Effect of Single *vs* Multiple Prophylactic Antibiotic Doses on Prosthetic Joint Infections Following Primary Total Hip Arthroplasty in Patients with a Fracture at Public and Private Hospitals in Denmark

Statistical Analysis Plan for the Nationwide Cross-Over, Cluster Randomized, Non-inferiority The Pro-Hip-Quality Trial

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BACKGROUND AND RATIONALE

A feared complication after total hip arthroplasty (THA) is prosthetic joint infection (PJI), associated with high morbidity and mortality (1-3). Perioperative antimicrobial prophylaxis is a well-established and documented part of standard care to reduce the risk of PJI after THA(4-6). There is however no consensus regarding the duration of prophylaxis. Danish national guidelines recommend both one single pre-operative dose as well as 24 hours of antibiotic coverage as strategies for antibiotic prophylaxis practice, i.e. a single preoperative dose or a 24-hour coverage using either cloxacillin or the second-generation cephalosporin, cefuroxime (7). The choice of antibiotic agent as well as duration, varies among the different orthopedic departments in Denmark which also reflects the clinical practice internationally.

Antimicrobial resistance poses a persistent and increasing global healthcare problem due to its limited treatment options. In addition, patients may experience systemic toxicity following prolonged use of antibiotics (8-12). Therefore, there is a need for optimizing the use of antibiotics and a reduction would be beneficial, but it should be without risking more infections. No randomized trial has compared one single preoperative dose with 24 hours of antibiotic coverage in THA. This comparison is important to establish the best evidence-based practice on antibiotic prophylaxis dosages in the future and combating antimicrobial resistance.

Objectives

The primary objective of this trial is to compare the effect of single versus multiple prophylactic antibiotic doses administered within 24 hours of primary THA due to fracture on the risk of revision due to PJI within 90 days. The non-inferiority of single prophylactic antibiotic will be shown if the upper boundary of the two-sided 95% confidence interval for the Odds Ratio is less than 2.1 for the single prophylactic doses as compared with multiple prophylactic antibiotic doses.

Key secondary objectives

To compare the effect of single versus multiple prophylactic antibiotic doses administered within 24 hours of primary THA due to fracture on critical outcomes assessed up to 90 days from surgery: Serious Adverse Events (SAEs), Potential PJI referred to as *PJI-likely,* Length of stay for hospitalization (LOS), Major Adverse Cardiovascular Events, Hospital-treated infections (Other than those listed above), Community-based antibiotic use, Opioid use, Use of prescribed acetaminophen or non-steroidal anti-inflammatory drugs, Any revision after THA.

STUDY METHODS

Trial design

The Pro-Hip-Quality OA trial is designed as a pragmatic registry-based, multicenter, open-label, cross-over, cluster-randomized, non-inferiority trial (13-16). The statistical analysis plan (SAP) and trial protocol are reported in accordance with a pragmatic combination of the following CONSORT statements: 'CONSORT for trials conducted using cohorts and routinely collected data (13)', 'Pragmatic Trials (14)' 'Cluster Randomized Trials (15),' 'Randomized Crossover Trials (16)' and 'Noninferiority and Equivalence Randomized trials (17).'This pragmatic registry-based trial design (18) will include cluster randomization of 36 different clinical departments, applying a crossover design. The trial was designed as a nationwide study where all public and private orthopedic departments participated, and all eligible patients were included.

The cluster randomization with embedded cross-over design across 36 clinical centers ensures that each center will administer a specific antibiotic regimen (i.e., either single-dose or multiple-dose) for one year. After the first year, centers will switch to the alternate regimen. This design ensures that each center experiences both interventions over the two-year study, facilitating a balanced comparison between the two treatment protocols. We do not anticipate significant variations in patient characteristics between those enrolled in year 1 and year 2 of the study. This expectation encompasses consistency in key factors: patient demographics (e.g., age, sex), comorbidities, baseline health conditions, disease severity, and treatment indications. Similarly, we do not foresee substantial changes in the clinical setting or study environment over the two years, including protocols for patient recruitment, infection prevention strategies, surgical methods, diagnostic approaches, revision surgery, or access to healthcare resources. Furthermore, the crossover approach means that the sites are randomized to receive each intervention once during separate periods (i.e., study years 1 and 2) acting as their control group. This may attenuate possible imbalances and variations in site characteristics (19, 20).

Trial registration was performed at ClinicalTrials.gov (NCT05530174) in August 2022. Patient enrolment started at the first departments in September 2022 and the last in December 2022. The last patient recruitment was completed on November 30, 2024. The trial has been approved by The Danish Medicines Agency (Case number: 021091723) and The Committees on Health Research Ethics for The Capital Region of Denmark (VEK) (Case number: 21069108) with

the option to opt out of informed consent, based on that both interventions follow standardized clinical practice described in national and international guidelines.

Randomization

In this cluster randomized trial, each cluster (any specific department of orthopedic surgery or center; e.g. C_1, C_2, C_3….., C_{36}) is the unit randomized. The outcomes of interest are recorded and analyzed for each participant individually nested within the cluster. Participants fulfilling the inclusion criteria will have data treated as planned (organized) conditioning on the local department depending on the year of surgery.

The senior biostatistician was responsible for the randomization process: Each center was allocated based on a code provided by the senior biostatistician responsible and reported to a central database. The randomization and allocation procedure will be known for the given year. To minimize the risk of protocol violations, the steering committee—comprising the study coordinator JSL, the principal investigator AAA, and the sponsor SO, conducted meetings with all departments before the recruitment of the first patient and again after the first year to ensure effective implementation of the cross-over. Local study coordinators have been assigned at each study site prior to study start. The local study investigators consist of a team of an orthopedic surgeon or anesthesiologist and a nurse. The team was responsible for the change of the standardized departmental instructions for antibiotic prophylaxis according to randomization, prior to study start. Furthermore, they have been responsible for the organization and thorough information of all relevant personnel at the respective study sites. Relevant material has been developed and organized by the authors and distributed to the local study coordinators. Meetings were held in the summer and autumn of 2022. New meetings were done one year later before the cross-over of treatment was planned. Furthermore, any protocol deviations or violations which could occur was reported by the local investigators to the principal investigator and sponsor at 6-month evaluations.

The ITT principle was implemented for all participants allocated to a treatment group ($X_{\text{Single-dose}}$ and $X_{\text{Multiple-dose}}$, respectively). All participants will be followed up, assessed, and analyzed as members of that group. This approach ensures that the results reflect real-world clinical scenarios and maintains the integrity of the randomized design. The study was blinded for the statistical analyst TH but not the patients, investigators, nor departments.

Sample size and power calculation

Based on existing Danish national statistics, we anticipate that we will be able to include app. 2,000 eligible individuals having a THA after hip fracture when enrolling consecutively across 36 clinical centers over the two-year period; i.e., that would potentially enable a pragmatic intention-to-treat (ITT) population of up to 1,000 patients in each group (i.e., up to 1,000 individuals exposed to single-dose antibiotics only).

Choice of the non-inferiority design will enable the deliverance of substantial evidence to change clinical practice if the prevention of PJI with a single dose of prophylactic antibiotic is "no less effective than" antibiotic practices of longer duration (i.e., multiple doses). Members of the Danish orthopedic community have been involved in deciding the potentially increased serious infection rate difference, we are willing to tolerate. Because the sample size is based on the standard flow of THA within the Danish real-world setting, we did not conduct formal power or sample size calculations. Initially, we defined "appreciably worse" serious infection rates and the chances of an erroneously significant result, that is, a false positive, that the medical community will tolerate. The PJI due to fracture rate in Denmark is expected to be 2.2%, (95% CI: 1.1 to 4.3) (21). It was decided that we will be willing to tolerate a potentially increased serious infection risk difference of up to 0.75% (7.5‰ more having a PJI).

