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Effect of single versus multiple prophylactic antibiotic doses on prosthetic joint infections following primary total hip arthroplasty in patients with osteoarthritis at public and private hospitals in Denmark: protocol for a nationwide cross-over, cluster randomised, non-inferiority trial [The Pro-Hip-Quality Trial]

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ABSTRACT

Introduction A feared complication after total hip arthroplasty (THA) is prosthetic joint infection (PJI), associated with high morbidity and mortality. Prophylactic antibiotics can reduce the risk of PJI. However, there is no consensus on the dosages and current recommendations are based on a low evidence level. The objective is to compare the effect of a single versus multiple doses of prophylactic antibiotics administered within 24 hours on PJI.

Methods and analysis The study is designed as a cross-over, cluster randomised, non-inferiority trial. All clinical centres use both antibiotic practices (1 year of each intervention). All Danish orthopaedic surgery departments will be involved: Based on quality databases, 2-year cohorts of approximately 20 000 primary THAs conducted at 39 public and private hospitals, will be included. Inclusion criteria: age ≥18 years, all indications for THA except patients operated due to acute or sequelae from proximal femoral or pelvic fractures or bone tumour or metastasis. The primary outcome is PJI within 90 days after primary THA. Secondary outcomes include (1) serious adverse events, (2) potential PJI, (3) length of hospitalisation stay, (4) cardiovascular events, (5) hospital-treated infections, (6) community-based antibiotic use, (7) opioid use and (8) use of acetaminophen and non-steroidal anti-inflammatory drugs. All outcome measures will be extracted from national databases. Analyses will be based on the intention-to-treat population. Non-inferiority will be shown if the upper limit of the two-sided 95% CI for the OR is less than 1.32 for the single dose as compared with multiple doses. The results will establish best practice on antibiotic prophylaxis dosages in the future.

Ethics and dissemination This study has been approved by Committees on Health Research Ethics for The Capital Region of Denmark (21069108) and The Danish Medicines Agency (2021091723). All results will be presented in peer-reviewed medical journals and international conferences.

Trial registration number NCT05530551.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A nationwide study including all public and private orthopaedic departments.
⇒ Data are collected through several validated national registries enabling a follow-up for long-term effects and an extensive exploration of a selection of relevant outcomes.
⇒ A prospective pragmatic cluster randomised trial with an unselected consecutive enrolment of all eligible patients ensures high external validity.
⇒ Insufficient gathering of biological samples during reoperation may hamper the primary outcome.
⇒ Prosthetic joint infection may not be captured within 90 days but is expected to be captured on planned analyses 1 year and 5 years after primary total hip arthroplasty, this renders a limitation.

INTRODUCTION

A potential and feared complication of total hip arthroplasty (THA) is prosthetic joint infection (PJI), associated with high morbidity and mortality.[1–4] PJI accounts for approximately 15% of reoperation procedures after THA.[5] Perioperative antimicrobial prophylaxis is a well-established and documented part of standard care to reduce the risk of PJI.[6–10] However, there is no consensus regarding duration of antibiotic prophylaxis for THA. While some of the well-established organisations and societies recommend use of a single preoperative dose[11 12] others recommend up to 24 hours of antimicrobial prophylaxis following THA.[13–15] Danish national guidelines recommend both strategies as options for antibiotic prophylaxis practice, that is, a single preoperative dose or a 24-hour coverage using either cloxacillin or the second-generation cephalosporin, cefuroxime.[16] Features of antibiotic prophylaxis include agent, dose, duration and timing. The choice of antibiotic agent as well as duration, varies among the different orthopaedic departments in Denmark.

The possibility to reduce the use of postoperative antibiotics without compromising patient safety will pose multiple advantages. These include a reduction of possible adverse events such as acute kidney injury,[17] opportunistic infections,[18] selection of multidrug-resistant bacteria[19] and most importantly, a reduction in the overall use of antibiotics. Use of antibiotics is regarded as the primary driver of the worldwide antimicrobial resistance, rendering the treatment of common infections difficult or even impossible.[20–22] Based on published systematic reviews, we recognise that there is no credible evidence to infer whether preoperative and postoperative dosages are more efficient than one single preoperative dose of prophylactic antibiotic.[23–25] A recently published cluster randomised trial found that antibiotic prophylaxis within 24 hours after surgery is non-inferior to a longer duration (within 48 hours) in prevention of healthcare-associated infections, including surgical site infections (SSI) after clean orthopaedic surgery.[26] A large retrospective study[27] and a recent large observational register-based study[28] suggest that a single dose may be non-inferior to multiple doses of prophylactic antibiotics in prevention of PJI after THA.

No randomised trial (RCT) has compared one single preoperative dose with 24 hours of antibiotic coverage in THA. Therefore, we designed the pragmatic, cross-over, cluster randomised, non-inferiority Pro-Hip-Quality osteoarthritis (OA) trial based on national quality databases, to investigate the effect of single versus multiple prophylactic antibiotic doses administered within 24 hours on PJI after primary THA. In this trial, primary and secondary outcomes are captured within 90 days from primary surgery. Studies confirm that most infections following arthroplasty occur within the first 90 days after surgery,[29 30] however, a certain percentage of up to 20% of PJIs, will not be captured in this period. These are expected to be captured within the 1-year and 5-year follow-up, respectively. If the study provides clear evidence supporting non-inferiority of a single dose, an inappropriate use of excessive antibiotics may be prevented.

