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Statistical analysis plan (SAP)

NCT03531463

Nordic Innovative Trials to Evaluate osteoPorotic Fractures (NITEP) Collaboration: The Nordic DeltaCon Trial protocol—non-operative treatment versus reversed total shoulder arthroplasty in patients 65 years of age and older with a displaced proximal humerus fracture: a prospective, randomised controlled trial

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SECTION 1: ADMINISTRATIVE INFORMATION

Trial registration: The trial is registered at www.clincaltrials.gov with the number NCT03531463.

Protocol version: This document has been written based on the information contained in the trial protocol published in BMJ Open (1).

Statistical Analysis Plan (SAP) revision history:

SAP version	Section changed	Description and reason for change	Date changed
1.0	Initial draft		
1.1	Analyses	specified	7.2.24
1.2	References	added	19.2.24
1.3	Final agreement of SAP		16.11.25

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SECTION 2: INTRODUCTION

Background

In the ageing population, the proximal humerus fracture (PHF) is one of the most common fractures (2). In addition to the significant disability caused by PHF among older individuals, such fractures are also associated with a high economic impact (3). In general, the operative interventions and rehabilitation after a shoulder fracture are resource-consuming.
The gender-specific fracture incidence for proximal humeral fractures for women in Sweden was 135 per 100000 person-years; in total, almost 10000 fractures were diagnosed in 2012 (4). The majority of PHFs are treated non-operatively and approximately 15%–33% of patients are treated surgically (5). Recent randomised controlled trials (RCTs) and meta-analyses have shown no difference in functional outcome between non-operative treatment and locking plate or hemi-arthroplasty (HA) in the treatment of PHF (6). However, operative treatment has a significantly higher risk of complications and reoperations of up to 30% (6). Originally, reverse total shoulder arthroplasty (RTSA) was used for osteoarthrosis in patients without cuff function to gain better functional outcomes. During the past decade, however, RTSA has gained popularity in the treatment of PHF. In a recent Medicare population analysis carried out between 2005 and 2012, the proportion of surgical procedures for PHF that were total shoulder arthroplasties (TSA) (of which RTSAs constituted 89% in 2011) increased from 3% to 17%, while the proportion of HA decreased from 42% to 24% during the same time period (5). There have been some systematic reviews based on case series and patient cohorts including one RCT that compared HA and RTSA. The results are equivocal; RTSA resulted in better functional outcomes compared with HA in some studies, with no difference seen in others (7, 8). In the RCT, the complication rate in the HA group was significantly higher than in the RTSA group (24% vs 10%, respectively). However, an arthroplasty registry analysis including 10844 operations (6658 TSA and 4186 RTSA) showed the RTSA postoperative complication rate to be 22% at 2 years (9).
Currently, there are no RCTs comparing RTSA to non-operative treatment after PHF. The current literature discourages the operative treatment of PHF with locking plate or HA, and there is no evidence that favors surgery over non-operative treatment (6). In spite of the

substantial costs and lack of evidence supporting the effectiveness of RTSA for PHF, it has become the accepted standard of care in the USA. Therefore, there is an urgent need for high-quality RCTs that compare RTSA with non-operative treatment.

Objectives and endpoint

SECTION 3: STUDY METHODS

Trial Design

This was a prospective, superiority, single-blinded, randomised, controlled, multicentre and multinational trial that compared RTSA and non-operative treatment in proximal humerus fractures in patients aged 65–85 years with displaced three-part and four-part fractures (B and C types) according to the recent AO/OTA 2018 revision.

The Statistical Analysis Plan (SAP) is reported in accordance with the "*Guidelines for the Content of Statistical Analysis Plan in Clinical Trials*" (10).

The Deltacon trial is registered at www.clincaltrials.gov with the number NCT03531463. The primary ethical approval for the trial has been given by the Regional Committee for Medical and Health Research Ethics, South-East Authority, Norway (2018/476 REK sør-øst D, https://rekportalen.no/#hjem/home). All sites gained institutional approval before the start of the trial. All patients included in the trial and those who declined but were asked to take part in the follow-up cohort were asked to give written informed consent.

