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Proximal Femoral Nail Unlocked Vs Locked (ProFNUL): A protocol for a multicentre, parallel armed randomised controlled trial for the effect of femoral nail screw configuration and mode of lag screw locking in the treatment of intertrochanteric femur fractures.

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ABSTRACT:

Introduction:

Intertrochanteric fractures are common fragility injuries in the elderly. Surgical fixation using intramedullary devices are one of the widely used management options. To date, evidence demonstrating the effects of lag screw configuration and the mode of lag screw locking in these devices is lacking. The purpose of this study is to investigate whether the lag screw configuration (single interlocking vs. integrated dual interlocking screw) and the mode of lag screw locking (static vs. dynamic) of a femoral nail device result in differences in clinical and functional outcomes.

Methods and analysis:

A multicentre, pragmatic, single-blinded randomised controlled trial with a three-arm parallel group design is proposed. Nine-hundred intertrochanteric fracture patients (A1 and A2 AO/OTA) will be randomised to fracture treatment using a Gamma3™ nail (Stryker) (proximally dynamic) or a Trigen™ Intertan™ nail (Smith and Nephew) in a dynamic or static lag screw configuration. The primary outcome measure consists of radiological evidence of device failure within six months following surgery, with failure being defined as breakage of the femoral nail, distal locking screw, a change in Tip-Apex Distance of more than 10mm or lag screw cut out through the femoral head. Secondary outcomes include surgical data (operation time, fluoroscopy time), complications (surgical site infection, reoperation, patient death), return to mobility and home circumstances, functional independence, Hip function and Pain. Patients with AMTS score > 8 will be asked to participate in 3D gait analysis at six weeks and six months to assess hip biomechanics from this cohort. Additional secondary measures of gait speed, hip range of motion, joint contact and muscle forces and gross activity monitoring patterns will be obtained in this subgroup.

Ethics and dissemination:

The Central Adelaide Local Health Network Human Research Ethics Committee has approved the protocol for this RCT (HREC/17/RAH/433). The results will be disseminated via peer-reviewed publications and presentations at relevant conferences.

Trial Registration:

This clinical trial has been registered on the Australia New Zealand Clinical Trials Registry (ANZCTR): ACTRN12618001431213.

ARTICLE SUMMARY

Strengths and Limitations of this study:

- Multicentre, pragmatic, single-blinded randomised controlled trial
- The first study to investigate the effects of femoral nail lag screw locking mode on clinical and functional outcomes.
- The first study to collect 3D motion capture data from these patients post-operatively.
- Powered to detect differences in device failure between the three parallel arm groups in a large sample size (900).
- Limitations of the study include an unpredictable loss to follow up from death or failure to attend.

INTRODUCTION:

Background and Rationale

Proximal femur fractures are a highly prevalent injury in the elderly,[1, 2] with an estimated 1.31 million fractures occurring worldwide each year.[3, 4] With a growing elderly population resulting from an increasing life expectancy, [5] there is an increasing global incidence of these fractures, [5-9] projected to reach 6.26 million by the year 2050.[10] Fractures within the intertrochanteric region represent approximately half of all proximal femur fractures. [11] Treatment typically consists of surgical fixation using either intramedullary (e.g. proximal femoral nail (PFN, Synthes™)) or extramedullary (e.g. Dynamic Hip Screw (DHS, Synthes™)) fixation devices.

Since its introduction in the 1990s, intramedullary fixation has become increasingly popular, [12] with the number of implanted femoral nails surpassing the number of extramedullary fixation devices in the united states in 2008. [13] Similar trends in device preference have also been recorded in Australia. [14] The increasing clinical use of the technique can be attributed to a number of factors, which in part relate to the biomechanical advantages of intramedullary fixation. The medialised implant position supports an in-line load distribution within the femur, [15, 16] which shortens the lever arm between the hip joint and the implant, decreasing bending moments on the implant, [17] and providing more effective stabilisation at the fracture site. [18, 19] This is advantageous particularly in elderly patients where immediate weight bearing mobilisation is an objective. Additional advantages over extramedullary fixation devices described in the literature include a shorter incision length, less operative time and lower intra-operative blood loss, [20] all which are deemed beneficial to recovery from surgery and the risk of complications. [21]

Numerous types of intramedullary fixation devices are available for clinical use, [22] however the optimum implant choice remains unknown. [23] While there is evidence to support the use of these devices in the treatment of intertrochanteric (IT) fractures, the evidence demonstrating whether variations in design characteristics influence patient clinical outcomes is conflicting. [12, 24-26] As no

rationale behind implant selection can be drawn from the literature, there is considerable diversity regarding the choice of implant between clinicians. [27]

The Gamma3™ nail (Stryker) is a well-established and widely used current generation single lag screw intramedullary device [12] which shows good clinical and radiographic outcomes. [28-30] However, complications still exist, with the most frequently reported complication being cut-out of the lag screw through the femoral head, [31-33] with an incidence rate ranging between 4% and 8%. [34-36] The Trigen™ Intertan™ nail (Smith & Nephew) is a similar current generation intramedullary device, featuring a dual lag screw configuration comprised of a larger superior lag screw and a smaller screw integrated within the superior screw. [37] Together, this dual-oval shaped composite screw allows for linear compression of the fragments at the fracture site while providing anti-rotation properties. [38] Clinical studies evaluating the Intertan nail against other single screw devices have recorded a significant reduction in the occurrences of implant failure, fracture site non-union, mal-union, lag screw cut out and uncontrolled varus fracture collapse. [37-41] Several authors have postulated the reduced complication rate being attributed to the design of this nail. [37] Moreover, ex vivo biomechanical studies have demonstrated superior biomechanical results with the Intertan™ nail. [42-45] However, despite the Gamma3™ nail and Trigen™ Intertan™ nail both being well-established implant choices used in the treatment of these fractures, very little direct comparative clinical evidence exists between these nails.

A meta-analysis by Ma et al [46] found only nine papers, four of which included the Gamma3™ and the Intertan™ . Of these four, three were randomised controlled trials comparing the two devices, but with relatively small cohort sizes. From these studies, the Intertan™ nail was shown to result in a lower incidence of implant cut out and femoral fractures which was of statistical significance. No statistically significant differences in time to union and post-operative complications were found between devices. Ma et al highlighted that a limitation of this statistical analysis was the relatively small sample size of the studies included, and indicated a need for more high quality RCTs to yield a more convincing test

power. [46] Hence, the literature reveals limited evidence of whether design characteristics of femoral nails affect clinical and patient outcomes in the treatment of trochanteric fractures.

In addition to the choice of the intramedullary implants, other aspects of these devices used in the practical management of intertrochanteric fractures need further evaluation. This includes the mode of lag screw fixation (static or dynamic). Technically, both the Gamma3™ and Intertan™ nails can be used in static or dynamic modes of the lag screw. In the dynamic mode, fracture collapse occurs under physiological loading, resulting in macro and micromotion of the fracture fragments as well as compression/ apposition of fracture fragments, [47-49] desired to stimulate fracture healing. However, excessive sliding of the lag screw has been shown by some authors to lead to mechanical complications and negatively affect patient function. [50-52]

Whilst there is evidence highlighting a reduced risk of lag screw cut out when utilizing a sliding lag screw in extramedullary devices, [51, 53, 54 55, 56] there is a paucity of similar evidence relating to the use of intramedullary devices. One study compared the static and dynamic modes of the proximal lag screw in the Gamma3™ nail in 80 patients. [57] From this study, no statistically or clinically significant difference in Harris Hip Scores, time to fracture healing or length of hospital stay was found. No such comparative evidence exists for the Intertan™ nail. Moreover, no clinical studies to date, comparing one intramedullary device to another has made any note of which mode of the lag screw was employed. Consequently, considerable variance in practice can be seen between clinicians.

For the Gamma3 nail, it is suggested by Stryker in their operative technique guide that the device has to be used in the dynamic mode, with the use of the nail in a static mode considered off label. [58] For the Intertan nail (Smith & Nephew), this decision is stated in their surgical technique guide as optional with both modes considered on label, [59] and left to the operating surgeons decision.

Considering the substantial costs attributed to the management of intertrochanteric fractures, we believe that more evidence is required to evaluate the effectiveness of a single or dual screw femoral nail, as well the use of these devices in the static and dynamic modes. Moreover, no previous studies

have compared postoperative lower extremity biomechanics in intertrochanteric fracture patients treated with these devices. This proposed multicentre, parallel, three-arm randomised controlled trial has been designed to fill these gaps in knowledge, and will include a two-way comparison between the Gamma3™ (dynamic) and Intertan™ (dynamic) nails, as well as the Intertan™ (dynamic) and Intertan™ (static) nails.

Objectives:

Primary Objective

The aim of this RCT is to investigate if there are differences in failure rates between the surgical management of intertrochanteric fractures using a single screw or dual screw femoral nail, as well as when using a femoral nail in either the static or dynamic modes of the lag screw.

It is hypothesized there will be no difference in failure rates between patients managed with a single screw or dual screw femoral nail device. It is also hypothesized that there will be no difference in failure rates between patients managed with a femoral nail in the static or dynamic mode of the lag screw.

Secondary Objectives

Several secondary objectives will also be studied for this RCT to evaluate the effectiveness of the devices used by quantifying and drawing inferences from observed differences between treatment groups in:

- Intraoperative surgical data (Operation time, fluoroscopy time, blood loss, Tip-Apex Distance)
- Pain within six months after surgery (VAS Pain Score).
- Patient function (Functional Independence Measure) and Hip function (Harris Hip Score) within six months after surgery.

- Post-operative hip biomechanics using objective measures from gait analysis up to six months after surgery.

Trial Design

The ProFNUL study is a multicentre, pragmatic, single-blinded randomised controlled trial with a three-arm parallel group design.

