BMJ Open

Migration and head penetration of Vitamin-E diffused cemented polyethylene cup compared to standard cemented cup in total hip arthroplasty. Study protocol for a randomized, double-blind, controlled trial (E1 HIP).

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-010781
Article Type:	Protocol
Date Submitted by the Author:	07-Dec-2015
Complete List of Authors:	Sköldenberg, Olof; Karolinska Institutet, Department of clinical sciences at Danderyd hospital; Danderyd hospital, Arthroplasty unit, Department of Orthopaedics Rysinska, Agata; Karolinska Institutet, Department of clinical sciences at Danderyd hospital; Danderyd hospital, Arthroplasty unit, Department of Orthopaedics Chammout, Ghazi; Karolinska Institutet, Department of clinical sciences at Danderyd hospital; Danderyd hospital, Arthroplasty unit, Department of Orthopaedics Eisler, Thomas; Karolinska Institutet, Department of clinical sciences at Danderyd hospital; Danderyd hospital, Arthroplasty unit, Department of Orthopaedics Muren, Olav; Karolinska Institutet, Department of Clinical Sciences at Danderyd Hospital; Danderyd hospital, Arthroplasty unit, Department of Orthopaedics Bodén, Henrik; Karolinska Institutet, Department of clinical sciences at Danderyd hospital; Danderyd hospital, Arthroplasty unit, Department of Orthopaedics Salemyr, Mats; Karolinska Institutet, Department of clinical sciences at Danderyd hospital; Danderyd hospital, Arthroplasty unit, Department of Orthopaedics
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Radiology and imaging, Research methods
Keywords:	Total hip arthroplasty, Vitamin-E, highly cross-linked polyethylene, cemented cup, Radiostereometry

Migration and head penetration of Vitamin-E diffused cemented polyethylene cup compared to standard cemented cup in total hip arthroplasty. Study protocol for a randomized, double-blind, controlled trial (E1 HIP).

Olof Sköldenberg, Agata Rysinska, Ghazi Chammout, Thomas Eisler, Olle Muren, Henrik Bodén, Mats Salemyr

All at Karolinska Institutet, Department of Clinical Sciences at Danderyd Hospital, Stockholm, Sweden.

Correspondence: Dr. Olof Sköldenberg, MD, PhD, Associate Professor, Department of Clinical Sciences, Unit of Orthopaedics, Karolinska Institutet at Danderyd Hospital, S-182 88 Danderyd, Sweden. Tel +46-8-6555000. Fax +46-8-7551476.

E-mail: olof.skoldenberg @ki.se

Word count: 2319

Key words: Total hip arthroplasty, vitamin-e, highly cross-linked polyethylene, cemented cup, radiostereometry.

Abstract

Introduction

In vitro, Vitamin-E diffused, highly cross-linked polyethylene (PE) have been shown to have superior wear resistance and improved mechanical properties as compared to that of standard highly cross-linked PE liners used in total hip arthroplasty (THA). The Vitamin-E used is alfa-tocopherol, a lipid-soluble antioxidant with oily consistency; theoretically affecting cemented fixation when used in acetabular components. The aim of the study is to evaluate the safety of a new acetabular cup with vitamin-E doped PE regarding migration, head penetration and clinical results.

Methods and analysis

In this single centre, double-blinded, randomized controlled trial, we will include 50 patients with primary hip osteoarthritis scheduled for THA and randomize them in a 1:1 ratio to a cemented cup with either argon-gas sterilized PE (control group) or Vitamin-E diffused PE (vitamin-e group). All patients and the assessor of the primary outcome will be blinded and the same uncemented stem used for all subjects. The primary endpoint will be proximal migration of the cup at 2 years after surgery measured with radiostereometry [RSA]). Secondary endpoints include proximal migration at other follow-ups, total migration, femoral head penetration, clinical outcome scores and hip-related complications. Patients will be followed-up at 3 months and at 1, 2, 5 and 10 years postoperatively.

Results

Results will be analysed using 95% CIs for the effect size. A regression model will also be used to adjust for stratification factors.

Ethics and dissemination

The ethical committee at Karolinska Institutet has approved the study. The first results from the study will be disseminated to the medical community via presentations and publications in relevant medical journals when the last patient included has been followed for 2 years.

Trial registration number: The trial is registered at www.clinicaltrials.gov (NCT02254980)

Strengths and limitations of this study

- Blinded assessment of primary outcome
- Randomized controlled trial
- High precision measurement of primary outcome using radiostereometry
- Proxy variable for loosening of implants
- Small study size
- Blinding of surgeons not possible

Introduction

The major factor limiting the lifespan of a total hip arthroplasty (THA) is periprosthetic osteolysis and loosening secondary to wear of ultrahigh-molecular weight polyethylene (PE) of acetabular components [1, 2]. In vitro, Vitamin-E doped highly cross-linked PE have been shown to have superior wear resistance and improved mechanical properties as compared to that of standard PE [3]. The first randomized clinical trials on vitamin-E PE in THA have recently been published by our research group and found a low wear rate up to two years postoperatively as compared to controls[4]. Others have confirmed these findings [5] also for larger-diameter femoral heads [6]. All of these trials use uncemented acetabular cups intended for biological fixation. In many countries the most common fixation method for the acetabular component is bone-cement[1] and there are now on the market acetabular components with vitamin-E doped PE intended for cemented fixation. The Vitamin-E used in implants is alfa-tocopherol, a lipid-soluble antioxidant with oily consistency; theoretically affecting cemented fixation when used in acetabular components. Radiostereometry (RSA) can be used to predict loosening of THA implants in vivo and is the gold standard in evaluating new prosthetic implants [7, 8]. A proximal migration of 1.0 mm up to 2 years after surgery significantly increases the risk of revision for acetabular cups [9] and this threshold can be implemented in a phased evidence-based introduction of new implants [10], since they allow early detection of high-risk cups while exposing a small number of patients[7-9].

The aim of the study is to evaluate the safety of a new acetabular cup with vitamin-E doped PE by comparing it to a clinically well proven cup with standard PE regarding migration, head penetration and clinical results. We hypothesized that the new vitamin-E PE is non-inferior to standard PE in terms of early (2 years) migration of the cup.