Randomisation

Patients were randomised using a random number matrix in a block allocation fashion, in blocks of 10. The blocks were stratified by age (65–75 years and >75 years) since age has been shown to associate with the main outcome measure. The treatment allocations from the matrix were acquired from an online randomisation system (website http:// randomize. net), where the researcher logged in after written consent and received the correct intervention. The randomisation system asked for stratified items: The hospital (site), gender and patient

age. Thereafter, the allocation will be shown. The patient was randomised after written consent and before baseline assessments. The physician responsible for the intervention or treatment did not participate in any part of the collection of patient outcomes during the follow-ups.

Sample Size

Assuming the effect size of a 14-point difference in the QuickDASH score and an SD (equal for both groups) of 26.8 points (from previous Olerud and MacDermid trials), the estimated sample size was 58 patients per group (delta=14, SD=26.8, alpha=0.05, power=0.8). With this age group, the estimate of loss in follow-up rate was set to 25% and resulted in a total of 154 patients in the trial. Total recruitment achieved 154 patients.

Framework

The overall objective of the trial was to determine whether surgical intervention results in a clinically and statistically significant better improvement compared to non-operative treatment on the short form of Disabilities of the Arm, Shoulder and Hand (Quick-DASH). The primary hypothesis is that surgical intervention produces better functional outcome and less pain compared to the non-operative treatment at 24 months.

Estimands

Clinical question

Among patients aged 65–85 years with displaced 3- or 4-part proximal humerus fractures (AO/OTA 11-B and 11-C types) who meet the trial eligibility criteria, what is the effect of initial randomisation to RTSA versus non-operative treatment on shoulder-related disability at 24 months?

Primary estimand components

Component	Specification
Treatment condition	Initial randomised assignment to RTSA versus non-operative treatment (exercise), regardless of subsequent treatment changes (treatment policy for most intercurrent events, see Section 4.x.2).
Target population	All randomized participants meeting the inclusion and exclusion criteria at baseline (intention-to-treat population), aged 65–85 years with AO/OTA 11-B1.1, 11-B1.2, 11-C1.1, 11-C3.1 low-energy PHF types as defined in the protocol.

Variable (endpoint)	Short form Disabilities of the Arm, Shoulder and Hand (QuickDASH) score (0–100, higher = greater disability) assessed at 24 months after randomisation.
Intercurrent events	Death before 24 months, secondary surgery (including revision, conversion to arthroplasty), crossover between treatment groups, additional non-protocol physiotherapy, and other changes in shoulder-related treatment after randomisation.
Strategy for intercurrent events	Treatment policy strategy for surgery/crossovers/other shoulder procedures; treatment policy for additional non-protocol rehabilitation; composite strategy for death (patients dying before 24 months assigned the worst possible QuickDASH score).
Population-level summary	Adjusted mean difference in QuickDASH score at 24 months between RTSA and non-operative treatment, estimated from the pre-specified linear mixed model, with 95% confidence interval.
Hypothesis	RTSA provides a clinically and statistically significant reduction (improvement) in QuickDASH score at 24 months compared to non-operative treatment.

Analysis model corresponding to the primary estimand

The primary estimand will be estimated using the pre-specified linear mixed-effects model:

- Random effect: patient (to account for repeated measures).
- Fixed effects: treatment group, follow-up time (3 months, 12 months, 24 months), treatment-by-time interaction, study centre, baseline QuickDASH, and age.
- Primary contrast: adjusted mean difference in QuickDASH at 24 months between RTSA and non-operative treatment, obtained as estimated marginal means from the model.

This analysis yields an estimate of the primary estimand under the assumption that missing data are missing at random conditional on the included covariates (see Missing Data section).

Secondary Estimands

For key secondary outcomes (VAS pain, grip strength, OSS, Constant Score, 15D, and reoperation/complication outcomes), estimands follow the same general structure:

- Treatment: randomised RTSA vs non-operative treatment (treatment policy).
- Population: all randomised eligible participants (ITT).
- Variables: respective secondary endpoints at prespecified time points (3, 12, 24 months).

