CLINICAL STUDY PROTOCOL

DAICY trial – Dual vs. Single-Antibiotic Impregnated Cement in Hemiarthroplasty for Femoral Neck Fracture: A Register-based cluster-randomized cross-over controlled trial

Clinicaltrials identifier	NCT
Version Number:	3.0
Date:	2021-11-23
Research Body:	Region Västerbotten
Principal investigator(s):	Sebastian Mukka

SYNOPSIS

Title: DAICY trial – Dual vs. Single-Antibiotic Impregnated Cement in Hemiarthroplasty for Femoral Neck Fracture: A Register-based cluster-randomized cross-over controlled trial

Rational for conducting the study: Periprosthetic joint infection (PJI) is the most feared complication following prosthetic replacement of the hip joint and is associated with increased mortality, morbidity and economic burden. The aim of the trial is to investigate whether the risk of periprosthetic joint infection after treatment with hemiarthroplasty performed due to femoral neck fracture is reduced after the use of dual-impregnated antibiotic loaded cement. Our ***primary outcome variable*** is the incidence of periprosthetic joint infection within one year after the index procedure. ***Secondary outcome variables*** include the occurrence of re-operations for any reason, bacteriology, antibiotic treatment, mortality and health care costs.

Study design: Register-based, cluster randomized controlled trial

Study population: Patients aged ≥60 years

Number of patients: 7,000

Inclusion criteria:
- Age ≥60 years
- Diagnosis: displaced femoral neck fracture type AO 31-B2 or B3/Garden type 3 or 4
- Eligible for hemiarthroplasty according to local guidelines and routines

Exclusion criteria:
- Previous inclusion of contralateral hip in the present study
- Pathological or stress fracture of the femoral neck, or fracture adjacent to a previous ipsilateral hip implant
- Unavailability of both interventions for a study participant (e.g., sensitivity to any of the components in the bone cement)
- Patients that have actively marked their hospital charts with an added privacy notice

Primary outcome variable:
The primary outcome will be the occurrence of periprosthetic joint infection of the index joint within one year.

Trial period: Jan 1st 2022 - Jan 31st 2027

SIGNATURE PAGE

I confirm that I have read and understood this protocol and that I will work according to the protocol. By my signature, I agree to personally supervise the conduct of this study in my affiliation and to ensure its conduct in compliance with the protocol, IRB/EC procedures, the Declaration of Helsinki, and local regulations governing the conduct of clinical studies.

Signature Principal Investigator	Date (yyyy-mm-dd)
Sebastian Mukka	
Printed name of Principal Investigator	
Signature Head of Department	Date (yyyy-mm-dd)
Printed name of Head of Department	

Copy for study site; to remain with study protocol

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Signature Principal Investigator	Date (yyyy-mm-dd)
Sebastian Mukka	
Printed name of Principal Investigator	
Signature Head of Department	Date (yyyy-mm-dd)
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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ASA	American Society of Anaesthesiologists
DIAC	Dual-Impregnated Antibiotic Cement
FNF	Femoral Neck Fracture
HA	Hip Hemiarthroplasty
ICD	International Classification of Diseases
PJI	Periprosthetic Joint Infection
NPR	National Patient Register
RCT	Randomized Controlled Trial
SAR	Swedish Arthroplasty Register
SDR	Swedish Drug Registry
SFR	Swedish Fracture Register

1. INTRODUCTION

1.1. Background

In Sweden, *hip fractures* annually affect close to 20,000 elderlies, often frail patients. Although the incidence of this injury seems to be stabilizing or even slightly declining, hip fractures cause an annual economic burden of no less than 800 million € in Sweden alone and the costs are increasing (1, 2).

Femoral neck fractures (FNFs) are mainly a fragility fracture in the elderly and frail, predominantly affecting women after menopause but reports have indicated an increased incidence in elderly men (3). The average age of patients suffering a hip fracture has been increasing over the last decade and is around 80 years with an exponential increase of incidence with age (4). The lifetime risk of hip fracture in Sweden is 20% for women and 11% in men (5). A hip fracture is related to a doubled risk of death during the first year after fracture in comparison to age-matched controls (6).