Patients and Methods

Setting and design

A single-center, randomized, double-blinded, controlled trial will be carried out from 2013 to 2025 at the Orthopaedic Department of Danderyd Hospital, Stockholm in collaboration with the Karolinska Institute, Stockholm. The Ethics Committee of the Karolinska Institute has approved the study (No. 2011/2003-31/1). The guidelines of Good Clinical Practise (GCP-ICH) will be followed [11]. The trial is initiated, designed, and performed as an academic investigation and registered at ClinicalTrials.gov (NCT02254980). The guidelines of the CONSORT Statement will be followed [12] for the final paper and the SPIRIT guidelines for the study protocol [13].

Randomization and blinding

Patients will be randomized in a 1:1 ratio to the control group or vitamin-e group using concealed envelopes. A randomly assigned batch size of 4 to 10 (in increments of 2; thus 4, 6, 8, or 10) will be used. We will use sex and age (<65 and ≥65 years) as stratification factors to ensure that the baseline characteristics are similar in the two groups. The patients and staff will be blinded to treatment. Because alfa-tocopherol taints PE yellow, the surgeons cannot be blinded to allocation. The outcome assessor of the migration primary and secondary endpoints will be blinded when performing the RSA analysis. The patients who are blinded fill out all forms for the clinical outcome scores.

Patients

Consecutive patients 40-75 years old who are being planned for THA will be eligible for inclusion in the study. We will include patients with a primary osteoarthritis of the hip and a willingness and ability to follow study-protocol. We will exclude patients with inflammatory arthritis or secondary osteoarthritis, with a femoral or pelvic anatomy after hip dysplasia not suitable for implantation of components, those who have ongoing oestrogen treatment or treatment with bisphosphonates, cortisol or cytostatic drugs 6 months prior to surgery and those, who are not suited for the study for other reason (for instance substance abuse).

Surgery and allocation

The randomization will allocate to THA with the cemented Muller Exceed ABT cup (Biomet, Warzaw, Indiana, USA) acetabular component with either Vitamin-E diffused polyethylene (vitamin-e group, E1™) or argon gas sterilized compression moulded PE (control group,

Arcom™ PE). A standard posterior approach with repair of the posterior capsule and external rotators will be used. The femoral component will be an uncemented, tapered, proximally porous- and hydroxyapatite-coated stem composed of a Ti-6Al-4V titanium alloy (Bi-Metric HA; Biomet, Warsaw, Indiana, USA) and a 32-mm chromium-cobalt head. The surgical technique as described by the manufacturers for the implants will be followed. Third generation cementation technique will be used. We have a long experience of using the Muller cup and Bi-Metric stem so no learning curve will be expected[14]. Intravenous tranexamic acid (Cyclokapron; Pfizer, Sollentuna, Sweden) will be administered before the start of surgery to reduce bleeding. Prophylactic antibiotics (cloxacillin; Meda, Solna, Sweden) will be administered thirty minutes preoperatively and twenty-four hours postoperatively, and dalteparin (Fragmin; AstraZeneca, Sodertalje, Sweden) for ten days postoperatively to prevent thrombosis. Patients will start rehabilitation on the first postoperative day. All patients will mobilize with full weight bearing, under supervision of a physiotherapist, with the use of suitable walking aids during the first 6 weeks.

End points and follow-ups

The primary end point variable will be proximal migration of the cup at 2 years, measured with RSA. This endpoint was chosen since every mm increase in 2-year proximal migration has been verified to increase the revision rate of an acetabular implant by 10% at 10 years [9]. This predictive power of early migration on future revision is widely used in RSA studies and is the reason the method is the gold-standard in evaluating new implants in joint arthroplasty [7-9, 15]. The secondary end points will include proximal migration at all other follow-ups, maximum total point motion (MTPM) of the cup, head penetration of the prosthetic head into the cup, migration of the femoral stem, development of radiolucent lines between bone and cement around the cup, functional outcome scores, serological markers of inflammation and hip related complications up to 10 years. Follow up will be done at inclusion and at 3 months and 1, 2, 5 and 10 years postoperatively (Figure 1) with the primary end point evaluated at 2 years.

Radiostereometry and radiological evaluation

Radiostereometry is a high-precision method of assessing three-dimensional (3D) micro movement from calibrated stereo radiographs and is used for evaluating new implants since early migration can predict loosening [7, 8]. Nine Tantalum-markers (1.0 mm) will be put in the pelvis surrounding the cup and the surgeon will fix nine tantalum markers in the implant

before cementing. We will follow the published guidelines for RSA [15]. We will use digital calibrated radiographs, a uniplanar calibration cage (Uniplanar digital 43; RSA Biomedical AB) and analyse all data using the UmRSA software (RSA Biomedical AB, Umeå, Sweden). The markers in the acetabulum form one segment and the markers in the cup another segment. The 3D translations and rotations of the calculated centre of gravity of the cup in relation to the acetabular bone segment will be calculated at each follow-up visit and compared with the immediate post-operative measurements. The proximal migration of the cup up to 2 years postoperatively, which has been found to be a clinically relevant endpoint for correlating RSA results to register data [9], will be used for the primary endpoint. A migration threshold of 1.0 mm during the first 2 years will be used [9]. The maximum total point movement (MTPM) of the cup, which is the 3D translation vector of the marker in the implant that has the largest movement and is seen as an indicator of the overall magnitude of migration, will be used for secondary end point of overall migration of the cups. The centre of the prosthetic head will also be measured with the built-in edge-detection technique of the software and used to measure head penetration into the PE and calculate linear head penetration. The centre of the prosthetic head and it´s movement in correlation to the femoral stem will also be used to measure the migration of the stem. At 1 year, we will perform two examinations 15 minutes apart on all patients with complete repositioning of the X-ray tubes and the calibration cage. We will use these measurements to calculate the precision of the calculated the precision as the 99% confidence interval (CI) (SD 2.7) of the difference between the examinations. The mean error of rigid body fitting will be used to evaluate the stability of the markers over time [16]. We will exclude examinations in which this value is > 0.3 mm because this indicates migration of the markers. The condition number is used to evaluate the distribution of the markers and a high value precludes accurate measurements of z-translation as well as segment rotation and MTPM. Therefore, in examinations in which the condition number exceeded 150, only transverse (x) and vertical (y) translations will be calculated [16]. In addition to the RSA evaluation, Digital anteroposterior and lateral radiographs will be taken (Bucky Diagnostics; Philips, Eindhoven, The Netherlands). With these, we will evaluate the presence of radiolucent lines between the bone and the cement in the DeLee and Charnley zones around the cup[17]. Heterotopic ossification will be evaluated according to the Brooker classification[18].