Confidence intervals and p-values

All 95% confidence intervals (95%CIs) and *P*-values will be two-sided. We will not apply explicit adjustments for multiplicity, rather we will interpret the key secondary endpoints with caution.

Primary endpoint: If we assume that the PJI risk is similar in the two groups (with 1,000 patients in each) we expect to achieve a precision (narrowness) in the two-sided 95% confidence intervals around the Odds Ratio (OR=1.000) from a Generalized Linear Mixed Model (GLMM), with 95% limits from 0.535 to 1.868; with a Random Effects factor for the 36 individual centers, and Fixed Effect factors for group, period and the interaction between group and period (Group×Period). This was validated through multiple simulations. The same simulations were carried out with a population of 800 in each group for sensitivity, resulting in 95 % limits around the Odds Ratio (OR=1.000) from 0.497 to 2.014. Based on the CIs from these simulations, which have very little variability, and the clinical importance of PJIs, a pragmatic non-inferiority margin should be chosen. Thus, it was decided that non-inferiority will be shown if the upper limit of the

two-sided 95% confidence interval for the odds ratio (derived from the GLMM) is less than 2.1 for the single dose as compared with the multiple doses group.

In addition to the simulations, a bootstrap analysis of 1,000 iterations using the 1,000-patient simulation yielded a 95% confidence interval from 0.457 to 1.972. The proximity of the bootstrap result (1.972) to the proposed margin (2.1) demonstrates that the margin accommodates the variability in the trial design while maintaining sufficient statistical power and clinical importance.

With this approach, we anticipate that the results from this cluster randomized, cross-over, non-inferiority trial will generate high-quality evidence that may advance and inform clinical practice on antibiotic prophylaxis dosages in the future.

Statistical interim analysis and stopping guidance

No statistical interim analysis was planned on any endpoint (index surgery to 90-day follow-up) between the two groups (i.e., single-dose and multiple-dose) between the two groups (single-dose and multiple-dose), as it was assessed that there would not be sufficient statistical power to conduct a meaningful interim analysis. Performing such an analysis could lead to premature conclusions, posing ethical concerns regarding participant safety and treatment efficacy. Therefore, no interim analysis was planned to uphold our study's scientific integrity and ethical responsibility. The final deadline for patient recruitment was set to 30. November 2024, corresponding to a 2-year study period for the departments that started patient inclusion as of December 1st, 2022.

Timing of final analysis

The final analysis for the between-group comparison (Single-dose vs. Multiple) for the primary endpoint (index surgery to 90-day follow-up) is planned to be performed after each randomized patient has completed the 90-day follow-up, corresponding to March 1st, 2025. The main publication of the trial will be prepared when these data have been received and cleaned. The data is anticipated to be received by May 2025, and the cleaning will be completed by July 2025. In subsequent manuscripts, including exploratory outcomes, secondary longer-term endpoints will be analyzed when the 12 months (corresponding to March 2026) and 60 months (March 2030) have been reached for all randomized patients, followed by preparation of manuscripts with one and five-year outcomes, respectively.

Timing of secondary outcome assessments

The time point of the assessment of the primary and secondary outcomes is within 90 days after index surgery: SAES, PJI-likely, LOS, MACE, Hospital-treated infections (other than PJI and PJI-likely), Community-based antibiotic use, use of acetaminophen or non-steroidal anti-inflammatory drugs, and any revision after THA. The outcome of opioid use will be evaluated within 6 months before index surgery and within 90 days after index surgery.

STATISTICAL PRINCIPLES

Adherence and protocol deviations

This is a pragmatic randomized trial, applying the intention-to-treat (ITT) principle. The main analysis uses the treatment policy estimand, which quantifies the average treatment effect among all the centers who had undergone randomization, regardless of adherence to treatment or crossover (i.e., the intention-to-treat population). The ITT approach ensures that the results reflect real-world clinical practice, accounting for adherence variations and any protocol deviations (22). Deviations from the protocol and adherence will be monitored and documented during data management, but they will not exclude participants from the primary analysis.

Analysis populations

The primary analyses will be based on the ITT population based on the Full Analysis Set; i.e., all patient's undergoing the prespecified surgery using the antibiotic dose corresponding to the specific cluster and year (cross-over, cluster randomization) (22). Accordingly, participants allocated to a treatment group ($X_{\text{Single-dose}}$ and $X_{\text{Multiple-dose}}$, respectively) will be followed up, assessed, and analyzed as members of that cluster, irrespective of the actual antibiotic regimen used in the specific clinic (i.e., independent of physicians' withdrawals and cross-over phenomena) (23, 24).

TRIAL POPULATION

Screening data

The total number of patients enrolled during the trial period of 2 years, will be collected and reported according to CONSORT flowchart (see **Figure 1**, Mockup below). Furthermore, the number of ineligible patients including reason for ineligibility and patients with loss to follow-up will be reported.

Eligibility

All patients ≥ 18 years receiving a primary THA conforming to the following inclusion and exclusion criteria are considered eligible for the trial.

Inclusion Criteria:

1. All patients receiving a primary THA due to either acute or sequelae of proximal femoral or acetabular fractures

Exclusion Criteria:

1. Patients receiving a primary THA due to primary and secondary causes of osteoarthritis, except acute/ sequelae from proximal femoral or pelvic fractures
2. Patients receiving a primary THA due to bone tumor or metastasis

Acute or sequelae of proximal femoral or acetabular fractures include:

Recruitment

The CONSORT flowchart will comprise number of patients screened, excluded (with reasons) eligible for inclusion in the trial, randomized, receiving their allocated treatment and lost to follow-up (with reasons), included in ITT analysis. The CONSORT flowchart is depicted in Mockup ***Figure 1.***

Follow-up

Follow-up are planned based on routine treatment practice and registration in administrative national validated databases and registries. Therefore, participation will not result in additional hospital visits.

Timing of loss to follow-up will be presented in the CONSORT flowchart with numbers and reasons for loss to follow-up given at the 90 days (primary end point) outcome assessment. Furthermore, the number (with reasons) of loss to follow-up during the course of the trial will be summarized by treatment group.

Baseline patient characteristics

The following data will be obtained from the patient at baseline: sex, age, height, weight, Body-mass index, American Society of Anesthesiologists classification (ASA), Comorbidity status, socioeconomic status (SES), whether the patient has diabetes (ICD-10 codes E10-E14 from DNPR), year of surgery, antibiotic agent applied as prophylaxis, duration of surgery, type of fixation, type of prosthesis and type of operating room as elaborated in Mockup **Table 1**.