Figure 1 Pro-Hip-Quality trial Logo.

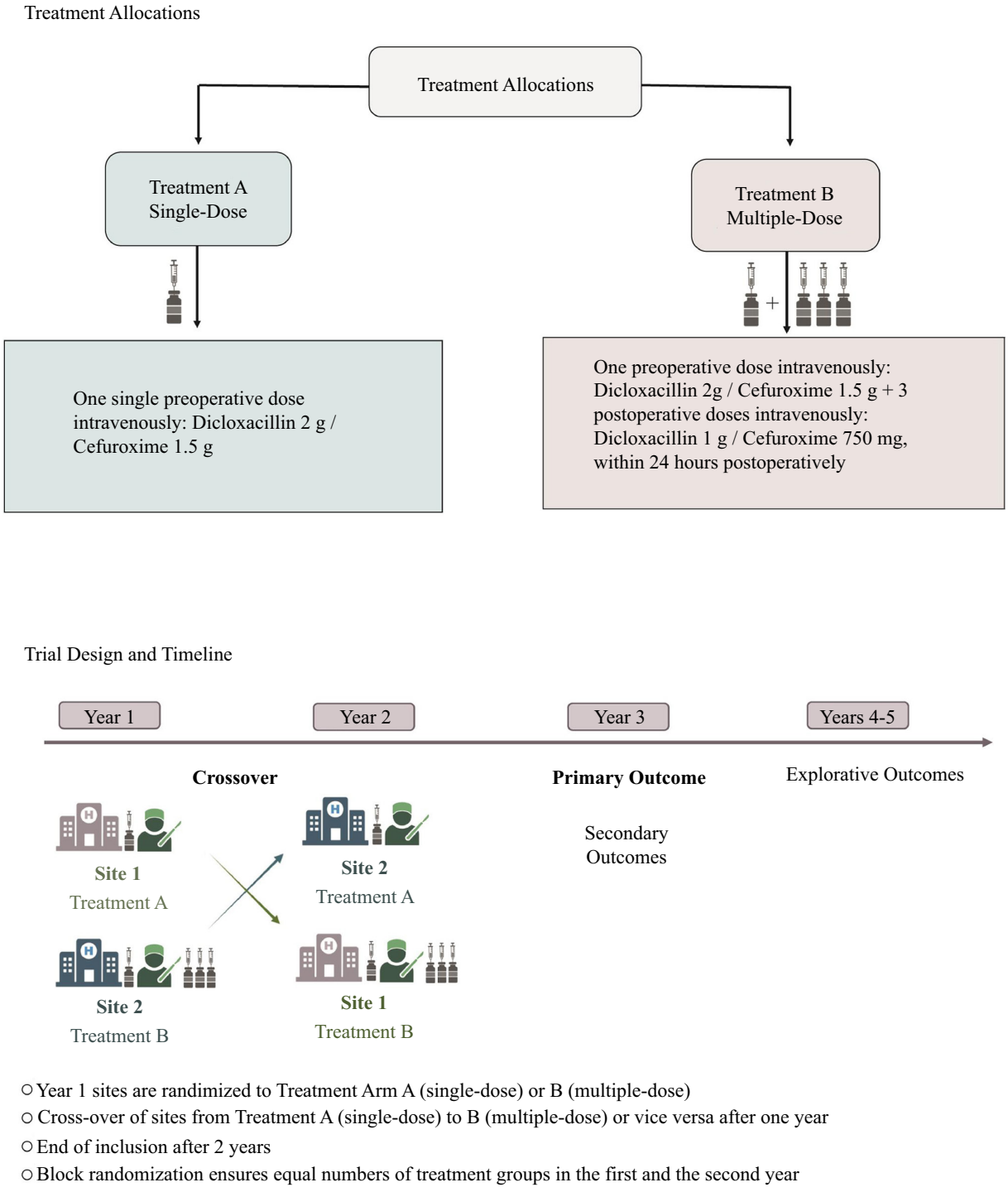
METHODS

Trial design

The Pro-Hip-Quality OA trial is designed as a pragmatic registry-based, multicentre, open label, cross-over, cluster randomised, non-inferiority trial.[31–34] Figure 1 represents the trial logo and figure 2 depicts the flow of the study.

The study will be reported according to a pragmatic combination of the following Consolidated Standards of Reporting Trials (CONSORT) statements: 'CONSORT for trials conducted using cohorts and routinely collected data',[31] 'Pragmatic Trials',[32] 'Cluster Randomised Trials',[33] 'Randomised Crossover Trials'[34] and 'Noninferiority and Equivalence Randomised trials'.[35] This pragmatic registry-based trial design[36] will include cluster randomisation of 39 different clinical departments, applying a cross-over design. This corresponds to all Danish public and private orthopaedic departments. Patient enrolment started at the first departments in September 2022 and the last departments in December 2022. Patient recruitment is expected to be completed in December 2024.

