# Administrative information:

**Title:** Comparing Nail versus Locking Plate in displaced three-part proximal humerus fractures; A multi-center randomized controlled trial (Otago PHINZ trial) investigating the effect on function post-operatively.

Trial registration:

Protocol version:

The Universal Trial Number (UTN): U1111-1288-0672

**Funding**

This trial is sponsored mainly by ‘University of Otago Christchurch - Orthopaedic Surgery and Musculoskeletal Medicine’, and ‘Christchurch hospital – Trauma Orthopaedic Surgery’.

**Role and responsibilities**

Dr Richard LIoyd (RL) conceived the research question. RL, Dr Zohreh Jafarian Tangrood (ZJT) and Dr Sam Arnold contributed to the design of the intervention. ZJT wrote the protocol with active contribution of RL. Authors revised and approved the protocol for the study. ZJT leads efforts for securing funding, registration and ethics approval.

# Abstract

Proximal humeral fractures (PHF) comprise the most common osteoporotic fractures after wrist and hip fractures in the elderly population. The mean age reported for the incidence of PHF is 70 years which increases with age. Accident Compensation Corporation (ACC) report in New Zealand showed an increase of more than two times of PHF in elderly in 2022 rising from 65 incidence at 50-54 years old to 139 at 70-74 years old. Low energy trauma in elderly consists of 19% and high energy trauma in young people consists of 43% displaced PHF requiring surgery treatments. Open Reduction Internal Fixation (ORIF) is the most common surgical method using intramedullary nail (IMN) or locking plates (LP) implants. The treatment effect of these two surgical approaches has remained controversial due to low power studies, poor quality of data presentation, and differences in sample population.

We aim to conduct a multi-center and single blinded randomized controlled trial comparing IMN with LP in patients with three-part PHF.

Patients above 18 years old with displaced three-part PHF will be randomized into IMN and LP groups. Patients will receive standard operation techniques for IMN and LP implants and a standard post-operative rehabilitation. They will be assessed at 3, 6, 12- and 24-months post-operative for pain using Visual Analogue Scale, and function using ‘Disability of the Arm, Shoulder and Hand’ (DASH), ‘Constant Murley’ and ‘American Shoulder and Elbow Surgeons’ (ASES). Complication rates including infection, fixation failures and metal work failures will be collected at 3- and 12-months post-operative. A sample size of 214 patients will allow us to show an 8-point difference at 12 months in DASH questionnaire with 80% power. The results of this trial will provide level one evidence comparing two surgical techniques addressing the need for investigation in three-part PHF.

# Comparing Nail versus locking plate in displaced three-part proximal humerus fractures; A multi-center randomized controlled trial (Otago PHINZ trial) investigating the effect on function post-operatively.

## Introduction

Proximal humeral fractures (PHF) comprise the most common osteoporotic fractures after wrist and hip fractures in the elderly population (C. Roux et al., 2012) and is accounted between 4 and 10% of all fracture types (Iglesias-Rodríguez et al., 2021). The mean age reported for incidence of PHF is 70 years old (Iglesias-Rodríguez et al., 2021; A. Roux et al., 2012) which increases up to two to four times higher in women than men after 50s (Iglesias-Rodríguez et al., 2021; A. Roux et al., 2012). Accident Compensation Corporation (ACC) report in 2022 showed a more than two times increase of PHF incidence in elderly rising from 65 cases at 50-54 years old to 139 cases for patients at 70-74 years old. The weekly compensation cost needed for rehabilitation was calculated almost 230.000 NZD for these patients.

Low energy trauma is the most frequent reason for fracture at elderly population in comparison with high energy trauma for patients at younger age (Lorenz et al., 2020). About 19% of fractures with low energy trauma and 43% of fractures with high energy trauma are categorized as displaced fractures requiring surgery treatments (Iglesias-Rodríguez et al., 2021). When the choice is made for surgical treatments, there are several options including closed reduction percutaneous pinning (CRPP), open reduction internal fixation (ORIF), hemiarthroplasty (HA) and reverse shoulder arthroplasty in which ORIF surgery is the most common method with better functional outcomes but higher complication rates amongst other three surgical methods (Dai et al., 2013; Gupta et al., 2015).

