DISCLOSE

Version 1.0 Final

CLINICAL TRIAL PROTOCOL

STUDY TITLE

A Randomized Controlled Trial Comparing No Reduction to Closed

Reduction for Distal Radius Fractures in Patients 65 Years and Older (DISCLOSE trial)

REFERENCE NUMBERS

Research ethical approval: R25001 Tampere Ethics committee

ClinicalTrials.gov: NCT07042139

STUDY SPONSOR

Wellbeing Services County of Pirkanmaa (PIRHA), Finland

COMPLIANCE STATEMENT

This trial is to be conducted in compliance with this protocol and with the principles of Good Clinical Practice.

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Document	Date of Issue	Summary of Change
Protocol version no.		
Original protocol 1.0 FINAL	6.7.2025	Not applicable

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1 BACKGROUND

Distal radius fractures (DRFs) are one of the most common fractures, occurring at a rate of 212 per 100,000 person-years.[1] These fractures typically result from low-energy trauma, such as fall from standing height and are associated with age-related increases in frailty. As general life expectancy rises, so does the number of these fractures [2 3], presenting a growing challenge in function and quality of life in both acute care and long-term management of the fracture. The majority of DRFs in patients aged 60 years or older are treated non-operatively due to a higher complication and reoperation rate without significantly better functional outcomes after surgery.[2 4-6]

Although anatomical alignment has traditionally been the primary goal of fracture reduction, evidence suggests that radiographic improvement is not necessarily associated with better functional outcomes, especially in older adults.[7-9] Even when closed reduction is initially successful and radiographic alignment is achieved, several studies suggest that alignment frequently deteriorates during follow-up, especially in elderly patients.[9-11] Especially radial shortening tends to return to the pre-reduction state by the time the cast is removed at 5-6 weeks, while dorsal angulation seems to be maintained better.[12-26] Reported total loss of reduction in adult patients with DRF range from 12 % to 100% [12-15 20 22 24 27], with patients aged 60 years or more having the highest rates (40% to 100%).[10 28 29] Despite the fact that reduction is nearly always lost, in a Finnish registry study, the incidence of corrective osteotomies is very low (0.3-0.7/100000 per person-years), especially in patients 65 years or older.[5]

Patients often perceive closed reduction as a painful and uncomfortable procedure.[30] Studies show that closed reduction increases pain when compared to casting alone in patients

awaiting surgery for DRFs.[31] There is also evidence that pain during closed reduction can decrease overall satisfaction and compliance with treatment.[32]

There is limited evidence regarding whether the closed reduction of DRFs in elderly patients improves clinical outcomes since only one randomized controlled trial has been published to compare closed reduction and casting to casting alone. In 1997, Kelly et al. reported no difference in functional outcomes between groups despite improved radiographic measures in the closed reduction group.[26] Since radiographic measures do not correlate to functional outcomes, it is uncertain whether the routine use of closed reduction in DRF is effective in improving functional outcomes and patient satisfaction in patients aged 65 or more.[7]

1.1 Objective

To evaluate whether casting without prior closed reduction is equivalent to casting following closed reduction with respect to wrist-related pain and disability, as measured by the Patient-Rated Wrist Evaluation (PRWE) score at 12 months, in patients aged 65 years or older with a displaced distal radius fracture.

2 METHODS AND ANALYSIS

2.1 Study setting

We will conduct a multicenter randomized controlled equivalence trial. We will also include a prospective observational group for eligible patients who decline participation in the randomization. The study will be conducted across multiple study centers located in Finland, Denmark, Sweden, and Estonia.

2.2 Participants

The study population will include patients aged 65 years or older having displaced distal radius fractures.

2.2.1 Inclusion criteria:

- Age 65 years or older
- Independent living patients
- Displaced distal radius fracture (AO/OTA 23A/23C) with 15-40 degree dorsal angulation; and/or shortening of the radius for more than 2 mm.
    - Associated ulnar styloid fracture is permitted
- Low energy injury, (fall from ≤1 m)

2.2.2 Exclusion criteria:

- Patient unable to provide consent
- Patients who are actively working in a paid position
- Volar angulation, partial articular fractures (AO/OTA 23B)

- Concomitant fracture of the ulna proximal to the base of the styloid process
- Associated fracture or dislocation in any other body part that would affect the use of the injured distal radius
- Distal radius fractures in both arms
- Open injury, Gustilo 2 or higher
- No bony contact between the main fragments
- High energy injuries

2.3 Interventions

Participants eligible for this trial will be recruited by orthopaedic residents/surgeons and emergency medicine doctors (recruiting personnel) in the emergency room. Eligible patients will be provided with a participant information sheet and given enough time to evaluate their willingness to participate and to ask questions about the trial. Patients who decline to be included in the randomized cohort of the study will be invited to participate in the observational cohort. Written consent will be obtained prior to inclusion in both study cohorts.

