in each hospital, along with routine peri-operative care including prophylactic antibiotics. The surgical fixation can be performed by using one of two routinely used methods; plates and screws are inserted through an incision that run along the length of the humerus. The correct length plate is chosen and then typically between 8 and 10 screws are inserted to hold the plate to the bone. Conversely, humeral nails are inserted through an incision at the top of the shoulder and passed down the hollow centre of the bone. The nails then have between 2 and 4 screws inserted above and below the fracture to give rotational stability to the arm (26).

The exact technique of surgical approach and insertion of the surgical implant will be left to the discretion of the treating surgeon according to their usual surgical technique. This surgical approach will be recorded.

There are a number of different manufacturers of surgical implants and no stipulation will be made as to which manufacturer to use.

9.6.2. Description of comparator

The use of cast, splints and slings are collectively described as ‘functional bracing’. This terminology reflects that these modalities (casts, splints and slings) are applied in a way that is

designed to allow the patient to continue to have some arm function whilst the bones unite. Throughout this trial we will use the term 'functional bracing.'

Following a diagnosis of a fracture of the humerus, a temporary cast is usually applied in the emergency department (depending on local hospital guidelines) to relieve pain and allow for swelling. After one to two weeks, when the swelling has settled, this temporary cast is removed and a thermo-plastic humeral brace is applied as per local hospital policy and guidelines. The humeral brace is worn until there is evidence of fracture union. Overall, this process takes approximately 8-10 weeks, after which patients have the humeral brace removed.

There are a number of suppliers of humeral braces but no stipulation will be made as to which brace to use. The type of brace will be recorded. As support for patients, we will provide written guidance on the application and care of humeral braces as our pre-application survey identified that some units do not have this information in written format.

9.6.3. Rehabilitation

Following the delivery of the selected treatment, rehabilitation will commence. In our pre-application survey of potential recruitment sites, it has become clear that many sites do not have documented rehabilitation programmes for this condition. We will therefore provide standardised written information sheets to all patients in the trial.

Both treatment methods stabilise the fracture to allow early mobilisation of the shoulder and elbow and early return to functional activity after the initial phase of soft tissue healing.

Any further therapy input, beyond the standardised exercise and advice sheet, will be at the discretion of the treating centre but will be recorded as part of the trial clinical reporting forms.

Both the operative and non-operative groups will be advised to begin active finger and wrist range-of-motion exercises; passive / active elbow range-of-motion exercises and non-weight bearing scapula setting exercises from day 1. No shoulder movement should begin in the first 2 weeks of treatment.

After 2 weeks, pendular/passive/active-assisted/active shoulder range-of-motion exercises and gentle isometric contraction exercises can begin and progress as comfort allows. There is no restriction in the range-of-motion allowed at the shoulder, however, no resistive or weight bearing exercises are allowed at this stage. Active finger, wrist and elbow range-of-motion exercises and non-weight bearing scapula setting exercises should continue. Patients at this stage will be allowed to begin gentle, functional activities with their affected arm, such as dressing; using cutlery; food preparation; writing and computer work. Resistive strengthening exercises and weight bearing exercises will begin following union.

9.7. Baseline Assessments

Baseline demographic data and retrospective pre-injury functional and pain data using the DASH and PROMIS physical function and PROMIS Pain interference questionnaires will be collected. Participants will also be asked to complete the EQ-5D-5L health-related quality-of-life questionnaire (27) to indicate their typical pre-injury health status and their current health status.

The presence or absence of a nerve injury at presentation, fracture type (simple or multi-fragmentary) and mode of injury (low energy or high energy) will also be recorded.

9.8. Clinic visit

Participants will usually attend at least three visits to the orthopaedic or trauma clinic after their initial treatment as part of standard care. With current changes in care-delivery, some of these reviews may now be made remotely, with X-rays taken at a satellite, linked, NHS centre and consultation performed over the telephone or video-call. Patients are not typically discharged from clinical review until radiographs confirm bony union. During each physical clinic visit, the clinical team will perform a clinical assessment and standard radiographs will be taken. If not performed physically, the assessment will be made at the same time as the virtual clinical review. The research team will record any early complications that have occurred at each of these reviews. The research team will transfer redacted radiographs taken in clinic, intra-operatively and in the time since their index treatment to the central office.