Comorbidity status will be evaluated using the Charlson Comorbidity index Score (CCI) (25). Information about comorbidities will be collected from DNPR (26, 27) after linkage using CRS(28) (26). The CCI score will be calculated based on all primary and secondary diagnoses from hospitalizations and outpatient visits registered as ICD-10 codes in the DNPR over a 10-year period before the primary THA. Although the positive predictive value (PPV) for diagnosis and treatment varies substantially in the DNPR (26), the overall PPV for the 19 Charlson conditions has been found to be 98.0% (29). For each patient that undergoes surgery during the trial period, information on SES will be based on retrieved information on marital status, cohabitation, highest obtained level of education, occupation, family income, and a measure of family liquid assets on the index date retrieved from Statistics Denmark (30). SES will be categorized into the following three domains: educational level, income, and employment status. Educational level will be categorized as low, medium, or high. Low includes no education or high school completed, medium includes vocational education or higher preparatory programs, and high includes a bachelor's or higher degree. Cohabitation status will be classified as living alone, cohabiting, or other. Cohabitation status will be classified as living alone or cohabiting with an adult partner (married, unmarried, or living in multifamily housing). Wealth will be determined using either family income (total in a co-housing family before taxes) or family liquid assets (including cash property value, bank deposits, and securities such as stocks, bonds, and mortgage deeds), depending on the patient's age. For patients aged ≥65 years, the standard retirement age in Denmark, family liquid assets will be used, as income may no longer accurately reflect financial status. For patients aged <65 years, family income will be used. Family income at the time of THA is calculated as the average annual pre-tax income in kroner (1 Euro ≈ 7.5 Kroner) over the 5 years prior to surgery. Income is classified as above or below the mean for each age group (0-59, 60-69, 70-79, 80+). To account for annual variations, both measures will be averaged over the 5 years preceding the primary THA. Family income and liquid assets will be each categorized into tertiles (low, medium, and high) for their age and combined into a single wealth variable. Numbers and percentages will be calculated and

presented for categorical variables. Means and SD will be computed and presented for continuous variables if data follows a normal distribution. In case, continuous variables are not normally distributed, median and interquartile range will be calculated. No tests of statistical significance will be conducted for any baseline characteristic variable. However, imbalances with clinical importance will be noted. The baseline characteristics will be presented as illustrated in Mock-up **Table 1.**

ANALYSIS

A flow diagram illustrating dataset construction, including codes where applicable (Appendix A). Every outcome was defined according to specific codes in well-defined registries and database (Table Appendix B).

Interventions

Patients will have received either one single dose of preoperative antibiotic (i.e. single dose) or one preoperative antibiotic dose followed by three postoperative dosages administered within the first 24 hours after index surgery (i.e. multiple dose) .The dosages and antibiotic agents applied have also been outlined in the protocol article (31) as well as the registration on ClinicalTrials.gov, registration ID NCT05530551 and are the following:

Antibiotic Practice Treatment A and B

		Single-Dose (A) / Multiple-Dose (B)	Multiple-Dose(B)		
Antibiotic	**Weight**	**Preoperative dose**	**6 hours postoperative**	**12 hours postoperative**	**18 hours postoperative**
Cloxacillin i.v.	< 120 kg	2 g	1 g	1 g	1 g
	> 120 kg	3 g	2 g	2 g	2 g
Cefuroxime i.v.	< 120 kg	1.5 g	750 mg	750 mg	750 mg
	> 120 kg	3 g	1.5 g	1.5 g	1.5 g

Possible transition to oral postoperative antibiotic treatment.

The first postoperative dose of cloxacillin or cefuroxime must be administered intravenously.

Antibiotic	**12 hours postoperative**	**18 hours postoperative**

Dicloxacillin oral	1 g	1 g
Amoxicillin and clavulanic acid oral	875 mg/125 mg*	875 mg/125 mg*

No weight adjustment.

*If the center or region does not have access to amoxicillin and clavulanic acid 875/125 mg, a dose of 1 g / 125 mg (i.e. amoxicillin 500 mg + amoxicillin and clavulanic acid 500 mg/125 mg) may be used.

Antibiotic Practice in cases of cephalosporin allergy or general beta lactam allergy

Antibiotic	**Weight**	**Preoperative dose**	**8 hours postoperative**	**16 hours postoperative**
Clindamycin i.v.	< 120 kg	900 mg	300 mg*	300 mg*
	≥ 120 kg	900 mg	600 mg*	600 mg*

*The postoperative dose may be administered orally in the same doses.

Outcome definitions and endpoints

All Danish residents and citizens are assigned a unique and permanent individual identification number (CPR number) at birth or on immigration. The Civil Registration System number goes through all Danish registries and enables an unambiguous linkage between registries and complete individual level follow-up (26, 27). The primary and key secondary outcomes will be included as endpoints, as illustrated in Mockup Table 2.

Primary endpoint: Incidence of PJI: The definition of PJI is based on revision surgery within 90 days of primary THA. Revision surgery is defined as a new surgical intervention the first time after the primary intervention including debridement alone or in combination with complete or partial removal or exchange of any implants.

PJI is defined as the presence of at least one of the following three criteria:

1. Two or more intraoperative deep-tissue samples of phenotypically indistinguishable bacteria isolated from at least three deep-tissue samples (32)

And/or

2. One or more positive intraoperative samples from a closed fluid aspirate AND a biopsy (fluid AND tissue) of phenotypically indistinguishable bacteria isolated (32)

And/or

3. A PJI when an indication of deep infection is reported to DHR by the surgeon upon revision surgery (33)

The definition of PJI is based on EBJIS(32), an International Consensus(34), and an algorithm developed to capture cases with PJI using national databases (35). For this trial, the definition of PJI is modified to include the most widely accepted definition of PJI with the main importance set to intraoperative cultures (36, 37). The definition of PJI by EBJIS(32) and the consensus from EBJIS and MSIS classifications of PJI(34) has been modified to exclude histological examination of intraoperative tissue biopsies, erythrocyte sedimentation rate, white blood cell count and biomarker analysis in joint fluid as these analyses are not routinely performed in Denmark. Furthermore, sinus tract communication with the joint or prosthesis visualization will be excluded as these are related to later infections than those occurring within 90 days after index surgery.

The definition has been simplified to allow for the capture of PJI through databases and registries without review of medical files and the modifications are expected only to give minor non-significant changes for the capture of PJI (33, 35). Data will be extracted from DNRP, DHR, MiBA and HAIBA. Positive culture samples (aspirations, tissue biopsies or fluid) must be obtained from the relevant hip joint. As part of standard care, a sample of at least 5 tissue biopsies are obtained at revision surgery. All samples are sent for microbiological analysis at one of ten regional departments of clinical microbiology who have standardized methods for handling of biopsies and culturing. The cumulative proportion of patients remaining PJI-free in the two groups will be presented as illustrated in Mockup Figure 2.

Key secondary endpoints evaluated within 90 days from primary THA

1) Serious Adverse Events (SAEs)

Number of patients with one or more SAEs. SAEs are defined according to the guidelines provided by the International Council for Harmonization of Technical Requirements for Human Use (ICH-GCP) (38). SAE refers to an event involving a significant risk of death or disability of the patient (or their offspring), including, but not limited to, an event that: (1) results in death, (2) is life-

threatening – in the investigator's opinion the patient was in immediate risk of death from the adverse event when it appeared, (3) requires hospitalization or prolongs existing hospitalization (4) results in permanent or significant disability. SAEs are recorded from DNPR. The list of ICD10 codes to identify SAEs is listed in Appendix C. This list has been curated to include diagnoses that are considered clinically significant, potentially life-threatening, requiring hospitalization, or resulting in persistent or significant disability/incapacity. To ensure comprehensive coverage and adherence to international standards, any additional codes that meet the criteria for SAEs as defined by the ICH-GCP guidelines will also be included.

2) Potential PJI referred to as *PJI-likely*

Incidence of potential PJI. PJI-likely is defined as at least one of the two criteria is fulfilled:

> A: One single intraoperatively obtained positive culture obtained from reoperation (aspiration fluid OR tissue biopsy) regardless of microorganism
>
> B: One single positive culture obtained from aspiration of synovial fluid regardless of microorganism AND any antibiotic prescriptions (ATC category J01) redeemed

These definitions of PJI-likely are based on a modified version of EBJIS (32) as described previously (see primary outcome) and the study by Milandt *et al*. (39) where first-time revisions with one positive culture were found to have a higher risk of re-revision for PJI.

Cases of PJI-likely, will be captured in HAIBA and MIBA, and registration of antibiotic prescription in NPR. Positive culture samples (aspirations, tissue biopsies or fluid) must be obtained from the relevant hip joint.

3) Length of stay for hospitalization (LOS)

Length of hospital stay (continuous measure [days]) is defined as number of postoperative overnight stays, including transferals to other departments and hospitals within 24 hours. Data on LOS is acquired from DNPR.