2.4 Randomization

Randomization will occur immediately after the written consent has been achieved in the emergency room. Randomization will be done using an online randomization system, Redcap. Randomization will be stratified by patients age (65-74 years and >74 years) and country using variable block sizes ranging from 2 to 6 and a 1:1 allocation ratio. The allocation sequence will be concealed from all study personnel through the use of an online randomization system.

2.5 Intervention group (No reduction)

A dorsal cast is applied to the patient's wrist after the initial radiograph in the no-reduction group. Following casting, a control radiograph is taken. Active range of motion exercises for the fingers and light use of the hand are recommended immediately.

2.6 Control group (Closed reduction)

Distal radius fracture reduction is performed in the emergency department under local anaesthetic infiltration, using lidocaine into the fracture site. The closed reduction is performed by the treating physician using their usual technique. Re-attempts at reduction are allowed in accordance with local practice. Post-reduction radiographs are taken to assess fracture alignment, although the findings do not influence the patient's treatment.

In both groups, the cast will be removed after 5 weeks at either the health center or the hospital's outpatient clinic, in accordance with the local treatment protocol. Following cast

removal, patients will be advised to resume everyday use of the injured wrist without restrictions. No radiographs will be taken during the casting period or before the 3-month follow-up.

2.7 Observational arm *(not part of the randomised equivalence trial)*

Eligible patients who decline participation in the randomization will be offered the opportunity to join an observational group. The patients will receive standard care (closed reduction and casting) and will provide consent for follow-up. The reduction of DRF is performed in the emergency department and post-reduction radiographs will be taken. Observational groups are treated according to local treatment protocols. Patients in the observational cohort will be followed at the same time points using the same outcome measures as the randomized group. Study follow-up of the observational group will be organized through remote controls.

2.8 Rehabilitation

All groups will receive a similar home exercise protocol. Outpatient physiotherapy and occupational therapy will be allowed according to the local practice.

3 PARTICIPANT TIMELINE

The schedule for enrollment, interventions and follow-up visits are presented in Table 1.

Participants will not be blinded due to the nature of the intervention. Recruiting personnel will only have access to the randomization module within the electronic REDCap software. The

outcome assessors (study nurse or orthopaedic resident or specialist) who collect the baseline data and outcome measures from follow-up visits will be blinded from the randomization result. Study personnel involved in follow-up visits will remain blinded to the randomization results, as the result is hidden in REDCap.

Participants will meet a research personnel or coordinator study nurse at the 3 and 12-month time point. At 3 months' time point, radiographs are taken. No additional radiographic follow-ups are organized. Follow-up appointments are carried out according to the participants' preference: All patients are invited to attend an in-person follow-up visit; however, if they decline, the follow-up will be conducted remotely via phone or via email link by a blinded study nurse. In the remote option, the accelerometer wristbands will be sent to the participants by mail. By offering a remote option, we aim to minimize the loss to follow-up. Participants will receive follow-up questionnaires via email or mail prior to their follow-up appointment. If they decline to complete the questionnaires, outcomes will be collected through a phone interview. The research data will be saved in a database with an online patient management program, REDCap. The 5-year follow-ups will be conducted by sending questionnaires via email or mail; if participants decline, outcomes will be collected through a phone interview.

All patients with unsettling symptoms will undergo physiotherapy rehabilitation for up to a year, as in standard care. If the symptoms do not improve during this time, the patient will be referred to an orthopaedic or hand surgeon for evaluation, where necessary procedures, such as a CT scan and, in cases of symptomatic malunion or nonunion, corrective osteotomy, will be considered.

4 OUTCOMES AND ENDPOINTS

4.1 Baseline data

Baseline variables will be collected by study personnel via phone within two working days following randomization. The study personnel will remain blinded to the randomization results.

Baseline variables include age, gender, hand dominance (right/left), height, weight, fracture type, smoking (yes/no), diabetes (yes/no), rheumatoid arthritis (yes/no), osteoporosis (yes/no), previous fractures in same wrist, use of analgesics and use of glucocorticoid treatment (yes/no), use of osteoporosis treatment (yes/no). Radiographic outcomes (dorsal angulation, ulnar variance, radial inclination, intra-articular gap) will be measured from the initial radiographs at baseline. Patient-Rated Wrist Evaluation (PRWE), Pain NRS, and EQ-5D-5L Index will be collected at baseline via phone, with patients asked to recall their status prior to the fracture (Appendix 1). Patient frailty will be assessed at baseline using the Clinical Frailty Scale (CFS)[33], as rated by the study nurse.

