Surgical Versus Non-Surgical Treatment of Humeral Shaft Fractures Compared By a Patient Reported Outcome: The Scandinavian Humeral Diaphyseal Fracture Trial (SHAFT) - A Study Protocol For a Pragmatic Randomized Clinical Trial

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Abstract

Background: The outcome of non-surgical treatment is generally good, but the treatment course can be long and painful with approximately a quarter of the patients acquiring a nonunion. Both surgical and non-surgical treatment can have disabling consequences such as nerve injury, infection and nonunion. The purpose of the study is to compare patient reported outcome after surgical and non-surgical treatment for humeral shaft fractures.

Methods: A pragmatic randomized controlled trial is planned with two study groups (SHAFT-Y and SHAFT-E). A total of 287 eligible acute humeral shaft fractures are scheduled to be recruited and randomly allocated to surgical or non-surgical treatment with the option of early crossover due to delayed union. The surgical method within the allocation is decided by the surgeon. The primary outcome is the Disability of Arm, Shoulder and Hand (DASH) score at 52 weeks, and is assessor blinded. The secondary outcomes are DASH score, EQ-5D-5L, pain assessed by visual analogue score, Constant-Murley score including elbow range of motion and anchor-questions collected at all timepoints throughout the trial. All complications will be reported including; infection, nerve or vascular injury, surgical revisions (implant malpositioning, hardware failure, aseptic loosening and peri-implant fracture), major adverse cardiovascular events, and mortality. Patients declining randomization will be asked to enroll into an observational cohort with same outcomes and post-treatment regimes.

Discussion: SHAFT will provide information on the effectiveness of two standard treatments for humeral shaft fractures, while taking the dilemmas within the population into account.

Trial registration: Clinicaltrials.gov, NCT04574336. Registered on 5 October 2020.

Background And Rationale

The incidence of humeral shaft fracture is between 13.5–20 per 100.000 annually(1,2). It is projected that the incidence of humeral shaft fractures will increase due to changing demographics(1). The fracture demography follows a typical bimodal pattern with young adults injured in sports, vehicular road-traffic accidents and other high energy traumas and the elderly injured with simple falls, respectively[2]. Considering this demographic difference, the importance of age in terms of patient expectations, upper limb function and patient-reported outcome measures (PROM) in humeral shaft fracture treatment is not well understood.

One of the main challenges with humeral shaft fractures is the choice between surgical and non-surgical treatment(3). Primary surgical treatment provides consistent high union rates, but patients are exposed to the risk of complications such as infection, iatrogenic radial nerve lesion and rotator cuff injury as well as shoulder impingement(4,5). In contrast, union rates from non-surgical treatment can vary from 75–100% (6–10). If nonunion occurs, it is not uncommon for patients to go through a prolonged treatment course up to 8 months before an additional procedure is offered(10,11). Although delayed surgical fixation leads to high union rates(12), the PROMs are inferior compared to primary fixation(11,13). These observations

may suggest that the prolonged course for patients with union problems is unfavorable. However, the challenge is to identify the patients that will benefit from early fixation. A way of determining early onset of union problems in a young cohort is by gently testing the fracture site at 6 weeks(14) and later for the elderly(15).

To our knowledge, three randomized controlled trials (RCT) have been completed and all trials compared plate osteosynthesis to non-surgical treatment without distinction of age(11,16,17). Four RCTs(18–21) are registered in clinicaltrials.gov, WHO and ISRCTN registry. Two RCTs are comparing plate osteosynthesis to non-surgical treatment and the last two RCTs are comparing plate and nails to non-surgical treatment. Adults of all ages are included, except in one RCT(20) that has an upper age limit at 65 years. Furthermore, in one already finished trial, the trial design had to be adjusted from an RCT to a prospective non-randomized comparative trial due to treatment allocation problems as there was a strong physician preference towards the surgical treatment option(22). A Cochrane review could not demonstrate any difference in union rate between different surgical procedures (intramedullary nail and plate osteosynthesis)(23).

This emphasizes the need for a pragmatic approach of interventions by including usual care of surgical treatment, considering the influence of age as well as accepting early secondary surgery as a part of treatment to improve disability and function after 12 months.

The SHAFT protocol conform with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)(24,25).

Methods: Participants, Interventions And Outcomes

Objectives

To compare surgical fixation of humeral shaft fracture to non-surgical treatment with early identification and treatment of delayed union by a patient-reported outcome after 52 weeks.

The trial population is divided in two groups by age due to the bimodal age distribution with more elderly than young and the treatment courses are different in terms of early crossover:

1. SHAFT-Y for the young with an age cut-off of 18 to 64 years. The early identification and treatment of delayed union is set to 6 to 12 weeks

2. SHAFT-E for the elder with an age cut-off + 65 years. The early identification and treatment of delayed union is set to 12 to 26 weeks

Trial design

A pragmatic multicenter, randomized, controlled, outcome assessor-blinded, clinical superiority trials. We have assessed the pragmatic design using PRECIS-2(26) which yielded 40 points out of possible 45

points (Fig. 1). This study furthermore collaborates with the NORCRIN Work Package 13 network.

Study setting

Sites from Denmark, Sweden and Norway have been recruited and spans from academic level I to level III trauma centers. The following is the current list of recruiting hospitals: Kolding Hospital; Hvidovre University Hospital of Copenhagen; Zealand University Hospital; Slagelse Hospital; Holbæk Hospital; New North Zealand University Hospital of Copenhagen, Odense University Hospital; Hospital of Southern Denmark; Aalborg University Hospital; Aarhus University Hospital; Herlev-Gentofte University Hospital of Copenhagen, Oslo University Hospital; Stavanger University Hospital; Østfold Hospital Trust; Sahlgrenska University Hospital; Uppsala University Hospital; Umeå University Hospital; Stockholm South General Hospital

Material

287 patients (n = 163 for SHAFT-Y, n = 124 for SHAFT-E) with a humeral shaft fracture will be equally randomized to surgical treatment or non-surgical treatment in each group. The overall trial flow and timeline of data collection is outlined in Fig. 2 + 3.