Intramedullary Nail (IML) and Locking plates (LP) are the two common surgical techniques used for ORIF surgeries that the treatment efficacy of them have remained controversial depending on the type of humeral head fractures, age of patients, and post-surgical complication rates (Lorenz et al., 2020). The LP technique is the most common surgery particularly in three-part fractures (Iglesias-Rodríguez et al., 2021) which is invasive in order to provide significant fixation. Some evidence has shown a noticeable rate of complications including avascular necrosis, screw perforation and loss of fixation following LP technique (Brorson et al., 2011; Dai et al., 2013; Lorenz et al., 2020). In comparison, the IMN is less invasive than LP and has evolved over the past 40 years to become a better alternative for the treatment of more complex PHFs particularly in patients with osteoporotic bone (Dilisio et al., 2016; Lindtner et al., 2017; Sosef et al., 2009). Overall IMN have demonstrated shorter surgery time, less bleeding loss and faster healing time than LP surgeries (Li et al., 2018; Shi et al., 2019); however, the clinical differences between these two methods still require more investigations.

Limited number of RCTs have indicated various clinical outcomes when comparing IML and LP surgeries. There was inconsistency in the type fractures (i.e., two, three and four-part proximal humerus fractures) and implant used in those studies that may contribute to conflicting findings of previous studies. Regarding function scores, for instance, two studies showed IMN resulted in superior functional outcome than LP (Boyer et al., 2021; Plath et al., 2019), while two other studies indicated no differences between two surgical methods (Gracitelli et al., 2016) or even lower functional outcome after IML surgery (Zhu et al., 2011). Similar conflicting outcomes were reported for total complication rates, while two studies showed IML can lead to lower complication rates (Boyer et al., 2021; Zhu et al., 2011), two other studies showed IML resulted in either equal (Plath et al., 2019) or higher complication rates (Gracitelli et al., 2016) than LP surgeries. Findings of previous systematic reviews when pooling data from non-randomized and randomized design studies, often showed no differences between IML and LP surgeries in terms of clinical outcomes (e.g., pain, function scores and ROM) and total complications rates (Li et al., 2018; Shi et al., 2019; Sun et al., 2017; Wang et al., 2015). However, caution needs to be used as studies pooled in those systematic reviews recruited participants with different fracture types and implants, and were classed as very low grade studies (Li et al., 2018). Thus, more high-quality studies are needed to identify the superiority of a surgical method based on the type of fracture and implants used for fixation.

Variation in the designs of implants over years may influence outcome measures and complication rates. Plates have little variability with proximal humeral internal locking system (PHILOS) and locking proximal humerus plate (LPHP) as the most common implants used for surgeries (Gracitelli et al., 2017). Although the designs of plates have shown to have no associations with the complication rates (Kavuri et al., 2018; Konrad et al., 2011), PHILOS implants was indicated with lower pain and disability scores in two, and three-part fracture surgeries than LPHP (Konrad et al., 2011). Overall, with plate fixations, the most complication rates included intra-articular screw penetration ranging from 5 to 20%, (Brorson et al., 2011; Kavuri et al., 2018), which may increase in osteoporotic bone conditions (Krappinger et al., 2011). In contrast, the third-generation nail implants have had great variations at proximal angulation, the number and the position of proximal locking screws in relation to the first generation (Dilisio et al., 2016; Gracitelli et al., 2017). These variations have been made to improve fixation in osteoporotic bone allowing superior biomechanical properties and lower complication rates (Dilisio et al., 2016; Gracitelli et al., 2017). The variability in the implant use contributes to the diversity of clinical outcome when comparing plates and nail surgeries in proximal humerus fractures. Additionally, there is not much information about the difference in the details of complication types between the two methods (Li et al., 2018; Shi et al., 2019). Despite the fact that the total complication rates were shown to be equivalent (Li et al., 2018; Wang et al., 2015) or lower (Shi et al., 2019) with nail implants compared with plates, only one systematic review showed nail implants results in lower screw penetration than plate surgeries (Sun et al., 2017). Thus, more studies are required to explicitly describe the types of complications occurring during each intervention.

We aim to compare the clinical outcomes and complication rates between PHILOS fixation and ‘Tornior Aequalis Intramedullary Humeral Nail’ (third generation IMN) surgical methods in participants with displaced three-part proximal humeral fractures. Our hypothesis is that IMN will result in better clinical outcomes and lower complication rates in comparison with plate surgery.