We have planned a nationwide study where all public and private orthopaedic departments will participate and all eligible patients will be included. Classic RCTs, exclude a high percentage of eligible patients. This may pose a limitation concerning external validity due to selected and specific populations as well as conduction under ideal clinical conditions.[37 38] Instead, we will apply a pragmatic registry-based, cluster randomised trial design.[36] This is a pragmatic trial due to the real-world setting of a broad, unselected, and representative patient group providing high external validity. We will test effectiveness of antibiotic prophylaxis regimens that are already available and standardised clinical practice. Another advantage of the design is that a classic RCT would be infeasible and very costly to conduct, given the small incidence of PJI. Furthermore, the randomisation at cluster level, enables a rapid inclusion of 2-year cohorts



- Year 1 sites are randimized to Treatment Arm A (single-dose) or B (multiple-dose)
- Cross-over of sites from Treatment A (single-dose) to B (multiple-dose) or vice versa after one year
- End of inclusion after 2 years
- Block randomization ensures equal numbers of treatment groups in the first and the second year

Figure 2 Pro-Hip-Quality treatment allocations, trial design and timeline.

of approximately 20 000 eligible patients, contributing to a sufficient study power facilitating clinical decision making based on strong evidence.

The incorporated block randomisation ensures equal numbers of sites in both treatment groups during the first and the second year, respectively. We do not expect variation among the patients included during year 1 and year 2 of the study. However, study participants from the same site are likely to have greater similarity to each other, compared with participants included from a different site.[39] Furthermore, the cross-over approach means that the sites are randomised to receive each of the interventions once during separate periods (i.e. study years 1 and 2) acting as own control group. This may attenuate possible imbalances and variations in site characteristics.[37 40]

Hypothesis

One single dose of prophylactic antibiotic is non-inferior to multiple doses of prophylactic antibiotics administered

within 24 hours on the cumulated incidence of PJI within 90 days after primary THA.

Eligibility

Inclusion criteria

1. All patients receiving a primary THA due to primary and secondary causes of OA.

Exclusion criteria

1. Patients receiving a primary THA due to either acute or sequelae of proximal femoral or acetabular fractures.
2. Patients receiving a primary THA due to bone tumour or metastasis.

Concerning developmental dysplasia, approximately 3% of the patients will have secondary OA due to acetabular dysplasia and 2% due to femoral head necrosis.[41]

Interventions

This trial incorporates a pragmatic registry-based design[36] and will include cluster randomisation of the 36 eligible sites corresponding to 39 different clinical departments, applying a cross-over design. The reason that the 39 clinical departments correspond to 36 sites in the randomisation, is that 3 of the departments have been merged due to pragmatic reasons as they apply common registration in the Danish Hip Arthroplasty Register (DHR).[42] Each clinical centre (1, 2, 3, …., 36) will be running a specific intervention (ie, single-dose or multiple-dose antibiotics) throughout 12 months, and then the subsequent year will be followed by the opposite intervention illustrated in figure 2. SSI preventive measures will remain fixed during the trial period.

Intervention period

Patient inclusion starts on the day of surgery, and follow-up is completed at 90-day and 1-year time points as part of the usual follow-up for the registry. Eighteen sites (i.e. clusters) will be randomly assigned to administer a single dose of antibiotics and 18 sites (i.e. clusters) will be randomly assigned to administer multiple doses of prophylactic antibiotics for 12 months from study start. The cross-over of each cluster to the alternate antibiotic duration will occur for the second 12 months of the study. Data collection will occur for 90 days post final recruitment for primary and secondary outcomes (figure 2).

Table 2 Possible transition to oral postoperative antibiotic treatment

Antibiotic	12 hours postoperative	18 hours postoperative
Dicloxacillin peroral	1 g	1 g
Amoxicillin and clavulanic acid peroral	875 mg/125 mg*	875 mg/125 mg*

No weight adjustment.
The first postoperative dose of cloxacillin or cefuroxime must be administered intravenously.
*If the centre or region does not have access to amoxicillin and clavulanic acid 875/125 mg, a dose of 1 g/125 mg (ie, amoxicillin 500 mg+amoxicillin and clavulanic acid 500 mg/125 mg) may be used.

The planned interventions, procedures and follow-up are planned in relation to implemented guidelines for admission and follow-up for databases and registries. Therefore, participation will not result in additional hospital visits.

Administration of antibiotics

The clusters will administer both treatment arms A and B listed in table 1. In treatment arm B: In cases of same-day surgery, the first postoperative dose (corresponding to 6 hours postoperatively), must be administered intravenously, the following postoperative may be administered orally due to pragmatic reasons. Doses and choice of antibiotic in these cases are listed in table 2. The preoperative antibiotic dose must be administered within 1 hour prior to surgical incision.[14 43] Cefuroxime may be used in cases of penicillin allergy including type 1 allergy as cross-reactivity is very low.[44] In case of cephalosporin allergy or general beta-lactam allergy; clindamycin may be used (table 3). Dose adjustments in case of delayed surgical start, prolonged surgery or affected liver or kidney function are listed in online supplemental appendix A. Other antibiotics may not be used in addition to the protocol-prescribed agents unless justified on medical assessment by the physician and reported accordingly.