Inclusion criteria

1. Fracture types 12A-C (OTA/AO classification)

a. Includes extra-articular fractures with extensions to the distal- and/or proximal ends of the humerus
2. Treatment within 14 days from trauma
3. Age 18–64 years for SHAFT-Y and ≥ 65 years for SHAFT-E

4. Patients must understand the information given and be able to read and speak Danish, Swedish or Norwegian to complete the study paperwork

Exclusion criteria

1. Inability to give informed consent

2. Undisplaced shaft fracture (less than a cortex-wide displacement in all radiographic plane)

3. Displaced fractures of the proximal and distal humerus (more than a 1 cm or 45 degree angulation(27))

4. Vascular injury in ipsilateral arm

5. Polytrauma (defined as a trauma with one or more absolute indications for surgical intervention)

6. Pathological fracture

7. Open fracture

8. Floating elbow fractures

9. BMI > 40

10. Health conditions preventing either treatment

Primary radial nervepalsy (RNP) is not an exclusion criterion as there has not been shown benefits in recovery time with early exploration(28).

Recruitment

Patients admitted to the emergency department (ED) in any of the trial sites will be clinically examined and plain radiographs will be obtained to confirm the diagnosis. If the patient fulfills the eligibility criteria's, they will be informed of the trial by staff and receive written information with patient participation information and "Researchers rights in a health science research project". They will be given time to consider and will be scheduled for an appointment with research staff within 10 days. If written consent is obtained at the consultation, randomization will occur immediately after. If patients do not wish to participate in the RCT, they will be asked to consider enrollment in an observational cohort.

The informed consent gives the investigators permission to obtain information from the patients' health records including; age, sex, height, weight, arm dominance, American Society of Anesthesiologists grade (ASA classification), UCLA activity score(29), list of current diagnosis and medication, mechanism of injury, radiographic images, previous surgery to the arm, tobacco (cigarettes, smokeless tobacco) and alcohol habits, employment and educational status. Patients will be provided with transport allowance to cover the costs for consultations at 26 weeks and 52 weeks. They further accept telephone calls if they miss follow-up visits to promote participant retention and complete follow-up.

Interim analyses

We will carry out two interim analyses after trial completion of 25% and 50% of the planned number of included patients, separately for the two age groups. We will use the O'Brian-Fleming rule(30) for determining appropriate significance levels for each analysis, which results in a significance level of 0.0006 for the first interim analysis, 0.0151 for the second interim analysis and 0.0471 for the final analysis. Interim analyses will be carried out for both the primary endpoint (DASH) and for serious complications (iatrogenic nerve injury, deep infection, major adverse cardiac events (MACE) and death) and will be conducted by one-sided tests to determine if the improvement in DASH is significantly above 25 points, respectively if the complication rate is at least 20% higher.

A Data Monitoring Committee (DMC) has been organized to monitor and evaluate the data from the interim analyses. The DMC consist of seven members in total; three members of the steering committee

and four independent members including the Patient Representative (PR), an orthopedic researcher, an orthopedic surgeon and a nurse.

In the event of one group having zero complications, the significance level cannot be computed by a Chi-square test, and the DMC will have to assess the data due to a statistical variation.

In the event of a patient sustaining several complications, the most severe complication will follow the patient. The complications are ranked in a hierarchy model describing the severity and is ranked from most severe to least severe: Death, MACE, deep infection with debridement, iatrogenic nerve injury.

The interim analyses will be conducted by a biostatistician, blinded to the treatment allocation. Data will then be presented to the DMC, in means and proportions and be accompanied with confidence intervals. The DMC will have access to the data unblinded, and if at least one of those two conditions are fulfilled or a statistical variation has occurred at an interim analysis the DMC will be asked to investigate the results in detail and present their recommendation to continue or stop the trial. In the event of disagreement, the steering committee will be involved in discussing the stopping of the trial.

Furthermore, the steering committee will be monitoring recruitment and drop-out. Any modification in design and recruitment will be registered in clinicaltrials.gov.

If it is observed that inclusion of patients in the two age groups is too slow, it can be decided to pool the age groups and analyze them as one total group instead. If this decision is made before the first interim analysis, above significance levels will be used for the total group. If the decision is made between the first and second interim analysis, O'Brian-Fleming significance levels for four analyses will be used, resulting in a significance level of 0.0184 for the second interim analysis and 0.0412 for the final analysis. If the decision is made after the second interim analysis, a significance level of 0.0417, corresponding to O'Brian-Fleming with five analyses, will be used for the final analysis.

Patient and public involvement

Patients were involved in the planning and development of the study protocol. A series of in-depth semi-structured interviews were conducted with the qualitative purpose of exploring the experiences acquired during the treatment course of a humeral shaft fracture. Beyond the qualitative study aim, a discussion of the most meaningful primary outcome measures was undertaken. All patients completed two questionnaires (DASH and QuickDASH) to solicit their feedback and to determine which PROM they found most appropriate when considering relevance, comprehensibility, comprehensiveness and length. The interviews further revealed complaints that were discussed with the patients and were subsequently priorities to be implemented as outcome measures of the trial.

One of the patients from the interviews accepted to be involved in the trial as the patient representative (PR). The PR is included in the steering committee and in the data monitoring committee (DMC). The study protocol was discussed with the PR in layman terms to facilitate a common understanding of the trial and to solicit feedback that could minimize patient burden and risk of missing data, as well as

providing insights from a patient perspective to optimize the communication between physicians and patients during the trial course and by written information. The feedback resulted in minor revisions of words in the patient information sheet to conform with patient concerns.

