A protocol for the conduct of a multicentre, prospective, randomized superiority trial of surgical versus non-surgical interventions for humeral shaft fractures

the HUmeral SHaft (HUSH) fracture study

From 40 NHS sites across the UK

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Aims

Fractures of the humeral shaft represent 3% to 5% of all fractures. The most common treatment for isolated humeral diaphysis fractures in the UK is non-operative using functional bracing, which carries a low risk of complications, but is associated with a longer healing time and a greater risk of nonunion than surgery. There is an increasing trend to surgical treatment, which may lead to quicker functional recovery and lower rates of fracture nonunion than functional bracing. However, surgery carries inherent risk, including infection, bleeding, and nerve damage. The aim of this trial is to evaluate the clinical and cost-effectiveness of functional bracing compared to surgical fixation for the treatment of humeral shaft fractures.

Methods

The HUmeral SHaft (HUSH) fracture study is a multicentre, prospective randomized superiority trial of surgical versus non-surgical interventions for humeral shaft fractures in adult patients. Participants will be randomized to receive either functional bracing or surgery. With 334 participants, the trial will have 90% power to detect a clinically important difference for the Disabilities of the Arm, Shoulder and Hand questionnaire score, assuming 20% loss to follow-up. Secondary outcomes will include function, pain, quality of life, complications, cost-effectiveness, time off work, and ability to drive.

Discussion

The results of this trial will provide evidence regarding clinical and cost-effectiveness between surgical and non-surgical treatment of humeral shaft fractures. Ethical approval has been obtained from East of England – Cambridge Central Research Ethics Committee. Publication is anticipated to occur in 2024.

Take home message

- The HUSH trial will give clarity regarding the safety and effectiveness of the two principle options for treating humeral shaft fractures (surgical fixation or cast/splint) and give unique insights into the trajectory of recovery after treatment.

Bone & Joint Open

Introduction

Fractures of the humeral shaft represent 3% to 5% of all fractures. They occur in a bimodal distribution, typically affecting younger males and older females.[1] Treatment goals are directed towards pain relief, the early restoration of function, and minimization of associated disability. It is recognized that providing stability at the fracture site, and hence 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 nonoperative, 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, which prevents the fractures from moving during activities of daily living, and this in turn reduces pain.

Functional bracing carries a low risk of medical complications. It does, however, require a prolonged period of immobilization in a brace, which is often painful in the early stages of healing. Importantly, functional bracing also has a recognized rate of nonunion (failure of the bone to heal) of approximately 20%.[2] Nonunion 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. It is claimed that surgical intervention may lead to quicker functional recovery and lower rates of fracture nonunion than functional bracing.[3] 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.[4]

There is both an increasing incidence as the population ages, and an increasing trend towards surgical fixation of humeral shaft fractures.[5,6] 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,[7] and systematic reviews.[8,9] 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 lack of information on cost-effectiveness for these two treatment strategies. Functional bracing initially appears to be the less expensive treatment option, with a relatively low immediate treatment cost (estimated at £1,100 per patient).[10] However, functional bracing does have a recognized nonunion rate of approximately 20%.[2] If a nonunion occurs, secondary surgical intervention is indicated, with a prolonged treatment period and costs estimated at £15.5 k per case, considering direct medical costs only.[11]

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 nonunion,[3] therefore requiring less additional surgery.

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.

The subject of identifying the optimal management for humeral shaft fractures is also under investigation by other research groups, with various study designs.[12] The FISH study found no difference in functionality at 12 months between surgery and functional bracing;[13] however, a power calculation based on currently available figures suggest a larger sample is required to ensure the study is sufficiently powered to change clinical practice in the UK.

Aims

The primary objective of the HUmeral SHaft (HUSH) trial is to compare function using the Disabilities of the Arm, Shoulder, and Hand (DASH)[14] patient-reported outcome measure (PROM) between functional bracing and surgical fixation at 12 months.

Secondary objectives are to: 1) quantify and draw inferences on observed differences in patient-reported outcomes between the trial treatment groups in the first 12 months; 2) 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) investigate the risk of complications between the trial treatment groups in the first 12 months; 4) investigate the resource use, costs, and comparative cost-effectiveness between the trial treatment groups at 12 months; and 5) record and compare the duration of time off work, for participants of working age, between the intervention groups.

Methods

Study design

This trial is a pragmatic, multicentre, two-arm, parallel group, randomized controlled superiority clinical trial with parallel economic analysis. Potentially eligible patients will be identified after referral to orthopaedic services from local emergency departments (EDs), minor injury units, or primary care, and highlighted to the research team at the daily trauma meeting or fracture clinics. After radiological confirmation of a fracture the local clinical team will confirm the eligibility of the individual patient to participate.

