Odense 2024-12-20

Arthroplasty Versus Internal Fixation for Undisplaced Femoral Neck Fracture (SENSE)

A statistical analysis plan

Identifiers:	NCT04075461
Unique Protocol ID:	S-20180036

This SAP has been written in accordance with *Guidelines for the Content of Statistical Analysis Plans in Clinical Trials (Ref: Gamble)*

Section 1: Administrative Information

Title and trial registration

1a

Statistical Analysis Plan (SAP) for: Arthroplasty Versus Internal Fixation for Undisplaced Femoral Neck Fracture (SENSE)

1b

The study is registered at clinicaltrials.gov (NCT04075461) February 1. 2020.

SAP version

The current version of the SAP is 1.0 (date)

Protocol version

The protocol being used for the study is …

SAP revision history

No revisions have been made

Roles and responsibilities

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Roles of SAP contributors:

BV is the principal investigator, AM acted as statistical advisor. Both contributed to all sections of the SAP.

AM will be conducting the analyses, and will together with BV remain blinded to treatment group allocation until all analyses are finalized.

Section 2: Introduction

Background and rationale

For an undisplaced femoral neck fracture (FNF) the primary choice of treatment is internal fixation (IF) in most guidelines (NICE, Roberts et al.). This means that the fracture is held in position by metal and needs to heal. Another option is to cut the femoral neck and head out, replace it with a metal part thereby creating an artificial hip, either a hemi arthroplasty or a total hip arthroplasty. The difference between IF or

arthroplasty is therefore the choice between a smaller initial surgical trauma inclusive waiting for the fracture to heal or a larger initial surgical trauma replacing the bone with an artificial hip. The latter is the treatment of choice for the displaced FNF due to a high reoperation rate of IF but is it the best treatment for an undisplaced fracture?

There are currently 2 randomised controlled trials (RCTs) comparing IF with arthroplasty for undisplaced FNF. Lu et al. found a slightly higher Harris Hip Score after 6 months and 1 year in favour of hemiarthroplasty but not thereafter. Dolatowski et al. found a faster mobility (TimedUp-And-Go) but no difference in the Harris Hip Score. These studies did not show a clinical difference in Harris Hip Scores, but this measure may not be the best primary outcome measure due to the ceiling effect and lack of validation for patients with hip fracture (Wamper et al.). Mobilisation on the other hand is perhaps the most important factor for mortality and should therefore be essential to measure in any hip fracture study (Kristensen et al.). There are other studie types comparing IF with arthroplasty for undisplaced FNF and a meta-analysis from 2021 (Xu and Xue) with 750 patients concluded that hemiarthroplasty provided a lower implant-related complication rate, lower reoperation rate, superior hip function without increased long-term mortality. Two later studies found lower reoperation rate for IF but otherwise no difference in mortality or functional outcome (Mukka et al., Wolf et al.) and one study did not find any difference in reoperation, mortality or functional outcome (Cordero-Ampuero et al.).

Overall there is a lack of high quality studies with large sample sizes in order to compare IF with arthroplasty for undisplaced FNF.

Objectives

The aim of this trial is to compare functional outcomes of arthroplasty with internal fixation for patients over 65 years old with an undisplaced FNF. The study is designed as a national single-blinded pragmatic 1:1 RCT. The hypothesis states that arthroplasty is superior to internal fixation using the New Mobility Score (NMS) as the primary outcome after 12 months.

Section 3: Study Methods

Trial design

The SENSE trial is a national, pragmatic, single-blinded randomized controlled trial (RCT) conducted across 19 public hospitals in Denmark thereby covering app. 94% of the Danish population.

Randomization

Patients are randomly assigned in a 1:1 ratio to either receive arthroplasty or IF.

Randomization is conducted electronically through REDCap, using randomly varied blocks of sizes 4 and 6, stratified by hospital.

Sample size

The primary outcome for the study is the New Mobility Score (NMS) measured at 12 months. Based on prior studies, a clinically meaningful difference in NMS of 1 point was selected, with an expected standard deviation of 2.2 points. To achieve 95% power at a 5% significance level, 127 participants are required per group. Accounting for an anticipated 30% loss to follow-up due to mortality or other causes, the target enrolment is set at 330 participants.

Framework

This study employs a superiority framework to determine whether arthroplasty provides significantly better functional outcomes than IF. Specifically, the hypothesis is that arthroplasty will result in higher NMS scores compared to IF at 12 months post-surgery.

Interim analysis and stopping guidelines

An interim analysis will be conducted after data collection from the first 70 participants, focusing on mortality and function. If a mortality difference of 10% or an NMS difference of 2 points between groups is observed at 30 days or 3 months, respectively, the trial steering committee will review whether the trial should continue. The interim analysis did not meet the set criteria's and the steering committee recommended to continue the trial.

Timing of final analysis

The final analysis will be performed after all follow-up data, including the 12-month assessments, are collected. It is estimated that the last follow-up data is collected by February 2025. Thus, the complete analysis will be conducted in spring 2025.