Interventions

Treatment will be performed within 14 days after injury. Eligible patients will be randomly allocated to one of two treatment options.

- Surgical treatment
- Non-surgical treatment with the option of early crossover surgery at 6–12 weeks(14) for SHAFT-Y and at 12–26 weeks for SHAFT-E

We anticipate that surgical treatment will include plate osteosynthesis (MIPO and ORIF), intramedullary nailing (antegrade and retrograde) and external fixation. Plate and nail types, screw configurations and surgical approaches will be decided by the surgeons. The procedure will be conducted or supervised by a senior consultant.

Non-surgical treatment will include sugar tong splint, plaster splints, hanging casts, or functional bracing such as the Sarmiento brace, and will be worn until a surgeon removes it.

All patients will be advised to follow this rehabilitation protocol.

Criterias for early crossover

Patients can be offered to undergo early crossover fixation with a surgical procedure of the surgeon's choice, if one of these criteria are met:

- Unacceptable pain experienced by the patient
- Severe pain with gross instability of the fracture site assessed by:
    - Unable to *en bloc* elevate the arm due to clear fracture instability
    - Gentle manipulation of the fracture site. Gentle manipulation should respect the risk of callus breakage
- Severe problems tolerating the brace, e.g. discomfort, skin irritation, wounds, hygiene problems.

The patients that undergo early crossover surgery will have the reason for crossover thoroughly noted. We anticipate the surgical procedures will be similar to the ones previously mentioned with the possible addition of bone graft.

Randomization

A computerized database software, Research Electronic Data Capture (REDCap)©(31) will be used to generate an irreversible random allocation sequence and perform block randomization with selected block sized of 2 and 4, which will be stratified on site and age (18–64 and + 65). Patients will be assigned to the trial with an allocation of 1:1 to either surgical treatment or non-surgical treatment. The trial worker acquires the allocated treatment from the central coordinator with randomization rights to REDCap. The trial worker then initiates the treatment, either by scheduling the surgery date or applying the chosen non-surgical method.

Protocol violation

- Lost to follow-up
- Treatment crossover outside the pre-defined interval for early crossover surgery

Patients that meet any of these criteria will remain in the study and be included in the intention-to-treat analysis but omitted from a per-protocol analysis.

Participant withdrawal

If the patient withdraws the consent, patients will be included in the statistical analysis through multiple imputation, if baseline data is obtained, otherwise imputation is not possible, and the patient will be replaced to meet the calculated sample size.

Blinding

The trial will consist of several levels of blinding:

- The primary outcome will be blinded to everyone involved in the trial, apart from the patients and a central trial worker (non-physician), who will only review the questionnaire for completion in REDCap
- The statistical analysis will be conducted by a blinded biostatistician

Primary outcome measure

The primary outcome is the Disability of Arm, Shoulder and Hand (DASH) score at 52 weeks(32). The DASH score is a 30-item self-reporting patient-reported outcome measure specific for physical function and symptoms of the upper limb. Scores range from 0 (no disability) to 100 (most severe disability). The DASH score is validated for the target population(33) and has undergone cross-cultural adaptation in Danish, Swedish and Norwegian(34).

Secondary outcome measures

Secondary outcomes consist of a self-reported measure of health-related quality of life (EQ-5D-5L), complication rates, visual analogue scale (VAS) for pain from the arm, a functional outcome score (Constant Murley) and anchor-questions including clinical anchors, retrospective global transition

questions and a binary repeat treatment question. Secondary outcome measures will be assessed at baseline, 3 weeks, 6 weeks, 12 weeks, 26 weeks, 52 weeks, 2 years and 5 years of the trial, Fig. 3:

- DASH score at 26 weeks (MIC(35), 7 and 10 respectively to age 18–64 and 65+)
- General health status questionnaire measured by EQ-5D-5L(36) (MIC(37), 0.074)
- Complications after treatment will be recorded and include local complications, early general complication and mortality:
    - Local complications: Infection (needing antibiotic treatment with or without debridement), nerve or vascular injury, surgical revision (due to implant malpositioning, hardware failure, aseptic loosening or peri-implant fracture) and tolerance problems with brace (discomfort resulting in non-compliance of wearing the brace
    - Early general complications needing hospitalization within 12 weeks(38,39):
    - Major adverse cardiac events (MACE) including myocardial infarction, heart failure, thromboembolism, cardiomyopathy and cardiac arrythmias.
    - Other major adverse events including pneumonia, renal failure, electrolyte abnormality and deficiency anemia and other unforeseen reasons for hospitalization.
    - Mortality
- Pain is assessed by using the visual analog scale (VAS) score. Patients are asked to assess their overall pain from the arm from 0-100 in a day (MIC(40), 16.55mm)
- Constant-Murley score(41) (MIC(35), 6.1). The subscales of strength and ROM will be depicted. ROM (flexion-extension) of the elbow will be recorded
- Clinical anchor (CA) questions presented with 5 response options (RO) and analyzed as a 5-point Likert scale:

Q: In general, would you say your health is?

RO: Excellent, Very good, Good, Fair, Poor

Q: How would you describe the results of the (operation / non-surgical treatment)?

RO: Excellent, Very good, Good, Fair, Poor

Q: How would you describe the function of your upper arm?

RO: Excellent, Very good, Good, Fair, Poor

Q: How would you describe the pain from your upper arm?

RO: None, Mild, Moderate, Severe, Extreme

- Retrospective Global transition questions (RGTQ) presented with 5 response option and analyzed as a 5-point Likert scale:

Q: Overall, how would you describe your general health now, compared to after the (operation / non-surgical treatment)?

