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Is arthroplaSty bEtter than interNal fixation for undiSplaced femoral nEck fracture? A national pragmatic RCT–the SENSE trial

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Abstract

Introduction

Undisplaced femoral neck fractures (FNFs) are usually treated by internal fixation but two randomised controlled trials (RCTs) have demonstrated advantages of treatment with arthroplasty. The complication rate was lowered but there were no clinically improved patient-reported outcome measures (PROM), which could be due to underpowering or choice of selected PROM as the studies does appear to report a better functional outcome. We will conduct an RCT comparing IF with arthroplasties in patients aged over 65 years with an undisplaced FNF.

Methods and analysis

Nineteen of twenty hospitals in Denmark treating hip fracture patients can provide patients for this study; therefore, the study can be considered a national RCT. Patients over 65 years old with an undisplaced FNF will be screened for eligibility and patients will only be excluded if they are unable to understand the study information (due to dementia or language), if they have a posterior tilt > 20 degrees, a pathological fracture, or they cannot walk. Participants will be electronically randomised (in alternating blocks of 4 or 6) into either internal fixation or arthroplasty. Postoperative care will follow the department standards.

Primary and secondary outcomes and measuring points have been established in collaboration with hip fracture patients by focus group interviews. The primary outcome measure is the New Mobility Score assessed after 1 year. Secondary outcomes are the Oxford Hip Score, EuroQol 5 domain (EQ-5D-5L), degree of posterior tilt, pain verbal rating scale, reoperation, and mortality.

Ethics and dissemination

All participants will sign an informed consent before entering the trial. Because this is a national trial, all relevant healthcare professionals in Denmark will automatically receive the trial results that will be published in international peer-review journals.

Registration details

The study is approved by the Danish Data Protection Agency (19/7429) and the scientific ethics committee (S-20180036).

Strengths and limitations of this study

- National RCT on undisplaced femoral neck fracture comparing internal fixation with arthroplasty
- It is a pragmatic RCT and each hospital can use their preferred implants
- Primary outcome is an easily understood functional score, the New Mobility Score
- Participants are only included if they are able to walk outside with no help for other indiviudals
- The participants and assessors are blinded concerning implant

Introduction

Arthroplasty for a displaced femoral neck fracture (FNF) in the elderly is recommended by most guidelines. [1 2] For the undisplaced FNF, internal fixation is the only recommendation; however, it is questioned whether there is an alternative treatment.

Recently, two randomised control trials (RCTs) comparing internal fixation with hemiarthroplasty have been published [3 4]. Both RCTs demonstrated a lower reoperation frequency in the hemiarthroplasty group (5%) compared to internal fixation (20–21%). Lu et al. [3] found a slightly higher Harris Hip Score after 6 months and 1 year in favour of hemiarthroplasty but not thereafter. Dolatowski et al. [4] found a faster mobility (Timed-Up-And-Go) but no difference in the Harris Hip Score. These studies did not show a clinical difference in Harris Hip Scores, but this measure may not be the best primary outcome measure due to the ceiling effect and lack of validation for hip fracture patients. [5]

Mobilisation after hip fracture is perhaps the most important factor for mortality after surgery [6] and surgery should, therefore, aim for fast mobilisation. Arthroplasty may be a good choice, as it may yield faster recovery than internal fixation. [7] A systematic review[8] in 2008 of mobility instruments for older patients showed that no existing instrument had the properties required to measure and monitor the mobility of older acute medical patients accurately. The New Mobility Score (NMS) developed by Parker may predict mortality [9], and Kristensen et al. have since shown that it can also predict function better than Timed-Up-and-Go. NMS is easy to use and has a very high inter-tester reliability. [10 11] Pedersen et al. [12] also demonstrated good correlation of NMS and gait function prediction with the same properties as Barthel-20 and Barthel-100 but with a lower ceiling frequency of 4 months postoperatively.

Even though the evidence is limited from the two RCTs [3 4], one could argue for implementing arthroplasty for undisplaced FNF since there are fewer reoperations and perhaps a faster mobilization. However, a cohort study has demonstrated a higher mortality percentage when using hemiarthroplasty compared to internal fixation. [13] This study does contain selection bias and confounding problems, as there are in general with cohort studies, which makes the resulting evidence limited for everyday clinical use. Therefore, we should conduct larger RCTs as hip fracture RCTs, in general, are small and underpowered. [14] In addition, external validity is often a problem in traditional RCTs, because a inclusion rate as little as 7% was seen in the FAITH study [15] thereby questioning whether hip fracture trials exclude too many patients. [16] A pragmatic RCT design includes a larger proportion of the eligible patients due to fewer exclusion criteria and could, therefore, be a better choice to test an intervention in everyday clinical setting [17]

The aim of this trial is to compare functional outcomes of arthroplasty with internal fixation for patients over 65 years old with an undisplaced displaced FNF. The study is designed as a national single-blinded pragmatic 1:1 RCT. The hypothesis states that arthroplasty is superior to internal fixation using the NMS as the primary outcome.

Methods: Participants, interventions, and outcomes

Study setting

The Danish National Health Service provides tax-supported free healthcare and general hospital care for all Danish citizens. [18] All hip fracture patients are treated at public hospitals in Denmark as no private hospital in Denmark have any acute fracture treatment. Twenty public hospitals in Denmark treat hip fracture patients, and nineteen of those hospitals participate in this study, making this trial a national RCT.

Trial design

The study is designed as a national pragmatic RCT, including all patients with an undisplaced FNF and an NMS of 5 and above. The current standard treatment in Denmark is internal fixation, and patients are randomised to either arthroplasty or internal fixation. The steering group has assessed the pragmatic attitude of the design and the study reaches five points in seven of the nine domains (Figure 1). [17] Reporting will be performed according to the extension of the CONSORT statements for a pragmatic RCT [19], and this protocol is reported according to the SPIRIT statement. [20]

Eligibility criteria

All patients with an undisplaced FNF classified as either Garden type I or II [21] are evaluated. The patients are included if

- Age ≥ 65 years
- Posterior tilt [22] < 20°
- Low energy fracture
- NMS = 5 and above, indicating an ability to walk prior to the fracture
- Cognitive state intact to achieve informed consent

Patients are excluded if

- The fracture is pathological
- The patient does not speak or understand Danish language

To ensure correct fracture classification, an adjudication committee will evaluate all included X-ray images.