Data sources

The outcome ascertainments and data are collected through several national registries. This is a great

Table 1 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 intravenous	<120 kg	2 g	1 g	1 g	1 g
	≥120 kg	3 g	2 g	2 g	2 g
Cefuroxime intravenous	<120 kg	1.5 g	750 mg	750 mg	750 mg
	≥120 kg	3 g	1.5 g	1.5 g	1.5 g

Table 3 Antibiotic practice in cases of cephalosporin allergy or general beta lactam allergy

Antibiotic	Weight	Preoperative dose	8 hours postoperative	16 hours postoperative
Clindamycin intravenous	<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.

advantage enabling investigation of several important outcomes and a follow-up duration where evaluation of long-term effects is made possible. All outcome measures will be extracted from the following national and validated databases: the Civil Registration System (CRS)[45]; DHR[46–48]; the Danish National Patient Registry (DNPR)[42]; The Hospital Acquired Infections Database (HAIBA)[49]; the Danish Microbiological Database (MiBa),[50] the Danish National Prescription Registry (NPR)[51] and the national database: Danish Agency for Labour Market and Recruitment registry (STAR).[52] Outcomes collected and details on the databases are listed in table 4. We will use the unique and permanent individual identification number known as the Civil Personal Register (CPR) number which goes through all Danish registries for an unambiguous linkage between registries.

Data sources for demographics

The following data will be obtained from the patient at baseline: sex, age, height, weight, American Society of Anesthesiologists classification, duration of surgery and socioeconomic status (SES). Comorbidity status will be evaluated using the Charlson Comorbidity Index Score (CCI).[53] Information about comorbidities will be collected from CRS[45] linked to the DNPR.[42] The CCI score will be calculated based on all primary and secondary diagnoses from hospitalisations and outpatient visits registered as International Classification of Diseases, Tenth Revision (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,[42] the overall PPV for the 19 Charlson conditions has been found to be 98.0%.[54]

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.[55]

Statistics Denmark holds registry data on socioeconomic characteristics on all Danish citizens at individual level. Information regarding family annual household income and liquid assets will be retrieved from The Income Statistics Register[52] and the data are primarily supplied by tax authorities. The Population Education Register[56] obtains information on the highest completed level of education and consists of data generated from administrative records of educational institutions and from surveys. The Register-based Labour Force Statistics obtains a description of the affiliation with the labour market. The registers are updated yearly and administered by the Danish government.

Data management

Entered data will be stored in REDCap at The Capital Region of Denmark. Data are entered via an encrypted connection and fulfil the demands for data security. All data entries and changes are logged in REDCap thus the database may store social security number and meets the good clinical practice (GCP) requirements for use of electronic case report form (eCRF), when conducting medical trials. After ended study (10 years after inclusion of last patient), all data will be pseudonymised.

Outcomes

The primary and secondary outcomes are captured within 90 days from index surgery. For this trial, a 90-day surveillance period has been chosen as recommended by the National Healthcare Safety Network[57] and studies confirm, that most infections following arthroplasty occur within the first 90 days after surgery.[29 30]

Primary outcome

Incidence of PJI: The definition of PJI is based on revision surgery within 90 days after 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 considered present when at least one of the following three criteria exists:

1. Two or more intraoperative deep tissue samples of phenotypically indistinguishable bacteria isolated from at least three deep tissue samples.[58]
2. One or more positive intraoperative samples from a closed fluid aspirate AND a biopsy (fluid AND tissue) of phenotypically indistinguishable bacteria isolated.[58]
3. A PJI when an indication of deep infection is reported to DHR by the surgeon on revision surgery.[46]

The definition of PJI is based on The European Bone and Joint Infection Society (EBJIS),[58] an International Consensus[15] and an algorithm developed to capture cases with PJI using national databases.[30] 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.[1 43] 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.[30 46] Data will