FNFs are classified according to the degree of fracture displacement and the most widely used is the Garden classification. As displacement increases, the risk of disruption of the blood supply to the femoral head increases. Displaced fractures represent two thirds of the FNFs. With a disrupted vascular supply, the risk for healing disturbances, complications and reoperations increases when treated with internal fixation with screws or pins. For displaced fractures in elderly patients treated with internal fixation, failure rates of 35-50% have been reported in the literature (7). The most frequent complications are avascular necrosis and pseudarthrosis due to disrupted vascular supply of the femoral head and mechanical failure due to inadequate fixation (8). Long-term follow-up studies have emphasized the superiority of replacing the joint by hip arthroplasty in comparison to internal fixation in regard to hip function (9-11). Hip arthroplasty with either a total or hemiarthroplasty is a reliable option due to its ability to restore hip function and reduce the need for secondary surgery after an FNF (12). In hip arthroplasty implants are fixed to the bone with or without the use of bone cement (polymethyl methacrylate). Uncemented fixation in FNF patients has been linked to an increased risk for periprosthetic femoral fractures (13). In Sweden cemented hip arthroplasties are most frequently used and are regarded as the gold standard for FNF patients.

Bone cement or polymethyl methacrylate (PMMA) is widely used for implant fixation in orthopaedic procedures. PMMA acts as a void-filler that creates a tight space which holds the implant against the bone and acts as a ‘grout’. Bone cements have no adhesive properties and rely instead on close mechanical interlock between the irregular bone surface and the prosthesis. PMMA is an acrylic polymer that is formed by mixing 2 sterile components, a liquid methyl methacrylate monomer and a powdered methyl methacrylate-styrene polymer. When mixed the liquid monomer polymerizes around the pre-polymerized powder particles to form hardened PMMA. An exothermic reaction generate heat in the process which reaches temperatures of around 82–86 °C in the body. In order to make the cement visible on radiographs, a contrast agent is added (zirconium dioxide or bariumsulphate).

Bone cement has proven useful as carrier of specific active substances, e.g., antibiotics added to the powder component. Antibiotics are delivered directly to the surgical site which in turn give a high

concentration and low systemic concentration well below the clinical routine dosages for systemic single injections. Various antibiotics have been successfully mixed and used with bone cements like gentamycin, clindamycin etc. Compared to intramuscular administration, systemic concentration levels of gentamycin are low with bone cement, usual maximum concentrations below 1 µg/ml (<10%) without any detectable systemic levels after 7 days. In Sweden, antibiotic loaded cement is routinely used and represents the standard of care in cemented primary total hip arthroplasty, always in combination with systemic prophylaxis to reduce the risk for revision surgery due to periprosthetic joint infection (PJI) (14-17). The type of antibiotic impregnated bone cement varies between regions, countries and type of surgical procedure performed.

In Sweden, the most commonly used cement is the low dose (≤ 2 g of antibiotic powder per 40 g cement) impregnated cement (Gentamycin). For revision procedures, a higher dose of gentamycin in combination with either vancomycin or clindamycin is often used and labelled dual-impregnated antibiotic cement (DIAC). For patients at risk for sustaining a PJI, i.e., hip fracture patients, some hospitals routinely use dual-impregnated antibiotic cement for hip arthroplasty procedures.

Surgical site infection (SSI) remains a severe complication linked to increased mortality, prolonged hospitalization, revision surgery, long-term treatment with antibiotics, dramatically increased costs and a strenuous rehabilitation (18). SSI is the third most commonly occurring healthcare-associated infection, accounting for 16% of reported infections (18). Rates of infection up to 7.3% for hemiarthroplasty have been reported (19). Parenteral antibiotics in elective primary total hip arthroplasty for osteoarthritis, have been shown to reduce SSI and antibiotic loaded cement, combined with systemic antibiotics is considered to be the most effective prophylaxis against infection (15, 16). The potential of developing resistance among infecting organisms by using local antibiotics in general and especially DIAC has been under discussion but the clinical evidence remains sparse (20, 21).