- Intercurrent events**:** handled as per Section 4.x.3 (same as for primary).
- Summary measures:
    - For continuous outcomes: adjusted mean differences at 24 months from mixed models.
    - For binary outcomes: absolute risk differences at each time point from logistic regression with marginal effects.

A per-protocol estimand for the primary outcome will be defined as the effect of RTSA versus non-operative treatment among participants who adhered to their allocated initial treatment and had no major protocol deviations. This provides a sensitivity estimand complementary to the primary ITT estimand.

Intercurrent Event Strategy

The table below specifies how each type of intercurrent event will be handled for the primary and key secondary estimands.

Intercurrent event	Definition / examples	Implementation in analysis
Death before 24-month follow-up	Patient dies from any cause before the 24-month outcome can be obtained.	Patients who die before the 24-month assessment will be considered as missing and all data until death is included in the analyses.
Crossover from non-operative to RTSA or other surgery	Patient randomised to non-operative treatment undergoes RTSA or other shoulder surgery during follow-up.	Patient remains analysed in the originally allocated group (non-operative) for ITT. All available QuickDASH measurements, including post-surgery, are used in the mixed model. Crossover is documented and will be explored in per-protocol (as-treated) sensitivity analyses.
Failure to receive allocated RTSA (no surgery or different procedure)	Patient randomised to RTSA does not receive RTSA (e.g. surgery cancelled, different procedure performed, or major deviation from planned implant).	Patient remains in the RTSA group for ITT analysis. All available outcomes are analysed as randomised. A per-protocol analysis will exclude or reclassify such patients according to predefined PP criteria.
Revision surgery or secondary surgery after the index procedure or initial care	Any reoperation on the index shoulder (e.g. revision arthroplasty, conversion to RTSA, hardware removal, re-fixation).	Outcomes collected after revision or secondary surgery are included as observed, reflecting the overall effect of the initial treatment strategy, including complications and subsequent interventions.

Additional or intensified physiotherapy / rehabilitation	Any non-protocol variation in physiotherapy intensity, duration or setting after randomisation.	Considered part of real-world management following the initial treatment assignment; outcomes included as observed. No adjustment will be made specifically for post-randomisation physiotherapy use or adherence in the primary analysis, but may be described descriptively.
Permanent institutionalisation or severe decline preventing clinic attendance	Patient becomes institutionalised, develops severe comorbidity, or is otherwise unable to attend physical follow-up, but remains alive.	Where feasible, outcome data may be collected by mail or telephone. If no data are obtained at 24 months, the mixed model will use available earlier measurements under MAR assumption.
Withdrawal of consent for further data collection (but permission to use prior data)	Patient withdraws consent to attend further visits but allows use of already collected data.	Previously collected data will be included; no further data collected. Mixed model estimates will rely on available data assuming MAR.
Withdrawal of consent including use of prior data	Patient withdraws consent and requests deletion/non-use of prior trial data.	All data from that participant will be excluded in accordance with applicable regulations and ethics. This change will be documented, and the effective analysis population will be reduced accordingly.
Discovery of ineligibility after randomisation	Patient is found after randomisation not to meet one or more inclusion/exclusion criteria (e.g., misclassified fracture type).	For ITT estimand, such patients remain included and analysed as randomised. For the per-protocol estimand, these participants will typically be excluded (see detailed PP definition).

Statistical interim analysis and stopping guidance

The external trial board had access to interim data and carried out the interim analysis after recruiting half of the patients. The report concentrated on the number of AEs and provided a recommendation on whether or not the trial should proceed. The board assessed the complication rates and compared them to the expected rates published in the available literature. An unexpectedly high rate of complications in either group would have indicated the end of the randomisation.

They advised the trial to continue. AEs and serious adverse events (SAEs) will be reported according to the guidelines provided by the Consort Group.

AE is defined in 3 categories (mild, moderate, severe) as follows:
1. For the RTSA intervention group, the primary focus will be postoperative deep infections requiring revision surgery, instability, periprosthetic fracture, radiographic early signs of loosening (within 2 years of the surgery) of the humeral stem or notching of the scapula neck.