4) Major Adverse Cardiovascular Events

Incidence of Major Adverse Cardiovascular Events (MACE). A MACE is defined a priori to include thromboembolic complications including venous thromboembolism, myocardial infarction,

atrial fibrillation and stroke based on the diagnostic ICD10 codes listed in Appendix B. VTE is defined a priori as both deep venous thromboembolisms confirmed by compression ultrasound and pulmonary embolism confirmed by spiral computed tomography (CT), ventilation-perfusion scintigraphy or pathological removal of an embolus and based on the following diagnostic ICD10 codes: I26, I80.1-I80.9, I82.1-I82.9, or T81.7B-D. Data will be extracted from DNPR.

5) Hospital-treated infections (Other than those listed above)

Patients with at least one hospital-treated infection are defined as those with first-time hospital admission for a primary or secondary infection diagnosis following discharge from the index THA surgery. Hospital-treated infections are identified from DNPR based on ICD-10 codes listed in Appendix B. The list of infections includes chronic and more rare infections, to detect possible flare-ups in any possible ongoing infections. This outcome does not include infections treated during index admission for arthroplasty surgery.

6) Community-based antibiotic use

Community-based antibiotic use (any community-treated infection or antibiotic use after discharge) is defined as at least one dispensing after discharge from index THA surgery and broad-spectrum antibiotics based on the Anatomical Therapeutic Chemical classification (ATC) codes. All antibiotics in Denmark require prescriptions from a physician. The Danish National Health Service Prescription Database has registered all reimbursed prescriptions from all community pharmacies since 2004. Medications are coded according to the ATC codes listed in Appendix B. All antibiotics in Denmark require prescriptions from a physician and these will be identified using NPR (40). We aim to specifically examine the redemption of ATC code J01E prescriptions within one week following the index operation to capture instances of post-operative urinary tract infections.

7) Opioid use

Patients who received at least one opioid prescription following primary THA surgery. All opioids in Denmark require prescriptions from a physician and these will be identified using NPR (40). The following ATC codes (including all subcodes) are included: N01AH (opioid anesthetics), N02A (opioids), N07BC02 (methadone), and R05DA04 (codeine). Given the lack of a clear definition for opioid users, we defined opioid users as patients who redeemed two opioid prescriptions within six

months prior to THA surgery. Conversely, patients who did not redeem two or more opioid prescriptions within this timeframe were classified as opioid naïve. For opioid naïve patients, opioid use post-THA is defined as the redemption of two opioid prescriptions within 90 days following surgery. We assert that two separate redeemed prescriptions confirm actual medication use. We will calculate the treatment dotation based on the number of packages and volume redeemed within 90 days post-surgery. To investigate dosages, all doses will be converted to morphine milligram equivalents using a conversion factor specific to the type of opioid (41, 42).

8) Use of acetaminophen or non-steroidal anti-inflammatory drugs

Patients who received at least one prescription for acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) following THA surgery. Prescriptions of analgesics will be identified using NPR (40). All analgesics in Denmark except 10-tablet packages of acetaminophen / ibuprofen of dose 200mg ibuprofen require prescriptions from a physician. Following ATC codes (including all subcodes) are included M01A (NSAIDs) and N02BE01 (paracetamol). Duration of treatment will be calculated based on number of packages and volume. Since there is no clear definition of acetaminophen or non-steroidal anti-inflammatory users, we define these users as patients who redeemed two prescriptions within 6 months before THA.

9) Any revision after THA

Revision surgery is defined as a new surgical intervention the first time after the primary intervention including debridement alone or in combination with complete or partial removal or exchange of any implants. Rate of revision is defined as revision due to any cause within 90 days from primary THA surgery. Any revision will be recorded from DHR and DNPR.

Analysis methods

All descriptive statistics and statistical analysis will be reported in accordance with the recommendations of the *"Enhancing the QUAlity and Transparency Of health Research"* (EQUATOR) network (43) and the CONSORT statement (44). Visual inspection (QQ-plot, histograms, and scatterplots) of the standardized residuals from the statistical model will be used to assess the assumption of normality and homogeneity of variances.

The primary analyses will be based on the Intention to Treat (ITT) population, i.e., all patients undergoing the prespecified surgery corresponding to the specific year (cross-over, cluster randomization). Two-sided 95% confidence intervals will be estimated and reported enabling (standard) superiority interpretations. The primary statistical analysis model will be based on a *Generalized Linear Mixed Model*, with a random effects factor applied indexing the clinical center (36 levels: 1, 2, 3, …, up to 36), a fixed effect will be applied for period (2 levels: 1st and 2nd year, respectively), and antibiotics group (2 levels: Single-dose and Multiple-dose, respectively), as well as the interaction between the two periods and antibiotics group (period×group; 4 levels: 2×2 levels). For the primary endpoint: Noninferiority will be shown if the upper limit of the two-sided 95% CI for the odds ratio is less than 2.1 for the single antibiotic dose as compared with multiple dose.

In addition, subgroup analyses will be performed to examine the following known and suspected baseline risk factors for PJI infection will be compared: age (≥65 versus <65 years), sex (male versus female), Anthropometric categories (BMI: ≥30 versus <30 kg/m^2), and presence of diabetes (with versus without). Additional analyses of the study will assess whether the difference of PJI risk in the two treatment arms differ in specific subsets of patients: femoral stem cementation (antibiotic-loaded bone cement versus bone cement with no antibiotic-load and cementless fixation vs fixation with bone cement) and type of antibiotic (beta-lactam antibiotics versus other). The rationale for these analyses is that we suspect the risk of infection to be different in these subgroups. The pharmacokinetics of the antibiotics might have an impact on the infection rates in the relevant groups. The statistical approach for this evaluation of potential effect modifiers is a test for statistical interaction to evaluate whether the treatment effect varies across levels of the effect modifier (45).

Finally, blinded results from the statistical analyses (single-dose compared to multiple-dose) will be presented to the author group followed by development of two written interpretations. The author group will sign a consensus statement comprising both interpretations prior to the unsealing of the randomization code.(46)

Missing data and sensitivity analyses

The main analyses will be based on the data as it appears in the database. Consequently, missing data is handled according to a Missing Completely At Random (MCAR) assumption (47).

Conducting sensitivity analyses in a randomized trial assessing the risk of PJIs following a single-dose versus multiple-dose antibiotic prophylaxis is essential to ensure the robustness and credibility of the findings. To evaluate the consistency of the primary endpoint and some or all the key secondary endpoints across various assumptions, missing data will be imputed using best-case, worst-case, best-worst-case, and worst-best-case imputations (48, 49) the results will be evaluated individually and combined using Rubin's rule.

Additional analyses

Stratified analysis

In secondary analyses, important contextual factors for a binary endpoint will be examined using statistical interaction tests, as proposed by Christensen et al. (45). Known and suspected baseline risk factors for PJI will be evaluated as potential effect modifiers: age group (<65 vs ≥65 years), sex (male vs female), anthropometric category (BMI: <30 vs ≥30 vs > 35 kg/m^2) and presence of diabetes (with vs without). Additional analyses of the study will assess whether the difference of PJI risk in the two treatment arms differ in specific subsets of patients: femoral stem cementation (antibiotic-loaded bone cement vs bone cement with no antibiotic-load and cementless fixation vs fixation with bone cement) and type of antibiotic (beta-lactam antibiotics vs other). The rationale for these analyses is that we suspect the risk of infection to be different in these subgroups. The pharmacokinetics of the antibiotics might have an impact on the infection rates in the relevant groups. The statistical approach for this evaluation of potential effect modifiers is a test for statistical interaction to evaluate whether the treatment effect varies across levels of the effect modifier (45). The subgroup analyses will be presented as demonstrated in Mock-up Figure 3A and B. No additional analyses on the primary and key secondary outcomes are planned from baseline to 90-day follow-up.