9.9. Remote Early phase follow-up up to 8 weeks

Participants will receive a weekly text/email/phone call (according to participant preference) up to week 8 post-randomisation with a link to a visual analogue scale asking them to indicate their level of pain in the previous 24 hours. They will also be asked whether they have returned to driving and work if applicable. At 4 weeks participants will also be asked to complete the PROMIS questionnaires and at 8 weeks they will be asked to complete the PROMIS, DASH, EQ-5D-5L, , and a complications questionnaire. If there are any queries with regards to the questionnaires, participants will be contacted by the research team.

9.10. Remote late phase follow-up (3, 6 & 12 months)

At 3, 6 and 12 months after randomisation, participants will be contacted by the central study office and invited to complete the DASH, PROMIS, EQ-5D-5L, , resource use and complications questionnaires. If there are any queries with regards to the questionnaires, participants will be contacted by the research team.

9.11. Early Discontinuation/Withdrawal of Participants

During the course of the trial a participant may choose to withdraw early from the study at any time, without giving reasons, and without prejudicing their clinical care.

Participants will **not** have the option to withdraw the data collected up until the point of withdrawal, as the data will be required for the intention-to-treat analysis and safety analysis. The options for withdrawal will be explained clearly in the Participant Information Sheet (PIS). The type of withdrawal and reason for withdrawal, if the participant is willing to provide one, will be recorded in the withdrawal Case Report Form (CRF).

9.12. Definition of End of Study

The end of the study is defined as the last follow up of the last participant and once all queries have been resolved.

10. SAFETY REPORTING

Safety reporting for each participant will begin from the first point of administration of the intervention (e.g. surgery) and will end when the participant has reached their final main follow up time point, at 12 months post-randomisation. This is a low risk, pragmatic trial where both of the trial interventions are in common use. In light of this, we do not anticipate many serious adverse events (SAEs) associated with either treatment.

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect

Other ‘important medical events’ may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

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 which hypothetically might have caused death if it were more severe.

10.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was ‘related’ (resulted from administration of any of the research procedures) and ‘unexpected’ in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website). As both arms are investigating procedures currently used as treatment methods, we will not be collecting unrelated SAEs.

When the local research team becomes aware of an SAE in a trial participant, the PI will review the SAE locally and make a decision about the causality (i.e. likelihood of the event to be related/attributed to the intervention). Further details on grades of causality can be found in the SAE reporting guidelines document available in the ISF. Following the assessment of causality

the PI will assess any related events for expectedness. For any SAEs assessed as unexpected and potentially related, the details of the event will be entered on an SAE reporting form on the database, and the local research team will notify the central trial team via email or telephone within 24 hours of the PI becoming aware of the event. Once the SAE form is received, causality and expectedness will be confirmed by the Chief Investigator (CI) or delegate (Nominated Person). In the event that consensus is not reached between the PI and Nominated Person about assessment of causality and expectedness, this will be escalated to the CI for further discussion. However, if no consensus decision is reached about expectedness after further discussion within one working day, and the SAE is judged to be unexpected by any one of either the PI, Nominated Person or CI, the event will be classified as an unexpected event.

10.3. Foreseeable Serious Adverse Events

SAEs that are foreseeable, or expected, in the treatment of these fractures do not need to be reported immediately, provided they are recorded in the 'Complications' section of the CRF and/or Patient Questionnaires.