Interventions

Participants are randomised to either arthroplasty or internal fixation. Because the treatment options at each hospital may be very different, arthroplasty can include total hip arthroplasty (cemented, uncemented, hybrid, dual-mobility cup) or hemiarthroplasty (cemented, uncemented) using the institution's regular surgical approach. Internal fixation can include either two or three screws/pins or a sliding hip screw. After discharge, all patients will be referred to standard rehabilitation in the municipalities and will be seen in their own home or at the orthopaedic department for outcome assessment after 3, 6, and 12 months. X-ray will be performed postoperatively within discharge and after 12 months.

Outcomes

Primary and secondary outcomes and measuring points have been established in collaboration with a focus group interview with hip fracture patients. The primary outcome measure is NMS assessed after 12 months. NMS will also be assessed at baseline, 3, and 6 months.

Secondary outcome measures evaluated at the same time points are the Oxford Hip Score (OHS), EuroQol 5 domain (EQ-5D-5L), pain verbal rating scale (VRS)[23], reoperation (any surgery related to the implants including closed reduction), and mortality. Explorative outcome measures are the de Morton Mobility Index (DEMMI) [7 24], Barthel-20 [25], Cumulated ambulation score (CAS)[26], X-ray measurements, and activity tracking.

Information will be retrieved from patient interview and healthcare records on the following:

- Demographics: age, sex, residency, pre-fracture mobility;
- Comorbidity: American Society of Anaesthesiologists Classification (ASA), diseases, medication, smoking, alcohol;
- Admission: time of admission, duration of hospital stay, concurrent infection, fracture time;
- Surgery: start and end of surgery, type of implant, surgical experience, blood loss;
- X-ray: quality of implant positioning[27-29]
- Biochemistry: haemoglobin, leucocytes, c-reactive protein (CRP), estimated glomerular filtration rate (eGFR), international normalised ratio (INR), blood transfusions;
- Complications: postoperative medical complications (all possible such as heart, lung, abdominal, brain, electrolytes, fall, and infection), readmissions.

A timeframe for the collection of data is provided in Table 1. Healthcare record information is collected for research purposes only to compare patient groups and treatment.

Sample size calculation

A minimal clinically important difference in NMS of 1 point was taken from Kristensen's thesis [30] and a 1-year average of 6.4 points with a standard deviation of 2.2 from Steihaug et al. [31]. The sample size was calculated using a 1-point difference, a standard deviation of 2.2, allowing a 5% probability of type 1 error and applying 95% statistical power. Consequently, 127 patients are required in each group and to allow for loss during follow-up due to mortality and other causes (30%). Therefore, a total of 330 patients are required for the study.

Recruitment

All patients are recruited in the emergency department when diagnosed with an undisplaced FNF. The admitting doctor or a senior consultant will inform the patient about the trial while the patient is in the emergency department. The information will be given verbally as well as by written participant information in an undisturbed room in the emergency department. If no next of kin are present, they will be invited to attend by phone if requested by the participant. Otherwise, an impartial assessor can be assigned. Because surgery is required to take place as quickly as possible due to a higher risk of mortality when delaying surgery, a reflection time of only 2 hours has been approved. Retrieval of informed consent will take place at either the emergency department or the ward.

Patient and public involvement

We conducted a focus group interview with hip fracture patients with internal fixation or arthroplasty at Hospital Lillebaelt, which involved 6 patients (and their relatives) aged 70 to 94 years who had received surgery 6–12 months prior to the interview. They were interviewed using a structured interview guide. The interview consisted of open questions regarding their hip fracture experience, their subsequent consequences/challenges, and what was important for them to regain. Further questions relating specifically to the study were also included. The questionnaires were easily understood, and all found them relevant. All questions were answered, and the most important outcome reported was for all functional outcomes, especially the ability to walk properly. Pain was also an important consideration, especially for the internal fixation group. All participants felt that the most important time for measuring outcomes would be after 1 year, but measuring during the first year was also important.

The study protocol was presented to the Patient and Relatives Council at Hospital Lillebaelt afterwards, with no additional remarks.

Methods: Assignment of interventions

Allocation

Treatment is divided into two strands and patients eligible for inclusion can be enrolled if they provide informed consent. Patients are entered into an electronic database (REDCap) and thereafter randomised using random blocks of n = 4 or n = 6 stratified by hospital. When the patient is called to the theatre, the surgeon will determine which implant to use by consulting REDCap; accordingly, REDCap will be used to create two groups representing each implant type.

Blinding

The surgeon and theatre staff cannot be blinded, but a standard phrase for the surgery will be used to blind the patient. According to standards of care and journal publication requirements, the coordinating staff can reveal the true surgery in case of severe pain or complications; otherwise, patients will not know until the end of the trial. The assessors will assess patients in their own home and will be blinded according to the type of surgery.

Methods: Data collection, management, and analysis

Data collection methods

Data will be collected by project staff. Baseline data will be collected during admission, and all data concerning patient-reported outcomes and physical assessment are collected by a physiotherapist in the patient's own home or in the outpatient clinic depending on the participant's wish.

Data management

Data will be entered directly into the projects' REDCap database when assessing or interviewing the participants.

Statistical methods

All variables are described according to their distribution. For group comparison with numerical data, a Student's t-test is used to determine whether data are normally distributed; otherwise, a non-parametric test will be used. For categorical data, a Chi-square test (or Fischer if data are small) will be used for group comparison. All other variables are tested by group comparison using intention-to-treat analysis and per-protocol analysis. For secondary analyses, linear and logistic regression analyses adjusting for demographic variables, comorbidity, mobility, type of implant, reoperation, and mortality will be used. Competing risks

and cluster analysis will be added for these analyses. Concerning mortality, a Cox-regression, including cluster analysis, will be used.

Methods: Monitoring

Data monitoring

After data retrieval from the first 70 patients, an interim analysis will be performed regarding mortality and function. If there is a difference of 10% in 30 days mortality, a consensus decision by steering group whether the trial should be stopped will be conducted. Likewise, if the NMS score shows 2 points or more difference after 3 months, all authors are asked whether the trial should be stopped. This is because the required sample size would then be 66 patients.

Potentially harm s

Any unforeseen complications that occur during the trial will be registered in the projects' REDCap database.

Auditing

An adjudication committee will audit all X-ray images.

Ethics and dissemination

Research ethics approval

The study is approved by the Danish Data Protection Agency (19/7429) and the Scientific Ethics Committee with the project id number S-20180036. It was first approved on the 15th October 2018 and a revision was approved 8th October 2019. The ClinicalTrials.gov identifier is NCT04075461.

Consent or assent

The orthopaedic surgeon on call is responsible for including patients. The patient have to give a written consent before entering the trial.

Confidentiality

Project data are securely stored in the project's REDCap database, and when the trial is completed, data are stored in the Danish Data Archive.