Harms

With regards to safety considerations, this trial will not involve any additional risks of adverse events of the antibiotics exceeding those considered normal for the surgical procedure and administration of antibiotics. Adverse events will be reported following usual practice, from the departments to the Danish Medicines Agency. Antibiotic prophylaxis in this study follows current guidelines for THA surgery. Both cloxacillin, cefuroxime, single dose, and multiple dose regimes

are already used as standard practice by Danish surgical centers. The dosage practices are therefore already current standard practices prior to this trial.

As one of the key secondary outcomes, SAEs will be defined in accordance with the *"International Conference on Harmonisation-Good Clinical Practice"* (ICH-GCP) guidelines.(50) The number (and percentage) of occurrences of all SAEs will be presented for each group. Statistical comparison will be conducted using Risk Differences and Relative Risks as illustrated in Mock-up **Table 3.**

Statistical software

All statistical analyses and calculations will be performed using R version 4.3.2 (2023-10-31 ucrt) with the packages tidyverse, lme4 and emmeans.

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Table 1. Baseline Characteristics of the Patients in the ITT population

	Single-dose (N=)	Multiple-dose (N=)
Age — yr		
Male sex — no. (%)		
Height — m		
Weight — kg		
Body-mass index — kg/m^2		
American Society of Anesthesiologists group, no. (%)		
1		
2		
3		
CCI group no. (%)		
Low		
Medium (1-2)		
High (3+)		
Diabetes no. (%)		
Antibiotic agent applied no. (%)		
Cloxacillin		
Cefuroxime		
Clindamycin		
Other		
Duration of surgery - minutes		
<60		
61-90		
≥91		
Type of fixation no. (%)		
Antibiotic-loaded bone cement		
Bone cement with no antibiotic-load		
Cementless fixation		
Patients with prior osteosynthesis material in the operated hip		
Year of Study		
Year 1, no. (%)		
Year 2, no. (%)		
Socioeconomic status		
Cohabitation		
Education		
Wealth		
Operating room		
LAF		
TAF		

* Plus–minus values will be mean ±SD unless otherwise indicated.

Table 2. Outcomes in the Intention-to-Treat Population*

Outcome	Single-dose (N =)	Multiple-dose (N =)	Odds Ratio (95% CI)	†Absolute risk difference (95%CI)
Primary Outcome				
Prosthetic Joint infection up to 90 days no. (%)				
Key Secondary Outcomes				
Serious adverse events (SAE), no. (%)				
PJI-likely, no. (%)				
Major Adverse Cardiovascular Events, no. (%)				
Length of stay (LOS), days				
Hospital-treated infections (excluding SSI), no. (%)				
Community-based antibiotic use, no. (%)				
Opioid use, no. (%)				
Use of acetaminophen/non-steroidal anti-inflammatory drugs , no. (%)				
Revision due to any cause, no. (%)				

* The primary analyses will be based on the Intention to Treat (ITT) population based on the Full Analysis Set; i.e., all patients undergoing the surgery corresponding to the specific year (cross-over, cluster randomization). Two-sided 95% confidence intervals will be estimated and reported enabling (standard) superiority interpretations. The primary statistical analysis model will be based on a *Generalized Linear Mixed Model*, with a random effects factor applied indexing the clinical center (36 levels: 1, 2, 3, …, up to 36), a fixed effect will be applied for period (2 levels: 1st and 2nd year, respectively), and antibiotics group (2 levels: Single-dose and Multiple-dose, respectively), as well as the interaction between the two (period×group; 4 levels: 2×2 levels). Hierarchical models account for variations in baseline risk across clusters (e.g., sites or patient subgroups).
†Absolute risk differences and their 95% confidence intervals will be derived from odds ratios and corresponding 95% confidence intervals estimated by the hierarchical model, incorporating the baseline risk in the reference group (multiple-dose).
The 95% confidence intervals will not be adjusted for multiplicity and should not be used in place of hypothesis testing.

Table 3. Serious Adverse Events within 90 days within each group. *

Events	Single-dose (N =)	Multiple-dose (N =)	Odds ratio (95% CI)	Absolute risk difference†
Serious adverse event — no. (%)				
Any infection requiring intravenous antibiotics				
Severe allergic reaction				
Organ failure				
Life-threatening events				
Musculoskeletal:				
Deep infection				
Hip dislocation				
Femoral fracture				
Aseptic loosening				
Cardiovascular:				
Vascular injury				
Pulmonary embolism				
Deep venous thrombosis				
Acute myocardial infarction				
Stroke				
Nervous system:				
Nerve injury				
Death (All-cause mortality)				
Discontinuation due to adverse event(s) — no. (%)				
Discontinuation due to serious adverse event(s) — no. (%)				

* This table includes all serious adverse events that occurred during the 3month study period, but which did not necessarily have a causal relationship with the treatment administered. An adverse event was classified as serious if it was fatal or life-threatening, required or prolonged inpatient hospitalization, was disabling, resulted in (a congenital anomaly or birth defect), or required medical or surgical intervention to prevent permanent impairment or damage.

† Absolute risk (multiple-dose vs single-dose group) will also be calculated. The 95% confidence intervals will not be adjusted for multiplicity.

FIGURE 1: CONSORT flow-chart.