## Methods

### Design and setting

We will conduct a multiple center and single blinded randomized controlled trial from April 2023 to November 2026. This is a superiority designed study recruiting eligible participants with dislocated 3-part proximal humerus fractures in parallel groups comparing intramedullary nail (IMN) with Locking plate (LP). This study will be reported following Standard Protocol Items: Recommendation for interventional trial statement (SPIRIT).

The study will be performed according to the Declaration of Helsinki. We will register the protocol at Australian New Zealand Clinical Trial. Ethical approval has been obtained from Maori committees (), and will be submitted to HDEC and Local ethics. Participants will be recruited from hospitals in Christchurch, Dunedin, Wellington, Auckland.

### Eligibility criteria

Patients above 18 years old with displaced three-part proximal humerus fractures based on Neer classification will be included. In three-part fractures, either the lesser or greater tuberosity is displaced with associated displacement of the surgical neck producing a rotational deformity (Giangarra & Manske, 2018). Displaced fractures will be defined as a dislocation more than 1 cm or with an angle greater than 45° between head and diaphysis of humerus (Carofino & Leopold, 2013). The type of fractures will be classified according to Neer-classification.

Exclusion criteria will be fractures extending to the humeral shaft or articular split, fractures more than 4 weeks old, or open fractures. Patients will be excluded if they are identified with concomitant ipsilateral fractures of distal humerus/ or elbow joint, previous surgery of affected shoulder, pathologic fracture (malignancy fractures), neurovascular injuries (e.g., stroke, or brachial plexus injuries), neurological disorders (e.g., Parkinson, or multiple sclerosis) or cognitive disorders (i.e., sever mental illness).

Intra operative changes of treatment due to small diameter of humerus shaft to use nail, fracture line through the nail entry point or severely reduced bone quality resulting in fixation problems with either implants will be excluded.

### Pre-operative evaluation

We will follow the standard of evaluation and diagnosis for injuries including the plain radiographs of orthogonal views (e.g., antero-posterior (AP) and axial views). CT-scan will be required to determine if patient suited for inclusion in trial.

### Surgical procedure

Orthopedic surgeons with experience of at least five Nail and Plate operations (N=10 in total) will operate on patients under general anesthesia in the beach chair position with the elbow fixed at 90°. Skin will be opened through deltopectoral or deltoid split approach at surgeon’s preference. Patients in the IMN group may have separate incisions as required. For both operational approaches, the greater and lesser tuberosities are re-approximated and sutured using non-absorbable suture. Once bony fragments are reduced, K-wires/sutures will be used under image intensifier guidance (fluoroscopy) to temporarily fix head before implant use. For patients in the IMN group, implant will be Tornier AEQUALIS Intramedullary Humeral Nail will be used. This is a straight nail, 130 mm length and 8 mm distal diameter. This nail has 4 cannulated proximal screws to provide fixation perpendicular to fracture lines and to avoid reduction loss due to the pull-out force of rotator cuff. Two distal screws are designed to control rotation. The medullary canal is opened using cannulated drill and nail will then be inserted once the reduction is stable. For patients in the LP group, PHILOS (DePuy-Synthes, Solothurn, Switzerland) stainless steel plate will be used. The PHILOS is designed with three or five holes based on distal fracture extension that will be replaced using locked screws with K-wires once the reduction is satisfactory. Previous studies have reported the intraoperative duration between 50 and 85 minutes for IMN surgery and 60 and 110 minutes for LP surgery (Plath et al., 2019; Zhu et al., 2011). The adherence to operation will be confirmed via plain radiography taken during the operation.

### Post-operative protocol

All patients will use slings for four weeks. Passive and active assistive exercises will be initiated between 7th and 10th days and continued to 6 weeks following operation. Active and resistive exercise will be instructed between 6 and 12 weeks. In each center one physiotherapist will be designated for rehabilitation protocol. The protocol of the rehabilitation will be provided for physiotherapists in order to standardize the postoperative rehabilitation program (Appendix 1).

