E-Poly versus Conventional HXLPE Liners for Total Hip Arthroplasty

Statistical Analysis Plan (SAP)

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Content

1. Introduction

This SAP is drafted by Kristian Kjærgaard with input from the other authors as listed on the first page. All authors have agreed on the final version of the SAP. Guidance on choice of statistical model was provided by Epidemiology, Biostatistics and Biodemography Department of Public Health University of Southern Denmark, J.B. Winsløws Vej 9B, DK-5000 Odense C.

This document describes how data will be described/presented and analysed for use in the article manuscript. Information provided here is written before data has been examined and is meant as a reference approach, and description and analyses may deviate if data require so.

2. Protocol summary

2.1. Background

Total hip replacement (THR) is one of the most common and successful procedures in joint replacement surgeries. In Denmark (DK) alone, around 9,000 patients receive a primary THA each year, revision rate is stable at 12-14%, and more than 75% of all primary THA last 20 years or more (1). Patients are often able to return to their previous profession within 1-14 weeks after surgery (2).

The two major causes of revision are aseptic loosening and dislocation, and the two together account for more than half of the revisions in 2015 in DK (1). To further improve THA survival rate, it is natural to investigate options for delaying or eliminating aseptic loosening and reducing dislocation.

This protocol aims to investigate the effect of material choice and head size on wear which may play a role in aseptic loosening. Moreover, clinical outcome and patient reported outcome measures (PROM), and a new method to assess wear are also investigated.

2.2. Objective

The objective of the study is to investigate liner wear, cup migration, and clinical outcome using a factorial design. Treatment groups are E-Poly versus ArComXL liners, and 36 mm versus 32 mm head size.

2.3. Specific research questions

Specific research questions regarding head penetration (primary outcome)

1. Does vitamin E diffused HXLPE (E-Poly) liners for THA show less penetration than conventional HXLPE liners (ArComXL) 5 years after surgery?
2. Do 36 mm heads for THA show more penetration than 32 mm heads up to 5 years after surgery?

Specific research questions regarding cup migration (secondary outcome)

3. Does the acetabular cup show less migration in relation to the pelvis, if the liner material is vitamin E diffused HXLPE (E-Poly) compared to conventional HXLPE (ArComXL) at 5 years after surgery?
4. Does the acetabular cup show more migration in relation to the pelvis, if the head size is 36 mm compared to 32 mm at 5 years after surgery?

Explorative outcome

5. Does clinical outcome and patient-reported outcome in patients with 36 mm head size improve more than in patients with 32 mm head size 5 years after surgery?

2.4. Trial design

The design used is a 2×2 factorial design with four groups as shown in the table below. Subjects received either an E-Poly or an ArComXL liner with a femoral head size of either 36 mm or 32 mm.

	Group 1	Group 2	Group 3	Group 4
Liner material	E-Poly	E-Poly	ArComXL	ArComXL
Head size	36 mm	32 mm	36 mm	32 mm

2.5. Participants

Patients were included from Odense University Hospital (OUH) and the former Middelfart Sygehus (now part of OUH) by three consultant orthopaedic surgeons. Inclusion and exclusion criteria are listed as follows.

Inclusion criteria are

- Patient is considered eligible for THA by an orthopaedic surgeon
- Reason for eligibility is unilateral primary idiopathic osteoarthrosis
- Choice of prosthesis is uncemented THA
- Age 40-70 years of age
- Cup size ≥ 54 mm

Exclusion criteria are

- Severe anteversion of femoral neck
- Dysplasia with Centre-Edge angle < 20°
- Malignancy
- Previous radiotherapy
- Any kind of physical or psychological illness renders it impossible for the patient to take part in our usual rehabilitation programme
- Complications during surgery that require the use of shell screws or cerclage around femur.

2.6. Interventions

2.6.1. Surgery

Standard posterior approach, cup/stem selection, cup/stem placement, antibiotic. Cup press fitted after a line to line-reaming at an optimal angle of 45 degree. Placement of ten tantalum beams (0.8 mm in diameter) in the periacetabular bone, ilium, ischium, and pubic bone.

2.6.2. Components

Stem: Biomet®, BiMetric uncemented stem. Head: 32 and 36 mm heads. Cup: Biomet®, Exceed ABT. Liner: Biomet® ArComXL, 32 and 36 mm liners or E-Poly, 32 and 36 mm liner. During the operation the patient had tranexamic acid and antibiotics.

2.6.3. Postoperative care

The rehabilitations and pain management will follow the orthopaedic unites usual care standard. Discharge criteria are when the patient can walk 50 meters on even surface and ambulate stairs.