Functional outcomes

The functional outcome scores will be the Harris hip score (HHS) [19] and the Hip disability and Osteoarthritis Outcome Score (HOOS) [20, 21]. Both are valid and widely used for evaluating hip function after THA. Health-related quality of life will be assessed by the EQ-5D (EuroQoL) [22, 23]. EQ-5D uses five dimensions: mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Other endpoints include pain in the operated hip evaluated with VAS.

Hip related complications and adverse events

All hip related complications will be recorded throughout the study period. To make sure that we capture all events, we will use the unique Swedish personal id-number and collect data prospectively throughout the study period through a combination of a search of our surgical and medical databases, follow-up visits and the Swedish Hip Arthroplasty Register. Other, non hip-related adverse events (AEs) and serious adverse events (SAEs) will also be collected throughout the study period

Serological markers

As a secondary endpoint, serological markers of inflammatory response (high-sensitivity c-reactive protein and interleukin-6) will be measured to investigate if the vitamin-E in the acetabular components reduces the inflammatory response during the study period [24, 25]. We will also measure the levels of serum C-terminal telopeptide of type I collagen (SCTx) and pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (1CTP), both of which can be used as biomarkers in the serum to measure the rate of bone turnover [26].

Data Quality Assurance

The study progress and study conduct will be monitored before, during and after the study by an external monitor to ensure that GCP-ICH [11], regulatory requirements, and all aspects of the protocol are followed. All study data will be collected and managed in a digital case report form (CRF) using REDCap electronic data capture tools hosted at Karolinska Institutet [27]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The medical records and other

documents will be reviewed for verification of agreement with data on the CRF. The subject has a right for a protection against invasion of privacy. In this study, each subject will receive a unique identification number, which will be linked to the CRF. The data will then be blinded correspondingly in all data analyses. However, the study monitor, auditor, representative from any regulatory authority, as well as the appropriate Ethical Committee are permitted to review the subject's primary medical records including laboratory test result reports, ECG reports, admission and discharge summaries, AE and SAE reports occurring during the study

Sample size

The study is designed to show that the vitamin-e group, compared to the control group, has neither lower nor higher proximal migration (y-translation) than the clinically relevant migration threshold of 0.2 mm[9]. A non-inferiority power analysis that with a power of 90% will show that the mean for the proximal migration at 2 years in the vitamin-e group is the same as the mean for the control group requires a sample size of 18 subjects in each group. This assumes that both groups has a common within-group standard deviation of 0.21, estimated from one of our previous studies [28], and that a difference of 0.2 mm or less is clinically irrelevant as reported in a recent meta-analysis [9]. The alpha (2-tailed) is set at 0.05. We will include 25 patients in each group (50 total) to allow for loss to follow-up and loss of data due to the technical nature of RSA.

Analysis

The analyses will be performed on the basis of the intention-to-treat principle, and all patients who are allocated to either group will be included in the analysis, regardless of actual surgery performed. Descriptive statistics (means and standard deviations) will be used to describe the patient characteristics and outcome variables at the measurement points. We will use the Student's t-test and Levene's test for comparison of the endpoints with 95% CI presented. An analysis of covariance (ANCOVA) of the primary endpoint will also be used to reduce variance, adjusted for exposure variable (control group/vitamin-e group) and stratification factors (male/female and <65/ ≥65 years). For subjects that withdrawn from the study before completion, the data from the last observation will be carried forward (imputed). The analyses will be performed with SPSS 22.0 for Windows (SPSS, Chicago, Illinois) statistical software.

Ethics and dissemination

The ethical committee at Karolinska Institutet has approved the study. The first results from the study will be disseminated to the medical community via presentations and publications in relevant medical journals when the last patient included has been followed for 2 years. Further publications will be presented at 5 and 10 years.

References

1. Garellick, G., et al. *Swedish Hip Arthroplasty Register Annual Report 2011*. 2011 2011-10-27]; Available from: http://www.shpr.se/Libraries/Documents/%C3%85rsrapport_2011_avseende_verksamhets%C3%A5ret_2011.sflb.ashx.
2. Harris, W.H., *Wear and periprosthetic osteolysis: the problem.* Clin Orthop Relat Res, 2001(393): p. 66-70.
3. Oral, E., et al., *Wear resistance and mechanical properties of highly cross-linked, ultrahigh-molecular weight polyethylene doped with vitamin E.* J Arthroplasty, 2006. **21**(4): p. 580-91.
4. Salemyr, M., et al., *Vitamin-E diffused highly cross-linked polyethylene liner compared to standard liners in total hip arthroplasty. A randomized, controlled trial.* Int Orthop, 2015.
5. Shareghi, B., P.E. Johanson, and J. Karrholm, *Femoral Head Penetration of Vitamin E-Infused Highly Cross-Linked Polyethylene Liners: A Randomized Radiostereometric Study of Seventy Hips Followed for Two Years.* J Bone Joint Surg Am, 2015. **97**(16): p. 1366-71.
6. Lindalen, E., et al., *E-vitamin infused highly cross-linked polyethylene: RSA results from a randomised controlled trial using 32 mm and 36 mm ceramic heads.* Hip Int, 2015. **25**(1): p. 50-5.
7. Kärrholm, J., et al., *Does early micromotion of femoral stem prostheses matter? 4-7-year stereoradiographic follow-up of 84 cemented prostheses.* J Bone Joint Surg Br, 1994. **76**(6): p. 912-7.
8. Selvik, G., *Roentgen stereophotogrammetry. A method for the study of the kinematics of the skeletal system.* Acta Orthop Scand Suppl, 1989. **232**: p. 1-51.
9. Pijls, B.G., et al., *Early proximal migration of cups is associated with late revision in THA: a systematic review and meta-analysis of 26 RSA studies and 49 survivalstudies.* Acta Orthop, 2012. **83**(6): p. 583-91.
10. Malchau, H., C.R. Bragdon, and O.K. Muratoglu, *The Stepwise Introduction of Innovation into Orthopedic Surgery The Next Level of Dilemmas.* Journal of Arthroplasty, 2010.
11. Vijayananthan, A. and O. Nawawi, *The importance of Good Clinical Practice guidelines and its role in clinical trials.* Biomed Imaging Interv J, 2008. **4**(1): p. e5.
12. Schulz, K.F., D.G. Altman, and D. Moher, *CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**: p. c332.
13. Chan, A.W., et al., *SPIRIT 2013 statement: defining standard protocol items for clinical trials.* Ann Intern Med, 2013. **158**(3): p. 200-7.
14. Boden, H., et al., *Total hip arthroplasty with an uncemented hydroxyapatite-coated tapered titanium stem: results at a minimum of 10 years' follow-up in 104 hips.* Journal of Orthopaedic Science, 2006. **11**(2): p. 175-9.