METHODS AND ANALYSIS

Patients will be randomised using an online computerised sequence generation service to test if there is a difference in outcomes between the treatment interventions. Recruitment, medical and surgical data collection will take place at the Royal Adelaide Hospital and Queen Elizabeth Hospital with other sites added later as required for participant numbers. Radiographic images will be collected at a diagnostic imaging practice and 3D motion capture data will be conducted at The University of Adelaide, South Australia.

This RCT has been registered with the Australian New Zealand Clinical Trials Registry (ANZCTR). Trial registration data is shown in Table 1.

This study protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.

Patient and Public Involvement

Patients and public were not involved in the design, conduct or reporting of this study.

Table 1. Trial Registration Data

Data Category	Information
Primary registry and trial identifying number	https://www.anzctr.org.au ACTRN12618001431213
Date of registration in primary registry	27/08/2018
Secondary identifying numbers	None
Source of monetary or material support	Smith & Nephew Pty Ltd
Primary sponsor	Royal Adelaide Hospital, Dept. of Orthopaedics & Trauma Contact person: MR (mark.rickman@sa.gov.au)
Secondary sponsor	University of Adelaide, Centre for Orthopaedic & Trauma Research. Contact person: AS (arjun.sivakumar@adelaide.edu.au) Contact person: DT (dominic.thewlis@adelaide.edu.au)
Contact for public queries	MR (mark.rickman@sa.gov.au)
Contact for scientific queries	DT (dominic.thewlis@adelaide.edu.au)
Public title	Evaluating the treatment methods of proximal femur fractures in elderly trauma patients
Scientific title	A multi-centre, single-blinded prospective randomised controlled trial of the Gamma3™ intramedullary nail to the unlocked and locked Intertan™ intramedullary nail for the treatment of proximal femur fractures.
Countries of recruitment	Australia.
Health problem studied	Proximal femur fracture
Interventions	Gamma3™ Trochanteric nail (Unlocked proximally) Trigen™ Intertan™ Trochanteric nail (Unlocked proximally) Trigen™ Intertan™ Trochanteric nail (Locked proximally)
Key inclusion and exclusion criteria	Inclusion criteria: Traumatic extracapsular hip fracture, Closed injury, Patient aged over 60 years, Ability to be followed for up to six months, Presentation to hospital within 14 days of injury Exclusion criteria: Patients with concomitant injuries affecting treatment and rehabilitation of the affected limb, Patients with associated neurovascular injuries requiring immediate surgery, Patients where consent is refused, Patient with limited English proficiency including family members.
Study type	Randomised controlled trial
Date of first enrolment	05/09/2018
Target sample size	900
Recruitment status	Recruiting
Primary Outcome	Device failure (time point: up to 6 months after intervention)
Key secondary outcomes	Incidence of Injury specific complications (time point: 6 months) Functional Independence (time point: 6 months) Reoperation incidence (time point: 6 months) Return to mobility circumstances (time point: 6 months) Hip joint range of motion (time point: 6 months) Hip joint contact forces (time point: 6 months) Post-operative hip muscle function (abductors, flexors, extensors) (time point: 6 months)

Eligibility

Patients over 60 years of age presenting to any of the participating hospitals with an isolated, closed intertrochanteric fracture will be recruited against the following eligibility criteria:

Inclusion criteria
1. Traumatic intertrochanteric femur fracture (A1 and A2 AO/OTA) where a decision has been made for surgical management using a femoral nail.
2. Closed injury.
3. Patients aged over 60 years.
4. Presentation to hospital within 14 days of injury.
Exclusion criteria
1. Patients with concomitant injuries affecting treatment and rehabilitation of the affected limb.
2. Patients with associated neurovascular injuries requiring immediate surgery.
3. Patients with limited English proficiency including family members.
4. Patients where consent is refused.

All eligible patients will be provided with a study information sheet and consent form by the hospital medical staff. Randomisation will then occur once consent has been obtained.

Randomisation and blinding

Patients will be randomised with allocation sequences generated using a computerised generation system managed by the Griffith University's Clinical Trial Unit (Griffith University, QLD, Australia) with stratified allocation factors of Abbreviated Mental Health Test Score (AMTS) and gender. Patients will be blinded to their allocation until the conclusion of the trial to reduce bias in patient reported outcome measures. The statistician performing the analysis will also be blinded to the group allocation. Surgeons and researchers will not be blinded to allocation.

Standard Treatment Pathway

The clinical pathway for recruited patients will be unchanged from the routine for each institution; surgery is typically carried out within 24-48 hours, and no changes will be necessary to any part of the surgical episode with the exception of the individual device used and mode of proximal locking as directed by the randomisation outcome. All fractures will be compressed proximally using the compression mechanism of the device being used at the time of surgery, just prior to the nail being either locked proximally or left unlocked. Similarly, post-operative management will remain unchanged from routine, including discharge timing and destination. All patients will be mobilised fully weight bearing as soon as possible after surgery.

Allocated Interventions

A total of 900 trauma patients with IT (31A1 and 31A2 AO/OTA) will be randomised to receive one of the three femoral nail interventions.

- Gamma3™ (Stryker) (Locked proximally)
- Intertan™ (Smith & Nephew) (Unlocked proximally)
- Intertan™ (Smith & Nephew) (Locked proximally)

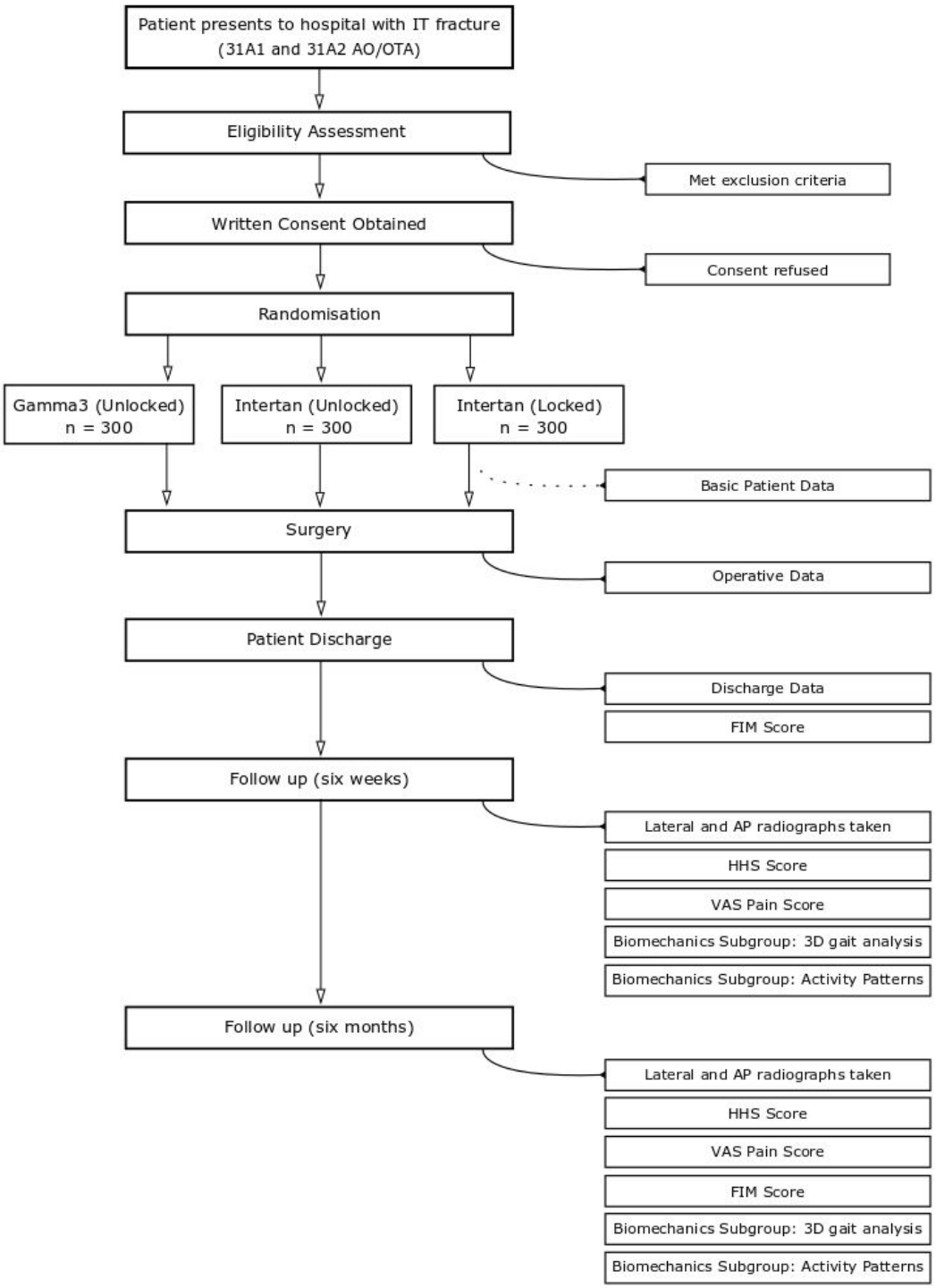
Participant Flow Timeline

A succinct summary of the patient timeline is described by Figure 1. Once a patient has been recruited and randomised, a baseline patient registration assessment will be completed through the use of an online form. Surgery will then proceed at the earliest available opportunity as per routine for the hospital. Following surgery, an operative information form will be completed by the operating surgeon using another online form. Upon patient discharge, medical staff will complete a patient discharge online form which includes a clinical assessment measure of functional independence (FIM score). Following discharge, follow up appointments will be scheduled to coincide with six weeks and six months with appointment letters and x-ray referrals sent from the

Royal Adelaide Hospital. A week prior to each patients appointment, patients will be called to confirm their appointments or reschedule, if required. AP and lateral hip radiographs will be taken, followed by a clinical examination with an orthopaedic and trauma specialist, where measures of hip pain (Visual Analog Scale from 0 to 10) and hip function (Harris Hip Score) will be recorded. At the six month follow up, AP and lateral hip radiographs will be taken, followed by a similar clinical examination with an orthopaedic and trauma specialist. At this appointment, a measure of functional independence (FIM score) will be recorded in addition to VAS and HHS scores.

