

# Bracing after Ankle Fracture (BAF): Statistical Analysis Plan (SAP)

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## Administrative information

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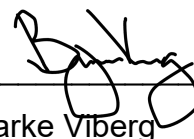
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## BACKGROUND

Ankle fractures are the third most common fracture in the emergency room (1, 2) resulting in pain and reduced ankle function (3). Also, emerging evidence indicates that immobilization prolongs patients' recovery (4-6). However, high quality evidence is necessary for finite conclusions.

In Scandinavia, foot-ankle braces (walkers) are used to immobilize the fracture while healing. Even though patients acknowledge the need for immobilization, a qualitative study of ten patients found that patients experienced difficulties in adhering to the recommendation of immobilization after ankle fracture (7). A randomized controlled trial (RCT) by Smeeing et al. 2020 (5) found that braces and elastic bandages, which allow more ankle movement than walkers, did not result in poorer functional outcomes and may facilitate a faster return to work without increasing complications. However, the RCT was terminated when only half of the required sample had been included, thus questioning the statistical power of the findings (5).

To further inform trial design, eight patients (male and female, aged 28 to 66 year) were interviewed and shared their perspectives on the walker, ankle-supporting elastic bandages, ankle stirrups, and research question. The Patients preferred ankle stirrups as they allowed movement during use. The same patients also expressed an aversion to the walker, while being concerned that ankle-supporting elastic bandages provided sufficient support.

## Objective

The BAF trial aims to test if an ankle stirrup is non-inferior compared to a walker in reducing ankle pain and improving function by the Manchester-Oxford Foot Questionnaire (MOXFQ) three months after ankle fracture.

## Methods

### Design

The study is a pragmatic, multi-center, non-inferiority trial.

### Randomization

Randomization is internet based using Redcap Randomize. For balanced treatment groups the randomization will be performed in blocks of four, six and eight. A data manager, uninvolved in the trial, prepares the randomization sequence to ensure an even distribution of surgical and non-surgical treated patients in groups and even distribution to the intervention and control group at each recruitment center.

### Blinding

The statistical analyst is blinded.

## Outcomes

### Primary outcome

The index score of the MOXFQ 3 months after ankle fracture is the primary outcome (8, 9). MOXFQ is a valid and reliable patient-reported outcome, preferred by patients, and is divided into three domains: pain, function, and social interaction (8-10). Response is on a 5-point Likert scale ranging from zero to four. The index score is calculated by summing

the raw scores of the 16 items to an index score ranging from 0 to 100, (100 most severe), using the formula  $\frac{i1+i2+\dots+i16}{64} \times 100$  (9).

MOXFQ was modified to enquire to the last seven days instead of the last four weeks due to patient feedback.

#### Secondary outcomes:

The subgroup analysis will assess non-inferiority in the following 7 subgroups: males 18-39, females 18-39, males 40-59, females 40-59, males 60+, females 60+ and in treatment groups (surgical and non-surgical).

Self-reported physical activity will be measured using the short-form International Physical Activity Questionnaire (IPAQ-SF) and grouping patients into low, moderate and high physical activity levels (11-13).

Health-related Quality Of Life (HRQOL) will be measured using the EuroQol five-dimension five-level questionnaire (ed-5d-5l) (14).

Ankle dorsiflexion is measured by clinicians using the knee-to-wall test, which measures ankle mobility in degrees of motion in standing.

Plantar flexor muscle strength for injured and contralateral ankle is measured, by clinicians, using the heel rise test. Patients perform as many single-leg heel raises at a cadence of one per second until fatigue or a maximum of 50 is reached.

Hospital Costs will be measured from a hospital perspective from ankle fracture and include cost of procedures.

Return to work is measured by the number of days from ankle fracture until the date patients return to work (full-time or part-time).

#### Exploratory outcomes

Physical activity will be objectively measured in a subgroup of patients (n = 280) using SENS accelerometer.