In a recent randomized study from England, the rate of infection following hemiarthroplasty for FNF was reduced from 3.5% with conventional single-impregnated antibiotic-loaded cement to 1.1% by using high-dose DIAC (22). Observational studies have indicated similar reduction in PJI (20, 23). At present there is one ongoing large scale clinical (White 8) trial to further entangle the potential effect of DIAC in the United Kingdom (24). The aforementioned study has a shorter follow-up and the occurrence of multi- and pan-resistant bacteria is higher in the United Kingdom. The differences motivate a Scandinavian multicentre trial, for better external validity. The chosen outcomes in the above mentioned and the present trial will enable us for a future comparison of the obtained results.

1.2. Rationale for conducting this study

Dual-impregnated antibiotic loaded cement is promising in lowering the incidence of periprosthetic joint infection, however there is a need for large, sufficiently powered randomized controlled trials in a Scandinavian setting. In this prospective register-based cluster randomized cross-over study, the aim of is to compare standard low dose antibiotic impregnated cement and DIAC in patients above 60 years old with a FNF amenable for HA according to local guidelines. The primary outcome will be reoperations due to infection within 1 year.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary objective

1) The primary objective is to assess whether DIAC reduces the risk of PJI in patients with a femoral neck fracture treated with a HA by 50% within one year.

2.2. Secondary objective(s)

The secondary objective(s) of this study are to evaluate whether there is a difference between the intervention and control group in:

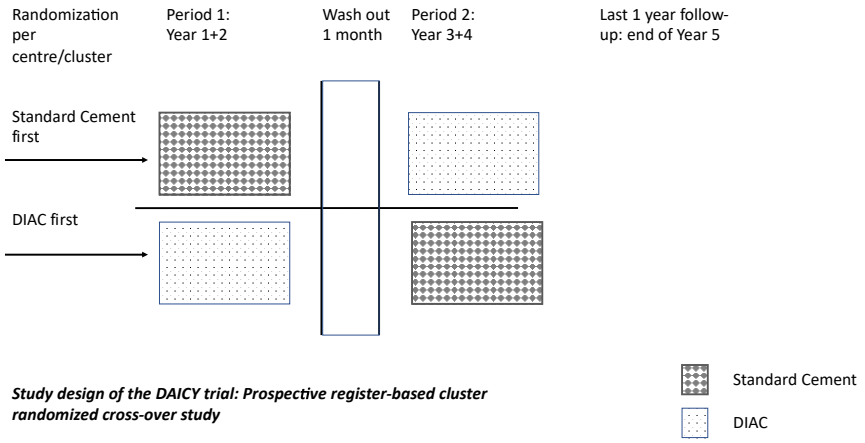
1) Antibiotic prescription obtained from the Swedish Drug register at 120 days and 1-year post-surgery.
2) Resistance patterns of infections; all infections identified in the primary endpoint will be assessed for antibiotic resistance profiles. Identified in the NPR or SAR and obtained by assessing the medical files.
3) Mortality obtained from the Swedish Fracture Registry (SFR) within 90 days and 1-year post-surgery.
4) Resource use; cost data will be obtained from national databases or will be estimated in consultation with the hospital finance department at 120 days and 1-year post-surgery.

3. STUDY DESIGN AND PROCEDURES

3.1. Overall study design and flow chart

The proposed study is designed as a prospective register-based cluster randomized cross-over study design. The study will be pragmatic, with broad eligibility criteria, participant inclusion by treating department (site), and great freedom for surgeons to choose between different implant brands, surgical approaches and post-operative regimes.

Two thirds of Swedish patients 60 years and above with a displaced femoral neck fracture receive a cemented HA. 2230 procedures were registered in the SFR during 2019 and were eligible for inclusion in the present study.