15. Valstar, E.R., et al., *Guidelines for standardization of radiostereometry (RSA) of implants.* Acta Orthop, 2005. **76**(4): p. 563-72.

16. Söderkvist, I. and P.A. Wedin, *On condition numbers and algorithms for determining a rigid-body movement.* Bit, 1994(34): p. 424-36.

17. DeLee, J.G. and J. Charnley, *Radiological demarcation of cemented sockets in total hip replacement.* Clin Orthop Relat Res, 1976(121): p. 20-32.

18. Brooker, A.F., et al., *Ectopic ossification following total hip replacement. Incidence and a method of classification.* J Bone Joint Surg Am, 1973. **55**(8): p. 1629-32.

19. Harris, W.H., *Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation.* J Bone Joint Surg Am, 1969. **51**(4): p. 737-55.

20. Nilsdotter, A.K., et al., *Hip disability and osteoarthritis outcome score (HOOS)--validity and responsiveness in total hip replacement.* BMC Musculoskelet Disord, 2003. **4**: p. 10.

21. Davis, A.M., et al., *Comparative, validity and responsiveness of the HOOS-PS and KOOS-PS to the WOMAC physical function subscale in total joint replacement for osteoarthritis.* Osteoarthritis and Cartilage, 2009. **17**(7): p. 843-7.

22. Burström, K., M. Johannesson, and F. Diderichsen, *Swedish population health-related quality of life results using the EQ-5D.* Qual Life Res, 2001. **10**(7): p. 621-35.

23. Rabin, R. and F. de Charro, *EQ-5D: a measure of health status from the EuroQol Group.* Ann Med, 2001. **33**(5): p. 337-43.

24. Chaganti, R.K., et al., *Elevation of serum tumor necrosis factor alpha in patients with periprosthetic osteolysis: a case-control study.* Clin Orthop Relat Res, 2014. **472**(2): p. 584-9.

25. Bergin, P.F., et al., *Comparison of minimally invasive direct anterior versus posterior total hip arthroplasty based on inflammation and muscle damage markers.* J Bone Joint Surg Am, 2011. **93**(15): p. 1392-8.

26. Rosen, H.N., et al., *Serum CTX: a new marker of bone resorption that shows treatment effect more often than other markers because of low coefficient of variability and large changes with bisphosphonate therapy.* Calcif Tissue Int, 2000. **66**(2): p. 100-3.

27. Harris, P.A., et al., *Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.* J Biomed Inform, 2009. **42**(2): p. 377-81.

28. Salemyr, M., et al., *Porous titanium construct cup compared to porous coated titanium cup in total hip arthroplasty. A randomised controlled trial.* Int Orthop, 2015. **39**(5): p. 823-32.

Acknowledgements

We gratefully acknowledge the support of our institution and department and most of all our research nurses Helene Sjöö, Paula Kelly-Pettersson, Marie Ax and Lise-Lotte Widmark

Authors' contributions

OS conceived the original study and developed the protocol with AR, GC, TE, OM, MS, HB. OS led the writing of the manuscript, with contributions from AR, GC, TE, OM, MS, HB. All authors contributed to the editing and redrafting.

Funding statement

The study will be supported from these foundations: Åke Wiberg stiftelse, Loo and Hans Ostermans Stiftelse, Sven Norén foundation, and The regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet. Biomet will partially fund the RSA examinations in the study but has no further input or participation in the trial.

Competing interests

None.

Ethics approval

Approved by the Ethics committee at the Karolinska Institute, Stockholm, Sweden

Data sharing statement

No additional data are available.

	< 2m	-2 v	0	+1 d	5d	3 m.	1 y	2 y	5 y	10 y
	Screening	Inclusion	Randomization and surgery	POD1	End of In-pt stay	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up
Screening for eligibility	x									
Informed consent		x								
Baseline data		x								
Randomization			x							
X-ray		x		x			x	x	x	x
RSA				x		x	x	x	x	x
HHS		x					x	x	x	x
HOOS		x					x	x	x	x
VAS		x					x	x	x	x
EQ-5D		x					x	x	x	x
Adverse events			x	x	x	x	x	x	x	x
Blood test		x		x		x	x	x	x	x

X-ray= Anterioposterior and lateral radiographs
RSA= Radiostereometry
HHS= Harris hip score
EQ-5D = Quality of life score
VAS= Visual Analogue Scale for hip pain
HOOS= Hip Osteoarthritis Outcome Score
Bloodtest =Serum C-terminal telopeptide of type I collagen (SCTx), pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (1CTP), C-reactive protein (CRP), IL-6, Hb
89x28mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on 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	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	na
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	13
	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)	na

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
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, noninferiority, exploratory)	5
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	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
	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)	na
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	na
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	6-7
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)	Figure 1

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	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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	5
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	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	na
Methods: Data collection, management, and analysis			
Data collection methods	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	8-9
	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	8-9

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	8-9
Statistical methods	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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	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	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	8
	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	na
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	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	na
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9-10
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)	na

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	5
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
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	na
Dissemination policy	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	9-10
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	na
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	na
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	na

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Migration and head penetration of Vitamin-E diffused cemented polyethylene cup compared to standard cemented cup in total hip arthroplasty. Study protocol for a randomized, double-blind, controlled trial (E1 HIP).