2. For the non-operative group, the primary focus will be on the rate of secondary surgery for any reason (eg, non-union, symptomatic avascular head necrosis, osteoarthrosis).

Both groups were monitored for SAE during the first four weeks after discharge for embolism (cardiac or brain) or death. The research nurse or physiotherapist filled out AE and SAE forms at 3 months control, if needed. At the halfway point of the trial (50% of patients recruited), an independent steering committee evaluated the complication rates and correlate them to the expected rates published in the available literature.

Timing of final analysis

The final analysis for the primary outcome, the end scores on QuickDASH at 24 months, will be performed after the last follow-up assessment at 24-months. The main publication of the trial will be prepared when these data are available.
In addition, papers on 5- and 10-years follow-up will be performed, when these follow-up assessments are available.

Timing of outcome assessments

The trial consists of six time points; baseline, 12-weeks, 12-months, 2 years, 5 years and 10 years. An overview of the assessments and procedures has been presented in the protocol.

SECTION 4: STATISTICAL PRINCIPLES

Confidence intervals and P values

For the primary outcome the statistical tests will be two-sided and a p-value <0.05 will be considered statistically significant. Confidence intervals will be 95% (95% CI) and two-sided.

No adjustments for multiplicity were made. For the secondary outcomes, p-values will be downplayed when interpreting the results. Secondary outcome are exploratory.

Analysis populations

The primary analysis will be based on the Intention to Treat (ITT) principle. Patients allocated to a treatment group (RTSA or exercise) should be followed up, assessed and analysed as members of that group, regardless of their adherence to the planned course of treatment. Per-protocol analysis population was defined as patients meeting protocol requirements, receiving either RSTA or nonoperative treatment, regardless of primary allocation, and not lost to follow-up immediately after randomisation (provided outcome data at least 1 time-point).

Changes from the Protocol

We have modified the primary statistical analysis from what was specified in the original protocol. The protocol originally described univariable comparisons at each time point. However, the updated analysis employs a linear mixed model, which more appropriately accounts for repeated-measures data. Dichotomous outcomes will still be analysed at each time point as originally planned, but the treatment effect will be estimated as the difference in proportions derived from marginal estimates of a logistic model.

The primary analyses described in the original protocol are now considered supplemental analyses.

The original protocol contained a typographical error in the sample size calculation (incorrect loss to follow-up). The corrected calculation is presented in this SAP and corresponds to the intended assumptions described in the protocol.

SECTION 5: TRIAL POPULATION

Screening data

At all hospitals patients eligible for treatment were screened for the inclusion and exclusion criteria. If they fulfilled the criteria, they were invited to participate. The number of patients who did not meet the criteria and the reason for ineligibility will be reported in a CONSORT flow chart. There were no pre-randomization withdrawals.

Eligibility

The following criteria was used throughout the study for patient selection.

- Inclusion criteria:
    - Low-energy AO/OTA group 11-B1.1, 11-B1.2 and 11-C1.1, 11-C3.1 (11). Both B and C type includes the subgroups: displaced,[2] impacted[3] or non-impacted[4] from the universal modifiers list.
- Exclusion criteria:
    - Radiographic
        - Mal-inclination less than varus 30°or valgus 45°.
        - Less than 50% contact between head fragment and metaphysis/diaphysis.
        - Head split fractures (group 11-C3.2 and 11-C3.3) with >10% of the articular surface in the main head fragment.
        - Dislocation or fracture dislocation of the gleno-humeral joint.
        - Pathological fracture.
        - Glenoid abnormality (retroversion, >15°; glenoid fracture; cuff arthropathy).
    - General
        - Refuses to participate in the study.
        - Aged <65 years or >85 years.
        - Serious poly-trauma or additional surgery.
        - Non-independent, drug/alcohol abuse or institutionalized (low co-operation).
        - Contraindications for surgery (severe cardiovascular, pulmonal or neurological comorbidity).
        - Does not understand written and spoken guidance in local languages.
        - Previous fracture with symptomatic sequelae in either shoulder.
        - Patients living outside the hospital’s catchment area.