Table 4 Data sources for outcomes

Database/registry	Description	Outcome collected
The Civil Registration System[42 45]	Contains continuously updated information on migration and vital status including date of death. All Danish residents and citizens are assigned a unique and permanent individual identification number (CPR number) at birth or on immigration. CPR number goes through all Danish registries and enables an unambiguous linkage between registries and complete individual level follow-up over time.	► Mortality
Danish Hip Arthroplasty Registry (DHR)[46–48]	Clinical data on primary THAs and revisions are prospectively collected through DHR. Preoperative data include hospital code and laterality of the affected hip. The perioperative data registered in the DHR include the date of surgery; antibiotic and thromboembolic prophylaxis; type of anaesthesia; duration of surgery; type of acetabular and femoral component and their fixation and type, size, and material of the prosthetic femoral head and the acetabular liner. For revisions, the following is registered: Indication, prosthetic status before revision, extent of revision and n of earlier revisions.	► PJI ► Any revision THA
The Danish National Patient Registry (DNPR)[42]	Contains data on all admissions and discharges from somatic hospitals in Denmark, including dates of admissions and discharges, surgical procedures performed and up to 20 diagnoses for every discharge.	► PJI ► SAE ► LOS ► Cardiovascular complications ► Hospital-treated infections ► Any revision THA
The Danish Microbiological Database (MiBa)[50]	Holds data on all microbiology results from all departments of clinical microbiology in Denmark since 2010.	► PJI, intraoperative aspirations ► PJI-likely: aspirations
The Hospital Acquired Infections Database (HAIBA)[49]	The database is an automated system for the surveillance of hospital acquired infection. HAIBA monitors specific types of infections, using algorithms, which combine data from the DNPR and MiBa. HAIBA provides continuous surveillance data, allowing for trend analysis.	► PJI
The Danish National Prescription Registry (NPR)[51]	NPR has recorded detailed information on prescriptions redeemed in Denmark. The NPR receives data recorded in the electronic dispensing systems of community pharmacies. The registry contains information related to the user, prescriber, the dispensing pharmacy and the drug prescribed.	► PJI-likely: antibiotic prescriptions ► Community-based antibiotic use ► Opioid use ► Acetaminophen or non-steroidal anti-inflammatory drug use
Danish Agency for Labour Market and Recruitment registry[52]	The agency monitors the labour market by combining own statistics and surveys with data from Statistics Denmark on unemployment and structural characteristics of the labour market.	► Incremental cost-effectiveness: Costs related to sick leave from work

LOS, length of stay; PJI, prosthetic joint infection; SAE, serious adverse event; THA, total hip arthroplasty.

be extracted from DNPR, DHR, MiBa and HAIBA. Positive culture samples (aspirations, tissue biopsies or fluid) must be obtained from the relevant hip joint. Sinus tract communication with the joint or prosthesis visualisation, is expected to be captured as an indication of deep infection reported to DHR by the surgeon on revision. Insufficient gathering of biological samples during reoperation may hamper the outcome. Any inaccuracy in identifying outcomes will likely be non-differential, that is, occurring evenly in the two arms. As part of standard care, multiple deep tissue samples are obtained at revision surgery. All samples are sent for microbiological analysis at one of ten regional departments of clinical microbiology. All samples are cultured aerobically and anaerobically for 5–14 days. Selected samples are examined by specific and/or broad-range 16S ribosomal RNA gene PCR. Microbiological results, including bacterial identification and susceptibility, can be obtained from MiBa.

In contrast to EBJIS,[58] we have not included histological examination of intraoperative tissue biopsies, erythrocyte sedimentation rate, white cell count nor biomarker analysis in joint fluid, as these analyses are not routinely

performed in Denmark. CRP levels must be interpreted with caution and cannot stand alone.[30]

Secondary outcomes

The secondary outcomes are captured within 90 days of primary THA.

Serious adverse events

Number of patients with one or more serious adverse events (SAEs). SAEs are defined according to the guidelines provided by the International Council for Harmonisation of Technical Requirements for Human Use (GCP).[59] 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:

- Results in death.
- Is life-threatening—in the investigator's opinion the patient was in immediate risk of death from the adverse event when it appeared.
- Requires hospitalisation or prolongs existing hospitalisation.
- Results in permanent or significant disability.

SAEs are recorded from DNPR.

Potential PJI referred to as PJI-likely

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

1. One single intraoperatively obtained positive culture obtained from reoperation (aspiration fluid OR tissue biopsy) regardless of microorganism.
2. One single positive culture obtained from aspiration of synovial fluid regardless of microorganism AND any antibiotic prescriptions (Anatomical Therapeutic Chemical, ATC category J01) redeemed.

These definitions of PJI-likely are based on a modified version of EBJIS[58] as described previously (see primary outcome) and the study by Milandt *et al*[60] where first-time revisions with one positive culture were found to have a higher risk of rerevision 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.

Length of stay for hospitalisation

Length of hospital stay is defined as number of postoperative overnight stays, including transferals to other departments and hospitals within 24 hours. Data on length of stay is acquired from DNPR.

Cardiovascular events

Incidence of cardiovascular events. Cardiovascular event is defined a priori to include thromboembolic complications including venous thromboembolism, myocardial infarction, atrial fibrillation and stroke based on the diagnostic ICD-10 codes listed in online supplemental appendix B. Data will be extracted from DNPR.

Hospital-treated infections (not PJI or PJI-likely)

Any hospital-treated infection is defined as any first-time hospital admission with a primary or secondary infection diagnosis after discharge from index THA surgery. Hospital-treated infections are identified from DNPR based on ICD-10 codes listed in online supplemental appendix C. The list of infections includes chronic and more rare infections, to detect possible flare-up in any possible ongoing infections. Infections treated during index admission for arthroplasty surgery, are not included in this outcome. Due to a high risk of different registration praxis for urinary tract infections (UTI) among Danish hospitals a sensitivity analysis is planned combining diagnosis-codes for UTI with UTI-specific antibiotic use in the general practice, obtained from NPR. There is no economic benefit for the departments when coding for UTI. The validity of the coding of UTI in the DNPR has been examined in the Danish context and the PPV for UTIs was 77%.[61]