Funding statement

This work is supported by the Novo Nordisk Foundation, Axel Muusfeldt Foundation, and A.P. Møller Foundation; however, neither has any influence on data or reporting. The trial has also received funds from two public foundations, the Region of Southern Denmark Foundation and the Hospital Lillebaelt Research Committee, neither of which has any influence on data or reporting.

Access to data

Due to Danish legislation, access to the trial data is limited to trial investigators.

Ancillary and post-trial care

Any patients who experience any harm due to this trial will have the same care as all other patients in Denmark through the independent Danish Patient Compensation Association.

Dissemination policy

Because this is a national trial, 19 of 20 hospitals providing hip fracture care are included. All relevant healthcare professionals involved in hip fracture treatment in Denmark will, therefore, automatically be informed of the trial results. The results will also be published in international peer-reviewed journals.

Perspective

By conducting a national pragmatic RCT, external validity will potentialle be high. A general problem with trials is the lack of clinical impact afterwards as one paper has shown that it takes an average of 17 years for new findings to reach clinical practice. [32] As this is a nation wide study, the impact of the results are expected to be immediate and high.

Author contributions

BV wrote first draft of the protocol. SK, HP, MSL, KH and OB were invited as the steering committee and the protocol was evaluated and rewritten in collaboration. All collaborators were invited to read, comment, and suggest alterations to the protocol. Each of the collaborators are in charge of onsite inclusion and data retrieval.

Competing interest statement

This study has received financial support by

- Novo Nordisk Foundation
- Axel Muusfeldt Foundation

- A.P. Møller Foundation
- Region of Southern Denmark Foundation
- Hospital Lillebaelt Research Committee

Neither of the foundations has any influence on data or reporting.

Outside the study, Bjarke Viberg has received payment for lectures held for Zimmer Biomet and Osmedic Swemac.

There are no other competing interests.

References

1. National Institute for Health and Care Excellence. Hip fracture: mangement. Clinical guideline [CG124]. National Institute for Health and Care Excellence, 2011, updated 2017.
2. Roberts KC, Brox WT. AAOS Clinical Practice Guideline: Management of Hip Fractures in the Elderly. *J Am Acad Orthop Surg* 2015;23(2):138-40. doi: 10.5435/JAAOS-D-14-00433
3. Lu Q, Tang G, Zhao X, et al. Hemiarthroplasty versus internal fixation in super-aged patients with undisplaced femoral neck fractures: a 5-year follow-up of randomized controlled trial. *Arch Orthop Trauma Surg* 2017;137(1):27-35. doi: 10.1007/s00402-016-2591-9 [published Online First: 2016/11/12]
4. Dolatowski FC, Frihagen F, Bartels S, et al. Screw Fixation Versus Hemiarthroplasty for Nondisplaced Femoral Neck Fractures in Elderly Patients: A Multicenter Randomized Controlled Trial. *J Bone Joint Surg Am* 2019;101(2):136-44. doi: 10.2106/JBJS.18.00316 [published Online First: 2019/01/18]
5. Wamper KE, Sierevelt IN, Poolman RW, et al. The Harris hip score: Do ceiling effects limit its usefulness in orthopedics? *Acta Orthop* 2010;81(6):703-7. doi: 10.3109/17453674.2010.537808 [published Online First: 2010/11/30]
6. Kristensen PK, Thillemann TM, Soballe K, et al. Are process performance measures associated with clinical outcomes among patients with hip fractures? A population-based cohort study. *Int J Qual Health Care* 2016 doi: 10.1093/intqhc/mzw093
7. de Morton NA, Harding KE, Taylor NF, et al. Validity of the de Morton Mobility Index (DEMMI) for measuring the mobility of patients with hip fracture during rehabilitation. *Disabil Rehabil* 2013;35(4):325-33. doi: 10.3109/09638288.2012.705220
8. de Morton NA, Berlowitz DJ, Keating JL. A systematic review of mobility instruments and their measurement properties for older acute medical patients. *Health Qual Life Outcomes* 2008;6:44. doi: 10.1186/1477-7525-6-44
9. Parker MJ, Palmer CR. A new mobility score for predicting mortality after hip fracture. *J Bone Joint Surg Br* 1993;75(5):797-8.
10. Kristensen MT, Foss NB, Kehlet H. [Timed Up and Go and New Mobility Score as predictors of function six months after hip fracture]. *Ugeskr Laeger* 2005;167(35):3297-300.
11. Kristensen MT, Bandholm T, Foss NB, et al. High inter-tester reliability of the new mobility score in patients with hip fracture. *J Rehabil Med* 2008;40(7):589-91. doi: 10.2340/16501977-0217
12. Pedersen TJ, Lauritsen JM. Routine functional assessment for hip fracture patients. *Acta Orthop* 2016;87(4):374-9. doi: 10.1080/17453674.2016.1197534
13. Sikand M, Wenn R, Moran CG. Mortality following surgery for undisplaced intracapsular hip fractures. *Injury* 2004;35(10):1015-9. doi: 10.1016/j.injury.2004.01.004 [published Online First: 2004/09/08]
14. Bernstein J, Weintraub S, Morris T, et al. Randomized Controlled Trials for Geriatric Hip Fracture Are Rare and Underpowered: A Systematic Review and a Call for Greater Collaboration. *J Bone Joint Surg Am* 2019;101(24):e132. doi: 10.2106/JBJS.19.00407 [published Online First: 2019/10/01]
15. Fixation using Alternative Implants for the Treatment of Hip fractures I. Fracture fixation in the operative management of hip fractures (FAITH): an international, multicentre, randomised controlled trial. *Lancet* 2017 doi: 10.1016/S0140-6736(17)30066-1
16. Hebert-Davies J, Laflamme GY, Rouleau D, et al. Bias towards dementia: are hip fracture trials excluding too many patients? A systematic review. *Injury* 2012;43(12):1978-84. doi: 10.1016/j.injury.2012.08.061 [published Online First: 2012/09/25]
17. Loudon K, Treweek S, Sullivan F, et al. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ* 2015;350:h2147. doi: 10.1136/bmj.h2147
18. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29(8):541-9. doi: 10.1007/s10654-014-9930-3

19. Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008;337:a2390. doi: 10.1136/bmj.a2390
20. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. doi: 10.1136/bmj.e7586 [published Online First: 2013/01/11]
21. Garden RS. Low-angle fixation in fractures of the femoral neck. *J Bone Joint Surg Br* 1961;43-B(4):647-63.
22. Palm H, Gosvig K, Krasheninnikoff M, et al. A new measurement for posterior tilt predicts reoperation in undisplaced femoral neck fractures: 113 consecutive patients treated by internal fixation and followed for 1 year. *Acta Orthop* 2009;80(3):303-7. doi: 10.3109/17453670902967281 [published Online First: 2009/07/28]
23. Bech RD, Lauritsen J, Ovesen O, et al. The Verbal Rating Scale Is Reliable for Assessment of Postoperative Pain in Hip Fracture Patients. *Pain Res Treat* 2015;2015:676212. doi: 10.1155/2015/676212 [published Online First: 2015/06/17]
24. de Morton NA, Davidson M, Keating JL. Validity, responsiveness and the minimal clinically important difference for the de Morton Mobility Index (DEMMI) in an older acute medical population. *BMC Geriatr* 2010;10:72. doi: 10.1186/1471-2318-10-72
25. Collin C, Wade DT, Davies S, et al. The Barthel ADL Index: a reliability study. *Int Disabil Stud* 1988;10(2):61-3. doi: 10.3109/09638288809164103 [published Online First: 1988/01/01]
26. Kristensen MT, Jakobsen TL, Nielsen JW, et al. Cumulated Ambulation Score to evaluate mobility is feasible in geriatric patients and in patients with hip fracture. *Dan Med J* 2012;59(7):A4464. [published Online First: 2012/07/05]
27. Chammout GK, Mukka SS, Carlsson T, et al. Total hip replacement versus open reduction and internal fixation of displaced femoral neck fractures: a randomized long-term follow-up study. *J Bone Joint Surg Am* 2012;94(21):1921-8. doi: 10.2106/JBJS.K.01615 [published Online First: 2012/09/28]
28. Baumgaertner MR, Curtin SL, Lindskog DM, et al. The value of the tip-apex distance in predicting failure of fixation of peritrochanteric fractures of the hip. *J Bone Joint Surg Am* 1995;77(7):1058-64. [published Online First: 1995/07/01]
29. Koldaas MIB, Pedersen JN, Hojsager FD, et al. Implant positioning (IMPO) in undisplaced femoral neck fractures: Association to reoperation and development of an IMPO scoring system. *Injury* 2019 doi: 10.1016/j.injury.2019.12.003 [published Online First: 2019/12/17]
30. Kristensen MT. Hip fractures - Functional assessments and factors influencing in-hospital outcome, a physiotherapeutic perspective. Lund University, 2010.
31. Steihaug OM, Gjesdal CG, Bogen B, et al. Does sarcopenia predict change in mobility after hip fracture? a multicenter observational study with one-year follow-up. *BMC Geriatr* 2018;18(1):65. doi: 10.1186/s12877-018-0755-x [published Online First: 2018/03/07]
32. Balas EA, Boren SA. Managing Clinical Knowledge for Health Care Improvement. *Yearb Med Inform* 2000(1):65-70. [published Online First: 2000/01/01]

Figure 1 Assessment of pragmatic design using the PRECIS-2 wheel

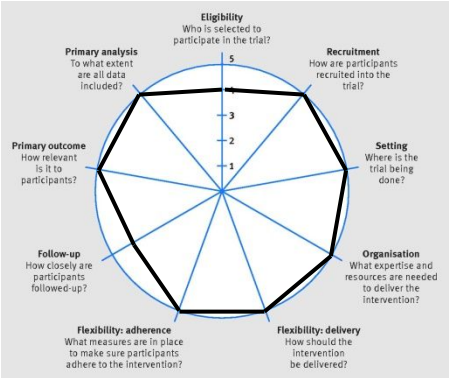

Table 1 Timeframe for collection of data

	Admission	2 weeks	6 weeks	3 months	6 months	12 months	At event
Demographics	X						
Comorbidity	X						
Admission	X						
Surgery	X						
Blood	X						
X-ray	X					X	
NMS	X			X	X	X	
Pain VRS	X	X	X	X	X	X	
OHS	X			X	X	X	
EQ-5D-5L	X			X	X	X	
DEMMI	X			X	X	X	
Barthel-20	X			X	X	X	
CAS	X		X	X			
Reoperation							X
Complications							X
Mortality							X

Appendix – Informed consent

Informeret samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt.

Forskningsprojektets titel: Is arthroplaSty bEtter than interNal fixation in the undiSplaced femoral nEck fracture? A national pragmatical RCT – the SENSE trial

Erklæring fra forsøgspersonen:

Jeg har fået skriftlig og mundtlig information og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til, at deltage i forskningsprojektet, og har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonens navn: _____

Dato: _____ Underskrift: _____

Ønsker du at blive informeret om forskningsprojektets resultat samt eventuelle konsekvenser for dig?:

Ja _____ (sæt x) Nej _____ (sæt x)

Erklæring fra den, der afgiver information:

Jeg erklærer, at forsøgspersonen har modtaget mundtlig og skriftlig information om forsøget.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Navnet på den, der har afgivet information:

Dato: _____ Underskrift: _____

Projektidentifikation: (Fx komiteens Projekt-ID, EudraCT nr., versions nr./dato eller lign.)

S-20180036

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.

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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	10
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	6-10
Protocol version	#3	Date and version identifier	09032020
Funding	#4	Sources and types of financial, material, and other support	10
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	11

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	11
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	11
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)	11
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	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-6
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)	6
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	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	6

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
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)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	7
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)	8+14
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	8
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	9

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
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	9
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 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	9
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	9
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	9
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	9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9

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)	9
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	10
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	10
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	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	10
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)	10
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to	10

		protect confidentiality before, during, and after the trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	11
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	11
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	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	14
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Is arthroplaSty bEtter than interNal fixation for undiSplaced femoral nEck fracture? A national pragmatic RCT–the SENSE trial

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Is arthroplaSty bEtter than interNal fixation for undiSplaced femoral nEck fracture? A national pragmatic RCT–the SENSE trial

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Abstract

Introduction

Undisplaced femoral neck fractures (FNFs) are usually treated by internal fixation (IF) but two randomised controlled trials (RCTs) have demonstrated advantages of treatment with arthroplasty. The complication rate was lowered but there were no clinically improved patient-reported outcome measures (PROM), which could be due to underpowering or choice of selected PROM as the studies does appear to report a better functional outcome. We will conduct an RCT comparing IF with arthroplasties in patients aged over 65 years with an undisplaced FNF.

Methods and analysis

All hospitals in Denmark treating hip fracture patients can provide patients for this study; therefore, the study can be considered a national RCT. Patients over 65 years old with an undisplaced FNF will be screened for eligibility and patients will only be excluded if they are unable to understand the study information (due to dementia or language), if they have a posterior tilt > 20 degrees, a pathological fracture, or they cannot walk. Participants will be electronically randomised (in alternating blocks of 4 or 6) into either IF or arthroplasty. Postoperative care will follow the department standards.