These include the following:

Surgery:

- Surgery, defined as unplanned return to theatre (including treatment for: mal-union, non-union, failed fixation, prominent implant correction, vascular injury, wound dehiscence, Compartment syndrome))
- Infection as a result of the intervention
- Nerve injury as a result of the treatment of the humeral diaphysis
- Symptomatic venous thrombosis
- Symptomatic pulmonary embolus
- Complex regional pain syndrome

Brace:

- Surgery, defined as unplanned return to theatre (including treatment for: mal-union, non-union, failed fixation, prominent implant correction, vascular injury, wound dehiscence, Compartment syndrome))
- Pressure sores (reported as partial thickness, grades 1 & 2; or full thickness, grades 3 & 4)
- Infection as a result of the intervention
- Nerve injury as a result of the treatment of the humeral diaphysis
- Symptomatic venous thrombosis
- Symptomatic pulmonary embolus
- Complex regional pain syndrome

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with full details of all analyses fully described in a statistical analysis plan. The SAP will be drafted early in the trial and finalised prior to the primary outcome analysis. The SAP will be reviewed by the TSC and the DSMC. Interim analyses of the efficacy outcomes are not planned and will be performed only if requested by the DSMC. It is anticipated that all analysis will be undertaken using Stata (28) or other well validated statistical packages.

11.2. Sample Size Determination

At 90% power and 5% (2-sided) significance, the proposed sample size needed is 266 (133 per treatment arm) participants providing data at 12 months in order to detect a standardised effect size of 0.4. Allowing for 20% loss to follow-up yields an overall target of 334 (167 per arm). These calculations are based on the primary outcome of DASH at 12 months. The minimum clinically important difference for the DASH questionnaire has been identified as 10 points, and the standard deviation available from the literature is variable with the closest to our target population being 21.7 (29). A standardized effect size of 0.4 (a small to moderate effect size) equates to a difference of 10 points when the standard deviation is as high as 25 or a difference of 8 points when it is as low as 20. The DSMC will review the sample size assumptions approximately half-way through recruitment to the study to ensure that this sample size would be able to provide a definitive answer to the research questions. In summary, a minimum of 266 participants with primary outcome data (DASH at 12 months) will provide a definitive answer to the research question with 90% power and 5% (2-sided) significance to detect a standardised effect size of 0.4. To achieve this number and allowing for loss to follow-up we aim to randomise 334 participants.

11.3. Analysis populations

The intention-to-treat population will include all participants with available data at time-points up to and including 12 months in the randomised groups to which they were allocated regardless of the treatment they actually received.

The per-protocol (PP) population will include all participants who received their allocated treatments and did not have any major protocol deviations. Major protocol deviations will be pre-specified in the Data management plan and SAP and will be finalised following a blinded review of the data prior to the primary analysis data-lock.

11.4. Description of the Statistical Methods

All available data from both treatment arms will be used in data analysis based on the intent-to-treat population. Reporting of the results will be in accordance with the CONSORT statement (30) using the extensions for non-pharmacological treatment interventions and patient-reported outcomes. Standard descriptive statistics will be used to describe the demographics between the treatment groups reporting means and standard deviations or medians and interquartile ranges as

appropriate for continuous variables and numbers and percentages for binary and categorical variables. Standard statistical summaries and graphical plots will be presented for the primary outcome measure and all secondary outcome measures.

The DASH at 12 months is the primary outcome in this study and will be compared between treatment groups as the dependent variable in a mixed-effects linear regression model including outcome information from all intermediate time-points. This model will adjust for stratification factors (recruitment centre, age and nerve injury at presentation), and baseline (preinjury) DASH score. A random effect will be included to account for any heterogeneity in the response due to recruitment centre, with the other variables being incorporated as fixed effects. The treatment effect will be based on the adjusted mean difference at 12 months which will be reported alongside the 95% confidence intervals and will be used to determine superiority. A fully adjusted analysis will also be undertaken adjusting for other important prognostic factors (diabetic-status, smoking status, Body Mass Index (BMI) and concomitant injuries which affect limb function) in addition to those specified above, and an unadjusted analysis will also be undertaken adjusting for baseline (pre-injury) DASH scores only. Sensitivity analyses using the per-protocol population will be undertaken.

Subgroups based on type of surgery/brace and stratification factors will be explored using treatment by subgroup interactions. Secondary clinical outcomes and patient reported outcomes will be similarly analysed using mixed effects regression, using logistic regression for binary data and linear regression for continuous data.