Community-based antibiotic use

Community-based antibiotic use is defined as proportion of patients with at least one dispensing of any antibiotic after discharge from primary THA surgery. Community-based antibiotic use is a surrogate measure of any community-treated infection and is defined as at least one dispensing for narrow-spectrum and broad-spectrum antibiotics based on the ATC classification codes. Medications are coded according to the ATC codes listed in online supplemental appendix D. All antibiotics in Denmark require prescriptions from a physician and these will be identified using NPR.[51]

Opioid use

Proportion of patients with at least one dispensing of any opioid after primary THA surgery. All opioids in Denmark require prescriptions from a physician and these will be identified using NPR.[51] Following ATC codes (including all subcodes) are included: N01AH (opioid anaesthetics), N02A (opioids), N07BC02 (methadone) and R05DA04 (codeine). Duration of treatment will be calculated based on no. of packages and volume. Since there is no clear definition of opioid users, we define opioid users as patients who redeemed two opioid prescriptions within six months before THA. We believe that two separated redeemed prescriptions supports that the patient is in fact using the medication.

Use of acetaminophen or non-steroidal anti-inflammatory drugs

Proportion of patients with at least one dispensing of any acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) after primary THA surgery. Prescriptions of analgesics will be identified using NPR.[51] All analgesics in Denmark except 10-tablet packages of acetaminophen/ibuprofen of dose 200 mg 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 six months before THA.

The validity of Danish Prescription Data to measure use of NSAIDs and quantification of bias due to non-prescription drug use has been examined. The prevalence of hospital sector-based and primary sector-based misclassification of true NSAID use as non-use was below 5.5%.[62]

Exploratory secondary outcomes

There will be several explorative outcomes focusing on the patient, health economy and the prognosis of the THA.

Incremental cost-effectiveness

The incremental cost-effectiveness will be calculated based on the costs per patient in the two antibiotic treatment arms. Costs related to antibiotic prophylaxis, hospital admissions and readmissions, hospital outpatient visits, visits to general practitioner and costs related to sick leave from work will be included. Hospital costs will include both those relevant to index surgery and those for other non-joint reasons. Data will be collected from DNPR, CRS and STAR.

Any revision after THA

Revision surgery is defined previously (see primary outcome). Rate of revision is defined as revision due to any cause within 1 year from primary THA surgery. Rate of revision will be recorded from DHR and DNPR.

Mortality

One-year mortality rate is defined by date of death due to any cause within 1 year after primary THA surgery. Data will be collected from CRS. Data will be collected for 1-year post final inclusion corresponding to a total of 3 years from December 2022.

Antimicrobial resistance and clonality

Changes in antimicrobial resistance and clonality of invasive pathogens between the two antibiotic treatment arms will be compared to detect signatures of potential selection. Data will be collected from HAIBA and using genomic analyses.

Sample size and power considerations

Based on existing Danish national statistics, we anticipate that we will be able to include up to 20 000 eligible individuals undergoing a THA when enrolling consecutively across 36 clinical centres over the 2-year period; that is, it would potentially enable a pragmatic intention-to-treat (ITT) population of up to 10 000 patients in each group (i.e. up to 10 000 individuals exposed to a single-dose antibiotics only).

Choice of the non-inferiority design will enable deliverance of substantial evidence to change clinical practice, if the effectiveness in prevention of PJI with a single dose of prophylactic antibiotic is comparable to antibiotic practices of longer duration (i.e. multiple doses). Members of the Danish orthopaedic community have been involved in deciding the potentially increased serious infection rate difference, we are willing to tolerate. Since the sample size was fixed a priori, conditioning on the standard flow of total hip arthroplasties in Denmark, we did not perform any formal power and sample size estimations. 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 baseline PJI rate in Denmark is between 0.5% and up to 5%, varying at departmental level.[63] It was decided that we will be willing to 'ignore' (i.e. tolerate) a potentially increased serious infection rate difference of up to 0.1% (1‰ more having a PJI, i.e. up to one per thousand). This will be the upper point for a potentially increased PJI rate difference, for which non-inferiority will be shown. In a cluster randomised trial like the present, it is not individuals who are randomised rather it is the clinical centres which need to be considered for the clustering effect when analysing the data. We will apply mixed-effects models (with random effects for clinical centres), including the correlation within clusters and thus provide appropriate standard errors.

If we assume that the PJI risk is similar in the two groups (with 10 000 patients in each group) we should be able to achieve a precision (narrowness) in the two-sided 95% CIs around the OR (OR=1.000) from a generalised linear mixed model, with 95% limits from 0.757 to 1.321; with a random effects factor for the 36 individual centres, assuming no main effect of period (year). Non-inferiority will be shown if the upper limit of the two-sided 95% CI for the OR is less than 1.32 for single dose as compared with multiple doses. With the precision we expect to achieve, we believe that the results of this cluster randomised, non-inferiority trial will deliver necessary evidence to potentially change clinical practice on antibiotic prophylaxis dosages in the future.

Another way to present our expected outcome and similarity between groups, is visualised in the precision plot in figure 3, with expected two-sided 95% CI range. If we (naively) assume that the outcome for all the individual patients is independent of clinical centre (i.e. with no clustering) and identically distributed, with 10 000 patients in each group and a 1% risk of PJI, we will expect a two-sided 95% CI in absolute terms range from −0.28% (−2.8‰) to +0. 28% (+2.8‰).