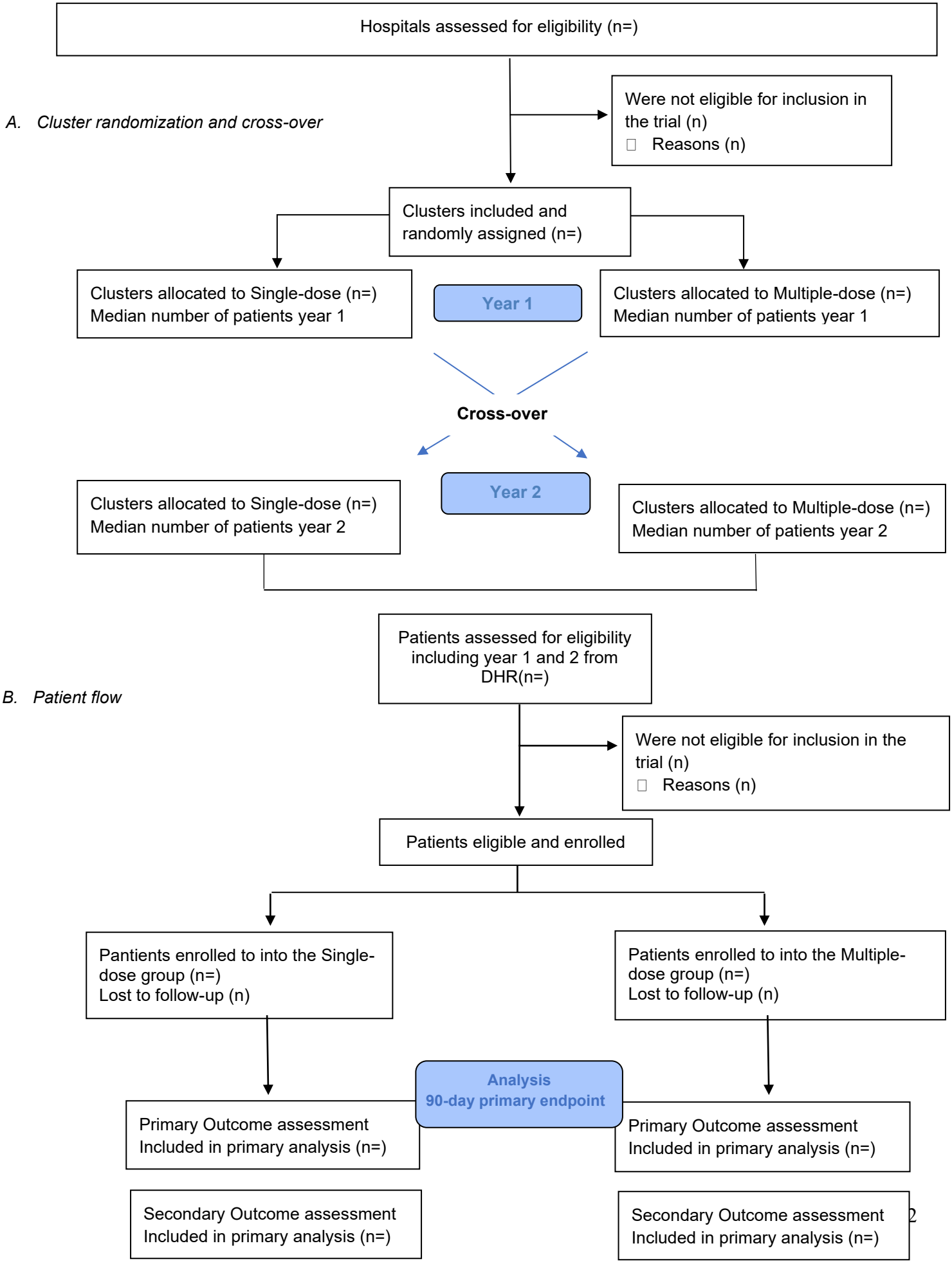


Figure 2. Kaplan Meier Curve. The cumulative proportion of patients remaining PJI-free in the two groups.

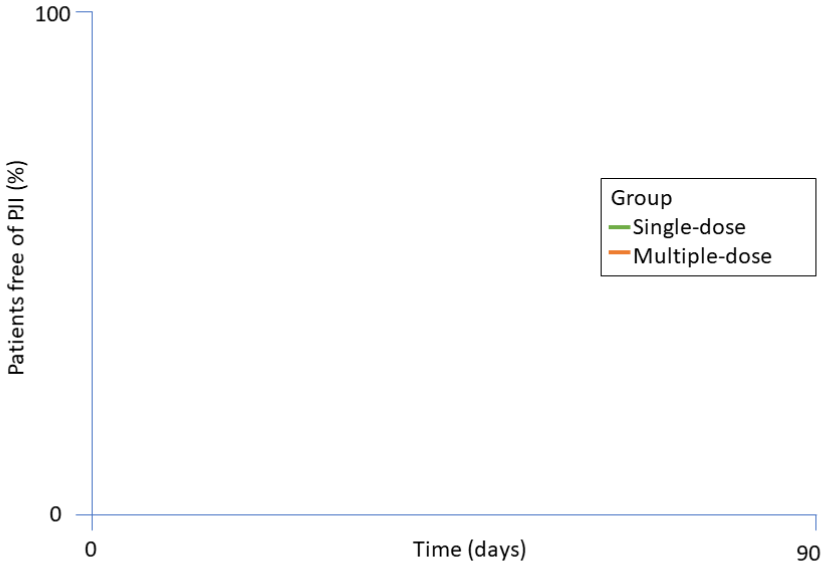
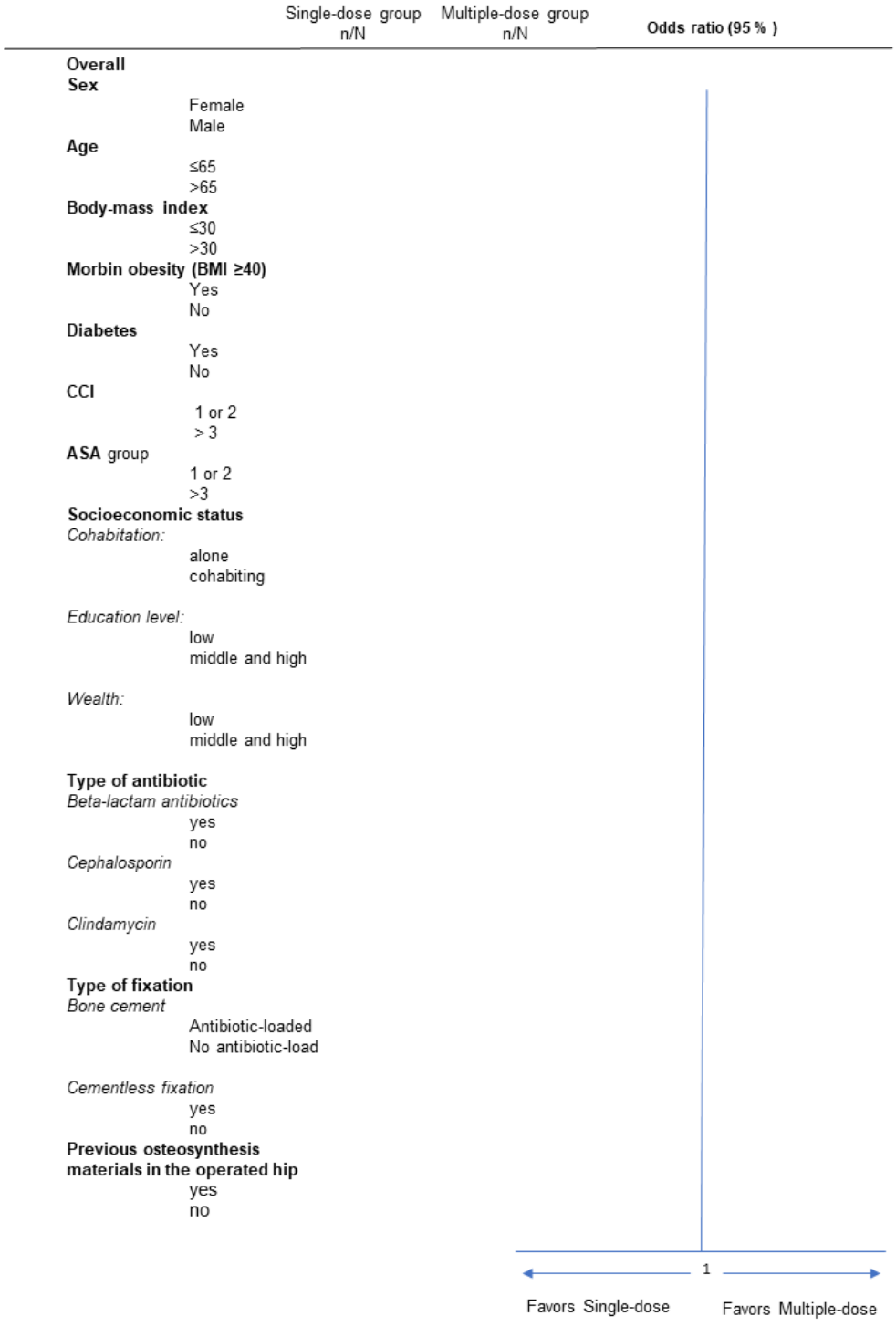
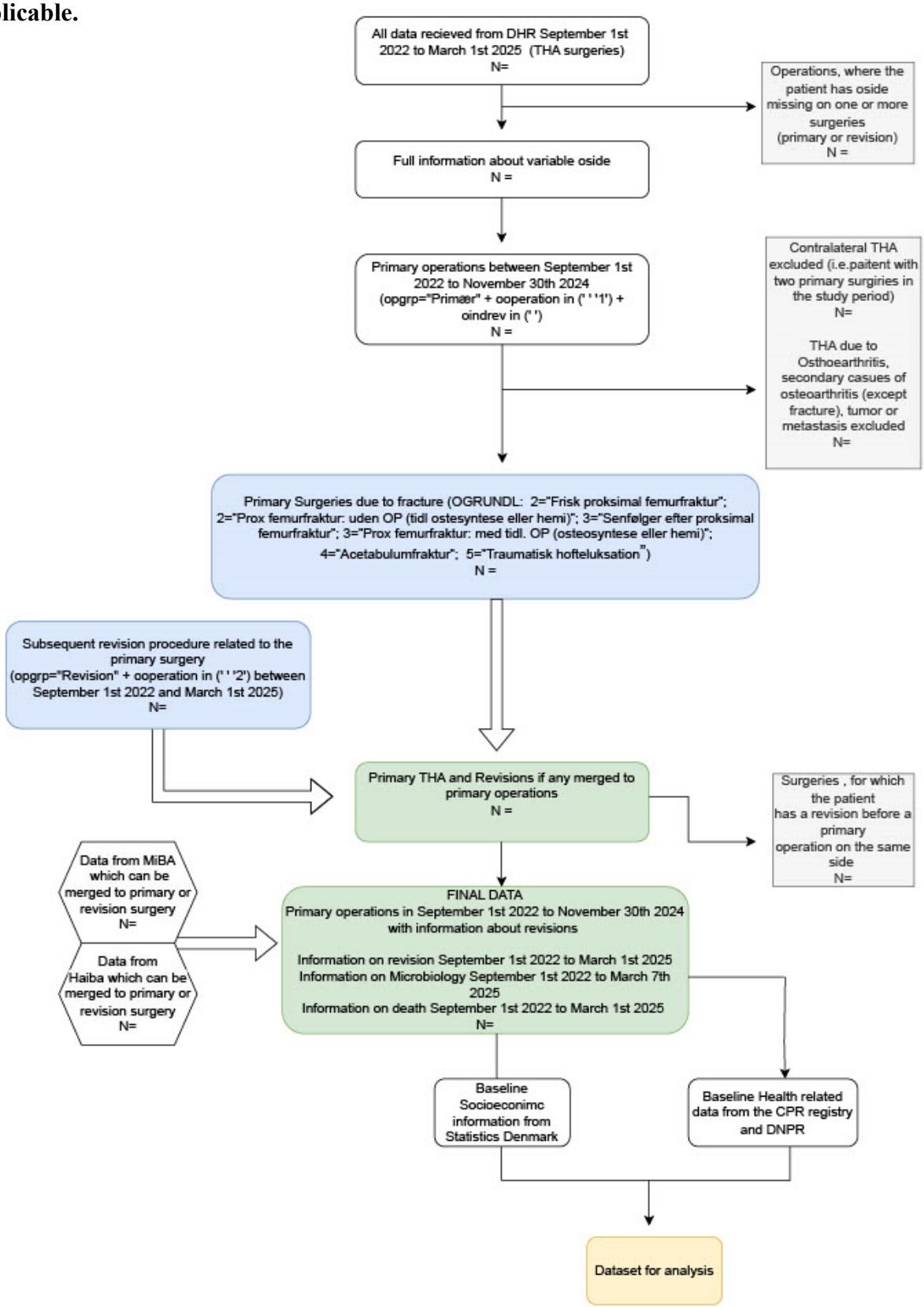