Patients with an AMTS score 8 or above will be included in a 'biomechanics sub-group' where 3D gait analysis will be performed at the six weeks and six month follow ups immediately following the clinical examination. After the gait analysis, patients will be provided with a wrist worn activity monitor (GeneActiv Original, Activinsights Ltd, Kimbolton, UK, 100 Hz) to wear for seven days at a time, providing information on 24 hour gross physical activity patterns of these patients. Patients will be asked to complete a sleep log during this period to better distinguish sedentary time from sleep. After seven days, patients will post the monitors back via pre-paid return envelopes. Patients living rurally and unable to attend follow up appointments will have x-ray appointments organised at locations convenient to them collected over the phone by an orthopaedics and trauma specialist. Patients presenting to clinics reporting complications, will be reviewed by a clinician and radiographs taken, as per standard procedure. In these events, the occurrence of these complications is recorded against the patient's hospital number.

Figure 1. Patient flow diagram



Outcomes

Primary outcome measure

The primary outcome measure is radiological evidence of device failure at any point up to six months following surgery and will be assessed via AP and lateral radiographs. Device failure will be defined as the occurrence of any of the following:

1. Breakage (mechanical fracture) of the femoral nail. [60]
2. Breakage (mechanical fracture) of the distal locking screw.
3. Protrusion of lag screw through the cortex of the femoral head (cut out). [61]
4. A change in TAD of more than 10mm.

The Tip-Apex Distance (TAD), [62] measured from the tip of the lag screw to the apex of the femoral cortex in lateral and AP radiographs is generally used in clinical practice and is desirable for this measurement to be under 25 mm. TADs larger than 25mm have been shown to serve as an accurate indicator of future protrusion of a lag screw through the femoral head (cut out). [63] The TAD has been shown to be reproducible to within 2-3 mm between measurements [62, 64] and highlighted to change by 2-3 mm over time. [65] A change in TAD of more than 10 mm has therefore been selected as a reference level which represents failure of the intramedullary device to maintain fracture stability.

Secondary outcome measures

Secondary outcomes will also assess differences in the effectiveness between the interventions using several measures, including:

Functional Independence: FIM score

The FIM score is a widely used instrument for measuring the severity of patient disability and dependence in rehabilitation medicine. [66] It has been demonstrated as a validated and reliable measure [67] with good interrater reliability of the total score (Intraclass correlation coefficient of 0.96). [68]

Pain: Visual Analog Scale

Pain will be assessed using a visual analog scale (VAS) [69] of categorical values from 0 to 10, with 0 indicating no pain, and 10 indicating excruciating pain. The VAS pain score is a commonly used and validated measurement for patient reported acute pain. [70]

Hip Function: Harris Hip Score

Hip function will be assessed by a clinician using the Harris Hip Score to evaluate hip function and disability across domains of pain, function, absence of deformity, and range of motion. [71] The Harris hip score is a well performing [72] and frequently used clinician based outcome measure that has shown high reliability and validity in evaluating hip function. [73, 74]

Perioperative Data

Perioperative data recorded in this trial will include surgery time, fluoroscopy time, Intra-operative Tip-Apex Distance, length of hospital stay, union time and intra-operative complications, all of which are commonly reported as valid measures across a number randomised controlled trials evaluating femoral nail devices. [46, 75-79] Intra-operative blood loss will also be recorded, however the reliability of this measure is unclear due to its underestimation during hip fracture surgery. [80]

Injury/Surgery Specific Complications

Surgical complications not only affect clinical outcome parameter, but appear to be a significant and often long-term predictor of patient postoperative psychosocial outcomes. [81, 82] Complications recorded will include the number and type of injury and surgery specific events and complications including, technical complications, surgical site infection, unplanned surgery and death up to one year following surgery. This has been reliably collected in previous studies. [83, 84]

Re-operation

The number of patients presenting to clinic requiring reoperation will be recorded in this trial. The rate of re-operation is a reliable measure in assessing quality of medical treatment. [85]

General Medical Complications

In this study, the number of patients suffering from general medical complications will be recorded. This has been collected and reported as a valid measure in the literature. [82]

Secondary outcome measures: Biomechanics Sub-group

Physical Mobility - Timed Up and Go

Physical mobility will be assessed using the timed "Up & Go" test (TUG) which has been widely used in the literature [86] and noted to be a practical and reliable performance indicator of physical mobility. [87] The validity of the TUG has been highlighted with its correlation with a number of mobility and performance measures such as the Berg Balance Scale [88] and gait speed [87, 89] with normative reference values available. [90]

Hip Biomechanics and Function: 3D Motion Analysis

Using a 10 camera motion capture system (Vicon Motion Systems Ltd., Oxford, UK, 100 Hz), 3D kinematic data will be collected as patients are asked to walk short distances between two marked points at their own comfortable pace. A set of 49 retroreflective markers will be placed on anatomical landmarks of each patient to identify positions of joints, in line with standardized position and coordinate system protocols established by the International Society of Biomechanics (ISB). [91] In addition to the recorded 3D marker trajectories using the above motion capture setup (Vicon Motion Systems Ltd., Oxford, UK, 100 Hz), ground reaction forces will be measured via two force platforms (AMTI Optima, Watertown, MA, 2000 Hz) and well as superficial muscle activity (i.e. activation, timing and amplitude) using passive surface electromyography electrodes (Delsys, Boston, MA, 2000 Hz, Contact Material 99.99% Silver, Inter-bar spacing 10mm, CMRR > 80 dB). These electrodes will be

placed on the hamstring (biceps femoris), gluteal muscles (gluteus maximus and gluteus medius), quadriceps (rectus femoris and vastus medialis) and hip adductor (adductor longus) of each leg, in line with SENIAM guidelines. This standardization ensures reliability im using 3D motion capture for the measurement gait parameters. [92]

An OpenSim [93] model will be scaled using the 3D motion data alongside the Musculoskeletal Atlas Program software (MAP) to produce patient-tailored musculoskeletal models. [94] Dynamic simulations will be run on the musculoskeletal models using OpenSim to calculate objective outcome measures from gait analysis including (but not limited to):

- Hip range of motion
- Hip joint contact forces
- Hip muscle force (simulated)

Gait Speed

Gait speed will be calculated from the motion capture trials as a valid and reliable measure of physical performance during gait, commonly reported in the literature. [95]

24-hour activity patterns

24-hour activity monitoring data over a seven day period will be collected at the six week and six month time points, using wearable accelerometers at the wrist (GeneActiv Original, Activinsights Ltd, Kimbolton, UK, 100 Hz). Patients will be asked to wear these activity monitors, at all times besides bathing. To better distinguish sedentary time from sleep time, patients will also be asked to fill in sleep logs. Physical activity measured using wrist worn accelerometers has been strongly correlated to gross motor activity patterns measured using waist worn monitors. [96] Wrist worn accelerometers will be used as opposed to waist or ankle worn accelerometers for better compliance.

Data Management:

Outcome data will be entered electronically and stored in a password protected shared drive and backed up weekly to a password protected folder on the University of Adelaide's network. Only investigators will have access to the data.

Sample size

Gamma3™ nail failure rates in the literature have been reported to vary from 2 to 15%. [97, 98] We opted for a conservative failure estimate of 7.5% as it represents the mid-range of reported data. [99] A clinically significant difference between the two groups would be a difference of 5% between the two intervention groups. Therefore using a significance level of 0.05 and power of 80%, allowing for 30% loss to follow up at six months (including 10% mortality) and a 1.5 variance inflation factor to allow for repeated measurements over time results in a requirement for 300 patients in each of the 3 groups (control group - Unlocked Gamma3™ Nail, and each of the Intervention Groups - Unlocked & Locked Intertan™ Nail).

Statistical Analysis

The primary outcome measure of device failure is considered a binary outcome (device failed/did not fail). A binary logistic regression model will be performed to assess the association between the outcome of device failure and the predictor of device type (Gamma3 Unlocked, Intertan Unlocked and Intertan Locked). Confounders of AMTS and gender will also be included in the model as covariates as they were stratification factors in the randomisation. Post-hoc comparisons will result in Odds Ratios, 95% confidence intervals, comparison P values and a global P value.

Some secondary outcomes are measured over two time periods. The FIM score is measured at patient discharge and at six months. Therefore, a linear mixed-effects model will be used for the outcome of FIM score and the interaction of time and device type, adjusting for repeated measurements over time as a random effect. A logarithmic transformation of the outcome may be

necessary. Similarly, as pain (VAS) and Harris Hip Score are measured at six weeks and six months, linear mixed-effects models will be used for these outcomes. For perioperative continuous outcomes, including surgery time, fluoroscopy time, Intra-operative Tip-Apex Distance, length of hospital stay and fracture union time, the association with device type will be investigated using a linear regression. For dichotomous secondary outcomes, including intra-operative complications, injury specific complication rates, re-operation rates and general medical complication rates, the association with device type will be investigated using binary logistic regression. Stratification variables AMTS and gender will be included as covariates in all secondary regression models.

For the biomechanics subgroup, secondary measures of gait speed, hip range of motion, hip muscle forces, and joint contact forces will be measured at six weeks and six months. Three linear mixed effects models will be used with the device type (Gamma3 Unlocked, Intertan Unlocked and Intertan Locked) as a fixed factor with timepoint as a repeated measure and the interaction of time and device type. Post hoc pairwise comparisons will then be used to identify the differences in the outcomes between the timepoints of six weeks and six months.

An intention-to-treat analysis will be performed (and as randomised analysis to deal with protocol non-adherence). Missing data will be handled on the basis of each outcome – if a patient is missing outcome data for a particular regression, they will be excluded from that regression. However, if they are not missing data for the remaining outcomes, they will be included in those analyses. The use of linear mixed-effects models also retains patient data when there is missing data from only one time period. Evidence for a statistically significant difference will be accepted as $p<0.05$. The statistical software that will be used is SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Trial oversight

The overall oversight of the trial will be under the responsibility of the head of the Department for Orthopaedics and Trauma at the Royal Adelaide Hospital and supported by the University of Adelaide's Centre for Orthopaedic & Trauma Research.