RO: Much worse, A little Worse, About the same, A little better, Much better

Q: Overall, how would you describe your upper arm now, compared to after the (operation / non-surgical treatment)?

RO: Much worse, A little Worse, About the same, A little better, Much better

Q: How would you describe the change in physical function in your upper arm since after the (operation/ non-surgical treatment)?

RO: Much worse, A little Worse, About the same, A little better, Much better

Q: How would you describe the change in pain from your upper arm since after the (operation/ non-surgical treatment)?

RO: Much worse, A little Worse, About the same, A little better, Much better

- Binary Repeat treatment (BRT) presented as a question with a binary response option:

Q: With the knowledge and experience you have gained of the treatment; would you then choose the same treatment again for a similar fracture?

RO: Yes, No

The DASH, EQ-5D-5L and CA questions will be sent by email or mail and patients are asked to complete the questionnaires before visits. The questionnaires will be reviewed for missing data by a trial worker and patients will be assisted with completing the questionnaires if any data is missing, without interference from the medical staff. The trial worker collects the questionnaires before consultation with the physician. The physician then collects the additional outcome measures at the consultation and enters data directly into REDCap.

Explorative outcome measures

- DASH score at all time points (pre-injury, 6 weeks, 12 weeks, 104 weeks, 260 weeks)
- Fracture type measured by the AO-classification and the location of the fracture
- Surgical procedure recorded as treatment modalities and subdivided in procedures and device/implant use

- Radiological variables measured as degree of displacement, angulation, comminution, callus formation and visibility of fracture line
- Gross instability of the fracture site is assessed by a physician through gentle manipulation. This is first tested at 6 weeks follow-up for SHAFT-Y and 12 weeks for SHAFT-E
- Return to work will be assessed by direct questioning at clinical visits. Five answers will be available: Unemployed, not returned, partially returned, fully returned and retired. If patients are still on sick leave they have 'not returned'. If they are back at work but not in full capacity as prior to the fracture, they are 'partially returned'; if they have returned as prior to the fracture they are 'fully returned'; and if the patients are a pensioner, they are "retired"
- Mechanism of injury measured as low-energy fractures e.g. fall from own height and high-energy fractures e.g. fall from heights, sports, motor vehicle accidents and other miscellaneous accidents
- Nonunion is defined as gross mobility at the fracture site after 12 weeks for SHAFT-Y and 26 weeks for SHAFT-E. Pain from the fracture site will also be noted to determine if the nonunion is symptomatic or asymptomatic. Radiological assessment of type of nonunion will also be assessed
- QALY-based cost analysis
- Successful primary treatment vs early crossover surgery
- Length of rehabilitation
- Level of activity by the UCLA activity score(42)

Other outcome measures

Any ancillary outcome measure or analysis will be reported.

Statistical analysis plan

Hypothesis

The null-hypothesis is:

- The DASH score at 52 weeks after surgical treatment is not superior to non-surgical treatment with the option of early crossover surgery in patients with humeral shaft fractures

Sample size

The two groups (SHAFT-Y and SHAFT-E) require individual sample size calculations due to our presumption that these groups cannot be compared in DASH scores. Based on the following assumptions, the total sample size is estimated to 163 patients for SHAFT-Y and 124 patients for SHAFT-E. The calculations are powered to detect a minimal important change (MIC) of 7 points in the young and 10 points in the elderly group in DASH, respectively. The MIC is determined on a population with the average age of 59 years(35). Our SHAFT-E will have a considerably higher average age; thus we assume a higher MIC is needed for this group. Two standard deviations were obtained from the data of the FISH

trial(11) and were separated in age groups of 18–64 years and 65 years and above. The standard deviations 14.91 and 18.59, respectively. We used an α-level of 0.05, a power of 0.80 and the allowance of attrition is set to 15%.

Patients will be included consecutively to an observational group until the sample size for the RCT is completed. The trial management committee can decide to pool data from both RCTs (SHAFT-Y, SHAFT-E) if recruitment is prolonged.

Statistical methods

The data will be analyzed using computerized statistical software and all data will be entered into REDCap.

Primary analysis

Descriptive statistics will be used to report demographic data. Demographic data and outcome measures will be tested visually and statistically (i.e. Shapiro Wilks test). Numeric variables will be summarized by means, standard deviations and 95% confidence intervals (95% CI). Median and interquartile ranges will be used when normal distribution is not met. Categorical variables will be summarized by frequency and proportion. For group comparison with numerical data, a student's t-test will be used if data is normally distributed, otherwise a non-parametric test will be used. For categorical data a Chi-square test will be used for group comparison. An intention-to-treat (ITT) analysis of the primary outcome will be conducted by univariable linear regression, including all patients that do not meet the withdrawal criteria and will be conducted to minimize bias within results. A sensitivity analysis will test the effects of non-adherence to protocol by conducting a per-protocol analysis and includes only patients who comply with the protocol. For missing data points in an outcome measure, a multiple imputation analysis using predictive covariates (sex, smoking, alcohol, UCLA activity, ASA score)(43–45) will be conducted to deal with nonresponse bias. For comparison we will carry out a sensitivity analysis excluding all the missing values.

Data will be considered statistically significant if p-values < 0.0471.

Secondary analysis

In order to re-ensure the validity of data a linear regression analysis will be computed with DASH score as the dependent variable and treatment modality as the independent variable. Additional regression analysis will be carried out between the early crossover group and the primary treatments. A multivariate regression analysis will be conducted to adjust for potential confounders. Variables adjusted for are: sex, smoking, alcohol, UCLA activity, ASA score. Data will be summarized as coefficients with 95% CIs and variance will be summarized as r-squares, adjusted r-squares, predicted r-squares, standard errors. Coefficients will be considered statistically significant if p-values < 0.05.