Figure 3 Subgroup analyses of the Primary Outcome in the Intention-to-Treat population. The primary outcome is prosthetic joint infection within 90 days after surgery. The reference group consists of patients assigned to the single-dose group. The confidence intervals for subgroup analyses are not planned to be adjusted for multiplicity and should not be used to infer definitive conclusions about treatment effects. The body-mass index is the weight in kilograms divided by the square of the height in meters. Additional analyses of the risk of PJI 90 days after surgery will assess whether the difference risk of PJI in the two treatment arms differs in specific subsets of patients: femoral stem cementation (antibiotic-loaded bone cement versus bone cement with no antibiotic-load versus cementless fixation) and type of antibiotic (beta-lactam antibiotics versus other). The reference group is patients assigned to the single-dose. The rationale for these analyses is that we suspect the risk of infection to be different in these subgroups.


Single-dose group n/N
Multiple-dose group n/N
Odds ratio (95 %)
Overall
Sex
Female
Male
Age
≤65
>65
Body-mass index
≤30
>30
Morbin obesity (BMI ≥40)
Yes
No
Diabetes
Yes
No
CCI
1 or 2
> 3
ASA group
1 or 2
>3
Socioeconomic status
Cohabitation:
alone
cohabiting
Education level:
low
middle and high
Wealth:
low
middle and high
Type of antibiotic
Beta-lactam antibiotics
yes
no
Cephalosporin
yes
no
Clindamycin
yes
no
Type of fixation
Bone cement
Antibiotic-loaded
No antibiotic-load
Cementless fixation
yes
no
Previous osteosynthesis materials in the operated hip
yes
no
1
Favors Single-dose
Favors Multiple-dose

Appendix A: Flow diagram illustrating dataset construction, including codes where applicable.



Appendix B: Registries, codes, and variables for each outcome

Outcome	**Registry**	**Codes for Registry**
Primary Outcome: Prosthetic Joint infection	Danish Hip Arthroplasty Registry (DHR) The Hospital Acquired Infections Database (HAIBA) The Danish Microbiological Database (MiBa)	Code for revision for infection in DHR: DHR: Variable 2: “Revision” HAIBA: Variable “SSI_acute_90 = 0 OR 1”, **0 = infection that occurred between 3 and 90 days after a planned index operation.** **1 = infection that occurred between 3 and 90 days after an acute index operation.** MiBA: "Prøvedato"=correspondning to date or revision, "Resultat"=positive for microorganism, "Prøvemateriale"=closed fluid aspirate taken intraoperatively, "Konklusion på undersøgelse" or "Dyrkningsfund" = phenotypically indistinguishable from bacteria found in tissue biopsy
Serious Adverse Events	The Danish National Patient Registry (DNPR)	Please see Appendix C for the complete outline of ICD-10 codes.

	The Civil Registration System	The civilregistration system: variable: date of death
PJI-likely	The Danish Microbiological Database (MiBa) The Danish National Prescription Registry (NPR)	MiBA: "Prøvedato"=**between 3 and 90 days after a planned index operation**, "Resultat"=positive for microorganism, "Prøvemateriale"=aspiration of synovial fluid OR closed fluid aspirate taken intraoperatively, "Lokation" = corresponding to THA from index surgery "Undersøgelse "= aspiration with or wihtout imaging guidance or biopsy "Konklusion på undersøgelse" or "Dyrkningsfund" = phenotypically indistinguishable from bacteria found in tissue biopsy From the prescription database (NPR): (ATC category J01
Length of stay for hospitalization	The Danish National Patient Registry (DNPR)	From date of index surgery to date of discharge.
Major Adverse Cardiovascular Events	The Danish National Patient Registry (DNPR)	The following ICD.10 codes: Venous thromboembolism: I26, I80.1 –I80.9, I82 or T81.7 Myocardial infarction: I20 – I25 Atrial fibrillation: I48.0 -I48.92