Study design of the DAICY trial: Prospective register-based cluster randomized cross-over study

3.2. Rationale for study design

The prospective register-based cluster randomized cross-over study design enables us to perform a national multicenter registry-based study without any additional follow-up visits. In this elderly population with a high prevalence of cognitive impairment, the main advantage is the possibility to recruit a large sample size without burden the patients with additional follow-up visits. The study population consists of an elderly and fragile group of patients, with a high burden of comorbidities, with the need of acute surgery with a HA after sustaining an FNF. This acute situation provides challenges to scientific evaluation and feasibility of participation in large multicenter clinical trials. The cluster randomized design is fundamental to the feasibility of recruitment and evaluation in this fragile group of patients.

The Swedish personal identity number allows the investigator to link registers on an individual level. Data on fracture classification, age, sex, type of trauma, time of diagnosis with radiography, time of surgical treatment will be collected in the SFR and the randomization will be performed within the SFR registry-platform. Further variables will be retrieved by cross-linking with the SAR with data on manufacturer and type of components (uni- or bipolar), cement type and any revision surgery performed. Data on reoperations are registered in the NPR. Mortality data is automatically available within the SFR and SAR, from the Swedish Tax Agency.

3.3. Study visits

There will be no formal clinical follow-up visits in addition to the local clinical routines. Data on reoperations and mortality is registered in the SFR, NPR and SAR.

4. STUDY POPULATION

4.1. Inclusion criteria

- Age ≥60 years
- Diagnosis: displaced femoral neck fracture type AO 31-B2 or B3/Garden type 3 or 4
- Eligible for HA according to local guidelines and routines

4.2. Exclusion criteria

- Previous inclusion of contralateral hip in the present study
- Pathological or stress fracture of the femoral neck, or fracture adjacent to a previous ipsilateral hip implant
- Unavailability of both interventions for a study participant (e.g., sensitivity to any of the components in the bone cement)
- Patients that have actively marked their hospital charts with an added privacy notice

4.3. Subject enrolment and randomization

In the first step of the study, the orthopedic departments included are randomized to start with either the control or intervention treatment. After the first period of 2 years is completed, the study site will change to use the other treatment for the patients included in the following period of 2 years. At each department, information regarding the study is made available on the official web page, the orthopedic ward and the outpatient department. All patients admitted and fulfilling the inclusion criteria and registered in the SFR or SAR will be included. After the index surgery, procedural details and patient characteristics will be collected within the SAR. Procedural details include type and brand of implant, type of components (uni- or bipolar head), type of cement (intervention: DIAC or control: Single-impregnated antibiotic-laden bone cement), surgical approach and type of antibiotic prophylaxis. Patient characteristics registered in the SAR include indication for surgery, age, sex, American Society of Anesthesiologists (ASA) grade and body mass index (BMI). Data on revision surgery performed and on reoperations are registered in the SAR. Data on reoperations are also registered in the NPR. Mortality data are automatically available within the SFR and SAR from the SDR.

4.4. Discontinuation and withdrawal of subjects

Subjects are free decline registration or to discontinue their participation in the SFR or SAR at any time without prejudice to further treatment. Already collected study data for these patients will be kept in the study database, however new data, including data from registries will not be added. Patients prematurely withdrawn from the study will not be replaced.

4.4.1. Premature termination of the study

The study group may decide to stop the trial or part of the trial at any time. Furthermore, the investigator should promptly inform the Ethics Committee and provide a detailed written explanation.

5. STUDY TREATMENTS

5.1. Identity of investigational implants

Group 1 (control): Cemented hemiarthroplasty with low dose single antibiotic cement Replacement of the femoral head and neck with choice of femoral head and stem. Cement used will be Heraeus Palacos R+G cement (Hanau, Germany) or Zimmer/Biomet Optipac cement – contains gentamicin 0.5 grams per 40 grams mix of cement.

Group 2 (exposed): Cemented hemiarthroplasty with high dose dual-impregnated antibiotic cement Replacement of the femoral head and neck with choice of femoral head and stem. Cement used will be Heraeus Copal G+C cement (Hanau, Germany) – contains gentamicin 1 g and clindamycin 1 g per 40 gram mix of cement.