Observational cohort

An observational cohort will be established and followed simultaneously with the RCT. Choice of treatment will be based on local decisions. Outcome measures, data collection and statistical plan will be similar. Follow-up can vary depending on each case, but all patients will be invited to follow the same timeline as the RCT.

The observational cohort will be subdivided into two groups of populations when statistical analysis will be conducted.

1) Patients who fulfil all eligibility criteria but decline randomization

2) Patients who fulfill all inclusion criteria but presents one or more exclusion criteria

Discussion

High level evidence on treatment of humeral shaft fracture treatment is sparse, but several RCT's are planned or ongoing(18–21). The current discussion on surgical treatment versus non-surgical treatment have been ongoing for more than a decade(3). The discussion has been intensified with recent RCTs showing surprisingly high nonunion rates in the non-surgical groups(11,46). The orthopedic research community has demanded the need of more high quality trials(47,48). Thus it is our aim that SHAFT will contribute to the increasing quality of evidence published for the decision-making of treatment of humeral shaft fractures by conducting a pragmatic, two-arm, multicenter, superiority, randomized controlled trial.

The trial is planned pragmatic by introducing real-life treatment courses, to comply with the trial objective of comparing the effectiveness of treatments and furthermore increase external validity.

The distribution of the study population is bimodal, but with a steep increase in incidences from the fifth decade(2,49). Our study group were humble recipients of demographic data from the FISH trial(11), which paradoxically, showed a clear difference in the number of recruited patients in the age-groups of 18–64 years versus + 65 years, favoring the "young" group. To protect the trial against imbalance, age is defined as a stratified variable to ensure equal distribution of age (18–64 and + 65) in the treatment groups. Furthermore, normative data from the general population suggests inferior DASH scores with increasing age and suggests that DASH scores of age-groups should not be compared(50,51). We further expect that the younger population can discriminate a smaller change in DASH than the elderly. The available data on MIC of DASH scores for humeral shaft fractures do not differentiate in age(35). Consequently, we have chosen to use two MICs, thereby having to recruit 163 young adults (SHAFT-Y) and 124 elderly (SHAFT-E) and to analyze data independently for each group.

Recruitment of 287 humeral shaft fractures present a challenge in a randomized setting as the annual incidence rate is 14.5 per 100.000(49). To overcome this, we will be recruiting from multiple sites across 3 Scandinavian countries with comparable health-care systems and with cultural and demographic similarities. Despite these overall similarities, surgical management can differ from site to site. To prevent

against bias in the surgical group, the randomization will be stratified by study site. One drawback of this type of stratification can be the risk of open blocks in multiple sites, which can give rise to allocation bias. To limit this the randomization will be conducted in small permuted blocks.

One RCT demonstrated a statistical significant difference in a subgroup analysis between late surgical crossover and primary surgical treatment after 12 months, favoring early surgery, with respect to possible confounding(11). The research group has furthermore in a recent study showed same difference between late surgical crossover and primary successful treatment after 2 years(13). To avoid prolonged failed treatment courses, and to minimize overall nonunion rates, the trial has implemented an option of early crossover of non-surgical treatment, if certain criteria for delayed union are met. The criteria for early crossover surgery are identical for each age-group but differ regarding the time of crossover. The term "early crossover" and "delayed union" were discussed intensively by the study group. "*When has the treatment failed?"* Crossover to surgical treatment after non-surgical treatment is not uncommonly performed within 12 weeks for the young and described due to lack of healing and early non-surgical failure(52,53). One can argue that a portion of these patients will unite without intervention(54), but multiple studies have currently shown association between gross mobility from the fracture site to nonunion in a young population after 6 weeks(14,43,54). For the elderly, our clinical experience is that healing first can be anticipated after 12 weeks. We therefore defined delayed union in SHAFT-Y between 6 and 12 weeks and SHAFT-E between 12 and 26 weeks. Furthermore endpoints were established to create a clear timepoint of when a treatment has failed, which we believe the orthopedic society needs, since there is no consensus in nonunion for humeral shaft fractures(7,10,12,55).

The DASH questionnaire is adopted by the study group as primary outcome as it is the best psychometrically validated and cross-culturally adapted PROM for humeral shaft fractures(35,56). The full DASH questionnaire is preferred over the Quick-DASH by patients through simple semi-structured interviews. The interviews were simple in a sense that the objective was to determine the "most preferred" questionnaire rather than asses the content validity of each questionnaires(57). The moderator was instructed in the conduct of qualitative interviews by an expert in qualitative research, but not proper trained. This could give challenges with bias, if the moderator preferred one questionnaire. This was sought to be reduced by the semi-structured guide, which was intended to make patients reflect, firstly on their treatment course and secondly on the questionnaires and its relevance, comprehensibility and comprehensiveness, to induce a thought-through answer to the question: *"Which questionnaire do you prefer?"*.

Through the interviews, it was furthermore recognized that around half of the patients failed to complete one or more questions, but none more than three, which is the cut-off for the score-calculation to be valid(32). To provide a margin of security for missing data, an unveiling trial worker will review the questionnaire for missing answers. Finally, to prevent performance bias, patients will complete the DASH questionnaire prior to visits with the physician, thereby blinding the physician.

The SHAFT trial is a pragmatic multicenter RCT, that will assess if there are a difference between surgical treatment versus non-surgical treatment in humeral shaft fractures, while taking the dilemmas within the population into account.

Trial Status

Protocol version 2.

Issue date: 30th of August 2021, Author DK.

Recruitment is anticipated to start on 1/1 2022 and is expected to be completed on 1/1 2024. If the sample size of 287 patients have not been meet, the extension of the study period will be discussed by the steering committee.