2.7. Outcomes

2.7.1. Primary outcome

The primary outcome is head penetration from baseline to 5 years postoperatively, assessed using roentgen stereogram analysis (RSA).

In addition to this, mean polyethylene wear from 1 year (after bedding-in) to 5 years is of interest.

2.7.2. Secondary outcome

The secondary outcome is mean migration of the acetabular cup in relation to the pelvis from baseline to 5 years postoperatively, assessed using RSA.

2.7.3. Explorative outcome

Hip function is assessed using Harris Hip Score from baseline to 5 years postoperatively (3,4). Averaged across treatment groups.

Quality of life is assessed using SF-36 and EQ-5D from baseline to 5 years postoperatively. Averaged across treatment groups.

Patient activity is assessed using UCLA Activity Score from baseline to 5 years postoperatively (5). The Likert-like scale correlates well with patient activity at population level and is analysed as continuous (5–7).

2.8. Participant timeline

Overall timing and frequency of data collection is shown in the table below. Baseline RSA measurements are performed on the third day after surgery.

			Study periods				
	Enrolment	Allocation	Post-allocation				Close-out
Time point	-2w	0	3m	1y	2y	3y	5y
Enrolment							
Eligibility screening	O						
Informed consent	O						
Allocation		O					
Intervention							
Surgery, total hip arthroplasty		O					
Assessments							
Baseline data		O					
RSA		O	O	O	O		O
HSS, SF-36, EQ-5D, UCLA Activity Score	O		O	O		O	O
Adverse events							O

2.9. Sample size

This study was originally designed and powered as a parallel group study with four arms.

We expect a wear reduction from 0.05 mm/year for ArComXL to 0.0005 mm/year for E-Poly (8). By using the formula

$$n = \frac{2(t_{2\alpha}) \times \delta^2}{\pi^2}$$

where n is number of patients required in each group, $t_{2\,\alpha}$ and t_β are parameters for type I and type II errors, δ is standard deviation, and π is minimal clinically important difference (9). We chose a minimal relevant difference of 0.05 mm/year, type I error (α) of 5%, and type II error (β) of 20%.

This results in $n \approx 15$, and at least 15 patients should be included in each group. We include 25 patients in each of the four groups (total of 100 patients), as is the international standard for this type of study.

2.10. Randomisation

Patients were randomised to either E-Poly or ArComXL liner with either 36 mm or 32 mm femoral head size. Using computer randomisation, 25 labels for each group were randomised and placed in sealed envelopes in one block. During surgery, just before insertion of the acetabular cup, the envelope was opened.

2.11. Blinding

The study is blinded for participants, care provider, investigator, and outcomes assessor.

2.12. Ethical considerations

This study has been approved by The Regional Scientific Ethical Committees for Southern Denmark (ID: S-20080151), The Danish Data Protection Agency (ID: 14/35949) and complies with The Declaration of Helsinki.

3. Data presentation and analysis

This chapter describes how data will be described/presented and analysed for use in the article manuscript. Information provided here is written before data has been examined and is meant as a reference approach, and description and analyses may deviate if data requires so.

3.1. Analysis population

Descriptions and analyses are performed as intention to treat (ITT) and per-protocol (PP) analyses.

3.1.1. Intention to treat (primary analysis)

All patients allocated to a treatment group are used. Missing data is not substituted.

3.1.2. Per-protocol

The per-protocol population is a subset of intention to treat, where the subjects attended all assessments and follow-up visits. Subjects, who did not attend all assessments or have otherwise missing data, are excluded from this analysis population.

3.2. Baseline data

Baseline data are reported for the whole study population as well as for each of the four individual treatment groups. Baseline data are not subject to statistical tests.

The proposed baseline data table is shown below.

Parameter	Total	Treatment groups			
		E-Poly + 36 mm	E-Poly + 32 mm	ArComXL + 36 mm	ArComXL + 32 mm
	n = ?	n = ?	n = ?	n = ?	n = ?
Male, n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age (years)	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)
BMI (kg/m2)	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)
ASA group					
1	n (%)	n (%)	n (%)	n (%)	n (%)
2	n (%)	n (%)	n (%)	n (%)	n (%)
3	n (%)	n (%)	n (%)	n (%)	n (%)
4-6	n (%)	n (%)	n (%)	n (%)	n (%)
Duration of operation (minutes)	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)
Blood loss (mL)	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)
Duration of hospitalisation (days)	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)
Cup size (mm)	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)
Preoperative patient-reported outcomes					
HSS	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)
EQ-5D-3L	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)
SF-36	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)
UCLA	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)

Proposed baseline data table. Data are means (m (SD) for mean and standard deviation) or numbers (n (%) for number and percentage).