Ethics and Dissemination

This protocol has received ethics approval by the Central Adelaide Local Health Network Human Research Ethics Committee and will be conducted in accordance to the NHMRC National Statement of Ethical Conduct in Human Research. This clinical trial has been registered on the Australia New Zealand Clinical Trials Registry (ANZCTR): ACTRN12618001431213.

Authors contributions:

MR, DT and AS contributed to the design and implementation of the study. AL will contribute to data collection and SE will contribute to the statistical analysis of the data. AS will be responsible for data collection, processing and analysis of the biomechanics subgroup. AS, AL, MR, DT and SE contributed to the writing of this manuscript. All investigators will communicate any protocol modifications such that amendments can be made to the relevant parties (ethics committee, trial registry).

Funding statement:

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Competing interests statement:

This project is funded through an investigator initiated grant by Smith & Nephew Inc Orthopaedic Division (SN). SN had no input into the study.

Patient Consent:

Obtained.

Protocol Version:

Protocol Version 6. Date: 26 Jun 2019

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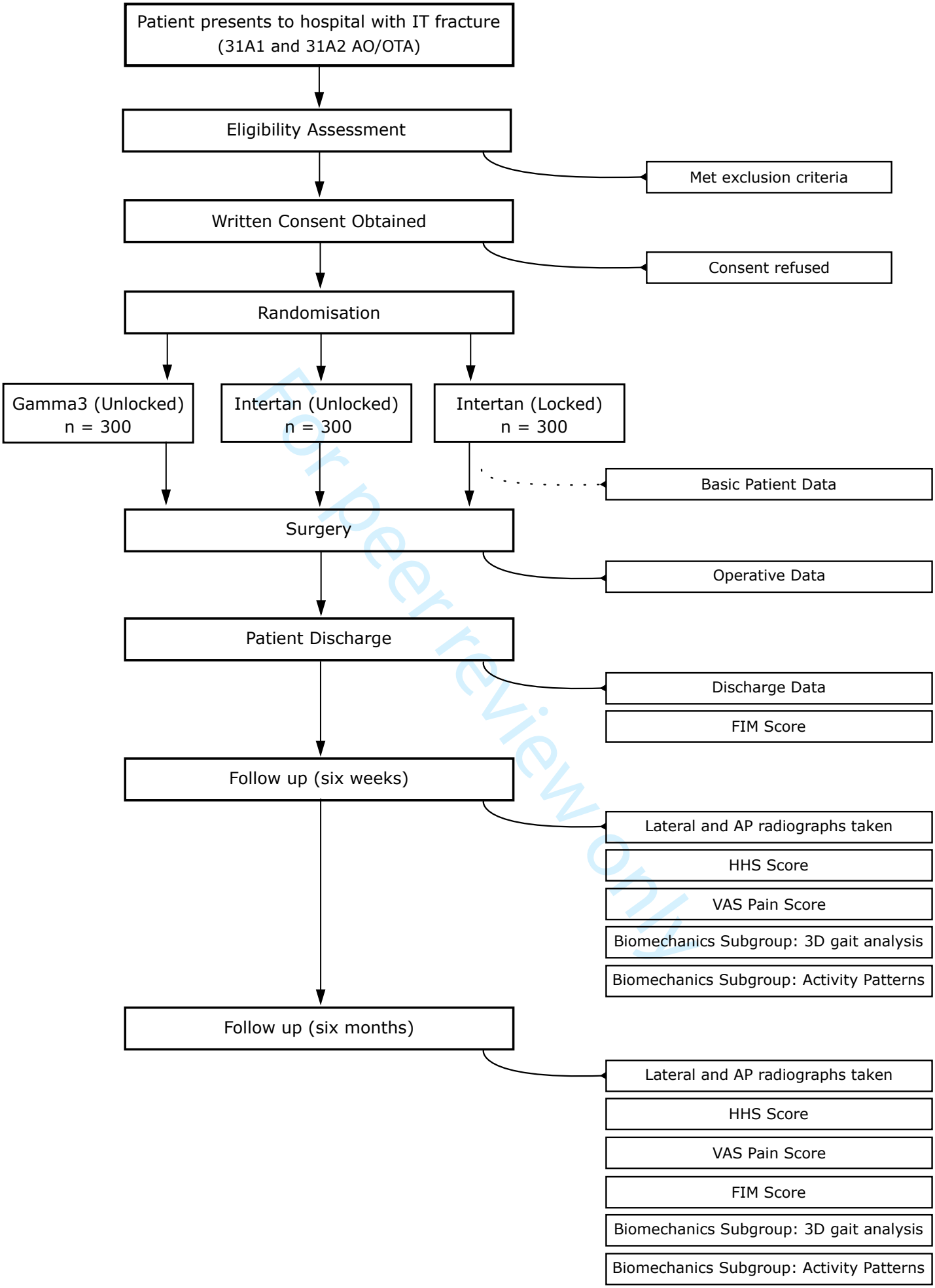

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	9
Protocol version	#3	Date and version identifier	20
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	20
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	9
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20

Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19,20
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11,12
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10,11
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-17
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-13

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered,	10

		opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a the appropriate medical staff are unblinded to the allocation and in the event of medical complications, the device type will be known by medical staff
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to	11,12,14-18

		promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12,13
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18,19

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a trial will continue until 900 patients are recruited

Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a in this trial, adverse events and harms are collected as complication information. This is described under secondary outcomes.
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	20
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or	10

		authorised surrogates, and how (see Item 32)	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a patients will be consented for the trial and informed that the data will be used for medical research.
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a all information collected is described in the protocol. See pg 11, 12-17
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a both devices used in this trial are FDA approved and widely used devices. Patients presenting with medical complications will be managed as standard

			procedure at the site patients present to.
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	20
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a No plans for participant level data to be made publically available
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Model consent forms will be uploaded as additional document
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	n/a

analysis in the current trial and for future use in ancillary studies, if applicable

Notes:

- 17b: n/a the appropriate medical staff are unblinded to the allocation and in the event of medical complications, the device type will be known by medical staff
- 18a: 11,12,14-18
- 21b: n/a trial will continue until 900 patients are recruited
- 22: n/a in this trial, adverse events and harms are collected as complication information. This is described under secondary outcomes.
- 26b: n/a patients will be consented for the trial and informed that the data will be used for medical research.
- 27: n/a all information collected is described in the protocol. See pg 11, 12-17
- 30: n/a both devices used in this trial are FDA approved and widely used devices. Patients presenting with medical complications will be managed as standard procedure at the site patients present to.
- 31c: n/a No plans for participant level data to be made publically available
- 32: Model consent forms will be uploaded as additional document This checklist was completed on 26. June 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Proximal Femoral Nail Unlocked Vs Locked (ProFNUL): A protocol for a multicentre, parallel armed randomised controlled trial for the effect of femoral nail mode of lag screw locking and screw configuration in the treatment of intertrochanteric femur fractures.

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Title: Proximal Femoral Nail Unlocked Vs Locked (ProFNUL): A protocol for a multicentre, parallel armed randomised controlled trial for the effect of femoral nail mode of lag screw locking and screw configuration in the treatment of intertrochanteric femur fractures.

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ABSTRACT:

Introduction:

Intertrochanteric fractures are common fragility injuries in the elderly. Surgical fixation using intramedullary (IM) devices are one of the widely used management options. To date, evidence demonstrating the effects of lag screw configuration and the mode of lag screw locking in these devices is lacking. The purpose of this study is to investigate whether the lag screw configuration (single vs. integrated dual interlocking screw) and the mode of lag screw locking (static vs. dynamic) of a femoral nail device result in differences in clinical and functional outcomes.

Methods and analysis:

A multicentre, pragmatic, single-blinded randomised controlled trial (RCT) with a three-arm parallel group design is proposed. Nine-hundred intertrochanteric fracture patients (A1 and A2 AO/OTA) will be randomised to fracture treatment using a Gamma3™ nail (Stryker) (proximally dynamic) or a Trigen™ Intertan™ nail (Smith and Nephew) in a dynamic or static lag screw configuration. The primary outcome measure consists of radiological evidence of construct failure within six months following surgery, with failure being defined as breakage of the femoral nail or distal locking screw, a change in Tip-Apex Distance (TAD) of more than 10mm or lag screw cut out through the femoral head. Secondary outcomes include surgical data (operation time, fluoroscopy time), complications (surgical site infection, reoperation, patient death), return to mobility and home circumstances, functional independence, function and Pain. Patients who are able to walk independently with or without a mobility aid and are able to answer simple questions and follow instructions will be asked to participate in three dimensional (3D) gait analysis at six weeks and six months to assess hip biomechanics from this cohort. Additional secondary measures of gait speed, hip range of motion, joint contact and muscle forces and gross activity monitoring patterns will be obtained in this subgroup.

Ethics and dissemination:

The Central Adelaide Local Health Network Human Research Ethics Committee has approved the protocol for this RCT (HREC/17/RAH/433). The results will be disseminated via peer-reviewed publications and presentations at relevant conferences.

Trial Registration:

This clinical trial has been registered on the Australia New Zealand Clinical Trials Registry (ANZCTR): ACTRN12618001431213.

ARTICLE SUMMARY

Strengths and Limitations of this study:

- Multicentre, pragmatic, single-blinded randomised controlled trial
- The first study to investigate the effects of femoral nail lag screw locking mode on clinical and functional outcomes.
- The first study to collect 3D motion capture data from these patients post-operatively.
- Powered to detect differences in device failure between the three parallel arm groups in a large sample size (900).
- Limitations of the study include an unpredictable loss to follow up from death or failure to attend.