### Outcome measures

#### Primary outcome

Patients functional impairment will be measured using a Disability of the Arm, Shoulder and Hand (DASH) as primary outcome measure. DASH has designed to test the physical function and symptoms of upper limb over 30-item questions scoring from 0-100 in which the greater score represents more functional difficulties. The minimal clinical importance for DASH was calculated to be a range between 8.1 to 13 (median =10.55) for proximal humerus fracture (Dabija & Jain, 2019). The clinometric characteristics of DASH was identified with high responsiveness for identifying functional improvement in patients who improve compared to those who do not improve and high test-retest reliability and internal consistency (>0.90) (Bot et al., 2004; Kolber et al., 2014).

#### Secondary outcome measures

Shoulder pain at rest and during activities will be assessed using 100 mm visual analogue scale (VAS). This scale has 11 score rating from 0 as no pain to 10 as the most severe pain. A change of 1.5 points was considered to indicate minimal clinical change (Tashjian et al., 2017). We will use Constant Murley and American Shoulder and Elbow Surgeons (ASES) scores to assess functional ability in patients. Constant Murley score ranges from 0 to 100 with greater score represents more functional impairment. The MCID for Constant Murley score was reported a range between 5.5 to 11.5 (median 8.5) for proximal humerus fractures (Dabija & Jain, 2019). ASES score was recommended by American Shoulder and Elbow Surgeons for patients with shoulder surgery, ranging from 0-100 with higher score indicates better functional results (Jones et al., 2020). The average MCID for ASES score was reported 15.5 for shoulder surgeries (Jones et al., 2020). These outcome measures are selected in order to keep consistency with previous studies that used different outcome measures. Participants arm ROM including arm flexion, abduction, external rotation and internal rotation will be measured by a goniometer and a tape measure.

Radiographs (anteroposterior and trans-scapular Y-view) will be used for diagnosis of possible complications (as binary data; Yes or No). Complications will include malreduction/malunion, nonunion, screw penetration/screw cut out, osteonecrosis of the humeral head, displacement of internal fixation, and hardware failure. Neck shaft angle (NSA) will be used to determine Malreduction and Malunion will be collected as composite data because malunion usually occurs following malreduction. Mal reduction will be defined as NSA ≤ 120°, or tuberosity displacement > 0.5 cm (Gracitelli et al., 2016). Presence of osseous abnormalities including malposition of greater or lesser tuberosity, incongruity of the articular surface, and malalignment of the articular segment will be referred as malunion (Beredjiklian et al., 1998; Duparc, 2013). Nonunion will be the lack of union requiring unplanned surgical intervention or incomplete radiologic healing at 12 months (Westgeest et al., 2016). Screw penetration/screw cut out will refer the screw violation from articular surface as a result of humeral head collapse (Kavuri et al., 2018). Osteonecrosis of the humeral head will be verified by MRI if features of osteonecrosis on x-ray indicated patient needs to be referred for MRI scan. The total complication (i.e., a composite incidence of superficial and deep wound infection, loss of fixation and metal work failures) will be reported at 12 months. Total complication rate will be reported by counting the ratio of patients with adverse events to total patients at 12 months.

### Follow-up time points

Clinical outcome measures including pain, function (i.e., DASH, Constant Murley and ASES) and ROM will be assessed at 3, 6, and, 12 months post-surgery by a blinded research assistant at each center. Radiographic images will be obtained and evaluated at 3 months, and 12 months post-surgery by independent radiologists.

### Sample size estimation

The sample size will be calculated for the superiority of Nail over Plate surgery for DASH score as primary outcome measure. Considering 80% of statistical power, a significant test set at 0.05 for two-tailed test, and a 8-point difference in DASH scores between two groups at 12 months (Plath et al., 2019), at least 89 participants is estimated for each arm (Portney & Watkins, 2015). For the potential of 20% drop-out, 107 participants will be required in each group. Retrospective data of operative PHF indicated 50 ORIF surgeries for three-part fractures in Christchurch hospital 2020 to 2022. If this trend continues, we anticipate recruiting 16 participants per year from Christchurch hospital. Given approximately the same amount of recruitment in other three centers (Auckland, Wellington, and Dunedin), it is estimated annual recruitment of 64 participants for a period of 3.5 years in each center.