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-010781.R1
Article Type:	Protocol
Date Submitted by the Author:	12-Apr-2016
Complete List of Authors:	Sköldenberg, Olof; Karolinska Institutet, Department of clinical sciences at Danderyd hospital; Danderyd hospital, Arthroplasty unit, Department of Orthopaedics Rysinska, Agata; Karolinska Institutet, Department of clinical sciences at Danderyd hospital; Danderyd hospital, Arthroplasty unit, Department of Orthopaedics Chammout, Ghazi; Karolinska Institutet, Department of clinical sciences at Danderyd hospital; Danderyd hospital, Arthroplasty unit, Department of Orthopaedics Eisler, Thomas; Karolinska Institutet, Department of clinical sciences at Danderyd hospital; Danderyd hospital, Arthroplasty unit, Department of Orthopaedics Muren, Olav; Karolinska Institutet, Department of Clinical Sciences at Danderyd Hospital; Danderyd hospital, Arthroplasty unit, Department of Orthopaedics Bodén, Henrik; Karolinska Institutet, Department of clinical sciences at Danderyd hospital; Danderyd hospital, Arthroplasty unit, Department of Orthopaedics Salemyr, Mats; Karolinska Institutet, Department of clinical sciences at Danderyd hospital; Danderyd hospital, Arthroplasty unit, Department of Orthopaedics
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Radiology and imaging, Research methods
Keywords:	Total hip arthroplasty, Vitamin-E, highly cross-linked polyethylene, cemented cup, Radiostereometry

Migration and head penetration of Vitamin-E diffused cemented polyethylene cup compared to standard cemented cup in total hip arthroplasty. Study protocol for a randomized, double-blind, controlled trial (E1 HIP).

Olof Sköldenberg, Agata Rysinska, Ghazi Chammout, Thomas Eisler, Olle Muren, Henrik Bodén, Mats Salemyr

All at Karolinska Institutet, Department of Clinical Sciences at Danderyd Hospital, Stockholm, Sweden.

Correspondence: Dr. Olof Sköldenberg, MD, PhD, Associate Professor, Department of Clinical Sciences, Unit of Orthopaedics, Karolinska Institutet at Danderyd Hospital, S-182 88 Danderyd, Sweden. Tel +46-8-6555000. Fax +46-8-7551476.

E-mail: olof.skoldenberg@gmail.com

Word count: 2319

Key words: Total hip arthroplasty, vitamin-e, highly cross-linked polyethylene, cemented cup, radiostereometry.

Abstract

Introduction

In vitro, Vitamin-E diffused, highly cross-linked polyethylene (PE) have been shown to have superior wear resistance and improved mechanical properties as compared to that of standard highly cross-linked PE liners used in total hip arthroplasty (THA). The aim of the study is to evaluate the safety of a new cemented acetabular cup with vitamin-E doped PE regarding migration, head penetration and clinical results.

Methods and analysis

In this single centre, double-blinded, randomized controlled trial, we will include 50 patients with primary hip osteoarthritis scheduled for THA and randomize them in a 1:1 ratio to a cemented cup with either argon-gas sterilized PE (control group) or Vitamin-E diffused PE (vitamin-e group). All patients and the assessor of the primary outcome will be blinded and the same uncemented stem used for all subjects. The primary endpoint will be proximal migration of the cup at 2 years after surgery measured with radiostereometry [RSA]). Secondary endpoints include proximal migration at other follow-ups, total migration, femoral head penetration, clinical outcome scores and hip-related complications. Patients will be followed-up at 3 months and at 1, 2, 5 and 10 years postoperatively.

Results

Results will be analysed using 95% CIs for the effect size. A regression model will also be used to adjust for stratification factors.

Ethics and dissemination

The ethical committee at Karolinska Institutet has approved the study. The first results from the study will be disseminated to the medical community via presentations and publications in relevant medical journals when the last patient included has been followed for 2 years.

Trial registration number: The trial is registered at www.clinicaltrials.gov (NCT02254980)

Strengths and limitations of this study

- Blinded assessment of primary outcome
- Randomized controlled trial
- High precision measurement of primary outcome using radiostereometry
- Proxy variable for loosening of implants
- Blinding of surgeons not possible

Introduction

The major factor limiting the lifespan of a total hip arthroplasty (THA) is periprosthetic osteolysis and loosening secondary to wear of ultrahigh-molecular weight polyethylene (PE) of acetabular components [1, 2]. In vitro, Vitamin-E doped highly cross-linked PE have been shown to have superior wear resistance and improved mechanical properties as compared to that of standard PE [3]. The first randomized clinical trials on vitamin-E PE in THA have recently been published by our research group and found a low wear rate up to two years postoperatively as compared to controls[4]. Others have confirmed these findings [5] also for larger-diameter femoral heads [6]. All of these trials use uncemented acetabular cups intended for biological fixation. In many countries the most common fixation method for the acetabular component is bone-cement[1] and there are now on the market new acetabular components with vitamin-E doped PE intended for cemented fixation. Radiostereometry (RSA) can be used to predict loosening of THA implants in vivo and is the gold standard in evaluating new prosthetic implants [7, 8]. A proximal migration of 1.0 mm up to 2 years after surgery significantly increases the risk of revision for acetabular cups [9] and this threshold can be implemented in a phased evidence-based introduction of new implants [10], since they allow early detection of high-risk cups while exposing a small number of patients[7-9].

The aim of the study is to evaluate the safety of a new acetabular cup with vitamin-E doped PE by comparing it to a clinically well proven cup with standard PE regarding migration, head penetration and clinical results. We hypothesized that the new vitamin-E PE is non-inferior to standard PE in terms of early (2 years) migration of the cup.