4.2 Primary endpoint

The primary outcome will be the Patient Rated Wrist Evaluation (PRWE) at 12 months.[34] PRWE is a 15-item questionnaire designed to measure wrist pain and disability in activities of daily living. The validity, reliability, and responsiveness of the questionnaire have been reported to be high for assessing the outcomes after distal radius fractures.[35-37] The questionnaire consists of two subscales (pain and function), and the score ranges from 0 (no disability) to

100 (severe disability). The minimal clinically important difference (MCID) in the PRWE is 11 points.[38] The validity and reliability of the Finnish PRWE are acceptable in patients with DRF.[37]

4.3 Key secondary endpoints

4.3.1 PRWE

PRWE is additionally measured at 3 months.

4.3.2 Pain

The Numeric Rating Scale (NRS) for Pain is a validated 11-point numerical rating scale for acute and chronic pain with terminal descriptors of 0 (no pain) and 10 (worst pain possible).[39] [40] Patients will be asked to evaluate the perceived pain during the last 7 days. Pain will be assessed at 3-months and 1-year.

4.3.3 Patient-acceptable symptom state

Patient satisfaction will be measured using the patient-acceptable symptom state (PASS).[41] Considering all the different ways your injury is affecting you, if you would remain in this state, do you feel that your current state is satisfactory (Yes/No)? PASS will be assessed at 3-month and 1 year. Patient satisfaction will be reported as percentage of patients with acceptable PASS.

4.3.4 Quality of life

EuroQol 5-dimension 5-level health-related quality of life questionnaire (EQ-5D-5L Index) is a general measure of health-related quality of life that has been validated for assessing quality of life in patients with upper extremity disorders.[42-44] Quality of life will be assessed at 3-months and 1-year.

4.3.5 Serious adverse events

Serious adverse events include, but are not limited to: late surgical interventions such as corrective osteotomy or internal fixation due to symptomatic nonunion; tendon repair; carpal tunnel release; acute nerve injury confirmed by electroneuromyography; and any other adverse event that results in hospitalisation, prolongation of existing hospitalisation, is life-threatening, or leads to persistent or significant disability (for example Complex Regional Pain Syndrome) or incapacity. Serious adverse events will be assessed at 3- and 12-months timepoints.

Asymptomatic malunion is not an adverse event, as most patients who undergo closed reduction after distal radius fracture develop malunion.[10 26 29] Symptomatic nonunion is defined as the presence of significant pain accompanied by the absence of a bony bridge on CT images. If a patient develops a symptomatic nonunion, a CT-scan will be taken at the 1-year time point in accordance with the standard treatment protocol.

4.3.6 Cosmesis

Participants are asked a question about wrist cosmesis: Does the appearance of the wrist bother you? (yes/no). Cosmesis will be assessed at 3-month time point.

4.4 Other endpoints

4.4.1 Radiographic measurements

Radiographic parameters are collected from radiographs taken at baseline and after casting, in accordance with the local treatment protocol**.** Control radiographs are taken at a 3-month time point, where we measure the loss of reduction and compare the final measurements between the groups. If a patient develops a symptomatic mal- or nonunion, a CT scan is taken at a 1-year time point, in accordance with the standard treatment protocol *(Appendix 2)*. Radiographic measurements will include dorsal angulation (degrees), ulnar variance (mm), radial inclination (degrees) and intra-articular gap (mm).

4.5 Exploratory endpoints

All exploratory endpoints are published in separate publications.

4.5.1 5 year follow-up

PRWE, Pain (NRS), quality of life, patient satisfaction, serious adverse events and mortality will be assessed at 5 years and are exploratory endpoints.

4.5.2 Tri-Axial Accelerometry

The upper-limb physical activity of the participants will be measured using a tri-axial (Axivity Ltd, Newcastle upon Tyne, UK) accelerometer. Activity is divided into four activity levels (inactivity, light, moderate and vigorous), and also sleeping time is counted and recorded. The participants will have an accelerometer sensor mounted on both wrists with a wristband. This

allows us to assess the asymmetry between the fractured and non-fractured arm. Patients in both groups are advised to use sensors for 7 days in 3- and 12-month follow-ups.