11.5. Decision points

This trial will have one decision point, at the end of the pilot phase.(31) The pilot phase represents the first six months of recruitment during which it is expected that a minimum of eight sites will be open to recruitment. The decision with regards to the continuation of the trial will be based on the total recruitment across recruitment centres. The stop-go criteria are given in Table 3. If recruitment fails to reach 20 participants by the end of the pilot phase (six months after trial opening), the DSMC may recommend that the trial is terminated.

Table 3: Stop/Go criteria for main trial

	Actual recruitment at the end of the pilot phase (6 Months)		
% Threshold	67%	68-99%	100%
Recruitment rate (per centre per month)	0.5	0.6-0.7	0.8
Number of sites opened	8	8	8

Trial Recruitment	<20 participants	21-29 participants	>30 participants
Stop-go outcome	Recruitment not feasible; decision not to proceed	Review recruitment strategies. Report to TSC. Continue but modify & monitor closely	Recruitment feasible; proceed with study

11.6. The Level of Statistical Significance

The HUSH trial has a single primary outcome, and therefore there will be no adjustment for multiple testing.

All outcomes will be assessed with 5% level of significance and will be presented with effect sizes and 95% confidence intervals. P-values will be reported with up to 3 decimal places.

11.7. Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data will be minimised by careful data management. Missing data will be described with reasons given where available; the number and percentage of individuals in the missing category will be presented by treatment arm. All data collected on data collection forms will be used, since only essential data items will be collected. No data will be considered spurious in the analysis since all data will be checked and cleaned before analysis. The nature and mechanism for missing variables and outcomes will be investigated, and if appropriate multiple imputation will be used. Sensitivity analyses will be undertaken assessing the underlying missing data assumptions. Any imputation techniques will be fully described in the Statistical Analysis Plan.

11.8. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any changes or deviations from the original SAP will be described and justified in the protocol, updated SAP, final report and publications as applicable, depending on the timing of the changes.

11.9. Health Economics Analysis

A prospectively planned economic evaluation of functional bracing versus surgical fixation will be conducted from an NHS and personal social services perspective, according to the recommendations of the NICE reference case (32).

Use of hospital and community contacts, made in connection with their surgery, will be recorded in the first 12 months (questionnaires at 3, 6 and 12 months). Healthcare resource use will be costed using most recently available published national reference costs, reflated to the most recent year (33). Generic health-related quality-of-life will be assessed at baseline, 8 weeks, 3, 6 and 12 months using the EQ-5D-5L questionnaire. EQ-5D-5L scores will be converted to health status scores using the UK value set recommended by NICE guidance at the time of analysis (34). Patient-level

QALY estimates will be estimated as the area-under-the-curve of health status scores over time using the trapezoidal rule. Baseline EQ-5D-5L will be included to minimise bias in the QALY calculation] (35), and to adjust subsequent analyses (36).

Within-trial analysis (to 12 months) using bivariate regression of costs and QALYs will inform a probabilistic assessment of incremental treatment cost-effectiveness. Mechanisms of missingness of data will be explored and multiple imputation methods will be applied to impute missing data. Imputation sets will be used to estimate incremental cost per QALY estimates and confidence intervals (37-39). Findings will be analysed and visualised in the cost-effectiveness plane, as cost-effectiveness acceptability curves, net monetary benefit and value of information analysis. Sensitivity analyses will be undertaken to explore uncertainty and to consider issues of generalisability of the study. If incremental costs and benefits are non-convergent within the trial follow-up then extrapolated modelling will be considered, drawing upon the best available information from the literature to supplement the trial data.

12. DATA MANAGEMENT

The data management aspects of the study are summarised here with full details described in the Data Management Plan.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, patient-reported outcome measures that are submitted directly to the sponsor and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.2. Access to Data

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

12.3. Data Recording and Record Keeping

The CRFs will be designed by the trial manager in conjunction with the trial management team, statisticians and health economists.