INTRODUCTION:

Background and Rationale

Proximal femur fractures are a highly prevalent injury in the elderly,[1, 2] with an estimated 1.31 million fractures occurring worldwide each year.[3, 4] With a growing elderly population resulting from an increasing life expectancy, [5] there is an increasing global incidence of these fractures, [5-9] projected to reach 6.26 million by the year 2050.[10] Fractures within the intertrochanteric region represent approximately half of all proximal femur fractures. [11] Treatment typically consists of

surgical fixation using either IM (e.g. proximal femoral nail (PFN, Synthes™)) or extramedullary (e.g. Dynamic Hip Screw (DHS, Synthes™)) fixation devices.

Since its introduction in the 1990s, IM fixation has become increasingly popular, [12] with increasing trends towards this device preference recorded in the United States [13] and Australia. [14] Numerous types of IM fixation devices are available for clinical use, [15] however the optimum implant choice remains unknown. [16] While there is evidence to support the use of these devices in the treatment of intertrochanteric fractures, the evidence demonstrating whether variations in design characteristics influence patient clinical outcomes is conflicting. [12, 17-19] As no rationale behind implant selection can be drawn from the literature, there is considerable diversity regarding the choice of implant between clinicians. [20]

The Gamma3™ nail (Stryker) is a well-established and widely used current generation single lag screw IM device [12] which shows good clinical and radiographic outcomes. [21-23] However, complications still exist, with the most frequently reported complication being cut-out of the lag screw through the femoral head, [24-26] with an incidence rate ranging between 4% and 8%. [27-29] The Trigen™ Intertan™ nail (Smith & Nephew) is a similar current generation IM device, featuring a dual lag screw configuration comprised of a larger superior lag screw and a smaller screw integrated within the superior screw. [30] Together, this interlocking dual-oval shaped composite screw mechanism allows for linear compression of the fragments at the fracture site while providing high rotational stability. [31, 32] Clinical studies evaluating the Intertan nail against other single screw devices have recorded a significant reduction in the occurrences of implant failure, fracture site non-union, mal-union, lag screw cut out and uncontrolled varus fracture collapse. [30, 31, 33-35] Several authors have postulated the reduced complication rate being attributed to the design of this nail. [30] Moreover, ex vivo biomechanical studies have demonstrated superior biomechanical results with the Intertan™ nail. [36-39] However, despite the Gamma3™ nail and Trigen™ Intertan™ nail both being well-established implant choices

used in the treatment of these fractures, very little direct comparative clinical evidence exists between these nails.

A meta-analysis by Ma et al [40] found only nine papers, four of which included the Gamma3™ and the Intertan™. Of these four, three were randomised controlled trials comparing the two devices, but with relatively small cohort sizes. From these studies, the Intertan™ nail was shown to result in a lower incidence of implant cut out and femoral fractures which was of statistical significance. No statistically significant differences in time to union and post-operative complications were found between devices. Ma et al highlighted that a limitation of this statistical analysis was the relatively small sample size of the studies included, and indicated a need for more high quality RCTs to yield a more convincing test power. [40] Hence, the literature reveals limited evidence of whether design characteristics of femoral nails affect clinical and patient outcomes in the treatment of trochanteric fractures.

In addition to the choice of the IM implants, other aspects of these devices used in the practical management of intertrochanteric fractures need further evaluation. This includes the mode of lag screw fixation (static or dynamic). Technically, both the Gamma3™ and Intertan™ nails can be used in static or dynamic modes of the lag screw. In the dynamic mode, fracture collapse occurs under physiological loading, resulting in macro and micromotion of the fracture fragments as well as compression/apposition of fracture fragments, [41-43] desired to stimulate fracture healing. However, excessive sliding of the lag screw has been shown by some authors to lead to mechanical complications and negatively affect patient function. [44-46]

Whilst there is evidence highlighting a reduced risk of lag screw cut out when utilizing a sliding lag screw in extramedullary devices, [45, 47, 48 49, 50] there is a paucity of similar evidence relating to the use of IM devices. One study compared the static and dynamic modes of the proximal lag screw in the Gamma3™ nail in 80 patients. [51] From this study, no statistically or clinically significant difference in Harris Hip Scores, time to fracture healing or length of hospital stay was found. No such comparative evidence exists for the Intertan™ nail. Moreover, no clinical studies to date, comparing one IM

device to another has made any note of which mode of the lag screw was employed. Consequently, considerable variance in practice can be seen between clinicians.

For the Gamma3 nail, it is suggested by Stryker in their operative technique guide that the device has to be used in the dynamic mode, with the use of the nail in a static mode considered off label. [52] For the Intertan nail (Smith & Nephew), this decision is stated in their surgical technique guide as optional with both modes considered on label, [53] and left to the operating surgeons decision.

Considering the substantial costs attributed to the management of intertrochanteric fractures, we believe that more evidence is required to evaluate the effectiveness of a single or dual screw femoral nail, as well the use of these devices in the static and dynamic modes. Moreover, no previous studies have compared postoperative lower extremity biomechanics in intertrochanteric fracture patients treated with these devices. This proposed multicentre, parallel, three-arm randomised controlled trial has been designed to fill these gaps in knowledge, and will include a two-way comparison between the Gamma3™ (dynamic) and Intertan™ (dynamic) nails, as well as the Intertan™ (dynamic) and Intertan™ (static) nails.

Objectives:

Primary Objective

The aim of this RCT is to investigate if there are differences in failure rates between the surgical management of intertrochanteric fractures using a single screw or dual screw femoral nail, as well as when using a femoral nail in either the static or dynamic modes of the lag screw.

It is hypothesized there will be no difference in failure rates between patients managed with a single screw or dual screw femoral nail device. It is also hypothesized that there will be no difference in failure rates between patients managed with a femoral nail in the static or dynamic mode of the lag screw.

Secondary Objectives

Several secondary objectives will also be studied for this RCT to evaluate the effectiveness of the devices used by quantifying and drawing inferences from observed differences between treatment groups in:

- Intraoperative surgical data (operation time, fluoroscopy time, blood loss, TAD)
- Pain within six months after surgery (VAS Pain Score).
- Patient function (Functional Independence Measure) and Hip function (Harris Hip Score) within six months after surgery.
- Post-operative hip biomechanics using objective measures from gait analysis up to six months after surgery.

Trial Design

The ProFNUL study is a multicentre, pragmatic (as defined by the Pragmatic–Explanatory Continuum Indicator Summary 2 Tool (PRECIS-2)[54]), single-blinded randomised controlled trial with a three-arm parallel group design.

METHODS AND ANALYSIS

Patients will be randomised using an online computerised sequence generation service to test if there is a difference in outcomes between the treatment interventions. Recruitment, medical and surgical data collection will take place at the Royal Adelaide Hospital and Queen Elizabeth Hospital with other sites added later as required for participant numbers. Radiographic images will be collected at a diagnostic imaging practice and 3D motion capture data will be conducted at The University of Adelaide, South Australia.

This RCT has been registered with the Australian New Zealand Clinical Trials Registry (ANZCTR). Trial registration data is shown in Table 1.

This study protocol was developed in accordance with the Standard Protocol Items:

Recommendations for Interventional Trials (SPIRIT) statement.

Patient and Public Involvement

Patients and public were not involved in the design, conduct or reporting of this study.

Table 1. Trial Registration Data

Data Category	Information
Primary registry and trial identifying number	https://www.anzctr.org.au ACTRN12618001431213
Date of registration in primary registry	27/08/2018
Secondary identifying numbers	None
Source of monetary or material support	Smith & Nephew Pty Ltd
Primary sponsor	Royal Adelaide Hospital, Dept. of Orthopaedics & Trauma Contact person: MR (mark.rickman@sa.gov.au) Smith & Nephew Inc Orthopaedic Division (SN)
Secondary sponsor	University of Adelaide, Centre for Orthopaedic & Trauma Research. Contact person: AS (arjun.sivakumar@adelaide.edu.au) Contact person: DT (dominic.thewlis@adelaide.edu.au)
Contact for public queries	MR (mark.rickman@sa.gov.au)
Contact for scientific queries	DT (dominic.thewlis@adelaide.edu.au)
Public title	Evaluating the treatment methods of proximal femur fractures in elderly trauma patients
Scientific title	A multi-centre, single-blinded prospective randomised controlled trial of the Gamma3™ intramedullary nail to the unlocked and locked Intertan™ intramedullary nail for the treatment of proximal femur fractures.
Countries of recruitment	Australia.
Health problem studied	Proximal femur fracture
Interventions	Gamma3™ Trochanteric nail (Unlocked proximally) Trigen™ Intertan™ Trochanteric nail (Unlocked proximally) Trigen™ Intertan™ Trochanteric nail (Locked proximally)
Key inclusion and exclusion criteria	Inclusion criteria: Traumatic extracapsular hip fracture, Closed injury, Patient aged over 60 years, Ability to be followed for up to six months, Presentation to hospital within 14 days of injury Exclusion criteria: Patients with concomitant injuries affecting treatment and rehabilitation of the affected limb, Patients with associated neurovascular injuries requiring immediate surgery, Patients where consent is refused, Patient with limited English proficiency including family members.
Study type	Randomised controlled trial
Date of first enrolment	05/09/2018
Target sample size	900
Recruitment status	Recruiting
Primary Outcome	Construct failure (time point: up to 6 months after intervention)

Key secondary outcomes	Incidence of Injury specific complications (time point: 6 months) Functional Independence (time point: 6 months) Reoperation incidence (time point: 6 months) Return to mobility circumstances (time point: 6 months) Hip joint range of motion (time point: 6 months) Hip joint contact forces (time point: 6 months) Post-operative hip muscle function (abductors, flexors, extensors) (time point: 6 months)

Eligibility

Patients over 60 years of age presenting to any of the participating hospitals with an isolated, closed intertrochanteric fracture will be recruited against the following eligibility criteria:

Inclusion criteria

1. Traumatic intertrochanteric femur fracture (A1 and A2 AO/OTA) where a decision has been made for surgical management using a femoral nail.
2. Closed injury.
3. Patients aged over 60 years.
4. Presentation to hospital within 14 days of injury.