5.2. Blinding

There will no blinding of the bone cement for the surgeon.

5.3. Randomization

All participating departments will be randomized in a 1:1 ratio to either the sequence dual impregnated antibiotic cement (intervention) period followed by standard cement (control) period, or the sequence control period followed by intervention period. All participating departments will be randomized once, using a single permuted block of size equal to the number of clusters (or the number of clusters plus one if the number of clusters is odd). We do not expect to enroll further clusters after trial start, but in that event, new clusters will be randomized to either treatment sequence using 1:1 simple randomization, to ensure that the decision to enter the trial is not affected by knowledge of treatment sequence allocation.

5.4. Concomitant medication

Patient will receive their ordinary medications and the standard pre- and postoperative treatment at each participating center including standard preoperative antibiotic prophylaxis.

6. STUDY MEASUREMENTS AND VARIABLES

6.1. Primary outcome variable

Periprosthetic joint infection of the index joint within one year

The definition of PJI will be that the treating physicians defined presence of a PJI and started treatment (re-operation, or suppressive antibiotics, or combinations thereof). The investigators will use the SFR, NPR, SAR and the SDR to identify potential PJI by the registration of any of the International Classification of Diseases (ICD; version 10) codes or NOMESCO codes indicative of

this complication (see Appendix 1). In cases when these codes are present a review of the medical records will be performed to identify patients.

The hazard of infection in the intervention compared to the control group will be assessed by fitting adjusted Cox proportional hazards models.
The review of medical records will capture any re-operation records for surgery related to the index hip fracture, details of antibiotics prescribed, microbiology reports if samples of the suspected infected tissues around the hip were sent for analysis.

6.2. Secondary outcome variable(s)

The relative hazard of the any re-operation of the index joint and mortality within 1 year in the intervention compared to the control group will be assessed by fitting adjusted Cox proportional hazards models (see *"Statistical methods"*), and a risk increase of >20% within one year will be considered clinically relevant.

Any re-operation

Re-operation will be treated as a binary categorical variable, recorded together with an underlying time-to-event variable, and will be defined as the occurrence of any surgical procedure performed on the previously treated hip within one year after surgery. The occurrence of re-operations is assessed by linking study participants with the NPR as described above, and will be defined by registration of at least one of the specified ICD or NOMESCO codes (Appendix 1).

Antibiotic suppression

Antibiotic prescription information will be obtained from the Swedish Drug Register at 120 days and 1-year post-surgery.

90-day and 1-year mortality

Occurrence of death (treated as a binary categorical variable), together with date and causes of death, are registered in the NPR and SFR, and 90-day and 1-year mortality will be obtained by cross-matching all study participants with the NPR and SDR.

Resistance patterns of infections

Resistance patterns of infections; all infections identified in the primary endpoint will be assessed for antibiotic resistance profiles. Identified in the NPR or SAR and obtained by accessing the medical files.

Cost-effectiveness

Procedural costs for intervention and control treatment will be recorded. Procedural costs of admissions for reoperations will also be collected from all units. This allows for basic health economic calculations using Markov modelling.

7. STATISTICS

Sample size calculation

Power was calculated for the proposed trial design and primary analysis using simulation. In addition to the hypothesized intervention effect, the power depends on the number of clusters, the number of yearly operations at each cluster, the PJI frequency in the control group, and intra-cluster and intra-cluster-period correlation.
10000 data sets were randomly generated from a model with individual outcome probabilities

$$\text{logit}(\Pr\{Y_{ijk}= 1|c_i, p_{ij}\}) = \mu + \beta_\tau\tau_{ij}+ \beta_\pi\pi_j+ c_i+ p_{ij},$$