Whenever possible, data will be collected in electronic format with direct entry onto the trial database, including the collection of documentary evidence of consent. Electronic data collection has the major advantage of building "data logic" and "edit checks" into forms, minimising missing data, data input errors and ensuring the completeness of consent forms. All data entered will be encrypted in transit between the participant's web browser and server. All identifiable information will be held on a server located in an access controlled server room at the University of Oxford. The data will be entered into a Good Clinical Practice (GCP) compliant data collection system and stored in a database on the secure server, accessible only to the research team based on their role within the study. The database and server are backed up to a secure location on a regular basis.

Details of the data collected, where it is stored and who has access to it along with a fair processing statement will be available for the public to see on the study website.

Paper forms with identifiable data will not be collected. Identifiable data will be limited to contact details and will be accessed separately from the outcome data obtained from/about the participants and managed within the rules of the clinical database system. In all other data, participants will be identified by a trial ID only. Direct access to source data/documents will be required for trial-related monitoring and/or audit by the Sponsor, NHS Trust or regulatory authorities as required. All electronic data will be retained for at least three years after publication of the trial. Contact details will be retained for 6 months after the last data collection. The data from consent forms (in most cases the consent will be given electronically) will be retained for one year after the last data collection.

The study team and the recruiting hospital will have access to all participant data.

Trial data will be collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the OCTRU, University of Oxford.

REDCap (40) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Wherever possible, trial data will be entered directly into the trial database by site staff or participants. If requested, paper forms will be provided for data collection. Data captured during phone calls to participants and trial data completed on paper forms by local site staff will be entered into the trial database by suitably trained central office staff. Full details will be recorded in the Data Management Plan. The participants will be identified by a unique trial specific number in any data extract. Identifiable data will only be accessible by members of the study team with a demonstrated need (managed via access controls within the application) and only used to communicate with the participant (e.g. sending follow-up reminders for online form completion). X-rays will be collected from each patient using an OCTRU specific system. This system will be hosted on OCTRU servers and validated as per OCTRU SOPs and the documentation held by OCTRU.; operation notes will be uploaded to REDCap.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and OCTRU Standard Operating Procedures (SOPs).

13.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Study monitoring

Quality control procedures will be undertaken during the recruitment and data collection phases of the study to ensure research is conducted, generated, recorded and reported in compliance with the protocol, GCP and ethics committee recommendations. The CI and the Trial manager will develop data management and monitoring plans.

13.3. Trial Oversight

The trial will be conducted in accordance with the principles of GCP and guidelines, the Declaration of Helsinki, OCTRU SOPs, relevant UK legislation and this Protocol. GCP-trained personnel will conduct the trial.

13.4. Trial Management Group

The day-to-day management of the trial will be the responsibility of the Trial Manager, supported by a Senior Trial Manager. This will be overseen by the Trial Management Group (TMG), who will meet monthly to assess progress. A Patient and Public Involvement (PPI) representative will be an integral member of the TMG. It will also be the responsibility of the Trial Manager to undertake training of the research staff at each of the trial centres. The trial statistician, health economist and the information specialist will be closely involved in setting up data capture systems, design of databases and clinical reporting forms.

13.5. Trial Steering Committee

The TSC, which includes independent members, provides overall supervision of the trial on behalf of the funder. Its terms of reference will be agreed with NIHR HTA and will be drawn up in a TSC charter which will outline its roles and responsibilities. Meetings of the TSC will take place at least once a year during the recruitment period. An outline of the remit of the TSC is to:

- monitor and supervise the progress of the trial towards its interim and overall objectives.
- review at regular intervals relevant information from other sources.
- consider the recommendations of the DSMC.
- inform the funding body on the progress of the trial.

The TSC will include at least one PPI representative as an independent member.