Inclusion criteria

Patients are included if they are aged 18 years and older with a fracture of the humeral shaft (diaphysis, defined as the section of bone outside one Muller-square of the proximal and distal ends of the humerus),[15] which the surgeon believes may benefit from surgical fixation, and who is willing to consent.

Exclusion criteria

Patients are excluded if: the fracture is open; the fracture is complicated by local tumour deposits; they have bilateral fractures; the index injury occurred more than 16 days prior to recruitment; they are unable to adhere to trial procedures (e.g. dementia or insufficient knowledge of the English language);

or they have other upper limb injuries which may reasonably be expected to affect responses to PROMs.

Consent

A member of the local research team will consent the participant into the trial.

Randomization

Once informed consent has been given, the participant will be randomized by the local research team using a web-based service. The randomization will be on a 1:1 basis, using a validated computer randomization programme managed through a secure (encrypted) web-based service by the Oxford Clinical Trials Research Unit (OCTRU), with a minimization algorithm to ensure balanced allocation across the treatment groups, stratified by centre, age (< 50 years vs ≥ 50 years), and nerve injury at presentation (Yes/No). The minimization algorithm will include a probabilistic element and a small number of participants randomized by simple randomization at the start of the trial to seed the algorithm in order to ensure the unpredictability of treatment allocation.[16]

Blinding

Due to the nature of the trial, neither the treating team nor the participants will be blinded.

Interventions

Non-surgical

The use of cast, splints, and slings are collectively described as 'functional bracing', which is the term we will use throughout this paper. Following a diagnosis of a fracture of the humerus, a temporary cast is normally applied in the ED to relieve pain and allow for swelling. After one to two weeks, when the swelling has settled, this temporary cast is removed and a thermoplastic humeral brace is applied. The humeral brace is worn until there is evidence of fracture union. Overall, this process takes approximately eight to ten weeks, after which the patient may remove the humeral brace. 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.

Surgical

General or regional anaesthesia will be used for surgery, as per routine practice in each hospital, along with routine perioperative care including prophylactic antibiotics. The surgical fixation can be performed by using one of two routinely used methods: plates and screws, or humeral nails.

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.

All concomitant care is permitted throughout the duration of the trial. All care throughout and after the trial is at the discretion of the treating care team; we will provide standardized written rehabilitation sheets to all patients in the trial.

Criteria for discontinuing or modifying allocated interventions

All participants are followed up by their local treating team, who decide on discontinuing or modifying the allocated intervention at their discretion.

Strategies to improve adherence to interventions

At each follow-up, participants will receive a text, email, or phone call (according to preference) and an additional reminder to complete the follow-up questionnaires.

Primary outcome

The primary outcome for this study is the DASH PROM, which is a 30-item, self-reported questionnaire designed to measure physical function and symptoms in patients with musculoskeletal disorders of the upper limb. The scores range from 0 (no disability) to 100 (most severe disability).[14,17]

Secondary outcomes

Pain: To assess pain recovery in the immediate post-injury period (up to week eight), a visual analogue scale (VAS) on a scale of 0 (no pain) to 100 (worst pain imaginable) will be used.[18]

DASH sports/performing arts module: An additional sub-section of the DASH questionnaire is used to investigate the effect of upper limb injury on a patient's participation in sports or playing instrument with scores ranging from 0 (not disabled) to 100 (most severe disability).[19]

PROMIS: The Patient-Reported Outcome Measurement Information System (PROMIS) questionnaires are computer-adaptive tests completed by the patient. The instrument covers a variety of domains and are scored from 0 to 100, with 50 points representing the mean score for the USA general population and higher scores indicating better function.[20,21] HUSH will utilize the Physical Function, which focuses on function and disability, and Pain-Interference PROMIS questionnaire, which investigates intensity and impact.

Quality of life: The EuroQol five-dimension five-level questionnaire (EQ-5D-5L) will be used to measure quality of life. It comprises a VAS measuring self-rated health on a scale from 0 (worst imaginable health) to 100 (best imaginable health), and a health instrument consisting of a five-level response, ranging from 'no problems' to 'unable' on five domains related to daily activities.[22]

Resource use: Patient- and hospital-reported resource use will be recorded. Return to work and driving will be recorded by weekly text or 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, nonunion, shoulder stiffness, elbow stiffness), and problems identified during the patient and public involvement process by those having undergone functional bracing (pressure sores, elbow stiffness).