A cost-utility analysis with a societal perspective and a one-year follow-up will be completed alongside the clinical trial and reported as the incremental cost per Quality Adjusted Life Year gained (ICER).

#### Baseline characteristics

Age, sex, fracture side, fracture type (AO classification), smoking status, Body Mass Index (BMI), length of education, type of surgical treatment, cohabiting status (living alone or with a partner), work-related physical requirements (blue-collar or white-collar) and usual employment status.

#### Sample size

A Minimum Clinically Important Difference (MCID) of 13 points is considered reasonable (9) and with a standard deviation of 14 points, the non-inferiority limit is set at 7 points (10). The statistical significance level will be one-sided at 2.5%, and the power (1-beta) will be 80%, resulting in a needed sample of 63 patients per arm. Fourteen extra patients (10%) will be recruited to mitigate potential drop-out. To ensure sufficient power for subgroups and representativeness to the population, Recruitment will continue across all subgroups until the last subgroup reaches 140 participants (probably females 18-39 years

as they comprising app. 10% of the ankle fracture population). As a result, some subgroups will exceed this number. To limit excessive recruitment, the total sample size will be capped at 1400 participants.

### Primary analysis

Non-inferiority will be assessed by a linear mixed regression model and 95% confidence interval (95% CI). The 95% CI must be above the non-inferiority margin for the ankle stirrup to be declared non-inferior in the Intention To Treat (ITT) analysis. The analysis will be adjusted for the randomisation stratification variable treatment (surgical or non-surgical) and subgroup defining variables age (continuous) and sex (male and female). Sites will be modeled as random effects. Missing outcome data will be handled using a linear mixed effects model, which yields unbiased estimates under a missing at random assumption, conditional on observed covariates and outcomes. Regression residuals will be examined for normal distribution in Q-Q plots and plots of residuals vs fitted values will be inspected to detect variance heterogeneity. If model assumptions are violated, confidence intervals will be estimated using non-parametric bootstrapping with 1,000 repetitions (for non-normal residuals) and/or by fitting a mixed model that allows for variance heterogeneity. Reporting will be the predicted between group change from baseline to 12-week follow-up.

### Sensitivity analysis

A sensitivity analysis will additionally include adjustment for: BMI, cohabiting status, smoking status, and baseline MOXFQ index score.

A per protocol analysis excluding patients who discontinue or crossover from stirrup to walker or vice versa before the primary outcome, will be completed.

### Secondary analyses

Using the same analysis, we will explore non-inferiority in 7 predefined subgroups: males 18-39, females 18-39, males 40-59, females 40-59, males 60+, females 60+ and in treatment groups (surgical and non-surgical). We hypothesize the intervention will be non-inferior in all 7 subgroups.

The remaining secondary outcomes will be ranked based on their patient perceived importance at 12-week follow-up. By asking each patient in the pilot to rank each secondary outcome from 1-6 (1 being most important). The ranking will be reported in the pilot. Appropriate analysis will be used to test differences from the zero hypothesis for each outcome until a zero hypothesis is confirmed. Hereafter groups are compared on descriptive statistics as counts, mean and frequencies.

Physical activity: Superiority in change in self-reported physical activity (low, medium or high) from baseline to 12-week follow-up will be analyzed using a multinomial mixed regression analysis adjusted for stratifying variables and sites modeled as a random effect. Reporting will be the predicted between group change from baseline to 12-week follow-up.

Return to work: superiority in return to work measured by the number of days from ankle fracture until the date patients return to work (full-time or part-time) will be analysed using a log rank test and visualized in Kaplan-meier plots.