where Y_{ijk} is the indicator for PJI in patient *k* in period *j* in cluster *i*, τ_{ij} indicates DIAC treatment in cluster *i* in period *j*, and π_j is the period indicator. For each simulated data set, the cluster and cluster-period effects c_i and p_{ij} were sampled from normal distributions with variance selected to provide the assumed intra-cluster and intra-cluster-period correlations. The overall period effect β_π is unimportant for the purpose of the simulations and was set to 0, and the intercept μ and treatment effect β_τ were set to provide the assumed control and intervention arm outcome probabilities.
The updated simulation model includes the 15 verified participating hospitals, using their recorded yearly number of operations for 2019 (64, 132, 209, 294, 224, 97, 67, 144, 71, 45, 32, 94, 97, 112, and 65). Hence the 4-year trial is assumed to include 7,000 patients in total.
The 1-year risk of PJI in the included population is assumed to be 3% in the control group. This estimate is based on the observed PJI frequency in Sweden (25, 26), and assumed to be conservative. Power was calculated under the hypothesis of 1.5% 1-year risk of PJI in the intervention group will be considered the minimal clinically significant difference motivating a general change in routines and recommendations from single-impregnated antibiotic-loaded cement to DIAC.
Unfortunately, there is no available data to estimate intra-cluster and intra-cluster-period correlations in PJI. For this reason, we simulated power under 3 scenarios; small correlations (0.01 within cluster and 0.008 within cluster-period), medium correlations (0.05 and 0.04 respectively), and large correlations (0.1 and 0.08 respectively), see (27). Under these scenarios, the power to obtain a 2-sided $p<0.05$ for the hypothesis of no difference was found to be 90%, 86% and 80%, respectively.

7.1. Statistical analysis

Generally, all statistical analyses will account for the cluster-randomized crossover design to ensure correct type I error rates and confidence intervals (CIs). Analyses will be performed using the intention-to-treat principle including all eligible patients with available follow-up data within a study site according to allocated treatment for the study site. The threshold of statistical significance will be set at a 2-sided p-value of 0.05.

As primary analysis, the difference in risk of PJI after the intervention treatment compared to the control group will be estimated using linear regression for aggregated cluster-period data, with proportion of events within a cluster period as dependent variable and treatment, cluster, period

and proportion of females within the cluster period as independent variables. Estimated difference in risk with 95% confidence interval and 2-sided p-value will be presented.
With the registry-based follow-up we assume that follow-up will be complete and the quality of data adequate with confirmation of data in an individual medical charts review. In the rare case that a patient has incomplete follow-up and a value for primary outcome is missing the patient will be excluded from analysis. Death before PJI will be handled as no PJI.
Secondary event outcomes will be analyzed and described in the same way as for the primary outcome.
Supplementary and sensitivity analyses will be performed for all event endpoints. An analysis of the primary outcome including all ITT patients will be performed using multiple imputation for individual outcomes based on individual patient characteristics, details to be described in the Statistical Analysis Plan. Sensitivity analyses to investigate the impact of handling death as non-event, in addition to analyzing death as a secondary outcome, will include analyses of the composite of PJI and death. As a sensitivity analysis for the asymptotic approximation in the linear model, a 2-sided p-value for no difference in proportion will be obtained by Monte Carlo randomization inference based on the likelihood ratio.
As a supplementary analysis, treatment contrasts as odds ratios will be presented for all event outcomes, with 95% confidence intervals. An appropriate method, accounting for the cluster-crossover design, will be pre-defined in the Statistical Analysis Plan. Note that while the linear model for aggregated data, used for the primary analysis, is often robust, asymptotic tests based on other models have a risk of inflated Type I error rates when the number of clusters is small (29).
For mortality, an additional supplementary analysis of time-to-event will be performed, using a method accounting for the cluster-allocated crossover design.
Allocated and actual performed treatments will be described in a CONSORT diagram, and additional per-protocol analyses will be undertaken as sensitivity analyses. Secondary outcomes will be presented without formal multiplicity adjustment. A detailed statistical analysis plan will be completed before data base lock.
For all event outcome variables, pre-defined subgroup/interaction analyses to assess the homogeneity of the treatment contrast will be performed, for sex, age, ASA class (I-II or III-IV) and for the procedural characteristics type of stem, head and surgical approach. For categorical subgroup indicators, events will be described in each subgroup as for the entire population, and the treatment contrast in each subgroup will be estimated using a linear model at the cluster level, with proportions summarized by cluster period and subgroup indicator as dependent variable, including treatment, cluster, period and subgroup and interaction between treatment and subgroup as independent variables, and presented with nominal 95% CI for each subgroup and the interaction p-value.
For health economic studies, analyses of cost per quality-adjusted life year will be described in a separate analysis plan.