Primary and secondary outcomes and measuring points have been established in collaboration with hip fracture patients by focus group interviews. The primary outcome measure is the New Mobility Score assessed after 1 year. Secondary outcomes are the Oxford Hip Score, EuroQol 5 domain (EQ-5D-5L), degree of posterior tilt, pain verbal rating scale, reoperation, and mortality.

Ethics and dissemination

All participants will sign an informed consent before entering the trial. Because this is a national trial, all relevant healthcare professionals in Denmark will automatically receive the trial results that will be published in international peer-review journals.

Registration details

The study is approved by the Danish Data Protection Agency (19/7429) and the scientific ethics committee (S-20180036). The ClinicalTrials.gov identifier is NCT04075461.

Strengths and limitations of this study

- National RCT on undisplaced femoral neck fracture comparing internal fixation with arthroplasty
- It is a pragmatic RCT and each hospital can use their preferred implants
- Primary outcome is an easily understood functional score, the New Mobility Score
- Participants are only included if they are able to walk outside with no help for other indiviudals
- The participants and assessors are blinded concerning implant

Introduction

Arthroplasty for a displaced femoral neck fracture (FNF) in the elderly is recommended by most guidelines. [1] [2] For the undisplaced FNF, internal fixation is the only recommendation; however, it is questioned whether there is an alternative treatment.

Recently, two randomised control trials (RCTs) comparing internal fixation with hemiarthroplasty have been published [3] [4]. Both RCTs demonstrated a lower reoperation frequency in the hemiarthroplasty group (5%) compared to internal fixation (20–21%). Lu et al. [3] found a slightly higher Harris Hip Score after 6 months and 1 year in favour of hemiarthroplasty but not thereafter. Dolatowski et al. [4] found a faster mobility (Timed-Up-And-Go) but no difference in the Harris Hip Score. These studies did not show a clinical difference in Harris Hip Scores, but this measure may not be the best primary outcome measure due to the ceiling effect and lack of validation for hip fracture patients. [5]

Mobilisation after hip fracture is perhaps the most important factor for mortality after surgery [6] and surgery should, therefore, aim for fast mobilisation. Arthroplasty may be a good choice, as it may yield faster recovery than internal fixation. [7] A systematic review[8] in 2008 of mobility instruments for older patients showed that no existing instrument had the properties required to measure and monitor the mobility of older acute medical patients accurately. The New Mobility Score (NMS) developed by Parker may predict mortality [9], and Kristensen et al. have since shown that it can also predict function better than Timed-Up-and-Go. NMS is easy to use and has a very high inter-tester reliability. [10] [11] Pedersen et al. [12] also demonstrated good correlation of NMS and gait function prediction with the same properties as Barthel-20 and Barthel-100 but with a lower ceiling frequency of 4 months postoperatively.

Even though the evidence is limited from the two RCTs [3] [4], one could argue for implementing arthroplasty for undisplaced FNF since there are fewer reoperations and perhaps a faster mobilization. However, a cohort study has demonstrated a higher mortality percentage when using hemiarthroplasty compared to internal fixation. [13] This study does contain selection bias and confounding problems, as there are in general with cohort studies, which makes the resulting evidence limited for everyday clinical use. Therefore, we should conduct larger RCTs as hip fracture RCTs, in general, are small and underpowered. [14] In addition, external validity is often a problem in traditional RCTs, because a inclusion rate as little as 7% was seen in the FAITH study [15] thereby questioning whether hip fracture trials exclude too many patients. [16] A pragmatic RCT design includes a larger proportion of the eligible patients due to fewer exclusion criteria and could, therefore, be a better choice to test an intervention in everyday clinical setting [17]

The aim of this trial is to compare functional outcomes of arthroplasty with internal fixation for patients over 65 years old with an undisplaced displaced FNF. The study is designed as a national single-blinded pragmatic 1:1 RCT. The hypothesis states that arthroplasty is superior to internal fixation using the NMS as the primary outcome.

Methods: Participants, interventions, and outcomes

Study setting

The Danish National Health Service provides tax-supported free healthcare and general hospital care for all Danish citizens. [18] All hip fracture patients are treated at public hospitals in Denmark as no private hospital in Denmark have any acute fracture treatment. Twenty public hospitals in Denmark treat hip fracture patients and all participate in this study, making this trial a national RCT.

The trial started 1st of February 2020 but has been paused due to COVID-19. The sites will start recruitment at different time points from 1st of July to 1st of October.

Trial design

The study is designed as a national pragmatic RCT, including all patients with an undisplaced FNF and an NMS of 5 and above. The current standard treatment in Denmark is internal fixation, and patients are randomised to either arthroplasty or internal fixation. The steering group has assessed the pragmatic attitude of the design and the study reaches five points in seven of the nine domains (Figure 1). [17] Reporting will be performed according to the extension of the CONSORT statements for a pragmatic RCT [19], and this protocol is reported according to the SPIRIT statement. [20]

Eligibility criteria

All patients with an undisplaced FNF classified as either Garden type I or II [21] are evaluated. The patients are included if

- Age ≥ 65 years
- Undisplaced femoral neck fracture
- Posterior tilt [22] < 20°
- NMS = 5 and above, indicating an ability to walk prior to the fracture
- Cognitive state intact to achieve informed consent

Patients are excluded if

- The fracture is pathological

- The patient does not speak or understand Danish language

To ensure correct fracture classification, an adjudication committee will evaluate all included X-ray images.

Interventions

Participants are randomised to either arthroplasty or internal fixation. Because the treatment options at each hospital may be very different, arthroplasty can include total hip arthroplasty (cemented, uncemented, hybrid, dual-mobility cup) or hemiarthroplasty (cemented, uncemented) using the institution's regular surgical approach (18 hospitals only use the posterior approach). Internal fixation can include either two or three screws/pins or a sliding hip screw. After discharge, all patients will be referred to standard rehabilitation in the municipalities and will be seen in their own home or at the orthopaedic department for outcome assessment after 3, 6, and 12 months. X-ray will be performed postoperatively within discharge and after 12 months.

Outcomes

Primary and secondary outcomes and measuring points have been established in collaboration with a focus group interview with hip fracture patients. The primary outcome measure is NMS assessed after 12 months. NMS will also be assessed at baseline, 3, and 6 months.

Secondary outcome measures evaluated at the same time points are the Oxford Hip Score (OHS), EuroQol 5 domain (EQ-5D-5L), pain verbal rating scale (VRS)[23], reoperation (any surgery related to the implants including closed reduction), and mortality. Explorative outcome measures are the de Morton Mobility Index (DEMMI) [7 24], Barthel-20 [25], Cumulated ambulation score (CAS)[26], X-ray measurements, and activity tracking.

