STATISTICAL ANALYSIS PLAN

Version 1.0

Date: 20.11.2025

LIMPER trials: Immediate mobilisation versus 2-week cast immobilisation after distal radius fracture treated with volar locking plate – a prospective, randomized, controlled trial

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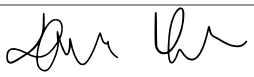
Last recruitment: NA

SAP Revision history

Date	Timing	Drafted/revised by	Version number	Description of amendments
20.11.2025	Prior to last recruitment	Ville Ponkilainen Laura Kärnä Aleksi Reito	1.0	First draft of SAP based on original trial protocol

Signatures

Date	Role	Name	Signature
20.11.2025	Author of the SAP and senior statistician responsible	Ville Ponkilainen	
20.11.2025	Chief investigator	Laura Kärnä	

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INTRODUCTION

Background

The LimperDRF trial is a multicentre, parallel-group, randomized controlled trial comparing immediate postoperative mobilisation with a 2-week postoperative cast in working-age patients undergoing volar plating for distal radius fractures (DRFs). Patients are randomized in a 1:1 ratio.

Objective

The coprimary objectives are to determine whether immediate mobilisation is equivalent to 2-week immobilisation after surgery for DRF, in terms of:

1. Wrist function at 2 months postoperatively, measured by patient-related wrist evaluation (PRWE)
2. Total length of postoperative sick leave

STUDY METHODS

Trial design

The LimperDRF trial is a randomised, controlled, 1:1, multicentre equivalence trial comparing immediate mobilisation versus 2-week cast immobilisation in working-age patients after DRF treated with open reduction and volar locking plate fixation.

Randomization

Randomisation will be performed after the wound has been sutured, because earlier randomisation might influence the surgeons' judgement, for example, in longer operating time. Thereafter, the allocation group will be revealed to the patient and the operating surgeon.

Participants will be included in the immediate mobilisation group or the 2-week cast group in a 1:1 allocation as per computer-generated randomisation matrix with randomised block size and stratified by work physical exertion level (sedentary/light vs medium/heavy/very heavy), fracture articulateness (intra-articular or extra-articular) and age (older or younger than 55 years).

Sample size

Full sample size calculation is presented in the original protocol publication[1]. The required sample size is 120 patients per group and equivalence margin was set at 6.3 points (PRWE).

Framework

This trial is an equivalence trial. The coprimary outcomes (PRWE and length of sick leave) will be evaluated within an equivalence framework.

Statistical interim analyses and stopping guidance

Both treatments are routinely used in clinical practice, and no serious harms or adverse events are expected from either intervention. Therefore, no formal stopping guidelines have been established.

Timing of outcome assessments

Primary and secondary outcomes are collected at 4 weeks, 2 months, 6 months, and 12 months.

Timing of final analysis

The final analysis will be based on 12-month follow-up data.

STATISTICAL PRINCIPLES

Confidence intervals and p values

All confidence intervals will be reported at the 95% level. All statistical tests will be two-sided, with a significance threshold of $p < 0.05$.

Adherence and protocol deviations

This SAP is based on the published protocol[1]. No protocol deviations affecting statistical methodology have been identified.

Analysis populations

All analyses will be performed on an intention-to-treat (ITT) basis.

TRIAL POPULATION

Screening data

We will report the screening data for all patients who were invited to participate in the trial, including withdrawals, crossovers and intercurrent events.

Eligibility

Inclusion criteria

- Patients with intra-articular or extra-articular DRF including Smith's and volar Barton's fracture
- Patients with or without accompanying fractures of the processus styloideus ulnae, and
- Patients who have been pragmatically chosen for operative treatment.