Data Management

7.2. Recording of data

All study data will be transferred from SFR, SAR, SDR and the NPR into the study database. Data relevant to assess known confounders and primary and secondary outcomes will be collected retrospectively from the registries mentioned above.
The investigator ensures that all source documents are accessible for monitoring.

Table. *Collection of data.*

	Swedish Fracture Registry	Swedish Hip Arthroplasty Registry	National Patient Registry	Swedish Drug Registry	Medical charts
PJI	X	X	X	X	X
Re-operation	X	X	X		X
Antibiotic suppression				X	X
Mortality: 90d and 1y	X		X		
Resistance patterns					X
Cost-effectiveness			X		X

7.3. Data storage and management

All data are recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification. All source data at each participating study center, a copy of the completed study database, original protocol with amendments and the final report will be stored at the Orthopedic Department at Umeå University Hospital for a minimum period of 15 years after termination of the trial.

At the conclusion of the study, the occurrence of any protocol deviations will be determined. Data from the SFR on all study participants will be fused with all data on the aforementioned study participants available in the SAR and the SDR one year after the inclusion of the last patient. This combined dataset will then be sent to the NPR to obtain all registered ICD and NOMESCO codes for all study participants from the date of inclusion and onward. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and available for data analysis.

8. QUALITY CONTROL AND QUALITY ASSURANCE

The coordinator will have regular contacts with the department/center to verify and to confirm that facilities remain acceptable, that the investigational team is adhering to the protocol, to verify inclusion/exclusion criteria. The investigator should ensure that all persons assisting with the trial are adequately informed and trained about the protocol, that the standardization defined in section 3.1 is adhered to.

8.1. Audits and inspections

Authorized representatives of the study group, or an Ethics Committee may perform audits or inspection at the center. The investigator must ensure that all study documents are accessible for auditing and inspection. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed and accurately reported according to the protocol, and any applicable regulatory requirements.

9. ETHICS

The study is performed in accordance with the protocol, with the latest version of the Declaration of Helsinki, and applicable regulatory requirements.

9.1. Ethics committee

The study has been approved by the Swedish Ethical Review Authority (dnr 2020-04815, Date of issue: 2020-10-22). The motivation of the waived individual informed consent is due to the nature of the intervention (Principle of Beneficence). The bone cement used in the intervention and control arms has essentially identical characteristics except for the mixture of the antibiotics. Both cements types are currently in clinical use. The Principal Investigator is responsible for informing the EC of any amendment to the protocol, in accordance with local requirements.

9.2. Informed consent

The local site investigator at each center will ensure that information for the present study is publicly visible on the web page of the hospital/region and on public display at the ward and outpatient clinic. The individual subject is not obliged to give written consent. The information is standardized and include about the nature, purpose and possible risks and benefits of the study. If a protocol amendment requires a change to the ICF, the Ethical committee must approve modifications that lead to a revised written information.

The monitor(s) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject.

The reasons for not applying individual informed consent are the following: The research poses no more than minimal risk. The bone cement is used in the present study is already routinely used in clincal practice in Sweden. The mechanical differences are minor and the differences in antibiotic concentrations appears only locally in the surgical area. At present, different orthopedic surgeons choose to use both types of bone cement for the present group of patients. Thus, the rights and welfare of subjects are not adversely affected. The feasibility of performing a large trial, to evaluate the true effect of bone cement on the rate of PJI including approximately 7,312 patients to a large extent having cognitive impairment, for an acute surgical procedure, are doubtful with written informed consent. When prospective research subjects are incapable of providing informed consent, a surrogate decision maker must provide consent on their behalf. The present study aiming as a stepwise introduction of DIAC bone cement in the present group of patients. The design improves the external validity of the study results and thus facilitate the implementation of the results to clinical practice.