The trial was registered on 5 October 2020 in clinicaltrials.gov (NCT04574336). Last updated 08/30/2021 to conform with protocol updates. https://clinicaltrials.gov/ct2/show/NCT04574336

Abbreviations

SHAFT: Scandinavian Humeral diaphyseal Fracture Trial; SHAFT-Y: Scandinavian Humeral diaphyseal Fracture Trial -Young; SHAFT-E: Scandinavian Humeral diaphyseal Fracture Trial – Elderly; RCT: Randomized Controlled Trial; WHO: World Health Organization; ISRCTN: International Standard Randomised Controlled Trial Number; SPIRIT: the Standard Protocol Items: Recommendations for Interventional Trials; PRECIS-2: PRagmatic Explanatory Continuum Indicator Summary-2; RNP: Radial nerve palsy; ED: Emergency department; ASA classification: American Society of Anesthesiologists classification; UCLA activity score: University of California, Los Angeles activity score; DMC: Data Monitoring Committee; DVT: Deep venous thrombosis; PROM: Patient reported outcome measure; The Patient Representative; REDCap: Research Electronic Data Capture; EQ-5D: EuroQol-5; VAS: Visual Analog Scale; CA: Clinical Anchors; RGTQ: Retrospective Global Transition Questions: BRT: Binary Repeat Treatment: BRT; QALY: Quality-Adjusted Life-Year; FISH: Finnish Shaft of the Humerus; ITT: Intention To Treat; DASH: Disability of arm, shoulder and hand; MIC: Minimal important change; SD: Standard deviations; ASA: American Society of Anesthesiologists Score; BMI: Body mass index; PROM: Patient reported outcome measure; ROM: Range of motion; MIPO: Minimal invasive plate osteosynthesis; ORIF: Open reduction internal fixation; MACE (Major adverse cardiac event)

Declarations

Ethics approval and consent to participate

The trial will conform with the ethical principles of the Declaration of Helsinki(58). The study is approved by the Danish scientific ethics committee (reference number S-20200130), including the informed consent form and patient information sheet. Written, informed consent will be obtained from all

participants. The management of personal data has been approved by the Data Protection Agency (reference number 20/60034). Any important protocol modification will be advertised to The Regional Committee on Health Research Ethics for East Denmark, and registered at ClinicalTrials.gov. Participants are covered by the insurance policies that apply to ordinary treatment. Separate ethical applications are sent and pending in Norway and Sweden. All important changes to the trial will be reported to the scientific ethics committee and be registered in clinicaltrials.gov.

Consent for publication

Not applicable.

Availability of data and materials

Study-related information about patients are secured in REDCap(31). REDCap is a secure web application with authentication and data logging for managing databases. Access to the database will be limited to trial workers currently working on the trial. Their rights will be limited to data entry only. Principal investigator will keep a list of persons with access. All published data will be fully anonymized of patient identifiers. Furthermore, the trial has been approved by the Danish Data Protection Agency and will conform to the Act on Processing Personal Data. Trial results are planned to be published in an international peer-review journal.

Competing interests

The authors declare that they have no competing interests.

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The trial is part of a PhD study and tuitions to the University of Southern Denmark are funded by the department of Orthopedic Surgery of Kolding Hospital and the PhD-fund of the Region of Southern Denmark. Furthermore, the principal investigator (DK) is guaranteed a salary from the department during the study period. Surgical and non-surgical devices are available at all trial sites as part of usual care and will be covered by the sites, if funding is not fully or partly obtained. External funding has been received by The free and Strategic Research Foundation of Southern Denmark (ref no.: 20/43018), The Cross-regional Research Foundation of The Southern and The Zealand Regions (ref no.: A789) and The Research Council of Lillebaelt Hospital (ref no.: 2020-16) for operational costs for a central and local coordinating project employee and for partly funding the costs connected to recruiting. The current and future funders had no role in the design, execution, analysis, data interpretation or decision to submit results. No industrial funding is involved.

Authors' contributions

Authorship conforms with the recommendations of ICMJE(59). DK: Conception and design, data analysis and interpretation, manuscript writing and approving the final version. KM, TF, AP, OW, PO and CE: Design,

data collection, critical review. SB and BV: Conception and design. Overall academic supervision. Critical review. All authors read and approved the final version and are accountable of ensuring the scientific integrity of the work.

SHAFT authorship agreement

The first authorship will be granted after the first patient has completed the trial endpoint at 52 weeks. A recruiting site will then be granted an additional authorship for every 5 patients that completes the trial endpoint at 52 weeks. All authors are expected to provide substantially to the data collection. The authorships are granted the departments and not individuals.

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All lead investigators will be SC members including the patient representative Miss Katharina Stohlmann. The SC is organized to administrate the trial by reviewing the progress of the study and if necessary, discuss changes to the protocol and/or investigators brochure to facilitate the smooth running of the study.