Patients and Methods

Setting and design

A single-center, randomized, double-blinded, controlled trial will be carried out from 2013 to 2025 at the Orthopaedic Department of Danderyd Hospital, Stockholm in collaboration with the Karolinska Institute, Stockholm. The Ethics Committee of the Karolinska Institute has approved the study (No. 2011/2003-31/1). The guidelines of Good Clinical Practise (GCP-ICH) will be followed [11]. The trial is initiated, designed, and performed as an academic investigation and registered at ClinicalTrials.gov (NCT02254980). The guidelines of the CONSORT Statement will be followed [12] for the final paper and the SPIRIT guidelines for the study protocol [13].

Randomization and blinding

Patients will be randomized in a 1:1 ratio to the control group or vitamin-e group using concealed envelopes. A randomly assigned batch size of 4 to 10 (in increments of 2; thus 4, 6, 8, or 10) will be used. We will use sex and age (<65 and ≥65 years) as stratification factors to ensure that the baseline characteristics are similar in the two groups. The patients and staff will be blinded to treatment. Because alfa-tocopherol taints PE yellow, the surgeons cannot be blinded to allocation. The outcome assessor of the migration primary and secondary endpoints will be blinded when performing the RSA analysis. The patients who are blinded fill out all forms for the clinical outcome scores.

Patients

Consecutive patients 40-75 years old who are being planned for THA will be eligible for inclusion in the study. We will include patients with a primary osteoarthritis of the hip and a willingness and ability to follow study-protocol. We will exclude patients with inflammatory arthritis or secondary osteoarthritis, with a femoral or pelvic anatomy after hip dysplasia not suitable for implantation of components, those who have ongoing oestrogen treatment or treatment with bisphosphonates, cortisol or cytostatic drugs 6 months prior to surgery and those, who are not suited for the study for other reason (for instance substance abuse).

Surgery and allocation

The randomization will allocate to THA with the cemented Muller Exceed ABT cup (Biomet, Warzaw, Indiana, USA) acetabular component with either Vitamin-E diffused polyethylene (vitamin-e group, E1™) or argon gas sterilized compression moulded PE (control group,

Arcom™ PE). A standard posterior approach with repair of the posterior capsule and external rotators will be used. The femoral component will be an uncemented, tapered, proximally porous- and hydroxyapatite-coated stem composed of a Ti-6Al-4V titanium alloy (Bi-Metric HA; Biomet, Warsaw, Indiana, USA) and a 32-mm chromium-cobalt head. The surgical technique as described by the manufacturers for the implants will be followed. Third generation cementation technique will be used. We have a long experience of using the Muller cup and Bi-Metric stem so no learning curve will be expected[14]. Intravenous tranexamic acid (Cyclokapron; Pfizer, Sollentuna, Sweden) will be administered before the start of surgery to reduce bleeding. Prophylactic antibiotics (cloxacillin; Meda, Solna, Sweden) will be administered thirty minutes preoperatively and twenty-four hours postoperatively, and dalteparin (Fragmin; AstraZeneca, Sodertalje, Sweden) for ten days postoperatively to prevent thrombosis. Patients will start rehabilitation on the first postoperative day. All patients will mobilize with full weight bearing, under supervision of a physiotherapist, with the use of suitable walking aids during the first 6 weeks.

End points and follow-ups

The primary end point variable will be proximal migration of the cup at 2 years, measured with RSA. This endpoint was chosen since every mm increase in 2-year proximal migration has been verified to increase the revision rate of an acetabular implant by 10% at 10 years [9]. This predictive power of early migration on future revision is widely used in RSA studies and is the reason the method is the gold-standard in evaluating new implants in joint arthroplasty [7-9, 15]. The secondary end points will include proximal migration at all other follow-ups, maximum total point motion (MTPM) of the cup, head penetration of the prosthetic head into the cup, migration of the femoral stem, development of radiolucent lines between bone and cement around the cup, functional outcome scores, serological markers of inflammation and hip related complications up to 10 years. Follow up will be done at inclusion and at 3 months and 1, 2, 5 and 10 years postoperatively (Figure 1) with the primary end point evaluated at 2 years.

Radiostereometry and radiological evaluation

Radiostereometry is a high-precision method of assessing three-dimensional (3D) micro movement from calibrated stereo radiographs and is used for evaluating new implants since early migration can predict loosening [7, 8]. Nine Tantalum-markers (1.0 mm) will be put in the pelvis surrounding the cup and the surgeon will fix nine tantalum markers in the implant

before cementing. We will follow the published guidelines for RSA [15]. We will use digital calibrated radiographs, a uniplanar calibration cage (Uniplanar digital 43; RSA Biomedical AB) and analyse all data using the UmRSA software (RSA Biomedical AB, Umeå, Sweden). The markers in the acetabulum form one segment and the markers in the cup another segment. The 3D translations and rotations of the calculated centre of gravity of the cup in relation to the acetabular bone segment will be calculated at each follow-up visit and compared with the immediate post-operative measurements. The proximal migration of the cup up to 2 years postoperatively, which has been found to be a clinically relevant endpoint for correlating RSA results to register data [9], will be used for the primary endpoint. A migration threshold of 1.0 mm during the first 2 years will be used [9]. The maximum total point movement (MTPM) of the cup, which is the 3D translation vector of the marker in the implant that has the largest movement and is seen as an indicator of the overall magnitude of migration, will be used for secondary end point of overall migration of the cups. The centre of the prosthetic head will also be measured with the built-in edge-detection technique of the software and used to measure head penetration into the PE and calculate linear head penetration. The centre of the prosthetic head and it´s movement in correlation to the femoral stem will also be used to measure the migration of the stem. At 1 year, we will perform two examinations 15 minutes apart on all patients with complete repositioning of the X-ray tubes and the calibration cage. We will use these measurements to calculate the precision of the calculated the precision as the 99% confidence interval (CI) (SD 2.7) of the difference between the examinations. The mean error of rigid body fitting will be used to evaluate the stability of the markers over time [16]. We will exclude examinations in which this value is > 0.3 mm because this indicates migration of the markers. The condition number is used to evaluate the distribution of the markers and a high value precludes accurate measurements of z-translation as well as segment rotation and MTPM. Therefore, in examinations in which the condition number exceeded 150, only transverse (x) and vertical (y) translations will be calculated [16]. In addition to the RSA evaluation, Digital anteroposterior and lateral radiographs will be taken (Bucky Diagnostics; Philips, Eindhoven, The Netherlands). With these, we will evaluate the presence of radiolucent lines between the bone and the cement in the DeLee and Charnley zones around the cup[17]. Heterotopic ossification will be evaluated according to the Brooker classification[18].