Information will be retrieved from patient interview and healthcare records on the following:

- Demographics: age, sex, residency, pre-fracture mobility;
- Comorbidity: American Society of Anaesthesiologists Classification (ASA), diseases, medication, smoking, alcohol;
- Admission: time of admission, duration of hospital stay, concurrent infection, fracture time;
- Surgery: start and end of surgery, type of implant, surgical experience, blood loss;
- X-ray: quality of implant positioning[27-29]
- Biochemistry: haemoglobin, leucocytes, c-reactive protein (CRP), estimated glomerular filtration rate (eGFR), international normalised ratio (INR), blood transfusions;
- Complications: postoperative medical complications (all possible such as heart, lung, abdominal, brain, electrolytes, fall, and infection), readmissions.

A timeframe for the collection of data is provided in Table 1. Healthcare record information is collected for research purposes only to compare patient groups and treatment.

Sample size calculation

A minimal clinically important difference in NMS of 1 point was taken from Kristensen's thesis [30] and a 1-year average of 6.4 points with a standard deviation of 2.2 from Steihaug et al. [31]. The sample size was calculated using a 1-point difference, a standard deviation of 2.2, allowing a 5% probability of type 1 error and applying 95% statistical power. Consequently, 127 patients are required in each group and to allow for loss during follow-up due to mortality and other causes (30%). Therefore, a total of 330 patients are required for the study.

Recruitment

All patients are recruited in the emergency department when diagnosed with an undisplaced FNF. The admitting doctor or a senior consultant will inform the patient about the trial while the patient is in the emergency department. The information will be given verbally as well as by written participant information in an undisturbed room in the emergency department. If no next of kin are present, they will be invited to attend by phone if requested by the participant. Otherwise, an impartial assessor can be assigned. Because surgery is required to take place as quickly as possible due to a higher risk of mortality when delaying surgery, a reflection time of only 2 hours has been approved. Retrieval of informed consent will take place at either the emergency department or the ward.

Patient and public involvement

We conducted a focus group interview with hip fracture patients with internal fixation or arthroplasty at Hospital Lillebaelt, which involved 6 patients (and their relatives) aged 70 to 94 years who had received surgery 6–12 months prior to the interview. They were interviewed using a structured interview guide. The interview consisted of open questions regarding their hip fracture experience, their subsequent consequences/challenges, and what was important for them to regain. Further questions relating specifically to the study were also included. The questionnaires were easily understood, and all found them relevant. All questions were answered, and the most important outcome reported was for all functional outcomes, especially the ability to walk properly. Pain was also an important consideration, especially for the internal fixation group. All participants felt that the most important time for measuring outcomes would be after 1 year, but measuring during the first year was also important.

The study protocol was presented to the Patient and Relatives Council at Hospital Lillebaelt afterwards, with no additional remarks.

Methods: Assignment of interventions

Allocation

Treatment is divided into two strands and patients eligible for inclusion can be enrolled if they provide informed consent. Patients are entered into an electronic database (REDCap) and thereafter randomised using random blocks of n = 4 or n = 6 stratified by hospital. When the patient is called to the theatre, the surgeon will determine which implant to use by consulting REDCap; accordingly, REDCap will be used to create two groups representing each implant type.

Blinding

The surgeon and theatre staff cannot be blinded, but a standard phrase for the surgery will be used to blind the patient. According to standards of care and journal publication requirements, the coordinating staff can reveal the true surgery in case of severe pain or complications; otherwise, patients will not know until the end of the trial. The assessors will assess patients in their own home and will be blinded according to the type of surgery.

Methods: Data collection, management, and analysis

Data collection methods

Data will be collected by project staff. Baseline data will be collected during admission, and all data concerning patient-reported outcomes and physical assessment are collected by a physiotherapist in the patient's own home or in the outpatient clinic depending on the participant's wish.

Data management

Data will be entered directly into the projects' REDCap database when assessing or interviewing the participants.

Statistical methods

All variables are described according to their distribution. Groups will be compared by linear mixed models for numerical data and logistic mixed models for dichotomous data including a random effect for hospital. Both unadjusted analyses as well as analyses adjusting for demographic variables, comorbidity, mobility, type of implant, reoperation, and mortality will be carried out. Distributional assumptions on residuals and random effects will be investigated by quantile-quantile plots, and in case of deviations from distributional assumptions bootstrapping with 1000 replicates will be utilized to estimate confidence intervals and p-

values. All group comparisons will be carried out both as intention-to-treat analysis and per-protocol analysis. Mortality well be analyzed by Cox-regression with baseline hazards stratified by hospital. As sensitivity analyses competing risk regression models will be applied.

Methods: Monitoring

Data monitoring

After data retrieval from the first 70 patients, an interim analysis will be performed regarding mortality and function. If there is a difference of 10% in 30 days mortality, a consensus decision by steering group whether the trial should be stopped will be conducted. Likewise, if the NMS score shows 2 points or more difference after 3 months, all authors are asked whether the trial should be stopped. This is because the required sample size would then be 66 patients.

Potentially harms

Any unforeseen complications that occur during the trial will be registered in the projects' REDCap database.

Auditing

An adjudication committee will audit all X-ray images.

Ethics and dissemination

Research ethics approval

The study is approved by the Danish Data Protection Agency (19/7429) and the Scientific Ethics Committee with the project id number S-20180036. It was first approved on the 15th October 2018 and a revision was approved 8th October 2019. The ClinicalTrials.gov identifier is NCT04075461.

Consent or assent

The orthopaedic surgeon on call is responsible for including patients. The patient have to give a written consent (Supplementary Appendix 1) before entering the trial.

Confidentiality

Project data are securely stored in the project's REDCap database, and when the trial is completed, data are stored in the Danish Data Archive.

Ancillary and post-trial care

Any patients who experience any harm due to this trial will have the same care as all other patients in Denmark through the independent Danish Patient Compensation Association.

Dissemination policy

This is a national trial and all 20 hospitals providing hip fracture care are included. All relevant healthcare professionals involved in hip fracture treatment in Denmark will, therefore, automatically be informed of the trial results. The results will also be published in international peer-reviewed journals.

Perspective

By conducting a national pragmatic RCT, external validity will potentialle be high. A general problem with trials is the lack of clinical impact afterwards as one paper has shown that it takes an average of 17 years for new findings to reach clinical practice. As this is a nation wide study, the impact of the results are expected to be immediate and high.