Exclusion criteria

1. Patients with concomitant injuries affecting treatment and rehabilitation of the affected limb.
2. Patients with associated neurovascular injuries requiring immediate surgery.
3. Patients with limited english proficiency including family members.
4. Patients where consent is refused.

All eligible patients will be provided with a study information sheet and consent form by the hospital medical staff (online supplementary appendix). If eligible patients are not able to consent due to cognitive impairment, consent will be sought from the family, in the same manner that consent for

surgery and anaesthesia occurs currently (online supplementary appendix). Randomisation will then occur once consent has been obtained.

Randomisation and blinding

Patients will be randomised via a computerised generation system managed by the Griffith University's Clinical Trial Unit (Griffith University, QLD, Australia), allocating patients to three study groups of equal weights using random block sizes of 6 and 9. Randomisation will be stratified by site (3 categories), gender (2 categories), and cognitive function via Abbreviated Mental Health Test Score (AMTS) (2 categories). Randomisation of the next subject will be computer-generated at the time of request by a medical research officer at the hospital via the online randomisation system.

Patients will be blinded to their allocation until the conclusion of the trial to reduce bias in patient reported outcome measures. The statistician performing the analysis will also be blinded to the group allocation. Surgeons and researchers will not be blinded to allocation.

Standard Treatment Pathway

The clinical pathway for recruited patients will be unchanged from the routine for each institution; surgery is typically carried out within 24-48 hours, and no changes will be necessary to any part of the surgical episode with the exception of the individual device used and mode of proximal locking as directed by the randomisation outcome. Training and observation will be provided to all surgeons throughout the duration of this study, from senior surgeons competent with the use of both devices; throughout the duration of the study it is anticipated that a large number of surgeons will carry out the procedures, using both devices at all sites. This adds to the pragmatic nature of the study. All fractures will be compressed proximally at the time of surgery, just prior to the nail being either locked proximally or left unlocked. Similarly, post-operative management will remain unchanged from routine, including discharge timing and destination. All patients will be mobilised fully weight bearing as soon as possible after surgery.

Allocated Interventions

A total of 900 trauma patients with IT (31A1 and 31A2 AO/OTA) will be randomised to receive one of the three femoral nail interventions.

- Gamma3™ (Stryker) (locked proximally)
- Intertan™ (Smith & Nephew) (unlocked proximally)
- Intertan™ (Smith & Nephew) (locked proximally)

Participant Flow Timeline

A succinct summary of the patient timeline is described by Figure 1. Once a patient has been recruited and randomised, a baseline patient registration assessment will be completed through the use of an online form. Surgery will then proceed at the earliest available opportunity as per routine for the hospital. Nail diameters are all fixed at 11mm for the Gamma3 nail, and 11.5mm for the Intertan Nail with the nail centrum collum diaphyseal (CCD) angle at 125 degrees. Following surgery, an operative information form will be completed by the operating surgeon using another online form. Upon patient discharge, medical staff will complete a patient discharge online form which includes a clinical assessment measure of functional independence (FIM score). Following discharge, follow up appointments will be scheduled to coincide with six weeks and six months with appointment letters and x-ray referrals sent from the Royal Adelaide Hospital. A week prior to each patients appointment, patients will be called to confirm their appointments or reschedule, if required. AP and lateral hip radiographs will be taken, followed by a clinical examination with an orthopaedic and trauma specialist, where measures of hip pain (Visual Analog Scale from 0 to 10) and hip function (Harris Hip Score) will be recorded. At the six month follow up, AP and lateral hip radiographs will be taken, followed by a similar clinical examination with an orthopaedic and trauma specialist. At this appointment, a measure of functional independence (FIM score) will be recorded in addition to VAS and HHS scores.

Patients who are able to walk independently with or without a mobility aid and are able to answer simple questions and follow instructions will be included in a 'biomechanics sub-group' where 3D gait analysis will be performed at the six weeks and six month follow ups immediately following the clinical examination. After the gait analysis, patients will be provided with a wrist worn activity monitor (GeneActiv Original, Activinsights Ltd, Kimbolton, UK, 100 Hz) to wear for seven days at a time, providing information on 24 hour gross physical activity patterns of these patients. Patients will be asked to complete a sleep log during this period to better distinguish sedentary time from sleep. After seven days, patients will post the monitors back via pre-paid return envelopes. Patients living rurally and unable to attend follow up appointments will have x-ray appointments organised at locations convenient to them collected over the phone by an orthopaedics and trauma specialist. Patients presenting to clinics reporting complications, will be reviewed by a clinician and radiographs taken, as per standard procedure. In these events, the occurrence of these complications is recorded against the patient's hospital number.

Outcomes

Primary outcome measure

The primary outcome measure is radiological evidence of device-bone construct failure at any point up to six months following surgery and will be assessed via AP and lateral radiographs. Failure will be defined as the occurrence of any of the following:

1. Breakage (mechanical fracture) of the femoral nail. [55]
2. Breakage (mechanical fracture) of the distal locking screw.
3. Protrusion of lag screw through the cortex of the femoral head (cut out). [56]
4. A change in TAD of more than 10mm.

The TAD, [57] measured from the tip of the lag screw to the apex of the femoral cortex in lateral and AP radiographs is generally used in clinical practice and is desirable for this measurement to be

under 25 mm. TADs larger than 25mm have been shown to serve as an accurate indicator of future protrusion of a lag screw through the femoral head (cut out). [58] The TAD has been shown to be reproducible to within 2-3 mm between measurements [57, 59] and highlighted to change by 2-3 mm over time. [60] A change in TAD of more than 10 mm has therefore been selected as a reference level which represents failure of the IM device to maintain fracture stability.

Secondary outcome measures

Secondary outcomes will also assess differences in the effectiveness between the interventions using several measures, including:

Femoral Neck Shortening

Femoral neck shortening will be measured from the anteroposterior radiograph along the long axis of the femur. This is a frequently used measure after surgical treatment of hip fractures [61, 62] and is regarded a reliable measure. [63]

Functional Independence: FIM score

The FIM score is a widely used instrument for measuring the severity of patient disability and dependence in rehabilitation medicine. [64] It has been demonstrated as a validated and reliable measure [65] with good interrater reliability of the total score (Intraclass correlation coefficient of 0.96). [66]

Pain: Visual Analog Scale

Pain will be assessed using a visual analog scale (VAS) [67] of categorical values from 0 to 10, with 0 indicating no pain, and 10 indicating excruciating pain. The VAS pain score is a commonly used and validated measurement for patient reported acute pain. [68]

Hip Function: Harris Hip Score

Hip function will be assessed by a clinician using the Harris Hip Score to evaluate hip function and disability across domains of pain, function, absence of deformity, and range of motion. [69] The Harris hip score is a well performing [70] and frequently used clinician based outcome measure that has shown high reliability and validity in evaluating hip function. [71, 72]

Perioperative Data

Perioperative data recorded in this trial will include surgery time, fluoroscopy time, Intra-operative TAD, length of hospital stay, union time and intra-operative complications, all of which are commonly reported as valid measures across a number randomised controlled trials evaluating femoral nail devices. [40, 73-77] Intra-operative blood loss will also be recorded, however the reliability of this measure is unclear due to its underestimation during hip fracture surgery. [78]

Injury/Surgery Specific Complications

Surgical complications not only affect clinical outcome parameter, but appear to be a significant and often long-term predictor of patient postoperative psychosocial outcomes. [79, 80] Complications recorded will include the number and type of injury and surgery specific events and complications including, technical complications, surgical site infection, unplanned surgery and death up to one year following surgery. This has been reliably collected in previous studies. [81, 82]

Re-operation

The number of patients presenting to clinic requiring reoperation will be recorded in this trial. The rate of re-operation is a reliable measure in assessing quality of medical treatment. [83]

General Medical Complications

In this study, the number of patients suffering from general medical complications will be recorded. This has been collected and reported as a valid measure in the literature. [80]

Secondary outcome measures: Biomechanics Sub-group

Physical Mobility - Timed Up and Go

Physical mobility will be assessed using the timed up & go test (TUG) which has been widely used in the literature [84] and noted to be a practical and reliable performance indicator of physical mobility. [85] The validity of the TUG has been highlighted with its correlation with a number of mobility and performance measures such as the Berg Balance Scale [86] and gait speed [85, 87] with normative reference values available. [88]

Hip Biomechanics and Function: 3D Motion Analysis

Using a 10 camera motion capture system (Vicon Motion Systems Ltd., Oxford, UK, 100 Hz), 3D kinematic data will be collected as patients are asked to walk short distances between two marked points at their own comfortable pace. A set of 49 retroreflective markers will be placed on anatomical landmarks of each patient to identify positions of joints, in line with standardized position and coordinate system protocols established by the International Society of Biomechanics (ISB). [89] In addition to the recorded 3D marker trajectories using the above motion capture setup (Vicon Motion Systems Ltd., Oxford, UK, 100 Hz), ground reaction forces will be measured via two force platforms (AMTI Optima, Watertown, MA, 2000 Hz) and well as superficial muscle activity (i.e. activation, timing and amplitude) using passive surface electromyography electrodes (Delsys, Boston, MA, 2000 Hz, Contact Material 99.99% Silver, Inter-bar spacing 10mm, CMRR > 80 dB). These electrodes will be placed on the hamstring (biceps femoris), gluteal muscles (gluteus maximus and gluteus medius), quadriceps (rectus femoris and vastus medialis) and hip adductor (adductor longus) of each leg, in line with SENIAM guidelines. This standardization ensures reliability in using 3D motion capture for the measurement gait parameters. [90]

An OpenSim [91] model will be scaled using the 3D motion data alongside the Musculoskeletal Atlas Program software (MAP) to produce patient-tailored musculoskeletal models. [92] Dynamic simulations will be run on the musculoskeletal models using OpenSim to calculate objective outcome measures from gait analysis including (but not limited to):

- Hip range of motion
- Hip joint contact forces
- Hip muscle force (simulated)

Gait Speed

Gait speed will be calculated from the motion capture trials as a valid and reliable measure of physical performance during gait, commonly reported in the literature. [93]

24-hour activity patterns

24-hour activity monitoring data over a seven day period will be collected at the six week and six month time points, using wearable accelerometers at the wrist (GeneActiv Original, Activinsights Ltd, Kimbolton, UK, 100 Hz). Patients will be asked to wear these activity monitors, at all times besides bathing. To better distinguish sedentary time from sleep time, patients will also be asked to fill in sleep logs. Physical activity measured using wrist worn accelerometers has been strongly correlated to gross motor activity patterns measured using waist worn monitors. [94] Wrist worn accelerometers will be used as opposed to waist or ankle worn accelerometers for better compliance.