Exclusion criteria

- Refusal to participate in the study.
- Open fracture with a severity greater than Gustilo grade 1.
- Patients aged less than 18 or more than 65 years.
- Patient does not understand written or spoken guidance in local languages.
- Pathological fracture
- Fractures that are operated on 3 weeks or more after the injury.
- Fracture assessed to need casting after operation: for example, severely comminuted fracture where the fracture morphology is assessed to need both the volar locking plate and postoperative casting.
- Previous fracture in the same wrist or forearm in the last 10 years that has led to impairment of function
- Ipsilateral fracture in upper extremity.
- Polytrauma.

Recruitment

Working-age patients with DRF who are scheduled for volar plating will be asked to participate in the study. Patients will be recruited at either preoperative visits to the outpatient clinic before surgery or on the ambulatory surgery ward the same day the surgery will be performed. The study participants will provide signed informed consent before the operation. Randomisation will be performed intraoperatively after the wound is sutured. Patients that refuse to participate, will be collected in screening log. Participants that are recruited, but are intraoperatively excluded for randomisation will be followed via questionnaires during the 1-year follow-up. Screening process is described in the flow chart (Figure 1).

Withdrawal/follow-up

Withdrawals and losses to follow-up will be collected in the REDCap at each time point.

Baseline patient characteristics

Baseline demographic and clinical characteristics will be summarized descriptively by treatment group as presented at Table 1. For continuous variables, data will be presented as mean (standard deviation [SD]) for approximately normally distributed variables, and as median (interquartile range [IQR]) if the distribution is non-normal. Dichotomous variables will be reported as counts (percentages). The normality of continuous variables will be assessed using visual inspection of histograms and Q–Q plots, supplemented by the Shapiro–Wilk test in cases of uncertainty.

OUTCOME MEASURES

Coprimary outcomes

1. Wrist function, measured as PRWE total score at 2 months, equivalence margin 6.3 points.
2. Total length of sick leave (days) up to 12 months, equivalence margin 4.1 weeks.

Analysis hierarchy for coprimary endpoints

The coprimary outcome will be tested according to the following hierarchy: We first test the PRWE at 2 months after the surgery. If the group difference is below the prespecified equivalence margin of 6.3 points, we will consider the groups equivalent and continue to test the second coprimary outcome. Only if both coprimary outcomes will result equivalent group differences, we will conclude that immediate mobilisation is equivalent to 2 week cast immobilisation in operatively treated DRFs in working aged population.

If the group difference exceeds the equivalence margin in either of the co-primary outcomes, the treatment with the greater effect will be considered superior.

Secondary Outcomes

1. Perceived working capacity, scale from 0 to 10, where higher score indicates higher ability to work
2. Pain (VAS), scale from 0 to 10 where higher score indicates higher pain
3. Patient satisfaction (PASS), including two items: 1. percentage of patients that are satisfied with the treatment and 2. percentage of patients that are willing to take the same treatment again if the treatment result was as it is now.
4. Complications (minor and major)

Other outcomes

Objective activity level (accelerometer)

ANALYSIS METHODS

PRWE, Pain-VAS and perceived work ability

The main comparison will be conducted by a repeated-measures mixed model (RMMM), including fixed effects for group allocation (cast or immediate mobilization), time point (baseline, 4 weeks, 2 months, 6 months, and 12 months), and stratification factors as covariates: age (older or younger than 55 years), fracture type (intra-articular or extra-articular), work physical exertion level (5 level factor, sedentary/light vs medium/heavy/very heavy), and study centre. A random intercept for patient (ID) will be included. The treatment effect will be expressed as the adjusted least-squares mean difference between groups at 2 months, along with the corresponding 95% confidence intervals (CI) and p-value.

Length of sick leave

Analysis for sick leave will be conducted with linear regression, including the same covariates as the RMMM model. The treatment effect will be expressed as the adjusted least-squares mean difference between groups at 2 months, along with the corresponding 95% confidence intervals (CI) and p-value.

PASS and complications

Binary outcomes (PASS and complications) will be analysed using logistic regression model. PASS is assessed at each time point separately and complications over the study period. Group allocation is the main exposure and above-mentioned covariates will be included in the model for adjustment. The main result will be the adjusted marginal risk difference between the groups from this model.