3.3. Primary outcome

Head penetration is expressed as the distance the head has penetrated the liner between first and subsequent measurements. The penetration will be presented as exemplified below.
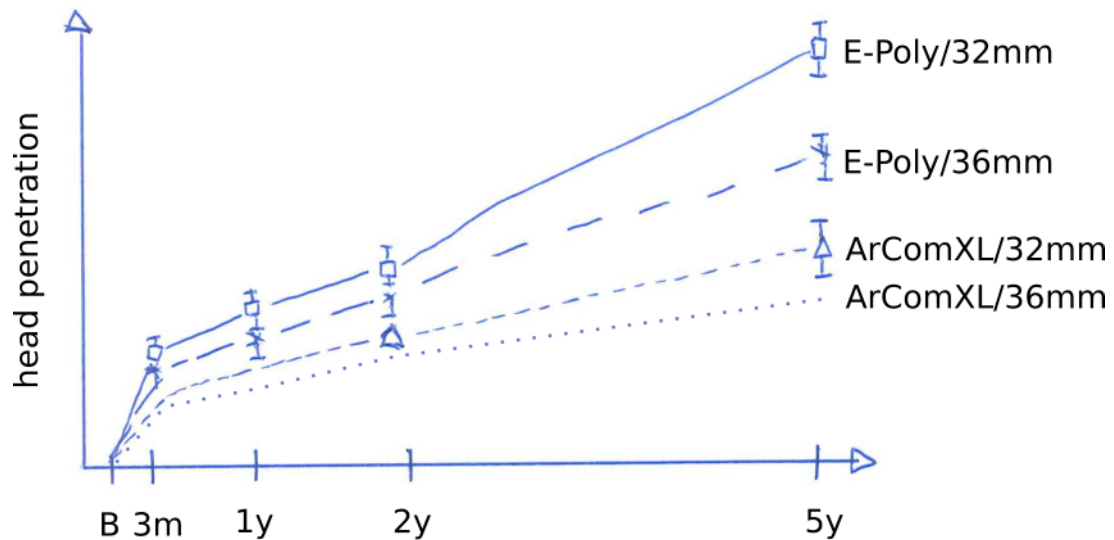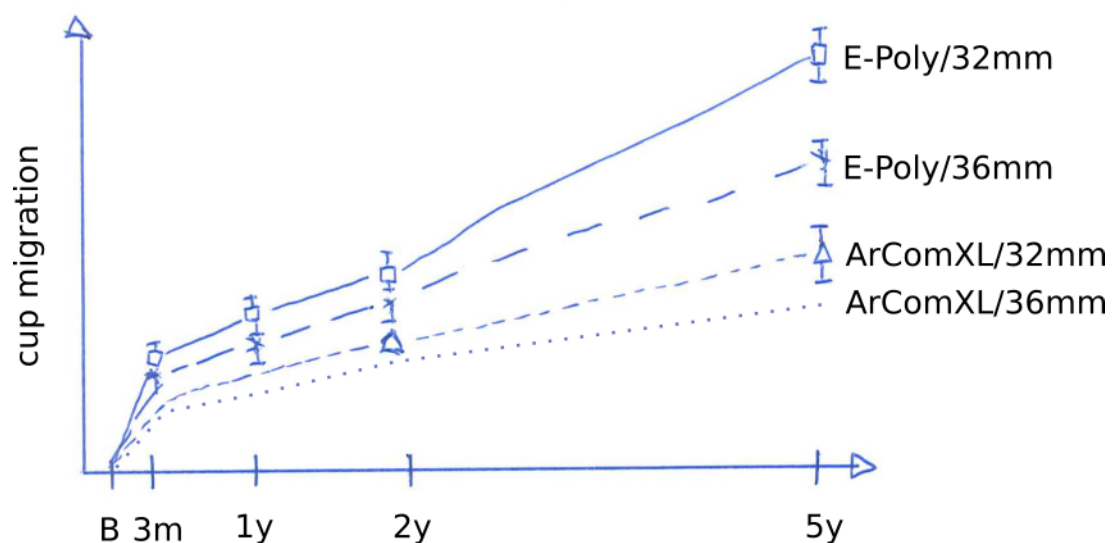

Head penetration is analysed using mixed model analysis with properties as:

Parameter	Description
Observation	Distance from centre of femoral head to centre of acetabular cup
Fixed effects	Material, head size, time
Random effects	Patient.