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Tables

Table 1

Rehabilitation protocol

Non-surgical		
Phases (approx. timepoints)	Treatment (mobilization)	Explanation
Phase 1 Emergency department (ED) (0 weeks)	Apply immobilization device. (Wrist and fingers are recommended to be moved within immobilization device for anti-edema).	Immobilization device should not be taken off. (dressing, hygiene) Await decrease of swelling and acute pain
Phase 2 (0–2 weeks)	Shift to brace, if not applied in ED. Physiotherapy can be introduced. (Unrestricted and unloaded active range of motion within the limitations of the brace are allowed).	Brace should always be carried. Patients allowed to lift objects, equivalently to a can of milk (max 1 kg). Physiotherapy can be started to introduce simple movements.
Phase 3a (6 weeks, can be extended to a maximum of 12 weeks)	Fracture is tested gently for instability in patients 18–64 years. If stable, continue to phase 4. If unstable or uncertain stability, return to phase 2 and extend period with brace or consider early crossover surgery.	a. The fracture is not sufficiently healed and needs more time with brace treatment. b. The fracture is grossly instable and there is a risk of nonunion. Surgical fixation could be beneficial.
Phase 3b (12 weeks, can be extended to a maximum of 26 weeks)	Fracture is tested gently for instability in patients ≥ 65 years. If stable, continue to phase 4. If unstable or uncertain stability, return to phase 2 and extend period with brace or consider early crossover surgery.	a. The fracture is not sufficiently healed and needs more time with brace treatment. b. The fracture is grossly instable and there is a risk of nonunion. Surgical fixation could be beneficial.
Phase 4 (Patients < 65 y: 6–12 weeks) (Patients > 65 y: 12–26 weeks)	Brace is removed. Continue physiotherapy. (Unrestricted active range of motion of shoulder and elbow with gradual loading).	Fracture is clinically healed. Physiotherapy to regain full range of motion and strength. Movements should be within the threshold of pain.
Surgical		
Phases (approx. timepoints)	Treatment (mobilization)	Explanation
Phase 1 (0 weeks)	Apply immobilization device. (Wrist and fingers are recommended to be moved within immobilization device for anti-edema).	Immobilization device should not be taken off. (dressing, hygiene) Await date of surgery.
Phase 1 (0–2 weeks)	Surgical treatment. Physiotherapy can be introduced. (Unrestricted active range of motion, unloaded).	Patients allowed to lift objects, equivalently to a can of milk (max 1 kg). Caution due to wound healing

Non-surgical		
Phase 2 (6 weeks)	Continue physiotherapy. (Unrestricted active range of motion, starting gradual loading).	Movements should be within the threshold of pain
Phase 3 (7 weeks -)	Continue physiotherapy. (No restrictions, active range of motion with full load).	Physiotherapy to regain full range of motion and strength