Objective activity level

As stated in the original protocol, all analyses with the activity data will be exploratory and hypothesis-generating. Exploratory analysis will assess differences in physical activity levels. Data will be analysed descriptively and using linear models. We will publish the accelometer data in a separate publication.

Missing data

Missing data for continuous outcome measures will not be imputed, as we are assuming data are missing at random, consistent with the underlying assumption of the model. The number of missing data items, including withdrawals and losses to follow-up at each time point, will be reported descriptively.

Multiplicity

The secondary analyses will be considered only to be supportive, explanatory or hypothesis-generating (or both), and as such, the p-values or alpha levels for these analyses will not be adjusted for multiple comparisons.

Harms

At 1-year follow-up, patient data will be reviewed to detect any complications. Complications are defined as problems with wound healing, deep infections, hardware failure (loss of reduction, malunion), tendon complications (both extensor and flexor irritations or ruptures), nerve-related problems (paresthesia, Complex Regional Pain Syndrome (CRPS)) or reoperation (for any reason). Complications are divided into major and minor complications. Problems with wound healing are categorised as minor complications and will be assessed via electronic questionnaires. Major complications include loss of reduction and hardware failure during follow-up resulting in reoperation, permanent nerve damage and CRPS.

Major and minor complications will be reported as counts with percentages, similar to other binary outcomes. Group differences at 12 months will be presented as odds ratios with 95% confidence intervals, derived from a logistic regression model.

Exploratory analyses

We have planned several additional analyses using the trial data. All these analyses are exploratory.

Accelometer analyses

We have planned to extract the raw Axivity data and process it with a open-source R algorithm GGIR. Patient activity per day is categorised to inactivity, low, moderate and vigorous activity. Primary Axivity analysis includes desciptive analysis of temporal changes in the activity level. Secondarily, we will compare average amount of each activity levels between the treatment groups. This analysis includes same covariates as the primary analysis of the trial.

We will also assess the association between Axivity levels and patient experienced pain and adverse events. With regard to pain, we plan to perform analysis at the 4 weeks time point and predictive analysis regarding pain at 2,6 and 12 months. Baseline variables will be included as covariates in the analyses.

If there are enough adverse events, we plan to do predictive analyses focusing on activity levels and adverse events during the 12 months follow-up period.

Ancillary MIC analyses

1) Minimal important change for return to work and work-related disability

Minimal important change is traditionally calculated using PROM and against some form of anchor question such as global improvement. In this trial we inquire patient rated work-related disability and return to work. We plan to investigate “work-related MIC” using PRWE as the outcome and return to work and work disability as an anchor question.

Radiological analysis

We will investigate the association between radiological parameters and patient reported symptoms at the 12 months follow-up. Main focus is to analysis to which degree radiological parameters angulation, inclination and articular step-off explain and predict 12 months PRWE together with other covariates.

Temporal analysis for PASS
PASS is a binary approach to assess if patient considers current symptom-state acceptable. We investigate what is the threshold for PRWE to achieve PASS at different time points. We also assess how achievement of PASS changes with follow-up and which temporal change is associated to PASS achievement.