Ankle dorsi fleksjon: superiority in ankle dorsiflexion will be analysed as the difference from 6-week to 12-week follow-up. Between group difference will be analysed using a linear regression analysis adjusted for stratifying variables. Missing outcome data will be assumed randomly. Regression residuals will be examined for normal distribution in Q-Q plots and

plots of residuals vs fitted values will be inspected to detect possible variance heterogeneity. If model assumptions are violated, confidence intervals will be estimated using non-parametric bootstrapping with 1,000 repetitions (for non-normal residuals) and/or by fitting a model that allows for variance heterogeneity.

Lower extremity strength: superiority in lower extremity strength will be analysed as the difference from 6-week to 12-week follow-up. Between group difference will be analysed using a linear regression analysis adjusted for stratifying variables. Missing outcome data will be assumed randomly. Regression residuals will be examined for normal distribution in Q-Q plots and plots of residuals vs fitted values will be inspected to detect possible variance heterogeneity. If model assumptions are violated, confidence intervals will be estimated using non-parametric bootstrapping with 1,000 repetitions (for non-normal residuals) and/or by fitting a model that allows for variance heterogeneity.

Superiority in Self-reported Health-related Quality Of Life (HRQOL) will be measured using the EuroQol five-dimension five-level questionnaire (ed-5d-5l) (14), pending on randomisation by the same mixed regression analysis as described for the primary analysis.

Non-inferiority in hospital costs measured from a hospital perspective including cost of procedures and readmissions pending on randomisation will be the total cost from baseline to 12-week follow up. Between group difference will be analysed using a linear regression analysis adjusted for stratifying variables. Missing outcome data will be assumed randomly. Regression residuals will be examined for normal distribution in Q-Q plots and plots of residuals vs fitted values will be inspected to detect possible variance heterogeneity. If model assumptions are violated, confidence intervals will be estimated using non-parametric bootstrapping with 1,000 repetitions (for non-normal residuals) and/or by fitting a model that allows for variance heterogeneity.

### Safety and adverse events

The number of adverse events (AE) and serious adverse events (SAE) are registered. The relatedness of the AE and SAE are assessed by the data monitoring committee.

Adverse Events (AE) are undesirable experiences that may occur during brace use:

- Skin irritation blisters, pressure sores due to poor fit, friction, or prolonged use
- Swelling or increased edema
- Pain or discomfort resulting from tightness, misalignment, or mechanical pressure.
- Delayed fracture healing due to excessive joint movement
- Muscle atrophy or joint stiffness from immobilization
- Reduced range of motion (ROM)
- Removal of material (e.g., screws) due to discomfort or healing complications

Serious Adverse Events (SAE) are complications requiring hospitalisation, surgical intervention, or posing a significant risk to the patient.

- Death (e.g., an unexpected cardiac event occurring during the study period)
- hospitalisation due to falls resulting from brace-related instability.
- Wound infection requiring inpatient treatment, potentially related to brace-induced irritation,
- deep vein thrombosis (DVT) or pulmonary embolism due to immobilisation
- Reoperation for malunion, non-union, or brace failure

- Fracture re-displacement necessitating surgical correction.
- Severe allergic reaction (e.g., anaphylaxis) to materials used in the brace.
- permanent nerve damage due to sustained compression from the brace and
- Serious skin ulceration requiring surgical debridement.

N (%)		walker	stirrup	Difference OR (95% CI)
Adverse Events				
	Related			
	Unrelated			
Serious Adverse Events				
	Related			
	Unrelated			
Relation is determined by the Data Monitoring Committee OR – Odds Ratio				

#### Statistical interim analyses and stopping guidance

Every six months, a data manager will perform a descriptive interim analysis for each subgroup and surgical and non-surgically treated patients on safety (number of adverse and serious adverse events) and recruitment rate to each subgroup. The interim analysis will be reported to the Data Monitoring Committee (DMC) and the steering committee. The DMC will at each meeting assesses if the trial an continue for each subgroup.

Interim outputs will be blinded by treatment arm.

#### Timing of final analysis

All analysis will be completed simultaneously when the last patient reaches the 12-week follow-up post-fracture.

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