4.5.3 Mortality

All-cause mortality data will be collected from medical health records at the 5-year follow-up.

4.5.4 Cost-effectiveness

Included unit cost components include hospital stays and outpatient visits, including imaging, surgical and anesthetic procedures, physiotherapy, complication management and re-operations and cast changes. Costs will be obtained directly from patients through questionnaires administered at the 3-month and 1-year follow-up, and from medical records. Cost data will be derived from the NordDRG classification system. Using the mean costs and mean health outcomes for each cohort, the incremental cost per quality-adjusted life-year (QALY) gained will be calculated.

4.5.5 DXA – Bone density scan (not part of the equivalence trial)

At selected sites, a subgroup of patients will be formed, from whom bone density Z-scores will be collected at 6 months. Results above -1 SD are regarded as normal. -1 to -2.5 SD are osteopenic, with reduced bone mineral density, and -2.5 SD and less are osteoporotic. DXA scans are used to assess bone mineral density (BMD), which provides information about bone strength and fracture risk. DXA data allows the stratification of participants based on

their underlying bone health (e.g., normal BMD, osteopenia, or osteoporosis). DXA data will be used to analyze incidence of osteoporosis and the correlation between bone density and loss of fracture reduction in patients with distal radius fractures. This data will be analyzed in separate publication.

5 SAMPLE SIZE

The sample size was determined based on an equivalence design, with an equal allocation ratio (1:1). We set the significance level (α) at 0.05, allowing a 5% probability of a Type I error. The power of the study was set at 90% (β = 0.1), corresponding to a 10% probability of a Type II error. The standard deviation of the outcome (PRWE) variable was estimated to be 21, based on previous studies.[9 22 45 46].

Based on the familiar minimal important difference (MID) for PRWE of 11.5 points, the equivalence margin was set at 6 units (half of MID), representing the maximum acceptable difference in means between the groups to still consider the groups as equivalent. This margin was intentionally set below the MID of PRWE to detect smaller differences, given the similar nature and cost of the two treatment approaches.

Using these parameters, a total sample size of 532 participants (266 per group) will provide 90% power to demonstrate equivalence between groups on the primary endpoint, assuming a true mean difference of < 0.01, a common standard deviation of 21, and equivalence margins of –6 to 6 on the PRWE score. The calculation was based on a 2-sided 90% confidence interval (α = 0.05) and used the exact method for two-sample means under normal distribution assumptions.

6 DATA COLLECTION

Primary data collection is conducted by the study personnel, who enters the data into an electronic system (REDCap) based on a phone interview or, if a patient prefers- through the e-mail link. All patients who attend an in-person follow-up visit will enter the data at the visit, while data for patients participating in remote follow-ups will be collected by study personnel via phone or through an e-mail link, based on their preference. These different follow-up options will be offered to minimize missing data.

7 DATA ANALYSIS

The primary hypothesis is that patients aged 65 and older with displaced distal radius fractures treated non-operatively with casting alone (without closed reduction) will have clinically equivalent-functional outcomes, as measured by the PRWE score at 12 months post-injury, compared to those treated with closed reduction and casting.

All primary and secondary analyses will follow the intention-to-treat principle. The findings will be presented in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. [47] The main comparison, PRWE total score between the study groups, will be analyzed using a repeated-measures mixed model (RMMM). Fixed factors in the analysis will include the study group and assessment time, while patients will be treated as random factors. The analysis will also incorporate interaction between the study group and the assessment time. The results will be presented as mean with 95% confidence intervals (CI) at 12 months following randomization. Missing data for continuous outcome measures will be handled using a mixed-effects linear model approach, assuming data are missing at random, consistent with the underlying assumption of these models[48]. For dichotomous

outcomes, missing data will be addressed using nonresponse imputation, in which patients who withdrew or did not provide a response will be considered non-responders.

Categorical endpoints will be analysed for each individual timepoint by logistical regression using randomised treatment, stratification groups as factors, and the baseline endpoint value as a covariate. For categorical efficacy outcomes, missing data will be addressed using nonresponse imputation, in which patients who withdrew or did not provide a response will be considered non-responders. The secondary analyses will serve only as supportive, explanatory, or hypothesis-generating. Serious adverse events will be reported in a descriptive manner.