Sequence generation and allocation concealment mechanism

In this cluster randomised trial, each cluster (any specific department of orthopaedic surgery or centre; e.g. C_1, C_2, C_3…, C_{36}) is the unit randomised (i.e. in a traditional RCT, the individual study participant is randomised). The outcomes of interest are recorded and analysed for each participant individually nested within cluster. Participants fulfilling the inclusion criteria will have data treated as

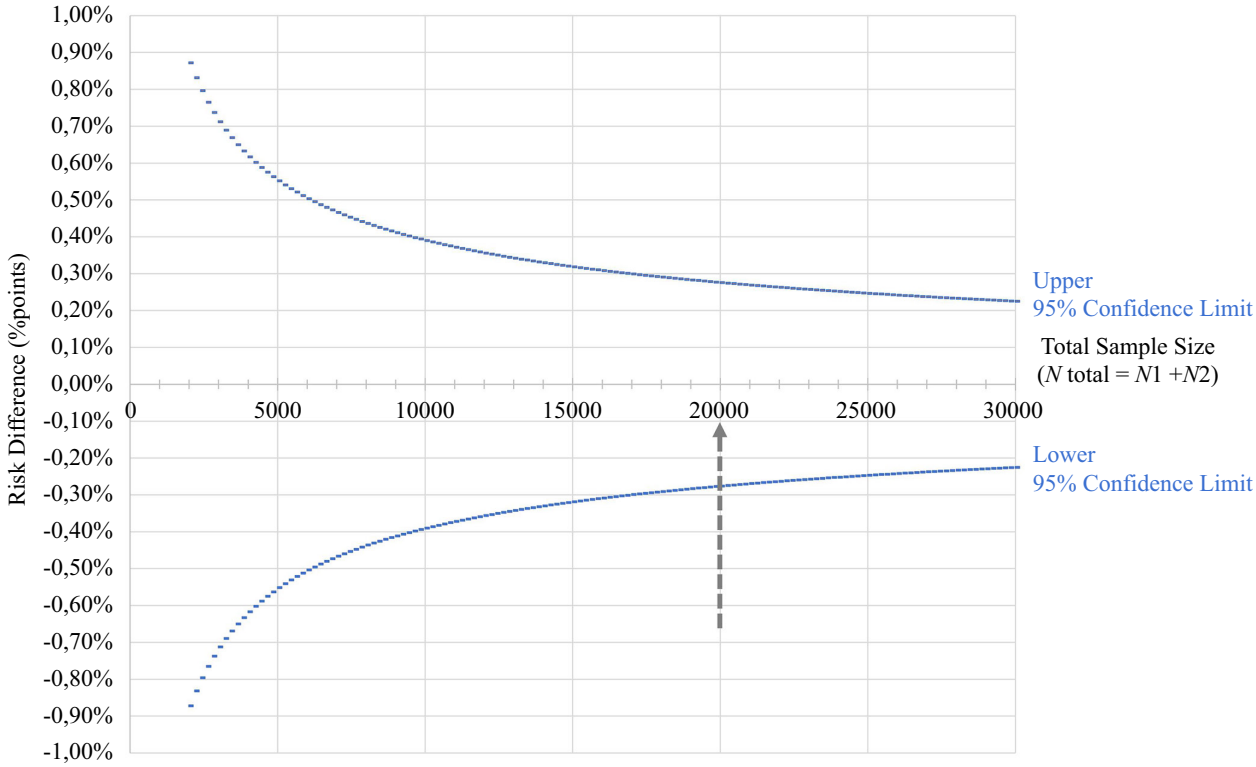


Figure 3 Precision plot. Expected two-sided 95% CI.

planned (organised) conditioning on the local hospital depending on the year of surgery.

Implementation

The senior biostatistician was responsible for the randomisation process. Each centre will be allocated a code by the senior biostatistician responsible and reported to a central database. The randomisation and allocation procedure will be known for the given year. To minimise the risks of unnecessary protocol violations, local study coordinators have been assigned at each study site prior to study start. The local study investigators consist of a team of an orthopaedic surgeon or an anesthesiologist and a nurse. The team was responsible for change of the standardised departmental instructions for antibiotic prophylaxis according to randomisation, prior to study start. Furthermore, they are responsible for organisation and thorough information of all relevant personnel at the respective study sites. Relevant material has been developed and organised by the authors and distributed to the local study coordinators. Meetings were held in the summer and autumn of 2022. New meetings are planned for the summer and autumn of 2023, where the cross-over of treatment is planned. Furthermore, any protocol deviations or violations which could occur, will be reported by the local investigators to the principal investigator and sponsor at 6-month evaluations. All patients with protocol deviations will be included in the ITT analysis. Any changes in departmental SSI preventive measures will also be reported at the 6-month evaluations.

Blinding

The study will not be blinded. It is considered infeasible to expose participants and clinical personnel to blinding as any specific clinic will follow the specific and known (single-dose or multiple-dose) antibiotic practice during an entire 1-year period (before switching).