13.6. Data and Safety Monitoring Committee

The DSMC is a group of independent experts external to the trial who assess the progress, conduct, participant safety and, if required critical endpoints of a clinical trial. The study DSMC will adopt a DAMOCLES charter which defines its terms of reference and operation in relation to oversight of the trial. The DSMC will advise the TSC on continuation of the trial at the end of the pilot phase. They will also review accruing data and summaries of the data presented by treatment group, and will assess the screening algorithm against the eligibility criteria. They will also consider emerging evidence from other related trials or research and review related SAEs that have been reported. The DSMC will review the sample size assumptions approximately half-way through recruitment to the study to ensure that the target sample size would be able to provide a definitive answer to the research questions. They may advise the chair of the TSC at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about participant safety. DSMC meetings will be held at least annually during the recruitment phase of the study. Full details including names will be included in the DSMC charter.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from GCP or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of GCP which is likely to affect to a significant degree –

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

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

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

16.2. Guidelines for Good Clinical Practice

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

16.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet and other study materials will be submitted to an appropriate Research Ethics Committee (REC), and Health Regulatory Authority (HRA) for written approval.

The CI will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties. The CI will submit progress reports to the funder at the end of each calendar month and at 6 monthly intervals.

16.5. Transparency in Research

Prior to recruitment of the first participant, the trial will have been registered on a publicly accessible database; [ISRCTN17108318].

The trial team undertakes to keep trial data up to date and to make the results publicly available.

16.6. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic databases. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.7. Expenses and Benefits

Participants will not undergo any hospital visits in addition to normal care, therefore no expenses will be payable.

17. FINANCE AND INSURANCE

17.1. Funding

This study is funded by the National Institute for Health Research Health Technology Assessment (NIHR127817).

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

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17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties; a contract will be drawn up between the Department of Health and the University of Oxford. Further collaboration agreements will be completed between the University of Oxford and the University of Warwick, University Hospitals of Leicester NHS Trust, Oxford University Hospitals NHS Foundation trust and South Tees Hospitals NHS Foundation Trust.

18. PUBLICATION POLICY

We intend to publish the protocol and Statistical Analysis Plan in open access journals before the end of the recruitment and follow-up phases respectively. The study monograph will be prepared for the funder by the trial management team when the primary end point is completed (one year follow-up) and a further publication will occur upon completion of the trial. The Investigators will be involved in reviewing drafts of manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge support from OCTRU and that the study was funded by the NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. No patient identifiable information will be contained in any form of dissemination of study results.

Dissemination will be via traditional and novel methods:

- Conference: Traditional conference dissemination will focus on presentations to include the key professional stakeholders (orthopaedic surgeons, physiotherapists, occupational therapists and trainees in orthopaedic surgery).
- Publications: Key outputs will be published in high-impact journals with publicity sought in other professional journals. We will ensure that plain English summaries are published alongside the full paper, along with links to other digital media on the trial website to

explain the trial result in an accessible format. Given the frequency of the injury, this is also likely to be of interest to international press outlets.

- Policy Makers: We will ensure the development of links with key organisations such as NICE and the British Orthopaedic Society to contribute to and capitalise on their networks. Most importantly the outputs will directly contribute to the NICE non-complex fracture recommendations at their scheduled update.
- Public Dissemination: To ensure a broad campaign we will target a range of social media outlets (e.g. NDORMS twitter) with an explainer video and infographic. We will seek to engage the NHS Dissemination centre.

19. DEVELOPMENT OF A NEW PRODUCT/PROCESS OR THE GENERATION OF INTELEECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

20. ARCHIVING

Documents and electronic systems will be archived as per the appropriate SOPs as prepared by OCTRU.