Data Management:

Outcome data will be entered electronically and stored in a password protected shared drive and backed up weekly to a password protected folder on the University of Adelaide's network. Only investigators will have access to the data.

Sample size

Gamma3™ nail failure rates in the literature have been reported to vary from 2 to 15%. [95, 96] We opted for a conservative failure estimate of 7.5% as it represents the mid-range of reported data. [97] A clinically significant difference between the two groups would be a difference of 5% between the two intervention groups. Therefore using a significance level of 0.05 and power of 80%, allowing for 30% loss to follow up at six months (including 10% mortality) and a 1.5 variance inflation factor to

allow for repeated measurements over time results in a requirement for 300 patients in each of the 3 groups (control group - unlocked Gamma3™ nail, and each of the intervention groups - unlocked & locked Intertan™ nail).

Statistical Analysis

The primary outcome measure of device failure is considered a binary outcome (device failed/did not fail). A binary logistic regression model will be performed to assess the association between the outcome of device failure and the predictor of device type (Gamma3 unlocked, Intertan unlocked and Intertan locked). Confounders of AMTS and gender will also be included in the model as covariates as they were stratification factors in the randomisation. Post-hoc comparisons will result in Odds Ratios, 95% confidence intervals, comparison P values and a global P value.

Some secondary outcomes are measured over two time periods. The FIM score is measured at patient discharge and at six months. Therefore, a linear mixed-effects model will be used for the outcome of FIM score and the interaction of time and device type, adjusting for repeated measurements over time as a random effect. A logarithmic transformation of the outcome may be necessary. Similarly, as pain (VAS) and Harris Hip Score are measured at six weeks and six months, linear mixed-effects models will be used for these outcomes. For perioperative continuous outcomes, including surgery time, fluoroscopy time, Intra-operative TAD, length of hospital stay and fracture union time, the association with device type will be investigated using a linear regression. For dichotomous secondary outcomes, including intra-operative complications, injury specific complication rates, re-operation rates and general medical complication rates, the association with device type will be investigated using binary logistic regression. Stratification variables AMTS and gender will be included as covariates in all secondary regression models.

For the biomechanics subgroup, secondary measures of gait speed, hip range of motion, hip muscle forces, and joint contact forces will be measured at six weeks and six months. Three linear mixed effects models will be used with the device type (Gamma3 unlocked, Intertan unlocked and Intertan

locked) as a fixed factor with timepoint as a repeated measure and the interaction of time and device type. Post hoc pairwise comparisons will then be used to identify the differences in the outcomes between the timepoints of six weeks and six months.

An intention-to-treat analysis will be performed (and as randomised analysis to deal with protocol non-adherence). Missing data will be handled on the basis of each outcome – if a patient is missing outcome data for a particular regression, they will be excluded from that regression. However, if they are not missing data for the remaining outcomes, they will be included in those analyses. The use of linear mixed-effects models also retains patient data when there is missing data from only one time period. Evidence for a statistically significant difference will be accepted as $p<0.05$. The statistical software that will be used is SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Trial oversight

The overall oversight of the trial will be under the responsibility of the head of the Department for Orthopaedics and Trauma at the Royal Adelaide Hospital and supported by the University of Adelaide's Centre for Orthopaedic & Trauma Research. A Trial Steering Committee and Data Safety and Monitoring Committee (DSMC) will be set up. The TSC will comprise of the chief investigator (CI) and associate investigator and will provide overall supervision. the DSMC will comprise of an associate investigator, clinicians and database management staff at the Royal Adelaide Hospital. The DSMC and TSC will meet prior to commencing the trial with further meetings arranged depending on the trial requirements.

Ethics and Dissemination

This protocol has received ethics approval by the Central Adelaide Local Health Network Human Research Ethics Committee and will be conducted in accordance to the NHMRC National Statement

of Ethical Conduct in Human Research. This clinical trial has been registered on the Australia New Zealand Clinical Trials Registry (ANZCTR): ACTRN12618001431213.

Authors contributions:

MR, DT and AS contributed to the design and implementation of the study. AL will contribute to data collection and SE will contribute to the statistical analysis of the data. AS will be responsible for data collection, processing and analysis of the biomechanics subgroup. AS, AL, MR, DT and SE contributed to the writing of this manuscript. All investigators will communicate any protocol modifications such that amendments can be made to the relevant parties (ethics committee, trial registry).

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Competing interests statement:

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Patient Consent:

Obtained.

Protocol Version:

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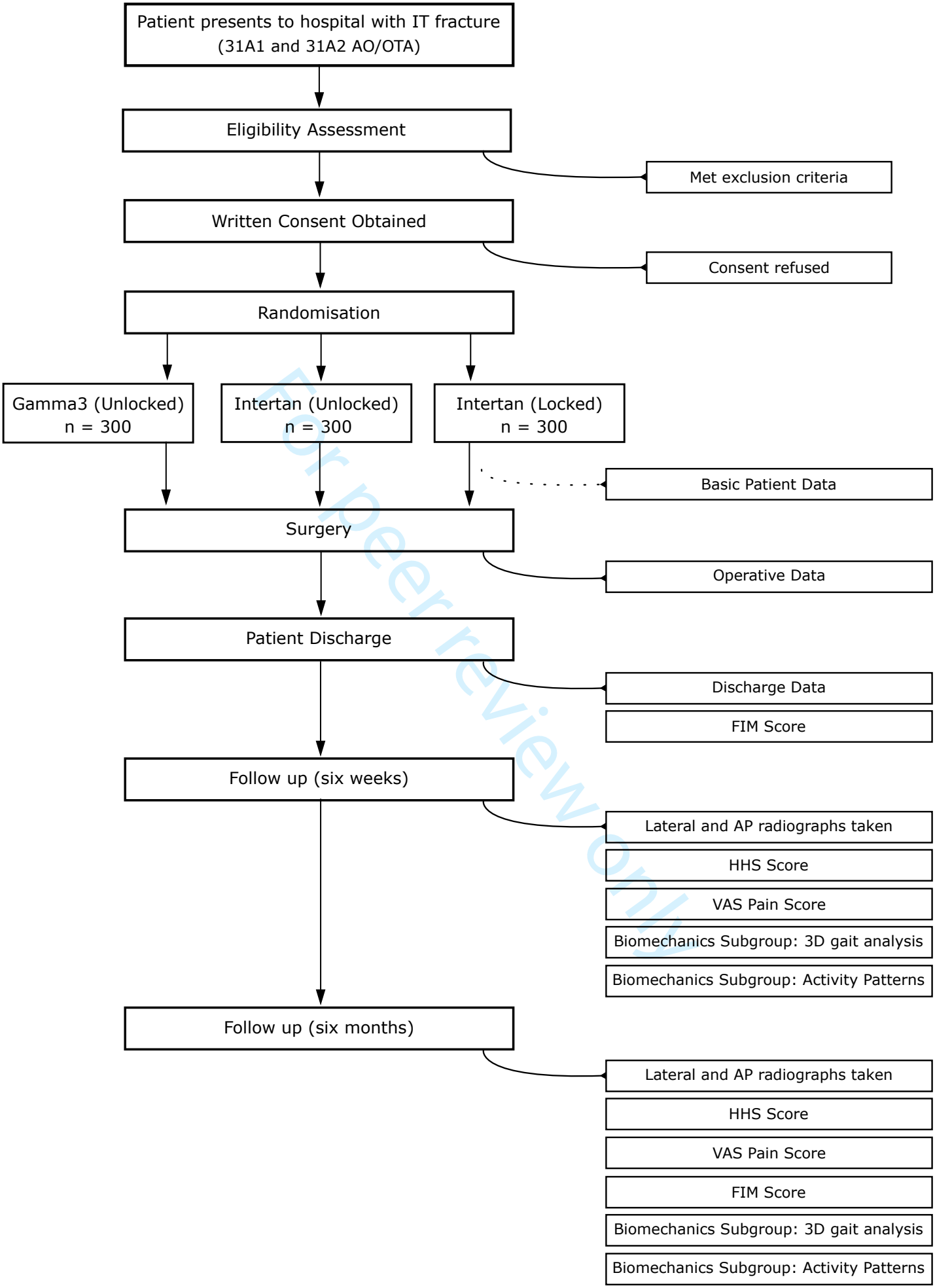
Figure Legends

Figure 1: Patient flow diagram.



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ProFNUL- Proximal Femoral Nail Unlocked vs Locked Trial – Participant Information Sheet

We are inviting you to take part in a clinical research study which is a comparison involving 2 different types of devices used to treat broken hips.

Before you decide whether to participate, it is important for you to understand why this study is being undertaken and what it will involve.

Please take time to read the following information carefully and discuss it with your family or other advisors, if you wish.

Please ask if you would like additional information or there is anything that is not clear.

Take your time to consider whether or not you wish to take part.

What is this trial about?

Broken hips such as yours are very common, and almost all are treated with an operation. At this hospital, around half of the operations for this injury involve using a device called a "Nail", which is a rod inserted down the middle of the thigh bone to help hold the break whilst it heals. At the top of this rod there is a long screw that is inserted up towards the hip joint, that adds more stability to the broken bone.