We will perform a series of sensitivity analyses to evaluate the robustness of the results to departures from the assumptions underlying the statistical analyses described below [49]. Because some patients are likely to experience important intercurrent events (e.g., undergoing surgery within the first 12 months from baseline; i.e., referred to as crossovers), sensitivity analyses will explore whether different assumptions about missing data could affect the conclusions[50]: For example, we will apply the hypothetical estimand, which corresponds to a while-on-randomized-treatment strategy. This approach aims to estimate the effect of the interventions up to, but not beyond, the occurrence of an intercurrent event. Specifically, the outcome value(s) prior to the intercurrent event will be used for analysis.

Among the prespecified ancillary analyses is an exploration of whether age group and sex modify the effect of treatment on the primary endpoint at 12 months. Specifically, outcomes will be compared between patients aged <75 years and ≥75 years, and between males and females

The observational cohort will be analyzed independently, employing statistical methods similar to those used for RCT study groups. 5-year results will be presented as a separate publication.

8 BLINDED DATA INTERPRETATION

To minimize the risk of biased interpretation, the results of this trial will be reported using a blinded data interpretation process [51]. Before reviewing the primary outcome data, the writing committee will prepare a "Background Assumptions" document outlining their predefined MIDs for the outcome measures, along with a brief summary of the planned statistical analyses. This document will be signed by all members of the writing committee and included as an appendix to the main publication.

Following this, the committee will conduct two separate interpretations of the primary outcome data, first assuming that Treatment A represents the no reduction group, and then assuming that Treatment A represents the closed reduction group. All decisions regarding key analyses and the format for presenting the primary results will be made prior to unblinding. These decisions, along with the meeting minutes, will be formally recorded, signed by the writing committee, and published as an appendix to the primary report.

8.1 Patient and Public Intervention

Patient and Public Involvement (PPI) was conducted in collaboration with Pirkanmaa Bone Association, following the GRIPP2 reporting checklist (Appendix 3). During a dedicated

meeting with association members, both primary and secondary outcomes were thoroughly reviewed. Pain and functional ability in daily tasks were identified as top priorities. Based on discussions with the association members, maximum grip strength was excluded from the outcomes, as it was not considered to have significant relevance to daily life. While the outcomes were considered appropriate, early recognition of pain emerged as a concern. In response, we improved the visibility of contact information to ensure patients know where to seek assistance in cases of severe wrist pain. To maintain ongoing patient and public engagement, we collaborated with a permanent PPI representative throughout the entire study period.

8.2 Data management

Each patient will be assigned a unique trial identification number (TIN) matched with the patient's personal identification number (ID). This is assigned when the patient has signed informed consent, and TINs are consecutive and never reused. The research data will only be handled with a TIN throughout the trial. For patients recruited in Tampere University Hospital, Patient personal ID is stored in the electronic secure server LOKERO at. Each research center has its code keys for its own patients, which only the centers themselves have access to ensure patient confidentiality. All research data will be saved on a database with an online patient management program REDCap (Research Electronic Data Capture, https://www.project-redcap.org/) and secured by two-factor authentication. Only trial researchers will have access to the REDCap data located on a secure study server at Tampere University Hospital. This approach ensures patient de-identification and guarantees

that individual identities will remain protected, even in the event of unauthorized access to the server data. The research data that study personnel use on the server will contain only de-identified TINs with a set of numbers acquired from the questionnaires, i.e., each question will be answered with a number. Patients e-mail is matched to patient's TIN to have the remote option (via email) to be available.

All primary and secondary data will be acquired and stored on the study server. Follow-up data will be entered either directly by patients, during visits using a tablet or remotely via an email link, or by a researcher or study nurse when questionnaires are returned by mail or completed through phone interviews. Patient-reported outcome data will be entered directly into the REDCap system by the patients using the "required fields" option activated to ensure there are no missing items from the completed questionnaires. Researchers from each participating hospital will have access to the secure study server where the trial research data is stored. An information security committee has approved the server at Tampere University Hospital.

The copyright of the trial research data will be owned and created by the collaboration parties. The data will be shared freely among the collaboration parties. All participating researchers will have access to the data after the trial. Due to EU General Data Protection Regulation (GDPR), public data sharing will be restricted until primary analysis and publication have been completed. Under certain circumstances, e.g., when a new member joins the collaboration, we will grant access to the data. All data will be stored for 15 years after the end of the trial.

A Data Safety Monitoring Board (DSMB) will oversee the study to ensure the rights, safety and well-being of participants throughout the trial. Monitoring will be conducted according to a pre-approved monitoring plan and in compliance with the principles of Good Clinical Practice (ICH GCP 5.18). The monitor will assess whether the trial is conducted, documented and reported in accordance with the protocol, regulatory requirements and applicable guidelines.

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