Table I displays at what timepoints the outcome measures are administered.

Adverse events

Safety reporting for each participant will begin from randomization and will end when the participant has reached their follow-up timepoint, at 12 months post-randomization. Both

Table I. Data collection timepoints.

Variable	Baseline (pre-injury)	Baseline	Weekly (up to 8 weeks)	4 weeks	8 weeks	3 months	6 months	12 months
DASH	X				X	X	X	X
VAS		X	X					
DASH sports/performing arts	X				X	X	X	X
PROMIS Upper Extremity		X		X	X	X	X	X
PROMIS Pain Interference		X		X	X	X	X	X
EQ-5D-5L	X	X			X	X	X	X
Return to work			X					
Return to driving			X					
Resource use					X	X	X	X
Complications					X	X	X	X

DASH, Disabilities of the Arm, Shoulder, and Hand questionnaire; EQ-5D-5L, EuroQol five-dimension five-level questionnaire; PROMIS, Patient-Reported Outcome Measurement Information System; VAS, visual analogue scale.

interventions are currently being used in the NHS. In light of this, we do not anticipate many unexpected serious adverse events (SAEs) associated with either treatments.

Foreseeable SAEs will be recorded in the 'complication' section of the case report form and/or patient questionnaires. When the local research team becomes aware of an unexpected SAE in a trial participant, the principal investigator (PI) will review the SAE locally and make a decision about the relatedness of the event to the intervention. Any SAEs that are considered to be unexpected and potentially related to the intervention will be reported to the central trial team within 24 hours of the PI becoming aware of the event. Once received, causality and expectedness will be confirmed by the chief investigator or delegate (nominated person). SAEs that are deemed to be unexpected and related to the trial will be reported to the research ethics committee within 15 days. All such events will also be reported to the trial steering committee (TSC) and data and safety monitoring committee (DSMC) at their next meetings.

Statistical analysis

Power and sample size

At 90% power and 5% (two-sided) significance, the proposed sample size needed is 266 participants (133 per treatment arm) providing data at 12 months in order to detect a standardized 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 target (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.[23–25] 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 halfway through recruitment to the study to ensure that this sample size would be able to provide a definitive answer to the research questions.

The trial will employ 1:1 treatment allocation, stratified by centre, age, and nerve injury, with patients randomized to either functional bracing or surgical fixation, based on the surgeons' usual surgical practice.

Screening and subsequent recruitment for the main phase will occur at a minimum of 16 NHS hospitals. 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.

All available data from both treatment arms will be used in data analysis based on the as-randomized population. Reporting of the results will be in accordance with the CONSORT statement,[26] using the extensions for non-pharmacological treatment interventions and PROMs. 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.

DASH score 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 previous timepoints. The longitudinal part of the model will consider interaction of treatment with time and adjust for stratification factors (recruitment centre, age, and nerve injury at presentation). Random effects will be included to account for within-individual participant variability and 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 and concomitant injuries that affect limb function), in addition to those specified above. Sensitivity analyses using the per-protocol population will be undertaken. If a substantial amount of non-compliance is observed or if the non-compliance is selective, then a complier average causal effect (CACE) will be undertaken as secondary analyses.[27]

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

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 National Institute for Health and Care Excellence (NICE) reference case.[28]

Use of hospital and community contacts, made in connection with their surgery, will be recorded in the first 12 months (questionnaires at three, six, and 12 months). Healthcare resource use will be costed using most recently available published national reference costs, reflated to the most recent year.[29] Generic health-related quality-of-life will be assessed at baseline, eight weeks, and three, six, and 12 months using the EQ-5D-5L questionnaire.[30] 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.[31] Patient-level quality-adjusted life year (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 minimize bias in the QALY calculation,[32] and to adjust subsequent analyses.[33]

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.[34–36] Findings will be analyzed and visualized 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 generalizability 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.

Data management

Personal data collected during the study will be handled and stored in accordance with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which requires data to be anonymized as soon as it is practical to do so. Data management will be performed in accordance with OCTRU standard operating procedures. Data are being entered directly into the REDCap electronic data capture tools hosted at the University of Oxford. Study-specific procedures will be outlined in a data management plan to ensure that high-quality data are produced for statistical analysis.

Potential risks

As both treatments are currently standard treatments used in the NHS, it is anticipated that the potential risks of this study are low and similar to those attributable to usual care.

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Data sharing

All data generated or analyzed during this study are included in the published article. However, as this a a protocol, it does not contain data or results.

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