Exact model selection is based on nested models and maximum likelihood estimation.

3.4. Secondary outcome

Cup migration is expressed as the overall migration of the cup in relation to the pelvis between first and subsequent measurements. The penetration will be presented as exemplified below.

Cup migration is analysed using a mixed model analysis with properties as follows:

Parameter	Description
Observation	Distance from acetabular cup to reference point in acetabular tantalum point (numerical).
Fixed effects	Material, head size, time.
Random effects	Patient.

Exact model selection is based on nested models and maximum likelihood estimation.

3.5. Exploratory outcomes

3.5.1. Clinical outcome, quality of life, and patient activity

Clinical outcome is assessed using Harris Hip Score (HHS). HHS yields an integer between 0 and 100.

Quality of life is assessed using SF-36 Health Survey that yields two real number indices: one for physical health and one for mental health.

Quality of life is also assessed using EQ-5D-3L that is a utility index for use in health economics.

The indices of HSS, SF-36 and EQ-5D are similar in data properties. Data is presented as shown below and analysed using a mixed model analysis with parameters as below.
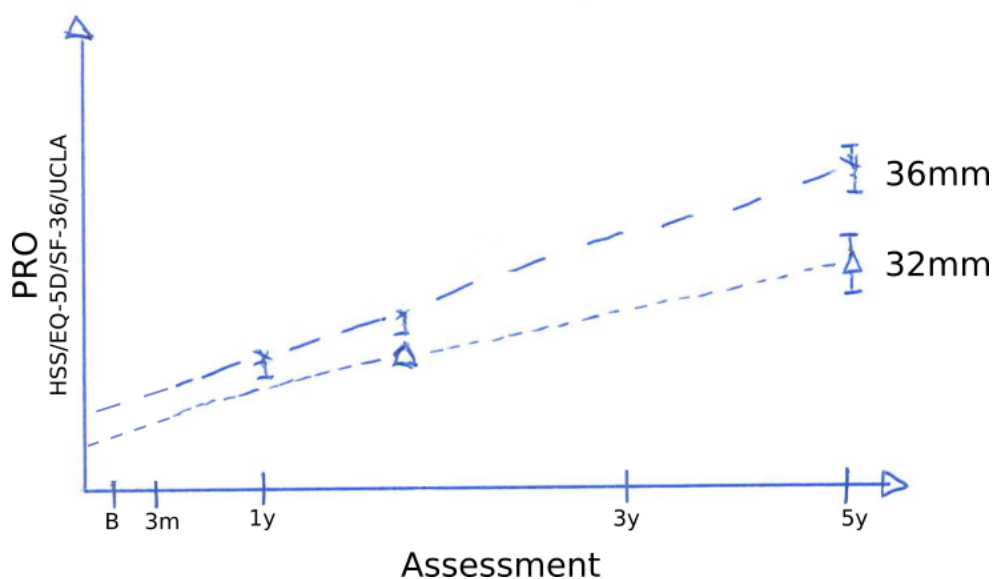
Liner material is not included in this model as we expect material to have little or no impact on clinical outcome and quality of life.

Mixed model analysis for clinical outcome (HSS) and quality of life (SF-36 and EQ-5D), and patient activity (UCLA Activity Score):

Parameter	Description
Observation	PRO index.
Fixed effects	Head size, PRO index at baseline
Random effects	Patient.

Exact model selection is based on nested models and maximum likelihood estimation.

Patient activity is assessed using the UCLA Activity Score which is a 10 level Likert-like scale (ordered categorical scale) (5). The scale is a priori considered numerical, and analyses are performed as for the other patient scores.

3.6. Adverse events

Adverse events are shown below. Adverse events are reported with number and standard deviation, and the hypothesis that the observation is caused by a certain liner-head size combination is reported with a p-value.

Adverse events are

- Luxation, both closed and open relocations
- Deep infection
- Periprosthetic fracture
- Revision surgery

3.7. Dissemination policy

It is our intent to publish selected results from the analyses described in this document in an international recognised peer-reviewed journal. All results from all analyses described in this document will be attached as appendices to the publication--regardless of significance.

4. Appendix

4.1. Assessment window ranges

Assessment	Window
3rd-day	Within first two weeks after surgery
3-month	After two weeks, within six months
1-year	After six months, within one year and six months
2-year	After one year and six months, within two years and six months
3-year	After two years and six months, within four years
5-year	After four years, within six years.

The average time and standard deviation from baseline to given assessment will be stated.

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