Funding statement

This work is supported by the Novo Nordisk Foundation (grant number NNF19OC0058674), Axel Muusfeldt Foundation (grant number 2019-0265), and A.P. Møller Foundation (grant number 19-L-0088); however, neither has any influence on data or reporting. The trial has also received funds from two public foundations, the Region of Southern Denmark Foundation (grant number 18/51820) and the Hospital Lillebaelt Research Committee (grant number 2019-05), neither of which has any influence on data or reporting.

Access to data

Due to Danish legislation, access to the trial data is limited to trial investigators.

Author contributions

BV wrote first draft of the protocol. SK, HP, MSL, KH and OB were invited as the steering committee and the protocol was evaluated and rewritten in collaboration. All collaborators were invited to read, comment, and suggest alterations to the protocol. Each of the collaborators are in charge of onsite inclusion and data retrieval.

Competing interest statement

Outside the study, Bjarke Viberg has received payment for lectures held for Zimmer Biomet and Osmedic Swemac.

There are no other competing interests.

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Graphics was designed by Lise Kryger Simonsen.

References

1. National Institute for Health and Care Excellence. Hip fracture: mangement. Clinical guideline [CG124]. National Institute for Health and Care Excellence, 2011, updated 2017.
2. Roberts KC, Brox WT. AAOS Clinical Practice Guideline: Management of Hip Fractures in the Elderly. *J Am Acad Orthop Surg* 2015;23(2):138-40. doi: 10.5435/JAAOS-D-14-00433
3. Lu Q, Tang G, Zhao X, et al. Hemiarthroplasty versus internal fixation in super-aged patients with undisplaced femoral neck fractures: a 5-year follow-up of randomized controlled trial. *Arch Orthop Trauma Surg* 2017;137(1):27-35. doi: 10.1007/s00402-016-2591-9 [published Online First: 2016/11/12]
4. Dolatowski FC, Frihagen F, Bartels S, et al. Screw Fixation Versus Hemiarthroplasty for Nondisplaced Femoral Neck Fractures in Elderly Patients: A Multicenter Randomized Controlled Trial. *J Bone Joint Surg Am* 2019;101(2):136-44. doi: 10.2106/JBJS.18.00316 [published Online First: 2019/01/18]
5. Wamper KE, Sierevelt IN, Poolman RW, et al. The Harris hip score: Do ceiling effects limit its usefulness in orthopedics? *Acta Orthop* 2010;81(6):703-7. doi: 10.3109/17453674.2010.537808 [published Online First: 2010/11/30]
6. Kristensen PK, Thillemann TM, Soballe K, et al. Are process performance measures associated with clinical outcomes among patients with hip fractures? A population-based cohort study. *Int J Qual Health Care* 2016 doi: 10.1093/intqhc/mzw093
7. de Morton NA, Harding KE, Taylor NF, et al. Validity of the de Morton Mobility Index (DEMMI) for measuring the mobility of patients with hip fracture during rehabilitation. *Disabil Rehabil* 2013;35(4):325-33. doi: 10.3109/09638288.2012.705220
8. de Morton NA, Berlowitz DJ, Keating JL. A systematic review of mobility instruments and their measurement properties for older acute medical patients. *Health Qual Life Outcomes* 2008;6:44. doi: 10.1186/1477-7525-6-44
9. Parker MJ, Palmer CR. A new mobility score for predicting mortality after hip fracture. *J Bone Joint Surg Br* 1993;75(5):797-8.
10. Kristensen MT, Foss NB, Kehlet H. [Timed Up and Go and New Mobility Score as predictors of function six months after hip fracture]. *Ugeskr Laeger* 2005;167(35):3297-300.
11. Kristensen MT, Bandholm T, Foss NB, et al. High inter-tester reliability of the new mobility score in patients with hip fracture. *J Rehabil Med* 2008;40(7):589-91. doi: 10.2340/16501977-0217
12. Pedersen TJ, Lauritsen JM. Routine functional assessment for hip fracture patients. *Acta Orthop* 2016;87(4):374-9. doi: 10.1080/17453674.2016.1197534
13. Sikand M, Wenn R, Moran CG. Mortality following surgery for undisplaced intracapsular hip fractures. *Injury* 2004;35(10):1015-9. doi: 10.1016/j.injury.2004.01.004 [published Online First: 2004/09/08]
14. Bernstein J, Weintraub S, Morris T, et al. Randomized Controlled Trials for Geriatric Hip Fracture Are Rare and Underpowered: A Systematic Review and a Call for Greater Collaboration. *J Bone Joint Surg Am* 2019;101(24):e132. doi: 10.2106/JBJS.19.00407 [published Online First: 2019/10/01]
15. Fixation using Alternative Implants for the Treatment of Hip fractures I. Fracture fixation in the operative management of hip fractures (FAITH): an international, multicentre, randomised controlled trial. *Lancet* 2017 doi: 10.1016/S0140-6736(17)30066-1
16. Hebert-Davies J, Laflamme GY, Rouleau D, et al. Bias towards dementia: are hip fracture trials excluding too many patients? A systematic review. *Injury* 2012;43(12):1978-84. doi: 10.1016/j.injury.2012.08.061 [published Online First: 2012/09/25]
17. Loudon K, Treweek S, Sullivan F, et al. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ* 2015;350:h2147. doi: 10.1136/bmj.h2147
18. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29(8):541-9. doi: 10.1007/s10654-014-9930-3

19. Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008;337:a2390. doi: 10.1136/bmj.a2390
20. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. doi: 10.1136/bmj.e7586 [published Online First: 2013/01/11]
21. Garden RS. Low-angle fixation in fractures of the femoral neck. *J Bone Joint Surg Br* 1961;43-B(4):647-63.
22. Palm H, Gosvig K, Krasheninnikoff M, et al. A new measurement for posterior tilt predicts reoperation in undisplaced femoral neck fractures: 113 consecutive patients treated by internal fixation and followed for 1 year. *Acta Orthop* 2009;80(3):303-7. doi: 10.3109/17453670902967281 [published Online First: 2009/07/28]
23. Bech RD, Lauritsen J, Ovesen O, et al. The Verbal Rating Scale Is Reliable for Assessment of Postoperative Pain in Hip Fracture Patients. *Pain Res Treat* 2015;2015:676212. doi: 10.1155/2015/676212 [published Online First: 2015/06/17]
24. de Morton NA, Davidson M, Keating JL. Validity, responsiveness and the minimal clinically important difference for the de Morton Mobility Index (DEMMI) in an older acute medical population. *BMC Geriatr* 2010;10:72. doi: 10.1186/1471-2318-10-72
25. Collin C, Wade DT, Davies S, et al. The Barthel ADL Index: a reliability study. *Int Disabil Stud* 1988;10(2):61-3. doi: 10.3109/09638288809164103 [published Online First: 1988/01/01]
26. Kristensen MT, Jakobsen TL, Nielsen JW, et al. Cumulated Ambulation Score to evaluate mobility is feasible in geriatric patients and in patients with hip fracture. *Dan Med J* 2012;59(7):A4464. [published Online First: 2012/07/05]
27. Chammout GK, Mukka SS, Carlsson T, et al. Total hip replacement versus open reduction and internal fixation of displaced femoral neck fractures: a randomized long-term follow-up study. *J Bone Joint Surg Am* 2012;94(21):1921-8. doi: 10.2106/JBJS.K.01615 [published Online First: 2012/09/28]
28. Baumgaertner MR, Curtin SL, Lindskog DM, et al. The value of the tip-apex distance in predicting failure of fixation of peritrochanteric fractures of the hip. *J Bone Joint Surg Am* 1995;77(7):1058-64. [published Online First: 1995/07/01]
29. Koldaas MIB, Pedersen JN, Hojsager FD, et al. Implant positioning (IMPO) in undisplaced femoral neck fractures: Association to reoperation and development of an IMPO scoring system. *Injury* 2019 doi: 10.1016/j.injury.2019.12.003 [published Online First: 2019/12/17]
30. Kristensen MT. Hip fractures - Functional assessments and factors influencing in-hospital outcome, a physiotherapeutic perspective. Lund University, 2010.
31. Steihaug OM, Gjesdal CG, Bogen B, et al. Does sarcopenia predict change in mobility after hip fracture? a multicenter observational study with one-year follow-up. *BMC Geriatr* 2018;18(1):65. doi: 10.1186/s12877-018-0755-x [published Online First: 2018/03/07]

Figure 1 Assessment of pragmatic design using the PRECIS-2 wheel

Table 1 Timeframe for collection of data

	Admission	2 weeks	6 weeks	3 months	6 months	12 months	At event
Demographics	X						
Comorbidity	X						
Admission	X						
Surgery	X						
Blood	X						
X-ray	X					X	
NMS	X			X	X	X	
Pain VRS	X	X	X	X	X	X	
OHS	X			X	X	X	
EQ-5D-5L	X			X	X	X	
DEMMI	X			X	X	X	
Barthel-20	X			X	X	X	
CAS	X		X	X			
Reoperation							X
Complications							X
Mortality							X

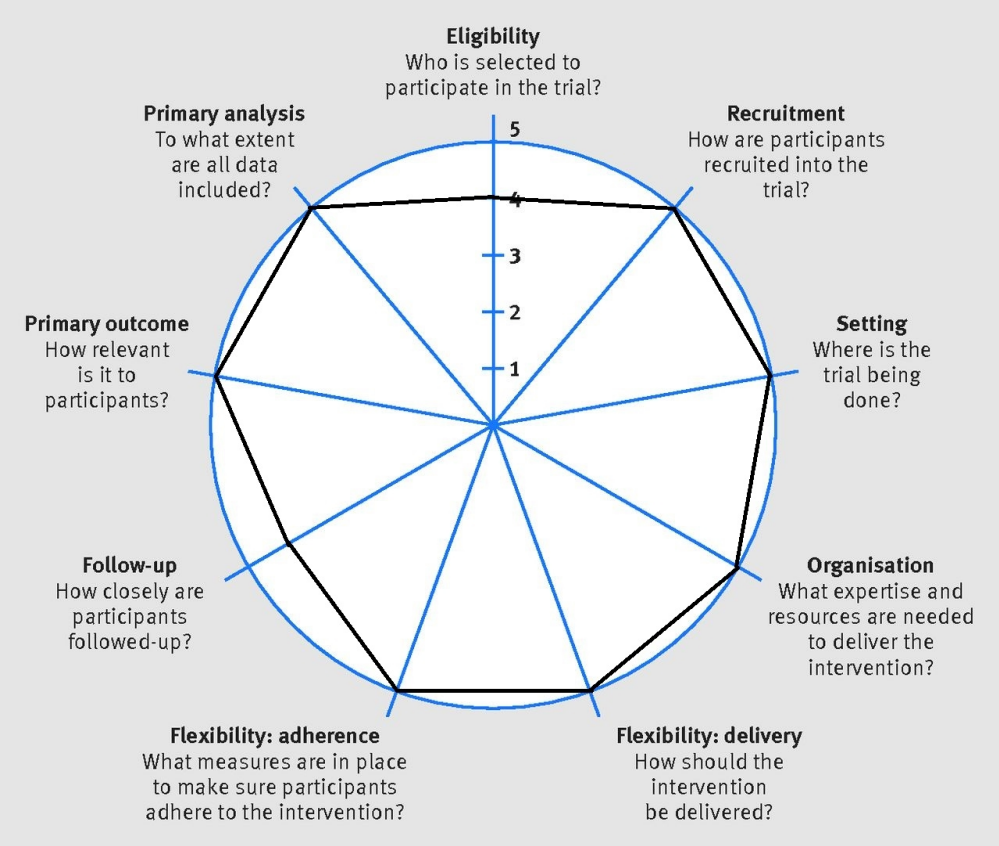

Figure 1 Assessment of pragmatic design using the PRECIS-2 wheel

108x91mm (300 x 300 DPI)

Informeret samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt.

Forskningsprojektets titel: Is arthroplaSty bEtter than interNal fixation in the undiSplaced femoral nEck fracture? A national pragmatical RCT – the SENSE trial

Erklæring fra forsøgspersonen:

Jeg har fået skriftlig og mundtlig information og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg kan trække mit samtykke tilbage inden operationen uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til, at deltage i forskningsprojektet, og har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonens navn: _____

Dato: _____ Underskrift: _____

Hvis der kommer nye væsentlige helbredsoplysninger frem om dig i forskningsprojektet vil du blive informeret. Vil du **frabede** dig information om nye væsentlige helbredsoplysninger, som kommer frem i forskningsprojektet, bedes du markere her:

Ønsker ikke information _____ (sæt x)

Erklæring fra den, der afgiver information:

Jeg erklærer, at forsøgspersonen har modtaget mundtlig og skriftlig information om forsøget.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Navnet på den, der har afgivet information:

Dato: _____ Underskrift: _____

Projektidentifikation: S-20180036

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	10
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	6-10
Protocol version	#3	Date and version identifier	09032020
Funding	#4	Sources and types of financial, material, and other support	10
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	11

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	11
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	11
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)	11
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	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-6
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)	6
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	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	6

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
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)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	7
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)	8+14
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	8
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	9

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
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	9
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 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	9
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	9
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	9
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	9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9

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)	9
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	10
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	10
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	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	10
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)	10
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to	10

		protect confidentiality before, during, and after the trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	11
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	11
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	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	14
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a