Statistical methods

The point of a non-inferiority test is to prove that results are at least not appreciably worse. A non-inferiority test can show that a single dose of antibiotics causes no more serious infections than multiple doses of antibiotics.[35] Non-inferiority will be shown if the upper limit of the two-sided 95% CI for the OR is less than 1.32 for the single-dose regimen compared with the multiple-dose regimen.

The primary analyses will be based on the ITT population based on the full analysis set; that is, all patients undergoing the prespecified surgery using the antibiotic dose corresponding to the specific year (cross-over, cluster randomisation). Two-sided 95% CIs will be estimated and reported enabling (standard) superiority interpretations. The primary statistical analysis model will be based on a generalised linear mixed model, with a random effects factor applied indexing the clinical centre (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 (two levels: single-dose and multiple-dose, respectively), as well as the interaction between the two (period×group; 4 levels: 2×2 levels).

Important premises to be aware of when considering the analysis of this pragmatic registry-based, multicentre,

open-label, cross-over, cluster randomised, non-inferiority trial, is the fact that results from participants enrolled (and operated) from the same centres cannot be assumed to be mutually independent (i.e. cluster randomisation). Also, the element of cross-over could also potentially introduce some complexities to the primary statistical models. In a cluster randomised trial like the Pro-Hip-Quality OA trial, the cluster (centre) is in principle the unit of analysis (i.e. in a traditional RCT, the individual study participant is randomised—and thus, the unit of analysis). In both types of trials, however, the outcomes of interest are recorded for each participant individually. The ITT principle asserts the effect of a treatment policy (i.e. the planned treatment practice (single-dose or multiple-dose antibiotics) implemented locally), rather than the actual treatment given (i.e. it is independent of treatment adherence—e.g. if more than one dose is given despite this being a protocol violation). Accordingly, participants allocated to a treatment group ($X_{\text{Single-dose}}$ and $X_{\text{Multiple-dose}}$, respectively) will be followed up, assessed and analysed as members of that group, irrespective of the actual antibiotic practice used in the specific clinic (i.e. independent of physicians' withdrawals and cross-over phenomena).

Subgroup analyses

In secondary analyses, the following known and suspected baseline risk factors for PJI will be compared: age (≥65 vs <65 years), sex (male vs female), body mass index categories (≥30 vs <30 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 vs cementless fixation) 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.[64]

Patient and public involvement

Patients have been interviewed and the clear message from the patients is that infection is a feared complication and that there is no reason to use more antibiotics than needed. A panel of two patient representatives from DHR has been present in the trial planning phase through meetings. They have been asked for inputs and to comment on the trial protocol. They find the study well designed and highly relevant.

ETHICS AND DISSEMINATION

This trial will be conducted in accordance with the principles of the Declaration of Helsinki and according to GCP standards.[65] It 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 an option without informed consent from the patient with the reason, that the patient's treatment in both interventions follow standardised clinical practice described in the departmental guidelines.

The study will be reported according to a pragmatic combination of the following CONSORT statements: 'CONSORT for trials conducted using cohorts and routinely collected data,'[31] 'Pragmatic Trials',[32] 'Cluster Randomised Trials',[33] 'Randomised Cross-over Trials',[34] and 'Noninferiority and Equivalence Randomised trials'.[35] The manuscript will follow Consolidated Standards of Reporting Trials.[66] Any important protocol amendments will be registered at ClinicalTrials.gov and an ethics amendment reported to The Danish Medicines Agency and The Committees on Health Research Ethics for The Capital Region of Denmark (VEK).

Authorship is granted according to the guidelines provided by International Committee of Medical Journal Editors.[67] Funding sources will have no influence on the interpretation of data. Access to the study data for other researchers can be requested. We commit to disseminate our findings from this trial by publication of the results in peer-reviewed medical journals and through scientific and academic meetings and conferences.

All data entries and changes are logged in REDCap at The Capital Region of Denmark. Data are entered via an encrypted connection and fulfil the demands for data security and thus the database may store social security number and meets the GCP requirements for use of eCRF, when conducting medical trials. After ended study (10 years after inclusion of the last patient), all data will be pseudonymised.

With regard to safety considerations, this trial will not involve any additional risks of adverse events exceeding those considered normal for the surgical procedure and administration of antibiotics. Adverse events will be reported following usual practice, from the respective departments to the Danish Medicines Agency. Antibiotic prophylaxis in this study follows current guidelines for THA surgery and both cloxacillin, cefuroxime, single-dose and multiple-dose regimens are already used as standard practice by Danish surgical centres. The dosage practices were therefore already current standard practices prior to this trial.

Data monitoring and safety committee

A data monitoring and safety committee will not be established. The Pro-Hip-Quality OA Trial follows well-known interventional drugs and follows already applied and well-established treatment standards, thus making interim decisions on termination difficult due to insufficient study power.

Timeline

2021: Application for approval from the Committees on Health Research Ethics for The Capital Region of Denmark (VEK) and The Danish Medicines Agency.

2022–2023: Enrolment of participants.

Spring/Summer 2024: Data analyses of primary and secondary outcomes, writing and submission of manuscript.

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Competing interests None declared.

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