This trial has two aims. The first is to compare two different makes of Nail – they are both well tried and tested designs, but from different companies, each considered 'standard practise' by different surgeons and at different hospitals. In spite of this, no direct comparison exists to help us decide which to use. The second aim of the study is related to the screw at the top of the nail. This screw can be inserted in two different ways – one is called "unlocked" which means it can slide up and down, whilst the other is called "locked" which means it is fixed in place. Some surgeons always use a "locked" mode, some always use an "unlocked" mode, and some decide for each individual case. There is no good evidence available to help guide this decision, and so we are aiming to get information from this trial to help us decide whether this screw should be fixed or allowed to slide, potentially

improving the future treatment of broken hips. In order to answer these questions we need to compare large numbers of patients, and our aim is to include a total of 900 patients in this study, over a 3 to 4 year period.

Why have I been asked to participate?

You have broken your hip, and your surgeon has already decided that you need an operation using a type of Nail. We would therefore like to consider enrolling you into this trial.

What will happen if I agree to take part?

If you agree to take part, you will be randomly assigned to receive one of the 2 different types of Nail, and also whether the screw at the top will be locked or unlocked. Randomisation is like flipping a coin – neither you nor your treating surgeon will be able to choose which device you receive, or whether the nail is locked or unlocked at the top.

Your operation will still take place in the normal way at the same time, by the same surgeon, the only difference will be which device is used in surgery, and how it is used with regard to the mode of the screw at the top.

After surgery we would normally review you up to one year after surgery, typically at six weeks, six months and 12 months. For this study, we are planning to review you in the clinic at six weeks and six months - we will ask you to fill out some forms to tell us about your hip pain and general function at each visit. This should take you around 20 minutes at each visit. There are no extra clinic visits required, and no extra X-rays to be taken.
You will not know which Nail has been used, although we will tell you if you want to know, after the 6 month final assessment.

In the event of general complications involving the treatment device (i.e. device failure), we may ask for consent for a bone biopsy to be taken. In this event, we will seek your consent before doing anything.

Are there any risks to me if I agree to take part?

There is no additional risk involved in the surgery or recovery process. It is possible that when the trial is complete you will have been randomly assigned to a group of patients that are shown to do less well, however it is not possible to tell that until the trial is completed. There are no out of pocket expenses associated with this trial.

What if something goes wrong?

All surgery has some risk, which will be discussed with you separately by your treating doctor or team. The additional risk of being involved in this study is felt to be very small. However, the study is indemnified by SA Health, and in addition you retain the right to seek compensation through the legal system.

What will happen if I refuse to take part?

If you don't want to take part in the trial then there is no problem with this. Your surgery will go ahead exactly as planned, and you will whichever Nail your surgeon chooses. There will be no change in your follow-up plans either.

What if I want to pull out of the study after surgery?

If you no longer wish to participate in the trial, then you are free to withdraw at any point. There will be no effect on your care as a result of this.

What are the potential benefits of this study?

You will not receive any direct benefits or payment for being in this study. however the information gained from this trial will help simplify decision making for future patients, and hopefully lead to also improved outcomes for the patients.

Who is organising and funding the research?

This study is being organised and run by Associate Professor Mark Rickman, as part of the department of Orthopaedics & Trauma at the Royal Adelaide Hospital.
The study will be performed according to the NHMRC National Statement on Ethical Conduct in Human Research, a document prepared to protect the rights of participants in medical research studies
Funding has been provided via a Research Grant, that was awarded by Smith & Nephew. Smith & Nephew manufacture one of the devices used in this study, however they do not have any control of any aspect of the study (it is independent of them as the funding was awarded as a grant). In addition, the data and outcomes from the study are owned by the University of Adelaide / Royal Adelaide Hospital and not by Smith & Nephew. The company however may benefit in that this will result in publication of a large volume of outcome data on patients managed with their device.

All research in medicine is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been carefully approved by the Central Adelaide Local Health Network Human Research Ethics Committee – HREC reference number: HREC/17/RAH/433

Confidentiality and Data Security

Access to your medical records for information related to your operation and any post operative events will be required by the research team.

All the information collected during the study will be kept confidential. Data will be held on a secure database in the Royal Adelaide Hospital, protected from unauthorised access.

On the database, you will be identified by a unique study number, date of birth, date of operation and surgeon who performed your operation. Only the surgeon, and members of the research team will be able to identify participant's names. All parties are bound by strict confidentiality guidelines under the Australian Data Protection Laws.

At the end of this study, the data will be stored in the same secure manner for 10 years, before being deleted.

If you agree to participate you will be asked to grant consent for our research team to access your medical notes for data entry and to auditors for the purpose of verifying accuracy of data entered.

In addition to the processes described above, data may otherwise be discoverable through processes of law or for assessing compliance with research procedures.

You have a right to access the information collected and stored by researchers about you. You also have a right to request that any information with which you disagree be corrected.

You have a right to ask that any stored specimens be destroyed but should be aware that data which has already

A description of this clinical trial will be available on www.anzctr.org.au, as required by the Ethics Committee. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What will happen to the results?

Whatever the trial shows, we plan to publish the outcome data as a paper in the medical literature, as well as present it at local and national meetings to disseminate the findings. No patients would be identified in any of these, and only total numbers of patients and outcomes will be shown.

Who do I ask if I have more questions?

If you have urgent questions, you can ask either the person who gave you this form, or your treating doctors. In addition, for less urgent questions you can ask the study co-ordinator A/Professor Mark Rickman, who can be contacted via his secretary on 08 707 42003.

If you wish to speak to someone not involved in the study about your rights as a participant, you may contact the Executive Officer of the Research Ethics Committee on 08 7117 2229 or CALHNResearchEthics@sa.gov.au

Study No: | | | |

ProFNUL – Proximal Femoral Nail Unlocked vs Locked Study

PATIENT CONSENT FORM

1. I confirm that I agree to take part in this study as described to me and that I was given the opportunity to ask all of the questions I had concerning my treatment and participation and that they were all answered to my satisfaction.

2. I also confirm that I have read and understood the patient information sheet and I have had the opportunity to discuss the patient information provided for me with members of my family and/or friends.

3. I understand that I will not benefit from taking part in this study.

4. I understand that if I withdraw or become unable to complete the study on medical grounds that data gathered prior to that time point may still be used for this study.

Patient Name ……

Signature …… Date ……

Consent Taken By …… Role……

Signature …… Date ……

Surgeon Name……

Surgeon Signature…….. Date……

Study No: | | | |

ProFNUL – Proximal Femoral Nail Unlocked vs Locked Study

Patient Consent Form for Gait Analysis & Activity Monitors

1. I confirm that I agree to take part in this part of the study as described to me and that I was given the opportunity to ask all of the questions I had concerning my treatment and participation and that they were all answered to my satisfaction.

2. I also confirm that I have read and understood the separate patient information sheet and I have had the opportunity to discuss the patient information provided for me with members of my family and/or friends.

3. I understand that I will not benefit from taking part in this study.

4. I understand that if I withdraw or become unable to complete the study on medical grounds that data gathered prior to that time point may still be used for this study.

Patient Name ……

Signature …… Date ……

Consent Taken By …… Role……

Signature …… Date ……

Surgeon Name……

Surgeon Signature…….. Date……

Study No: | | | |

ProFNUL – Proximal Femoral Nail Unlocked vs Locked Study

3rd Party Consent Form

1. I confirm that I agree for ……..to take part in this study as described to me and that I was given the opportunity to ask all of the questions I had concerning their treatment and participation, and that they were all answered to my satisfaction.

2. I also confirm that I have read and understood the patient information sheet and I have had the opportunity to discuss the patient information provided for me with members of my family and/or friends.

3. I understand that there is no benefit to us from taking part in this study.

4. I understand that if the patient becomes unable to complete the study on medical grounds that data gathered prior to that time point may still be used for this study.

Name …… Relationship to Patient……

Signature …… Date ……

Consent Taken By …… Role……

Signature …… Date ……

Surgeon Name……

Surgeon Signature…….. Date……

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	8
Protocol version	#3	Date and version identifier	20
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	19
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	8
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19

Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18,19
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10,11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11,12

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10,11
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11,12
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-16
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10-12

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17,18
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered,	10

		opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a the appropriate medical staff are unblinded to the allocation and in the event of medical complications, the device type will be known by medical staff
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to	10,11,12-16

		promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11,12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16,18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17,18

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a trial will continue until 900 patients are recruited

Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a in this trial, adverse events and harms are collected as complication information. This is described under secondary outcomes.
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18,19
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or	9

		authorised surrogates, and how (see Item 32)	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a patients will be consented for the trial and informed that the data will be used for medical research.
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a all information collected is described in the protocol. See pg 10, 11-16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16,18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a both devices used in this trial are FDA approved and widely used devices. Patients presenting with medical complications will be managed as standard

			procedure at the site patients present to.
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a No plans for participant level data to be made publically available
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Model consent forms will be uploaded as additional document
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	n/a

analysis in the current trial and for future use in ancillary studies, if applicable

Notes:

- 17b: n/a the appropriate medical staff are unblinded to the allocation and in the event of medical complications, the device type will be known by medical staff
- 18a: 10,11,12-16
- 21b: n/a trial will continue until 900 patients are recruited
- 22: n/a in this trial, adverse events and harms are collected as complication information. This is described under secondary outcomes.
- 26b: n/a patients will be consented for the trial and informed that the data will be used for medical research.
- 27: n/a all information collected is described in the protocol. See pg 10, 11-16
- 30: n/a both devices used in this trial are FDA approved and widely used devices. Patients presenting with medical complications will be managed as standard procedure at the site patients present to.
- 31c: n/a No plans for participant level data to be made publically available
- 32: Model consent forms will be uploaded as additional document This checklist was completed on 26. June 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai