PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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.
AUTHORS	Sivakumar, Arjun; Thewlis, Dominic; Ladurner, Andreas; Edwards, Suzanne; Rickman, Mark

VERSION 1 - REVIEW

REVIEWER	Matthias Knobe Cantonal Hospital Lucerne, Switzerland
REVIEW RETURNED	15-Jul-2019

GENERAL COMMENTS	The paper deals with an important subject of orthopedic trauma, regarding the treatment of proximal femoral fractures. The objective of the study is the comparison of two intramedullary implants (nails) sometimes considered the “third and fourth generation” from the viewpoint of fixation of trochanteric stable and unstable fractures (31A1 and 31A2). In general the paper is well-written and the study well conducted. Using a prospective randomised clinical design authors plan to include 900 patients. 3 study arms are conducted using the Gamma3 nail (unlocked) and the Trigen nail in the unlocked and the locked way hampering lag screw sliding. Despite the well conducted approach I have some remarks: 1) The title is misleading in some way: your trail is about 2 nail designs (single screw, double screw) and in only one specific nail design (Trigen) the effect of the locking mechanism should be examined. Please change the first part of the title. 2) What is a pragmatic trial? 3) Why the study doesn’t include 31A3 fractures? Assuming a more unstable fracture configuration, the difference in the hip biomechanics between the 1- and 2 screw nail design should be greater. 4) Please change the phrase: “Device failure” regarding the primary outcome as it describes only the implant breakage which is very rare: Cut-out, excessive migration, excessive sliding and fracture collapse should be referred to “fracture or osteosynthesis failure”. 5) Please mention the basic differences between the intramedullary implants (interlocking lag screw mechanism, rotational stability of the Intertan nail in comparison to the Gamma3) in the Introduction section. Please refer to

	biomechanical studies as the implant anchorage in the femoral head plays a crucial role. (See Knobe M, Gradl G, Buecking B, Gackstatter S, Sönmez TT, Ghassemi A, Stromps JP, Prescher A, Pape HC. Locked minimally invasive plating versus fourth generation nailing in the treatment of AO/OTA 31A2.2 fractures: A biomechanical comparison of PCCP(®) and Intertan nail(®).Injury. 2015 Aug;46(8):1475-82). 6) You mentioned that ex vivo biomechanical studies have demonstrated superior biomechanical results with the Intertan™ nail. However, despite its high rotational stability the Intertan nail showed a significant migration tendency at higher loads (See Knobe M et al. Injury 2015 Aug;46(8):1475-82). That's why a measurement of migration tendency additionally to TAD is reasonable. 7) Which nail diameter and nail CCD angle do you want to use? Is a reaming of the femoral channel planned? 8) What is the previous experience of the authors´ department with the two implants (learning curve), number of surgeons and their practical experience? 9) Furthermore, because "Excessive sliding of the lag screw has been shown by some authors to lead to mechanical complications and negatively affect patient function", a measurement of the femoral neck shortening should be considered. 10) Results depend on reduction quality. It is necessary to provide data regarding the surgical quality (medial shaft displacement, CCD (125 or 130 degrees?), limb length). All this is essential in comparing intramedullary implants. 11) A highlight of the study is the planned biomechanical evaluation in the clinical setting with gait analysis, muscle force evaluation, gait speed, activity monitoring etc. Literature lacks in such data. Congratulation for this test set-up! In general the study design is very good and I wish you all the best in realization of this study. Thank you for your effort planning the trial and preparing the manuscript. I would be happy to read the results.

REVIEWER	Xavier Griffin University of Oxford, UK CI or co-applicant on a number of hip fracture trials funded by National Institute of Health Research and/or X-Bolt Ltd, Hereaus.
REVIEW RETURNED	27-Sep-2019

GENERAL COMMENTS	Overall a well written protocol. I have some very minor concerns: 1. The introduction is a not balanced representation of the data supporting extra versus intramedullary devices in the treatment of pertrochanteric fractures. Whilst the trial is not addressing this question the introduction does make reference to the debate but presents a very one sided view in favour of intramedullary devices. This should be revised or indeed removed entirely as it has little relevance to the research question. 2. The sequence generation detail is lacking please expand. The implementation of the allocation is also unclear, please expand.

	3. Please clarify the eligibility regarding cognitive impairment. I assumed that consent was sought only from the patient and there were no arrangements for including participants with cognitive impairment. Later there is mention of participants with AMTS less than or greater than 8 however - please make the eligibility criterion explicit. 4. Oversight - please clarify whether there is DSMc and/or TSC. 5. Publication & IP - (item 5 in the SPIRIT checklist is incompletely reported) please also state whether the funder or sponsor owns the IP and whether the sponsor is free to publish. 6. I cannot see that the Sponsor is stated on page 9 as per the SPIRIT checklist.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Reviewer Name: Matthias Knobe

Institution and Country: Cantonal Hospital Lucerne, Switzerland

Comment 1: The title is misleading in some way: your trail is about 2 nail designs (single screw, double screw) and in only one specific nail design (Trigen) the effect of the locking mechanism should be examined. Please change the first part of the title.

Response 1: The title of the trial has been reversed (pg. 1, Title).

Changed from: “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.”

Changed to: “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.”

Comment 2: What is a pragmatic trial?

Response 2: As defined by the Pragmatic–Explanatory Continuum Indicator Summary 2 (PRECIS-2) Tool, a pragmatic trial is a clinical trial that focuses on the correlation between treatments and outcomes in a real world health system and assessed for pragmatism under nine domains. This has been added to the text in the manuscript.

Author Action:

Line added (Page 8, Trial Design, line 172).

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

Changed to: “The ProFNUL study is a multicentre, pragmatic (as defined by the Pragmatic–Explanatory Continuum Indicator Summary 2 Tool (PRECIS-2)1), single-blinded randomised controlled trial with a three-arm parallel group design.”

Comment 3: Why the study doesn’t include 31A3 fractures? Assuming a more unstable fracture configuration, the difference in the hip biomechanics between the 1- and 2 screw nail design should be greater.

Response 3: We chose not to look at these fracture types in order to simplify the clinical question being answered by the trial. Many people would not use this type of device, especially in a dynamic mode, for the 31A3 fractures, which then invites criticism of the trial outcomes.

Comment 4: Please change the phrase: “Device failure” regarding the primary outcome as it describes only the implant breakage which is very rare: Cut-out, excessive migration, excessive sliding and fracture collapse should be referred to “fracture or osteosynthesis failure”.

Response 4: We have changed the phrase “device failure” to “”construct failure”. (pg. 2, Abstract, Methods and analysis, pg. 10, Trial Registration Data, primary outcome).

Comment 5: Please mention the basic differences between the intramedullary implants (interlocking lag screw mechanism, rotational stability of the Intertan nail in comparison to the Gamma3) in the Introduction section. Please refer to biomechanical studies as the implant anchorage in the femoral head plays a crucial role. (See Knobe M, Gradl G, Buecking B, Gackstatter S, Sönmez TT, Ghassemi A, Stromps JP, Prescher A, Pape HC. Locked minimally invasive plating versus fourth generation nailing in the treatment of AO/OTA 31A2.2 fractures: A biomechanical comparison of PCCP(®) and Intertan nail(®).Injury. 2015 Aug;46(8):1475-82).

Response 5: Line changed in the introduction to better convey the interlocking lag screw mechanism and high rotational stability for the intertan nail with this paper cited. (pg. 5, introduction).

Page 5, Introduction, paragraph 3, line 104-106.

Changed from: “Together, this dual-oval shaped composite screw mechanism allows for linear compression of the fragments at the fracture site while providing anti-rotation properties.”

Changed to: “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.2”

Comment 6: You mentioned that ex vivo biomechanical studies have demonstrated superior biomechanical results with the Intertan™ nail. However, despite its high rotational stability the Intertan nail showed a significant migration tendency at higher loads (See Knobe M et al. Injury 2015 Aug;46(8):1475-82). That’s why a measurement of migration tendency additionally to TAD is reasonable.

Response 6: This is a good point however, in-vivo, a reliable, consistent measure of migration is difficult.

Comment 7: Which nail diameter and nail CCD angle do you want to use? Is a reaming of the femoral channel planned?

Response 7: Nail diameters are all fixed at 11 (Gamma) and 11.5 (Intertan). CCD angle is 125 degrees.

Author Action:

Line added (Page 12, Participant Flow Diagram, line 241-242).