Blinded Analysis

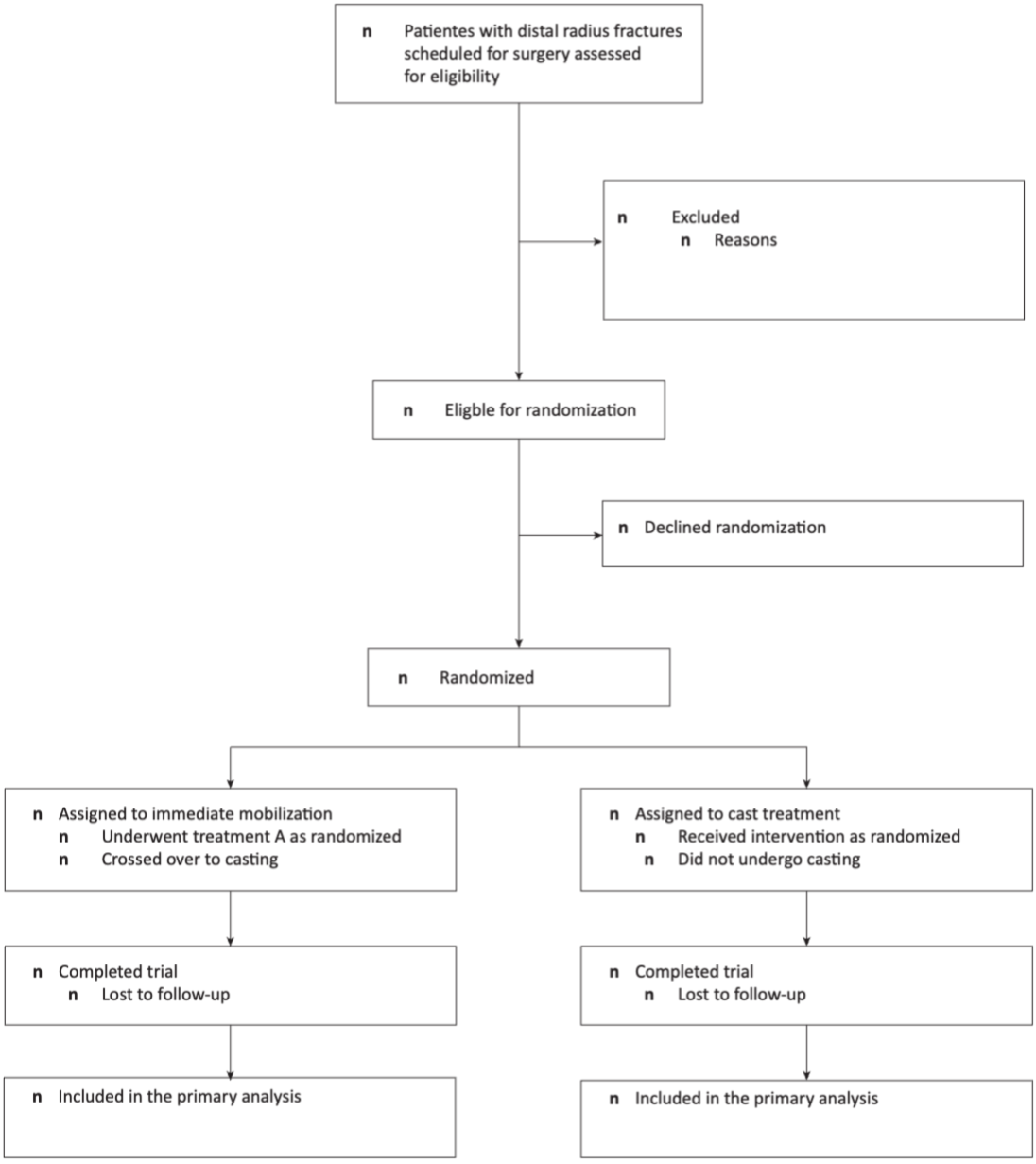
The primary analysis will be conducted using blinded data interpretation. Treatment groups will be labeled using coded identifiers (e.g., Treatment A and Treatment B). All statistical analyses and interpretations will be completed based on these blinded group assignments before unblinding occurs.

Statistical software

Analyses will be conducted using R software, version 4.4.1 (R Foundation for Statistical Computing, Vienna Austria). Data cleaning will be performed using the R packages janitor, dplyr, and tidyr; analyses will be conducted using lme4, emmeans, lm, glm; and figures will be generated using ggplot2.