Functional outcomes

The functional outcome scores will be the Harris hip score (HHS) [19] and the Hip disability and Osteoarthritis Outcome Score (HOOS) [20, 21]. Both are valid and widely used for evaluating hip function after THA. Health-related quality of life will be assessed by the EQ-5D (EuroQoL) [22, 23]. EQ-5D uses five dimensions: mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Other endpoints include pain in the operated hip evaluated with VAS.

Hip related complications and adverse events

All hip related complications will be recorded throughout the study period. To make sure that we capture all events, we will use the unique Swedish personal id-number and collect data prospectively throughout the study period through a combination of a search of our surgical and medical databases, follow-up visits and the Swedish Hip Arthroplasty Register. Other, non hip-related adverse events (AEs) and serious adverse events (SAEs) will also be collected throughout the study period

Serological markers

As a secondary endpoint, serological markers of inflammatory response (high-sensitivity c-reactive protein and interleukin-6) will be measured to investigate if the vitamin-E in the acetabular components reduces the inflammatory response during the study period [24, 25]. We will also measure the levels of serum C-terminal telopeptide of type I collagen (SCTx) and pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (1CTP), both of which can be used as biomarkers in the serum to measure the rate of bone turnover [26].

Data Quality Assurance

The study progress and study conduct will be monitored before, during and after the study by an external monitor to ensure that GCP-ICH [11], regulatory requirements, and all aspects of the protocol are followed. All study data will be collected and managed in a digital case report form (CRF) using REDCap electronic data capture tools hosted at Karolinska Institutet [27]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The medical records and other

documents will be reviewed for verification of agreement with data on the CRF. The subject has a right for a protection against invasion of privacy. In this study, each subject will receive a unique identification number, which will be linked to the CRF. The data will then be blinded correspondingly in all data analyses. However, the study monitor, auditor, representative from any regulatory authority, as well as the appropriate Ethical Committee are permitted to review the subject's primary medical records including laboratory test result reports, ECG reports, admission and discharge summaries, AE and SAE reports occurring during the study

Sample size

The study is designed to show that the vitamin-e group, compared to the control group, has neither lower nor higher proximal migration (y-translation) than the clinically relevant migration threshold of 0.2 mm[9]. A non-inferiority power analysis that with a power of 90% will show that the mean for the proximal migration at 2 years in the vitamin-e group is the same as the mean for the control group requires a sample size of 18 subjects in each group. This assumes that both groups has a common within-group standard deviation of 0.21, estimated from one of our previous studies [28], and that a difference of 0.2 mm or less is clinically irrelevant as reported in a recent meta-analysis [9]. The alpha (2-tailed) is set at 0.05. We will include 25 patients in each group (50 total) to allow for loss to follow-up and loss of data due to the technical nature of RSA.

Analysis

The analyses will be performed on the basis of the intention-to-treat principle, and all patients who are allocated to either group will be included in the analysis, regardless of actual surgery performed. Descriptive statistics (means and standard deviations) will be used to describe the patient characteristics and outcome variables at the measurement points. We will use the Student's t-test and Levene's test for comparison of the endpoints with 95% CI presented. An analysis of covariance (ANCOVA) of the primary endpoint will also be used to reduce variance, adjusted for exposure variable (control group/vitamin-e group) and stratification factors (male/female and <65/ ≥65 years). For subjects that withdrawn from the study before completion, the data from the last observation will be carried forward (imputed). The analyses will be performed with SPSS 22.0 for Windows (SPSS, Chicago, Illinois) statistical software.

Ethics and dissemination

The ethical committee at Karolinska Institutet has approved the study. The first results from the study will be disseminated to the medical community via presentations and publications in relevant medical journals when the last patient included has been followed for 2 years. Further publications will be presented at 5 and 10 years.

References

1. Garellick, G., et al. *Swedish Hip Arthroplasty Register Annual Report 2011*. 2011 2011-10-27]; Available from: http://www.shpr.se/Libraries/Documents/%C3%85rsrapport_2011_avseende_verksamhets%C3%A5ret_2011.sflb.ashx.
2. Harris, W.H., *Wear and periprosthetic osteolysis: the problem.* Clin Orthop Relat Res, 2001(393): p. 66-70.
3. Oral, E., et al., *Wear resistance and mechanical properties of highly cross-linked, ultrahigh-molecular weight polyethylene doped with vitamin E.* J Arthroplasty, 2006. **21**(4): p. 580-91.
4. Salemyr, M., et al., *Vitamin-E diffused highly cross-linked polyethylene liner compared to standard liners in total hip arthroplasty. A randomized, controlled trial.* Int Orthop, 2015.
5. Shareghi, B., P.E. Johanson, and J. Karrholm, *Femoral Head Penetration of Vitamin E-Infused Highly Cross-Linked Polyethylene Liners: A Randomized Radiostereometric Study of Seventy Hips Followed for Two Years.* J Bone Joint Surg Am, 2015. **97**(16): p. 1366-71.
6. Lindalen, E., et al., *E-vitamin infused highly cross-linked polyethylene: RSA results from a randomised controlled trial using 32 mm and 36 mm ceramic heads.* Hip Int, 2015. **25**(1): p. 50-5.
7. Kärrholm, J., et al., *Does early micromotion of femoral stem prostheses matter? 4-7-year stereoradiographic follow-up of 84 cemented prostheses.* J Bone Joint Surg Br, 1994. **76**(6): p. 912-7.
8. Selvik, G., *Roentgen stereophotogrammetry. A method for the study of the kinematics of the skeletal system.* Acta Orthop Scand Suppl, 1989. **232**: p. 1-51.
9. Pijls, B.G., et al., *Early proximal migration of cups is associated with late revision in THA: a systematic review and meta-analysis of 26 RSA studies and 49 survivalstudies.* Acta Orthop, 2012. **83**(6): p. 583-91.
10. Malchau, H., C.R. Bragdon, and O.K. Muratoglu, *The Stepwise Introduction of Innovation into Orthopedic Surgery The Next Level of Dilemmas.* Journal of Arthroplasty, 2010.
11. Vijayananthan, A. and O. Nawawi, *The importance of Good Clinical Practice guidelines and its role in clinical trials.* Biomed Imaging Interv J, 2008. **4**(1): p. e5.
12. Schulz, K.F., D.G. Altman, and D. Moher, *CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**: p. c332.
13. Chan, A.W., et al., *SPIRIT 2013 statement: defining standard protocol items for clinical trials.* Ann Intern Med, 2013. **158**(3): p. 200-7.
14. Boden, H., et al., *Total hip arthroplasty with an uncemented hydroxyapatite-coated tapered titanium stem: results at a minimum of 10 years' follow-up in 104 hips.* Journal of Orthopaedic Science, 2006. **11**(2): p. 175-9.