"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."

Comment 8: What is the previous experience of the authors´ department with the two implants (learning curve), number of surgeons and their practical experience?

Response 8: 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, a large number of surgeons with varying levels of surgeon experience including junior doctors, SET trainees, fellows and consultants will carry out the procedures, using both devices at all sites.

Author Action:

Lines added (Page 11, Standard Treatment Pathway, line 223-226).

"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."

Comment 9: Furthermore, because "Excessive sliding of the lag screw has been shown by some authors to lead to mechanical complications and negatively affect patient function", a measurement of the femoral neck shortening should be considered.

Response 9: A specific measurement of the femoral neck shortening will also be calculated from start and end X-rays.

Author Action:

Lines added to include a measure of femoral neck shortening as a secondary outcome (pg. 16, Secondary outcomes, lines 301-304).

"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 3, 4 and is regarded a reliable measure. 5"

Comment 10: Results depend on reduction quality. It is necessary to provide data regarding the surgical quality (medial shaft displacement, CCD (125 or 130 degrees?), limb length). All this is essential in comparing intramedullary implants.

Response 10: This is true, but complex to do. Hence the large patient numbers, and randomisation in this pragmatic trial, which means we don't have to look at these closely.

Reviewer 2

Reviewer Name: Xavier Griffin

Institution and Country: University of Oxford, UK

Comment 1: The introduction is a not balanced representation of the data supporting extra versus intramedullary devices in the treatment of pertrochanteric fractures. Whilst the trial is not addressing this question the introduction does make reference to the debate but presents a very one sided view in favour of intramedullary devices. This should be revised or indeed removed entirely as it has little relevance to the research question.

Response 1: This is a good point and the feedback taken on board. Paragraph two removed from introduction (pg. 4, Introduction, lines 80-91).

Paragraph two now reads: "Since its introduction in the 1990s, intramedullary fixation has become increasingly popular, with increasing trends towards this device preference recorded in the united states and Australia…"

Comment 2: The sequence generation detail is lacking please expand. The implementation of the allocation is also unclear, please expand.

Response 2: Additional detail on sequence generation and implementation of allocation provided. (pg. 10, Randomisation and blinding, lines 204-209).

Changed from: "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."

Changed to: "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."

Comment 3: Please clarify the eligibility regarding cognitive impairment. I assumed that consent was sought only from the patient and there were no arrangements for including participants with cognitive impairment. Later there is mention of participants with AMTS less than or greater than 8 however - please make the eligibility criterion explicit.

Response 3: As a pragmatic trial, patients with cognitive impairment are eligible for the trial but if they are unable to provide consent due to their cognitive impairment, consent will be sought from the family, in the same manner that consent for surgery and anaesthesia occurs currently. Eligibility and consent for patients with cognitive impairment has been clarified to reflect this.

Author Action:

Lines added (pg. 10, Eligibility, lines 199-200)

“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.”

For the biomechanics sub group; lines added (pg. 13, participant flow timeline, lines 252-253)

“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”

Comment 4: Oversight - please clarify whether there is DSMc and/or TSC.

Response 4: Information on TSC and DSMc added. Lines added (pg. 21, trial oversight, lines 430-435)

“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. TSC meetings will be held weekly and DSMC meetings will be held annually. The DSMC and TSC will meet prior to commencing the trial with further meetings arranged depending on the trial requirements.”

Comment 5: Publication & IP - (item 5 in the SPIRIT checklist is incompletely reported) please also state whether the funder or sponsor owns the IP and whether the sponsor is free to publish.

Response 5: This is not an industry sponsored trial, it’s an investigator initiated trial (pg. 22, Competing interests statement, lines 453-454). Line added to competing interest statement (pg. 22, Competing interests statement, lines 454-455):

“IP is owned by the Royal Adelaide Hospital/University of Adelaide.”

Comment 6: I cannot see that the Sponsor is stated on page 9 as per the SPIRIT checklist.

Response 6: Listed Smith and Nephew as a sponsor on pg 9.

VERSION 2 – REVIEW

REVIEWER	Matthias Knobe Lucerne Cantonal Hospital Switzerland
REVIEW RETURNED	14-Nov-2019

GENERAL COMMENTS	Revision was done successfully. I recommend publication and wish you all the best in realization of this study.