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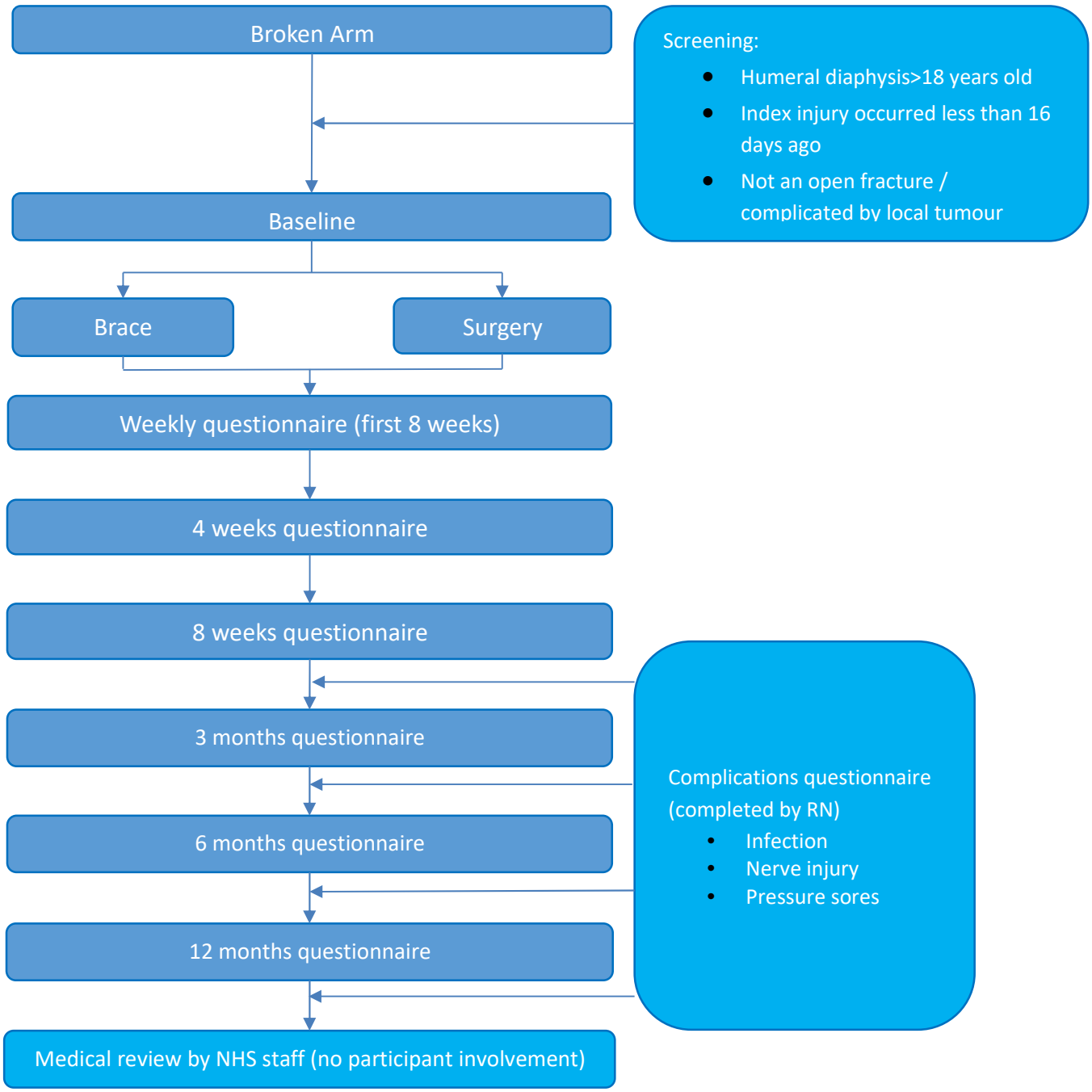
22. APPENDIX A: STUDY FLOW CHART



23. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
N/A – 1st Version	V1.0	27Apr2020		
N/A before REC approval	V2.0	01Jun2020	Marloes Franssen	• Addition of WPAI at 8 weeks • Addition of details on contacting participants in case of queries
Amendment 01	V3.0	26Aug2020	Marloes Franssen, Amrita Athwal	• Updated duration of study in line with NIHR funding (corrected initial error) • Added description of pilot phase and overview of decision points in line with NIHR request • Additional possibility of virtual recruitment • Updated 'clinic visit' section following changes due to COVID-19
Amendment 09	V4.0	26Aug2021	Kylea Draper Steve Gwilym Anita Mansouri Susan Dutton	• Removal of WPAI questionnaire from trial CRFs • Minor grammar and updating of titles • Statistical method update
Amendment 12	V5.0	09Nov2021	Marloes Franssen Steve Gwilym	• Addition of wording in

				section 9.6 to reflect policy in all hospitals