PROPOSED FIGURES AND TABLES

Figure 1. Flow chart



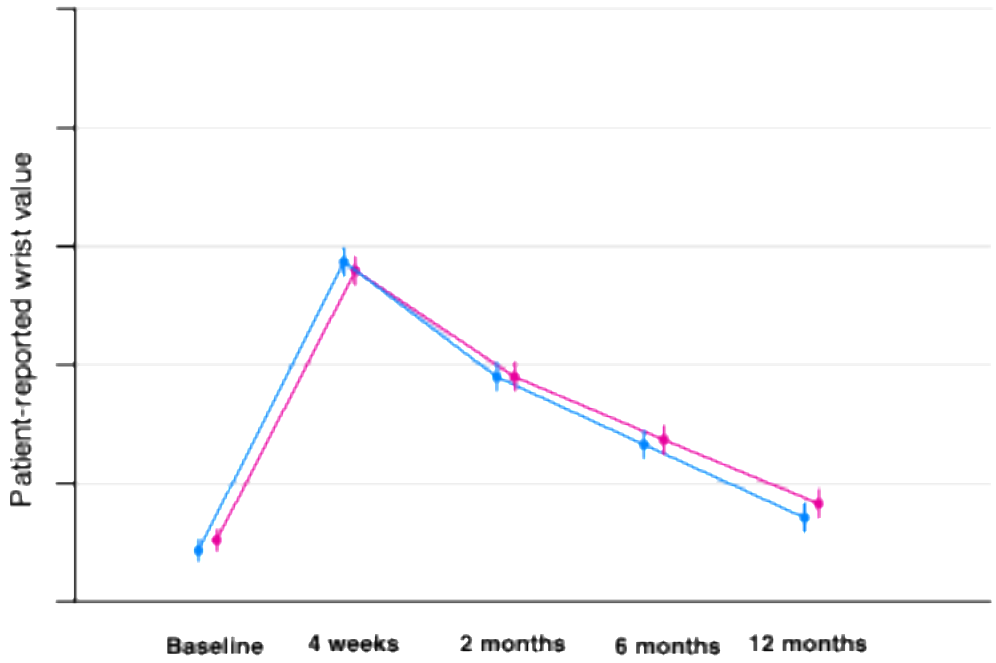


Figure 2. The trajectory of PRWE will be displayed as a point plot, with error bars indicating the confidence intervals at each time point. Each point represents the least-squares mean at the corresponding time point by group, derived from RMMM model (described above).

Table 1. Baseline patient characteristics will be reported as mean ± SD, median IQR, or count with percentage (%), as appropriate based on variable distribution.

	Group A	**Group B**
Age, years		
Sex		
Female		
Male		
Height, cm		
Weight, kg		
Body Mass Index, kg/m^2		
Handedness		
Comorbidities (DM, rheumatoid dicease, stroke, osteoporosis, neurological disorders, ASO)		
Injury mechanism		
Date of injury		
Time to surgery (days)		
Fracture classification		
Work status		
Education level		
Workability (0-10)		
Smoking, yes/no		
Physical work exertion level (1-5)		
PRWE total score		
Pain VAS		

Table 2. Primary results at 12 months

	Group A	**Group B**	**Adjusted mean difference (95% CI)**
Primary outcomes			
PRWE total score (0-100)			
Length of sick leave (days)			
Secondary outcomes			
Pain VAS (0-10)			
Perceived work ability (0-10)			
Satisfaction, n (%)			
Patient Acceptable Symptom State			
Willing to take the same treatment			

Table 3. Major and minor complications at 12 months

	Group A	**Group B**	**Risk difference (95% CI)**
Major complications			
Minor complications			

References

1. Kärnä L, Launonen AP, Karjalainen T, et al. LIMPER trials: immediate mobilisation versus 2-week cast immobilisation after distal radius fracture treated with volar locking plate–a study protocol for a prospective, randomised, controlled trial. *BMJ open* 2022;12(11):e064440.