		Stroke: I60.0 - I64.0
Hospital-treated infections (Other than PJI and PJI-likely)	The Danish National Patient Registry (DNPR)	A20 -A38, A42 -A44, A48 -A49, A65 -A79, A3, A49.9, A39.4, A40 -A41, B37.7, A32.7, A54.8G, A02.1, A22.7, A26.7, A42.7, A28.2B, A06.5, A54.1, B43, D73.3, E06.0A, E23.6A, E32.1, G06, G07, H00.0A, H05.0A, H44.0A, H60.0, J34.0A, J36, J38.3D, J38.7G, J39.0, J39.1, J39.8A, J85.1, J85.2, J85.3, K04.6, K04.7, K11.3, K12.2, K13.0A, K14.0A, K20.9A, K35.3A, K35.3B, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K75.0, K81.0A, K85.8A, L02, L05.0, L05.9, M60.8A, M86.8A, M86.9A, N15.1, N34.0, N41.2, N45.0, N48.2, N49.2A, N61.9A, N61.9B, N70.0A, N70.0B, N71.0A, N73.0A, N73.0B, N73.2A, N73.2B, N73.3A, N73.5A, N73.8A, N73.8C, N75.1, N76.4, N76.8A, **Except:** A54.1B, B43.0, B43.8, B43.9, K57.0B, K57.0C, K57.2B, K57.2C, K57.4A, K65.0M, K65.0N, K65.0O, K65.0P, A46, H01.0, H03, H60.0, H60.1, H60.2, H60.3, H62, K12.2, K13.0, K61, M72.6, L01, L08, L03, J34.0, L00, L02, L04, L05, L06, L07, L30.3, L73.8, H00, H01.0, H03.0, H03.1, H04.3, H05.0, H06.1, H10, H13.0, H13.1, H15.0, H19.1, H19.2, H22.0, H32.0, H44.0, H44.1, H60, H61.0, H62.0, H62.1, H62.2, H62.3, H65, H66, H67.0, H67.1, H68, H70, H73.0, H75.0, H83.0, H94.0 **Except:** H60.4, H60.4A, H605, H60.5B, H60.8, H608.A, H65.2, H65.3, H65.4, H65.4C, H66.1, H66.2, H66.3, H68.1, H70.1, H70.8,

		G00 -07, A80 - A89, G00, G01, G02, G03, A32.1, A39.0, A17.0, A20.3, A87, A54.8D, A02.2C, B37.5, B00.3, B01.0, B02.1, B05.1, B26.1, B38.4, A00 -A09, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, K83.0, K85.9, I00 -I02, I30.1, I32.0, I33, I38, I40.0, I39.8, B37.6, J00 - J06, J36, J39.0, J39.1, J12 -J18, J20 - J22, J44.0, J85.1, J86, J20 -J22, J34.0, J35.0, J38.3C, J38.3D, J38.7B, J38.7F, J38.7G, **Except:** J34.0E, J34.0F, J34.0G, J34.0H, N10, N11, N12, N15.1, N15.9, N30, N33.0, N34, N39.0, N08.0, N13.6, N16.0, N28.8D, N28.8E, N28.8F, N29.0, N29.1, **Except:** N30.1, N30.2, N30.4, A50 -A64, N41, N45, N48.1, N48.2, N49, N51.1, N51.2, N70 -77, O23, O26.4, O41.1, O74.0, O75.3, O85, O86, 088.3, O91, O98, M00, M01, M86, M63.0, M63.2, T80.2, T81.4, T82.6, T82.7, T83.5, T83.6, T84.5, T84.6, T84.7, T85.7, T88.0, T89.9, B90 -B99, K04.0, K05.2 Codes for specific Hospital-treated infections Pneumonia: J12-J18 Urinary tract infections N10, N11, N12, N15.1, N15.9, N30, N33.0, N34, N39.0, N08.0, N13.6, N16.0, N28.8D, N28.8E, N28.8F, N29.0, N29.1, Except: N30.1, N30.2, N30.4

Community-based antibiotic use	The Danish National Prescription Registry (NPR)	Narrow spectrum antibiotics: J01CE, J01CF, J01DB Broad spectrum antibiotics: J01DC, JO1DD, J01DE, J01DH, J01DI, J01CR, J01CA, J01F. J01E, J01MA, J01AA
Opioid use	The Danish National Prescription Registry (NPR)	Following ATC codes (including all subcodes) are included: N01AH (opioid anesthetics), N02A (opioids), N07BC02 (methadone), and R05DA04 (codeine).
Use of acetaminophen or non-steroidal anti-inflammatory drugs	The Danish National Prescription Registry (NPR)	Acetaminophen ATC codes: N02BE01 and N02BE51 Non-steroidal anti-inflammatory drug ATC codes: M01A
Any revision after THA	Danish Hip Arthroplasty Registry (DHR) and The Danish National Patient Registry (DNPR)	Code for revision for infection in DHR: DHR: Variable 2: “Revision”

Appendix C: International Classification of Diseases, 10th Revision Diagnosis Codes for Serious Adverse Events

Serious Adverse Event	**ICD-10 Diagnostic Code**
Sepsis	A40 - A41
Shock not elsewhere classifies R67	R67
Anaphylactic Shock, unspecified	T78.2
Other types of shock included in codes below	• anesthesia (T88.2) • anaphylactic (due to): o serum (T80.5) • postoperative (T81.1) • traumatic (T79.4)
Staphylococcal scalded skin syndrome	L00
Infectious arthropathies	M00-M03
Osteomyelitis	M86
Injuries to the hip and thigh	S70-S79
Poisoning by drugs, medicaments and biological substances	T36 – T50
Certain early complications of trauma, not elsewhere classified	T79
Complications of surgical and medical care, not elsewhere classified	T80 – T88
Pneumothorax	J93
Respiratory failure, not elsewhere classified	J96

Postprocedural respiratory disorders, not elsewhere classified	J95
Adult respiratory distress syndrome	J80
Pulmonary oedema	J81
Cardiac arrest	I46
Other forms of heart disease	I30 – I52
Ischemic heart diseases	I20 – I25
Acute and subacute endocarditis	I33
Acute myocarditis	I40
Heart failure	I50
Complications and ill-defined descriptions of heart disease	I51
Pulmonary heart disease and diseases of pulmonary circulation	I26-I28
Arterial embolism and thrombosis	I74
Phlebitis and thrombophlebitis	I80
Portal vein thrombosis	I81
Other venous embolism and thrombosis	I82
Intracranial and intraspinal phlebitis and thrombophlebitis	G08

Postprocedural disorder of circulatory system, unspecified	I97.9
Acute kidney failure	N17
Type 1 diabetes mellitus with diabetic ketoacidosis	E10.1
Type 2 diabetes mellitus with diabetic ketoacidosis	E11.1
Other specified diabetes mellitus with diabetic ketoacidosis	E13.1
Stroke	I60-I64
External causes of morbidity and mortality	Y40 – Y84
Acute appendicitis	K35
Acute peritonitis	K65
Perforation of intestine	K63.1
Abscess (perianal, ischiorectal, intrasphincteric)	K61
Hemoperitoneum	K66.1
Other and unspecified intestinal obstruction	K56.6
Ileus	K56
Hematemesis	K92.0
Melena	92.1
Gastrointestinal hemorrhage unspecified	92.2

Acute Pancreatitis	K85
Cholangitis	83.0
Acute cholecystitis	K81.0
Perforation of gallbladder	K82.2
Abscess of liver	K75.0
Perforation of the esophagus	K22.3
Gastric ulcers with bleeding or perforation	K25.0 to K25.6
Duodenal ulcers with bleeding or perforation	K26.0 to K26.6
Gastrojejunal ulcers with bleeding or perforation	K28.0 to K28.6
Diverticular disease with perforation, abscess, or bleeding	K57.0, K57.2, K 57.4, K57.8
Diaphragmatic hernia with obstruction or gangrene	K44.0, K44.1
Peritonitis	K65
Abscess of intestine	K63.0
Perforation of intestine	K63.1 (non traumatic)

Serious Adverse Event	**ICD-10 Diagnostic Code**
Surgical site infection	T81.40, T81.41, T81.42, T81.43, T81.49
Venous thromboembolism	I26, I80, T81.7B

Cardiac Arrest	I46, I97.12
Acute myocardial Infarction	I21
Stroke	I60 - I64
Pancreatitis	K85
Pneumonia	J13, J14, J15, J16, J17, J18, J85.1, T81-4P
Acute kidney injury	N17
Wound dehiscence	T81.3