Figures

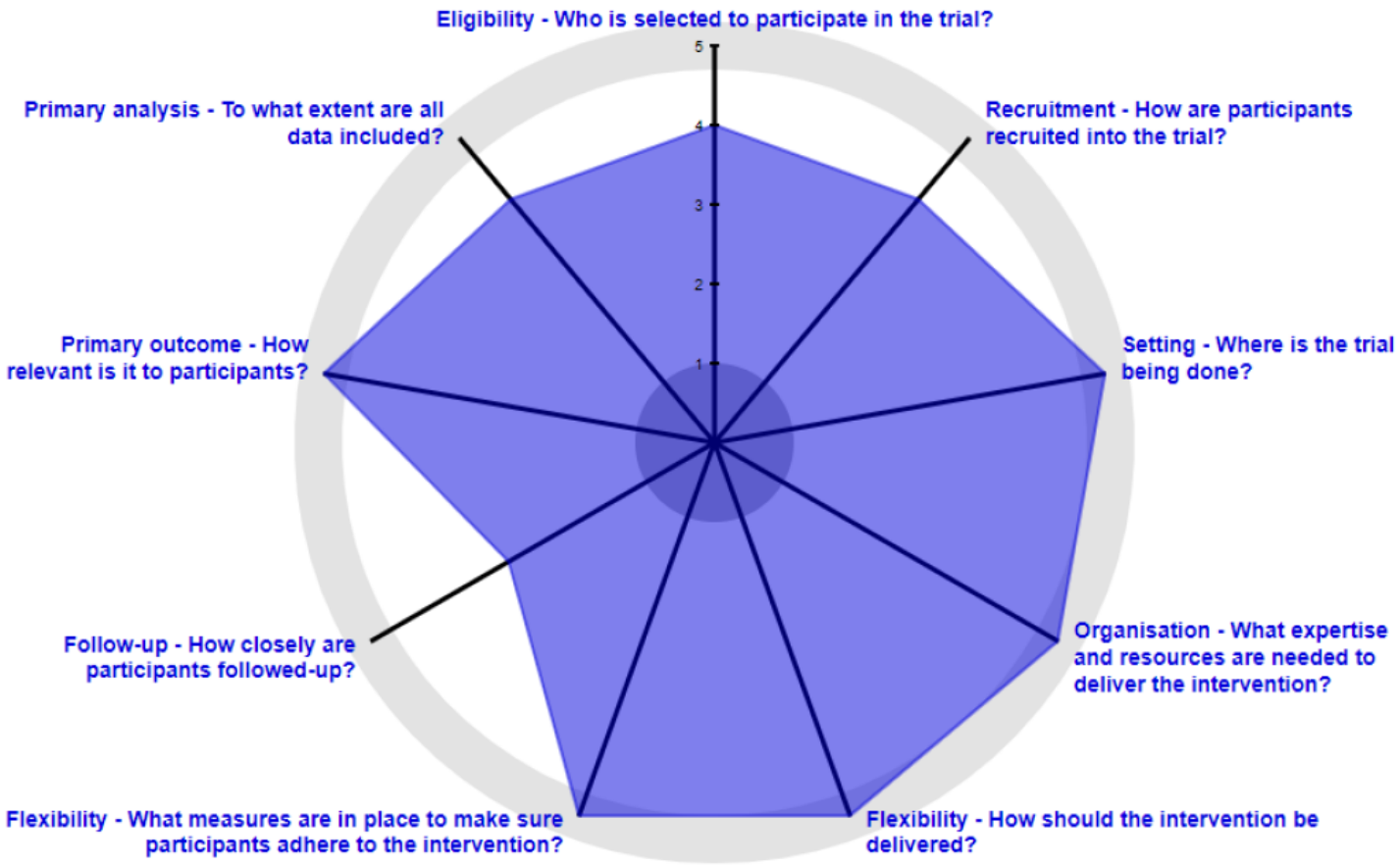

Figure 1

Assessment of the pragmatic design using the PRECIS-2

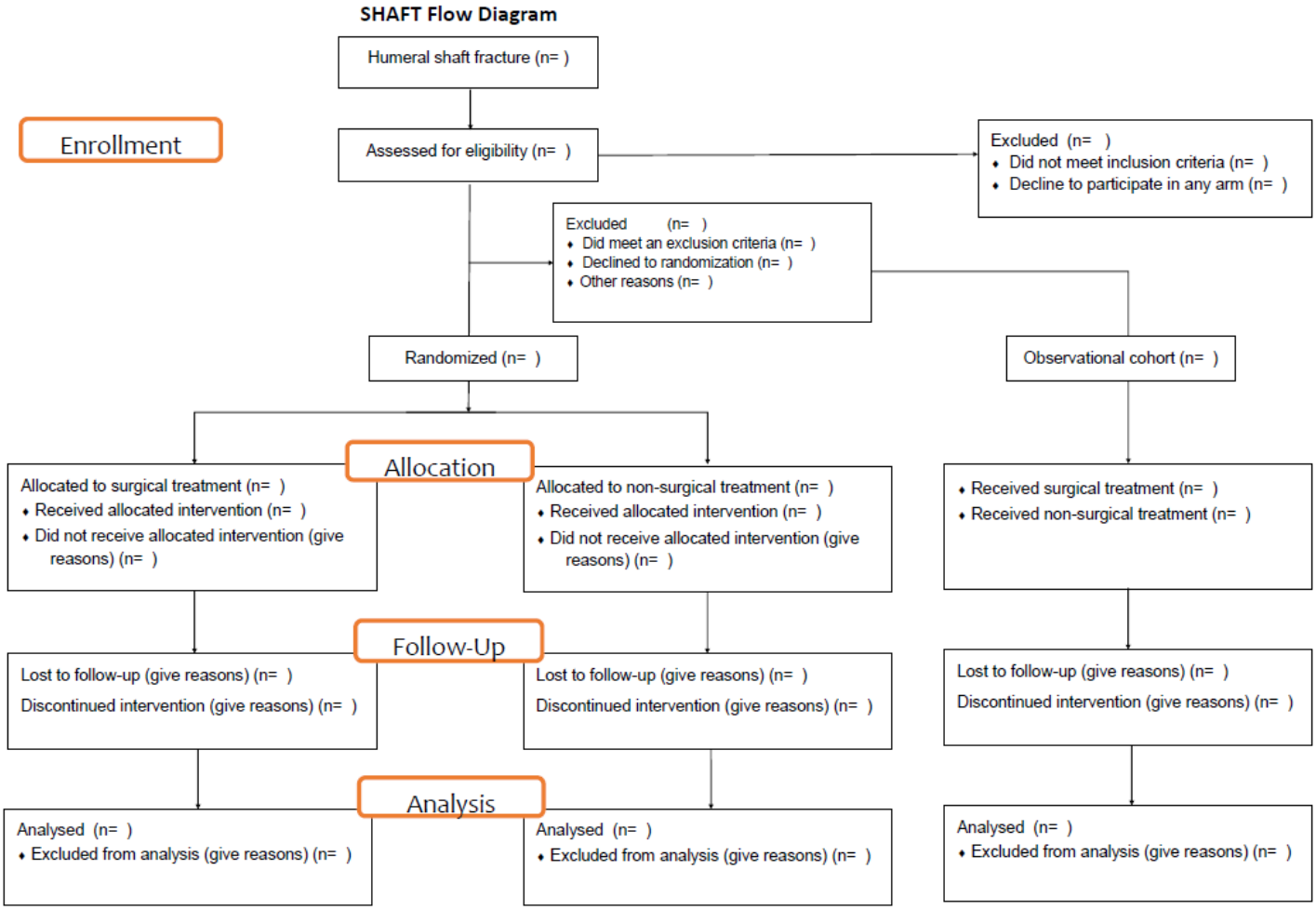

Figure 2

Trial flow

	SCREENING	ENROLMENT/ ALLOCATION	Electronic follow-up	POST-ALLOCATION				Electronic follow-up	Electronic follow-up
	Pre-randomization *(Emergency department)*	Baseline / Randomization *(1. follow-up)*		*2.follow-up*	*3.follow-up*	*4.follow-up*	*5.follow-up*		
Time point	*0-10 days*	*10 days*	*3 weeks*	*6 weeks*	*12 weeks*	*26 weeks*	*52 weeks*	*104 weeks*	*260 weeks*
ENROLLMENT									
Eligibility screen	x								
Informed consent		x							
Baseline data		x							
Allocation		x							
INTERVENTIONS									
Surgical		x							
Non-surgical SHAFT-Y		x		x[1] →					
Non-surgical SHAFT-E					x[2] →				
ASSESSMENTS									
DASH		x[3]		x	x	x	x	x[4]	x[4]
EQ-5D		x[3]		x	x	x	x	x[4]	x[4]
Constant-Murley				x	x	x	x		
UCLA activity		x[3]		x	x	x	x		
Complications		x		x	x	x	x		
VAS		x		x	x	x	x		
Clinical anchors			x[4]	x	x	x	x		
RGTQ							x		
BRT							x		

[1]Option of converting to early surgical crossover within 6-12 weeks in the non-surgical group, age 18-64 years
[2]Option of converting to early surgical crossover within 12-26 weeks in the non-surgical group, age +65 years
[3]Pre-injury scores
[4]By email/phone

Figure 3

Timeline and overview of enrollment, interventions and assessments for SHAFT

Supplementary Files

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- SPIRITchecklistSHAFT.docx