### Recruitment procedure:

Staff in orthopaedic department (e.g., trauma coordinator nurse and trauma fellows) will identify the potential participants with proximal humerus fractures and let them know that someone from the research team will speak to them about Otago PHINZ trial. Trauma coordinator nurse and trauma fellow will inform research team of potential participants with proximal humerus fractures. The research team will approach potential participants to introduce the study. At this stage, they collect participants’ eligibility criteria in an online data capture that has been set for this purpose. This information will be used to report the recruitment rate indicating the percentage of eligible participants per participants screened. Eligible participants, then, will be provided with an information sheet and consent form and will be given some time to consult with their family and friends about their participation in the study. Due to emergency of the situation, this time will be varied depending on the operation room and surgeon available for the patient. Once eligible participants showed interest, the treating surgeon will ask them to sign the consent form before being randomized into groups. Randomization will be executed in REDCap (Research Electronic Data Capture) where patients and treating members are aware of group allocation. Participants’ demographic information will be collected from electronic medical records after operation by ZJT who is unblinded to the group allocation.

### Randomization:

A statistician who is not involved in the study will prepare a computer-generated random sequence using blocks of 4 with a 1 to 1 ratio, nail and plate groups. Stratified randomization based on age group (18-40 Y, 41-70 Y, 71-80 Y, and 81 Y and above) will be performed in each treating center to ensure the normal distribution of patients for each arm (Kim & Shin, 2014).

### Blinding:

Research Assistants who are unaware of group allocation will conduct the objective measurement of pain, function and ROM at follow-up time points. Patients will be asked to wear a short-sleeved T-shirt to conceal the surgery scars and will be instructed not to reveal their treatment group. In each treating centre, a radiologist not-involved the intervention, will report post-surgical complications based on regular radiographs taken in each follow-up. The data will be collected and managed by REDCap electronic data capture tools hosted by University of Otago.

### Measurement procedure:

Anteroposterior radiograph views at neutral position will be used to measure the neck shaft angle. The angle will be measured between a line bisecting humeral shaft and a line perpendicular to the center of humeral head (Zhu et al., 2011).

Arm ROM including arm active flexion, abduction, and external rotation will be measured using goniometer. For flexion and abduction, the angle between body and arm will be measured in the supine position. For external rotation, arm rests besides the body with elbow in 90° flexion in supine position, and at the end point of external rotation, the angle between vertical line and forearm will be measured. For arm internal rotation, patients will be asked to raise their hand behind the body in the standing position. The distance between the tip of the thumb and a line joining two PSIS together will be measured with a tape measure (Beshara et al., 2022).

Arm strength will be measured using a validated electronic isometric strength dynamometer at 90° arm abduction at scapular plane in affected side in pounds. This tool will be used to determine the arm strength item in Constant Murley score.

## Statistical analysis

All statistical analysis will be completed using SPSS (version 28.0; IBM Corporation, Armonk, NY). The Skewness and Kurtosis analysis will be performed to test the normal distribution of data. Continuous normally distributed data will be presented as mean and SD and non-normally distributed data will be reported as median and range to summarize characteristics of participants at baseline and each time points. For continuous data with normal distribution, we will use paired t-test for within group differences, and independent t-test for between group differences. For continues data with non-normal distribution, we will use Wilcoxon signed ranks test for calculating within group and Mann-Whitney U test for between group differences. Categorical data will be reported as number and percentage. The frequency of variances between two groups will be compared using chi-squired test (χ2). We will use multiple regression analysis to estimate the effects of age, sex, and treatment group on function scores. For categorical data, we will use logistic regression to estimate the effects of age, sex and intervention on complication rates. Age, sex, and group allocation will be considered as independent variables and function scores (DASH, ASES and Constant Murley Score) and complication rates will be considered as dependent variables. For all statistical analysis, P-value will be set at ≤ 0.05. Patients will be analysis according to intention to treat and multiple imputation will be used for missing data at random.

## Importance of this study

This is the first multi-center RCT comparing Nail and Locking plate for three-part proximal humerus fractures. Previous systematic reviews pooled the composite data of studies recruiting participants with 2, 3, and 4-part proximal humerus fractures. Therefore, the efficacy of treatment based on fracture type have remained unclear. We will create reliable information about safety and benefit of Nail and Locking plate approaches for three-part proximal humerus fractures. We will use stratified randomization to ensure equal distribution of participants based on age group in each arm. Recruiting participants with wide age group and from different treating centers will raise the external validity of the trial and tests how the treatment works under usual circumstances. Electronic data collection will facilitate the timely possibility of collecting data from participants who may have difficulties to access hospitals.

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