15. Valstar, E.R., et al., *Guidelines for standardization of radiostereometry (RSA) of implants.* Acta Orthop, 2005. **76**(4): p. 563-72.

16. Söderkvist, I. and P.A. Wedin, *On condition numbers and algorithms for determining a rigid-body movement.* Bit, 1994(34): p. 424-36.

17. DeLee, J.G. and J. Charnley, *Radiological demarcation of cemented sockets in total hip replacement.* Clin Orthop Relat Res, 1976(121): p. 20-32.

18. Brooker, A.F., et al., *Ectopic ossification following total hip replacement. Incidence and a method of classification.* J Bone Joint Surg Am, 1973. **55**(8): p. 1629-32.

19. Harris, W.H., *Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation.* J Bone Joint Surg Am, 1969. **51**(4): p. 737-55.

20. Nilsdotter, A.K., et al., *Hip disability and osteoarthritis outcome score (HOOS)--validity and responsiveness in total hip replacement.* BMC Musculoskelet Disord, 2003. **4**: p. 10.

21. Davis, A.M., et al., *Comparative, validity and responsiveness of the HOOS-PS and KOOS-PS to the WOMAC physical function subscale in total joint replacement for osteoarthritis.* Osteoarthritis and Cartilage, 2009. **17**(7): p. 843-7.

22. Burström, K., M. Johannesson, and F. Diderichsen, *Swedish population health-related quality of life results using the EQ-5D.* Qual Life Res, 2001. **10**(7): p. 621-35.

23. Rabin, R. and F. de Charro, *EQ-5D: a measure of health status from the EuroQol Group.* Ann Med, 2001. **33**(5): p. 337-43.

24. Chaganti, R.K., et al., *Elevation of serum tumor necrosis factor alpha in patients with periprosthetic osteolysis: a case-control study.* Clin Orthop Relat Res, 2014. **472**(2): p. 584-9.

25. Bergin, P.F., et al., *Comparison of minimally invasive direct anterior versus posterior total hip arthroplasty based on inflammation and muscle damage markers.* J Bone Joint Surg Am, 2011. **93**(15): p. 1392-8.

26. Rosen, H.N., et al., *Serum CTX: a new marker of bone resorption that shows treatment effect more often than other markers because of low coefficient of variability and large changes with bisphosphonate therapy.* Calcif Tissue Int, 2000. **66**(2): p. 100-3.

27. Harris, P.A., et al., *Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.* J Biomed Inform, 2009. **42**(2): p. 377-81.

28. Salemyr, M., et al., *Porous titanium construct cup compared to porous coated titanium cup in total hip arthroplasty. A randomised controlled trial.* Int Orthop, 2015. **39**(5): p. 823-32.

Acknowledgements

We gratefully acknowledge the support of our institution and department and most of all our research nurses Helene Sjöö, Paula Kelly-Pettersson, Marie Ax and Lise-Lotte Widmark

Authors' contributions

OS conceived the original study and developed the protocol with AR, GC, TE, OM, MS, HB. OS led the writing of the manuscript, with contributions from AR, GC, TE, OM, MS, HB. All authors contributed to the editing and redrafting.

Funding statement

The study will be supported from these foundations: Åke Wiberg stiftelse, Loo and Hans Ostermans Stiftelse, Sven Norén foundation, and The regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet. Biomet will partially fund the RSA examinations in the study but has no further input or participation in the trial.

Competing interests

None.

Ethics approval

Approved by the Ethics committee at the Karolinska Institute, Stockholm, Sweden

Data sharing statement

No additional data are available.

	< 2m	-2 v	0	+1 d	5d	3 m.	1 y	2 y	5 y	10 y
	Screening	Inclusion	Randomization and surgery	POD1	End of In-pt stay	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up
Screening for eligibility	x									
Informed consent		x								
Baseline data		x								
Randomization			x							
X-ray		x		x			x	x	x	x
RSA				x		x	x	x	x	x
HHS		x					x	x	x	x
HOOS		x					x	x	x	x
VAS		x					x	x	x	x
EQ-5D		x					x	x	x	x
Adverse events			x	x	x	x	x	x	x	x
Blood test		x		x		x	x	x	x	x

X-ray= Anterioposterior and lateral radiographs
RSA= Radiostereometry
HHS= Harris hip score
EQ-5D = Quality of life score
VAS= Visual Analogue Scale for hip pain
HOOS= Hip Osteoarthritis Outcome Score
Bloodtest =Serum C-terminal telopeptide of type I collagen (SCTx), pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (1CTP), C-reactive protein (CRP), IL-6, Hb
89x28mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on 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	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	na
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	13
	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)	na

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
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, noninferiority, exploratory)	5
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	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
	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)	na
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	na
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	6-7
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)	Figure 1

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	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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	5
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	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	na
Methods: Data collection, management, and analysis			
Data collection methods	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	8-9
	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	8-9

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	8-9
Statistical methods	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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	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	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	8
	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	na
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	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	na
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9-10
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)	na

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	5
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
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	na
Dissemination policy	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	9-10
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	na
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	na
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	na

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.