Timing of outcome assessments

Assessments occur at:

Baseline:	During hospital admission with demographics, comorbidity, admission, surgery, blood samples, x-rays, NMS, Pain ratings using the Verbal Rating Scale (VRS), Oxford Hip Score (OHS), and Cumulated Ambulation Score (CAS).
2 and 6 weeks:	Pain VRS, CAS at 6 weeks
3 months:	NMS, CAS, Pain VRS, OHS, EuroQol 5-Dimension 5-Level (EQ-5D-5L), Barthel-20, and the de Morton Mobility Index (DEMMI).
6 months:	NMS, Pain VRS, OHS, EQ-5D-5L, Barthel-20, and DEMMI.
12 months:	NMS (primary endpoint), Pain VRS, OHS, EQ-5D-5L, Barthel-20, DEMMI, reoperation rates, and mortality.

Timeframe for collection of data

	Admission	2 weeks	6 weeks	3 months	6 months	12 months	At event
Demographics	X						
Comorbidity	X						
Admission	X						
Surgery	X						
Blood	X						
X-ray	X					X	
NMS	X			X	X	X	
Pain VRS	X	X	X	X	X	X	
OHS	X			X	X	X	
EQ-5D-5L	X			X	X	X	
DEMMI	X			X	X	X	
Barthel-20	X			X	X	X	
CAS	X		X	X			
Reoperation							X
Complications							X
Mortality							X

Section 4: Statistical Principles

Confidence intervals and P values

The statistical significance level is determined to 5% ($p<0.05$)

No correction for multiple testing will be performed, as the study has one clearly specified main hypothesis.

The confidence intervals to be reported are 95% (95% CI)

Adherence and protocol deviations

Adherence is defined as receiving the allocated surgical procedure as per randomization. Participants will be considered adherent if they undergo the surgical procedure they were allocated to.

Adherence rates will be reported as the proportion of participants in each group who received their allocated intervention. Non-adherence, including reasons for any deviations, will be documented and categorized. Adherence to intervention will be presented as frequencies and percentages of participants adhering to intervention and participants not adhering to the intervention.

Definition of protocol deviations in the trial: Protocol deviations are defined as any deviation from the procedures described in the protocol for the study.

Description of which protocol deviations will be summarized: All deviations form protocol will be described.

Analysis population

We define the Intention-to-Treat (ITT) population includes all randomized participants analyzed according to their allocated group, regardless of the surgery performed or follow-up completion. The Per-Protocol (PP) population consists of participants who received their allocated surgical procedure without major protocol deviations. The Complete-Case population includes participants with no missing data for the primary outcome.

Section 5: Trial Population

Screening data

Screening data was not collected as part of this trial; therefore, no reporting on the representativeness of the trial sample based on screened individuals is available.

Eligibility

All patients with an undisplaced FNF classified as either Garden type I or II21 are evaluated. The patients are included if:

- Age ≥65 years
- Undisplaced FNF
- Posterior tilt <20°
- NMS=5 and above, indicating an ability to walk prior to the fracture
- Cognitive state intact to achieve informed consent

Patients are excluded if:

- The fracture is pathological
- The patient does not speak or understand Danish language

Recruitment

All patients are recruited in the emergency department when diagnosed with an undisplaced FNF. The admitting doctor or a senior consultant will inform the patient about the trial while the patient is in the emergency department. The information will be given verbally as well as by written participant information in an undisturbed room in the emergency department. If no next of kin are present, they will be invited to attend by phone if requested by the participant. Otherwise, an impartial assessor can be assigned. Because surgery is required to take place as quickly as possible due to a higher risk of mortality when delaying surgery, a reflection time of only 2 hours has been approved. Retrieval of informed consent will take place at either the emergency department or the ward.

Withdrawal/follow-up

Withdrawal and loss to follow-up will be recorded throughout the study. Timing and reasons will be summarized descriptively, with frequencies by treatment group. Participants with available data will remain in the ITT analysis

Baseline patient characteristics

Baseline patient characteristics include age, sex, residency, pre-fracture mobility, comorbidity (using the American Society of Anaesthesiologists Classification), diseases, medication, smoking, and alcohol.

Section 6: Analysis

Outcome definitions (primary, secondary, and other measures)

Outcome Definitions

Primary Outcome

New Mobility Score (NMS): The NMS will be assessed at baseline (pre-fracture recall), 3, 6, and 12 months, with the 12-month assessment serving as the primary endpoint. The NMS ranges from 0 to 9.

Secondary Outcomes

Oxford Hip Score (OHS): The OHS will be assessed at baseline (pre-fracture recall), 3, 6, and 12 months. Scores range from 0 to 48, with higher scores indicating better hip function.

EuroQol 5-Dimension 5-Level (EQ-5D-5L): The EQ-5D-5L measures health-related quality of life, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each rated from 1 to 5. A visual analog scale (VAS) from 0 to 100 (worst to best health) is also included. The EQ-5D-5L will be assessed at baseline, 3, 6, and 12 months. Scores will include an index value derived from the EQ-5D-5L scale and a VAS score ranging from 0 to 100. EQ-5D-5L scores at 12 months are a secondary outcome.