Recruitment

The CONSORT flowchart will present the number of patients screened, excluded (with reasons), eligible for inclusion, randomized, receiving allocated treatment, withdrawals (with reasons), lost to follow-up (with reasons), included in the ITT analysis, included in the per protocol analysis.

Withdrawal/follow-up

Throughout the trial period, the included patients were allowed to withdraw from the study at any time. Participants who decided to withdraw will be encouraged to continue in the study as if they have received the intervention.

Baseline patient characteristics

Baseline characteristics will be presented. Categorical variables will be presented as numbers and percentages. Continuous variables will be presented as mean with standard deviation (SD), if normally distributed and ad median with interquartile range (IQR) if not normally distributed. No tests of significance will be conducted for the baseline characteristics, imbalances of importance will be noted. Baseline and follow-up values for the primary and secondary outcomes will be presented as part of the analysis.

From the baseline variable, age and baseline QuickDASH were included for adjustment in the analyses. Missing baseline data is reported.

SECTION 6: ANALYSIS

Outcome definitions

QuickDASH

The primary outcome will be presented as the 24-month adjusted mean difference. QuickDASH is a valid and reliable patient-reported questionnaire assessing shoulder pain and function with 11 items. The final score is between 0 to 100, where higher score indicates greater disability.

Secondary outcomes

General visual analogue scale (VAS) for pain, grip strength, the Oxford Shoulder Score (OSS), the Constant score (CS) and the number of reoperations and complications. Quality of life will be assessed with 15-D. Difference in treatment costs between the groups will be calculated and health economic analysis performed.

Analysis methods

The primary analysis method for QuickDASH will be a linear mixed model. The patient is included as a random factor. Study group and follow-up assessments (3 months, 1 year, 2 years) will be included as a fixed factor. Study centre, baseline QuickDASH and patient age will also be included as fixed factors. The main model will include the interaction between the study group and the follow-up assessment. Primary treatment effect at 2 years will be estimated as the estimated marginal means between the study group from time-spesific contrast. Similar estimates will be obtained for 3 months and 1 year also. Similar analysis will be done for key secondary outcomes VAS pain, VAS grip strength, OSS, CS and 15D. Results will be presented with 95% CIs.

For categorical variables we will estimate the group absolute risk difference using a logistic regression based on marginal effects. Separate models will be run at each follow-up time-points. Logistic models include study group and patient age as adjusting covariates.

No residual diagnostics were done as LMM is robust against normality violations (12). Baseline imbalances were addressed including age and baseline QuickDASH in the LMM analysis. Age is the single most important variable affecting the outcome.

Missing data

As stated above, imputations will not be applied in this study due to the repeated mixed model analysis. We assume missing at random (MAR) model. Each randomized patient will be included in the intention-to-treat analysis with the collected data. In an attempt to collect data from all randomized patients, participants deciding to withdraw from the study, are still encouraged to attend the follow-up test.

Additional analyses

For primary and key secondary outcomes an additional analysis will be done with a crude between-group comparison. For continuous variables we will assess the study group difference using Welch t-test at each time point as a supplementary analysis. Categorical variables will be compared using Fisher exact test for 2x2 tables and Chi-squares test for other comparisons.

The subgroup analyses for the primary outcome will be done according to following variables: of age (per stratification), sex, fracture group, smoking and ASA class. These analyses are as stratified not using interaction analysis. No adjustment for multiplicity is done and all analyses are purely exploratory.

Additional analyses will be performed with the purpose of testing the robustness of the intention-to-treat analysis, including a per-protocol analysis for the primary outcome; Crossover patients are defined as patients allocated to the non-operative group who undergo RSA during follow-up or patients allocated to surgery, but who do not undergo the procedure to any reason. Between operated patients, a sensitivity analysis will be conducted comparing different models of prostheses.

Harms

Adverse and serious adverse events will be presented as numbers and percentages for each event.

Statistical software

All statistical analysis will be made using the latest R software and/or Stata

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