9.3. Subject data protection

The study information presented at the web page of the hospital/region, at the orthopedic ward and outpatient department will incorporate wording that complies with relevant data protection and privacy legislation, the collection and by those persons who need that information for the purposes of the study.
The study information presented at the web page of the hospital/region, at the orthopedic ward and open clinic will explain that study data will be stored in a computer database, maintaining

confidentiality in accordance with national data legislation. All data computer processed by the study group will be identified by ten-digit personal registration numbers.
The study information presented at the web page of the hospital/region, at the orthopedic ward and open clinic will also explain that for data verification purposes, authorized representatives of the study group, a regulatory authority or an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

9.4. Insurances

The study subjects are covered by the Swedish Patient Injury Act by LÖF, the Swedish patient insurance.

10. PROTOCOL DEVIATIONS AND AMENDMENTS

Modifications to the signed protocol are only possible through approved protocol amendments and with the agreement of all responsible persons. Details of non-substantial amendments are to be clearly noted in the amended protocol.
A change that concerns; a new trial site, new principal investigator and or a new informed consent form should only be submitted to the concerned Ethics Committee.
In case of a substantial protocol amendment (e.g., change of; main purpose of the trial, primary/secondary variable, measurement of primary variable), the concerned Ethics Committee must be informed and should be asked for its opinion/approval prior implementation of amended protocol, as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The Investigator must not implement any deviation from, or change to the protocol, without discussion with, and agreement by the study group and prior review and documented approval/favorable opinion of the amendment from the relevant ethics committee, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study (e.g., change of telephone numbers).

11. REPORT AND PUBLICATIONS

After completion of the study, the results will be analyzed and a clinical study report will be prepared according to the CONSORT statement for cluster randomized studies (29). Within 1 year after the end of the study, the study group will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited Ethics Committee. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12. STUDY TIMETABLE

12.1. Study period

Estimated subject enrollment start: 2022-01-01
Subject enrollment preliminary end: 2025-12-31
Subject preliminary last follow-up: 2027-01-31

12.2. Definition of “End of study”

The study group will notify the concerned Ethics Committee of the end of the study within a period of 90 days. End of study is defined as 1 year after inclusion of the last subject.

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Appendix

1. ICD codes for primary and secondary outcomes.

Endpoint	ICD	NOMESCO
Periprosthetic joint infection	M00.0, M00.0F, M00.1, M00.2, M00.2F, M00.8, M00.8F, M00.9, M00.9F, M86.0F, M86.1F, M86.6, M86.6F, T81.4, T84.5, T84.5F, T84.5X, T84.7, T84.7F	NFSx, NFA12, TNF05, TNF10
Any reoperation		Any of the codes above, and: NFA00-22, NFA31-32, NFCx, NFF01-12, NFL09-19, NFL39-49, NFL69-99, NFM09-29, NFM49, NFM79-99, NFTx, NFWx

Endpoint	ATC	Minimum number of tablets
Drug prescription	J01XX08: 56 st J01XA02: 28 st J01XA01: 56 st J04AB02: 28 st J01XX09: 28 st J01XC01: 168 st J01CF05: 84 st J01FF01: 56 st J01CA04: 84 st P01AB01: 84 st J01MA02: 56 st J01MA06: 56 st, J01MA12: 28 st J01MA14: 28 st J01EE01: 56 st J01CE02: 168 st J01DB05: 56 st J01DB01: 56 st J01DC02: 56 st J01DC08: 56 st J01DD14: 28 st J01DD04: 28 st J01FA06: 56 st J01FA01: 112 st J01FA09: 56 st J01FA10: 28 st J01FA15: 56 st J01CR02: 56 st	56 st 28 st 56 st 28 st 28 st 168 st 84 st 56 st 84 st 84 st 56 st 56 st, 28 st 28 st 56 st 168 st 56 st 56 st 56 st 56 st 28 st 28 st 56 st 112 st 56 st 28 st 56 st 56 st