Verbal Rating Scale for Pain (VRS): The VRS for pain will measure patient-reported pain intensity on a scale from 0 (no pain) to 10 (worst possible pain). This outcome will be recorded at multiple time points to capture immediate and longer-term pain levels (2 weeks, 6 weeks, 3 months, 6 months, and 12 months). The Pain score is measured on a 0-10 scale. The VRS at 12 months is a secondary outcome.

Reoperation Rate: This outcome captures any surgical procedures related to implant failure or complications following the initial surgery. Reoperations will be tracked up to 12 months and will include any additional surgery required. This measure is categorical (yes/no), indicating whether a reoperation occurred within 12 months. Reoperations will be subdivided in to major and minor: major is defined as any surgery that leads to the change of an implant or parts of it, removal of an implant (not simple removal of internal fixation), open reduction of a dislocated hip, operation due to periprosthetic fracture, or a DAIR (Debridement, antibiotics, and implant retention) procedure. Minor is defined as simple hardware removal of internal fixation or closed reduction of a dislocated hip.

Mortality: Mortality will be recorded as a binary outcome (alive/deceased) whenever the event occurs within the study period.

Exploratory Outcomes

These outcomes will not be included in the primary paper and consists for de Morton Mobility Index (DEMMI), Cumulated Ambulation Score, and X-ray measurements.

Analysis method

Primary Outcome Analysis

The primary outcome will be analyzed using a linear mixed-effects model to account for repeated measures across time points (baseline, 3, 6, and 12 months). The model will include fixed effects for time, and the

interaction between time and treatment, along with random intercepts for both hospital and individuals to account for within-subject correlation.

Time will be treated as a categorical variable.

t = 0, …, T (observations time points) (fixed effect)

i = 1, ..., I (participants) (random effect as random intercept γi)

Treatment arm as fixed effect exposure with interaction with time

Baseline measurements will be included as time point 0.

Treatment effect at each time point

$$Y_{i,t}=b_{treatment,t}Treatment_i time_t+b_t time_t+\gamma_i+\varepsilon_{i,t}$$

We will use an unstructured covariance structure for the random effects. If it improves model fit, time will also be added as a random effect to account for variability in NMS across time points within individuals.

Presentation: Estimated differences in NMS scores between treatment groups will be presented with β-coefficients, 95% confidence intervals (CIs), and p-values. Treatment effects will be displayed graphically across time points to illustrate trajectories by group, with error bars representing 95% CIs.

Secondary Outcome Analyses

Oxford Hip Score (OHS), EQ-5D-5L, and Verbal Rating Scale for Pain (VRS)) will each be analysed using mixed-effects models as described for the primary outcome.

Reoperation Rate and Mortality: Binary outcomes (reoperation and mortality within 12 months) will be analysed using logistic regression models with treatment as a fixed effect and hospital as a random effect. Additionally, for mortality, time-to-event analysis will be conducted using Cox proportional hazards models with baseline hazards stratified by hospital.

Presentation: For secondary outcomes, results will be presented with β-coefficients, odds ratios (for binary outcomes), hazard ratios (for time-to-event mortality analysis), 95% CIs, and p-values.

Adjustments for Covariates

Analyses of the primary and secondary outcomes will be done twice, once unadjusted, and once adjusted for following covariates: Age (continuous), Sex (male/female), Comorbidity (measured by the American Society of Anesthesiologists classification).

Assumptions Checking for Statistical Methods

Linear Mixed-Effects Models: Assumptions of normality and homoscedasticity for residuals will be checked by examining quantile-quantile (Q-Q) plots and residual-vs-fitted plots.

Logistic and Cox Models: Assumptions of linearity and proportional hazards, respectively, will be assessed. The proportional hazards assumption in Cox models will be evaluated using Schoenfeld residuals. Deviations from linearity in logistic models will be reviewed by adding polynomial terms or piecewise splines as needed.

Alternative Methods if distributional assumptions do not hold

If normality assumptions are violated in the linear mixed-effects model, non-parametric bootstrapping with 1,000 replicates will be used to estimate 95% CIs for treatment effects.

If the proportional hazards assumption is violated in the Cox regression model for mortality, we will conduct a Kaplan-Meier survival analysis. The survival curves for each treatment group will be plotted, and differences between groups will be tested using the log-rank test.

Sensitivity Analyses

Intention-to-Treat vs. Per-Protocol: The primary analysis will be conducted as intention-to-treat (ITT). A sensitivity analysis will be conducted per-protocol to assess treatment effects among participants who fully adhered to assigned interventions.

Missing Data

No missing data is expected for the Cox regression outcome (mortality and reoperation rate). For all other outcomes, mixed-effects models inherently account for missing data under the assumption that it is Missing at Random (MAR). A dropout table will be presented, summarizing the number and timing of participants lost to follow-up by treatment group.

Harms

A table summarizing all recorded harms, excluding reoperations, will be presented.

Statistical Software

All statistical analyses will be performed using Stata 18.

References

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