| RESEARCH ARTICLE `OPEN ACCESS`

The Adverse Effects Associated With Ibuprofen Use After Major Orthopaedic Surgeries—A Detailed Statistical Analysis Plan for the PERISAFE Randomized Clinical Trial

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ABSTRACT

The PERISAFE trial aims to assess the adverse effects associated with an 8-day postoperative treatment with ibuprofen after hip and knee arthroplasties. This paper outlines the detailed statistical analysis plan for the primary data. The PERISAFE trial is a randomized, placebo-controlled, blinded multicentre trial allocating 2904 hip- or knee-arthroplasty patients 1:1 to ibuprofen 400 mg ×3/day or identical placebo ×3/day for 8 days postoperatively. The primary outcome is a composite of death, acute myocardial infarction, stroke, pulmonary embolism, deep venous thrombosis, renal failure, major bleeding, re-operation, gastrointestinal ulcer, or readmission within 90 days postoperatively. Secondary outcomes are hospital-free days within 90 days postoperatively, a composite of ibuprofen and opioid-related adverse reactions based on an 8-day postoperative diary, and health-related quality of life after 90 days postoperatively. All randomized patients who undergo surgery will be included in all analyzes. Binary data will be analyzed using a mixed-effects generalized linear model, count data will be analyzed using the van Elteren test, and continuous data will be analyzed using a mixed-effects linear regression. Additionally, the win ratio will be calculated for the primary outcome. The statistical analyzes will be conducted in accordance with this pre-planned statistical analysis plan with one interim analysis after the inclusion of 1400 patients. All

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analyzes will be adjusted for site. We expect that the PERISAFE trial will provide high-quality data based on predefined detailed methodology regarding the safety of postoperative treatment with ibuprofen after elective hip and knee arthroplasties.

1 | Background

Hip and knee arthroplasties are common surgeries in the Western World, with approximately 172 and 119 per 100,000 population for hip and knee arthroplasties, respectively [1].

Ibuprofen, a non-steroid anti-inflammatory drug (NSAID), is frequently used for pain relief after hip and knee arthroplasties in combination with paracetamol, local anaesthetics (for knee arthroplasty), glucocorticoids, and opioids as needed [2–5]. However, NSAIDs may be associated with serious adverse events, including gastrointestinal ulcers [6, 7], bleeding [8, 9], renal impairment [10, 11], and cardiovascular morbidity and mortality [12, 13]. The risk of adverse events varies with the type of NSAID, dosage, and treatment duration [14].

Limited evidence exists on the risk of NSAID adverse effects in surgical patients [15]. Previous trials focused on efficacy with short intervention periods, short-term follow-up, and a limited focus on adverse events. Large pragmatic trials are needed to investigate the risk of adverse effects following hip and knee arthroplasties.

The PERISAFE trial is an investigator-initiated, superiority, randomized, blinded, multicentre clinical trial of ibuprofen vs. placebo for the treatment of acute postoperative pain in 2904 patients undergoing hip or knee arthroplasties.

We have previously published the PERISAFE trial protocol [16] but the full detailed statistical analysis plan (SAP) extends beyond it. To enhance transparency and prevent selective outcome reporting and data-driven analysis, we here present the pre-specified SAP, finalized and published before enrolment of the final patient. This is in accordance with International Conference on Harmonisation (ICH) of Good Clinical Practice (GCP) guidelines [17].

2 | Materials and Methods

2.1 | Trial Overview

The PERISAFE trial is a randomized, multicentre clinical trial comparing ibuprofen vs. placebo in 2904 hip or knee arthroplasty patients. The trial aims to assess the adverse effects associated with eight-day postoperative treatment with ibuprofen after elective hip and knee arthroplasties. Adult patients planned to receive NSAIDs for pain treatment after elective primary hip and knee arthroplasties are randomly assigned (1:1) to receive ibuprofen or placebo three times daily for the 8 days beginning on the evening of surgery.

Currently, nine sites in Denmark are actively screening and randomizing patients for the PERISAFE trial. One site, Capio Gildhøj Private Hospital, closed after randomizing 122 patients in the spring of 2024. A detailed protocol including the trial background, design, and rationale has been published previously [16].

The PERISAFE trial is registered at ClinicalTrials.gov (NCT05575700; 10-07-2022) and the European Clinical Trial System (EU CT no. 2022-502502-32-00; 29-03-2023). It is conducted in accordance with the Declaration of Helsinki and follows Good Clinical Practice standards [18]. The trial has been approved by the Danish Data Protection Agency (REG-149-2022; 07-02-2023), the Danish Medicine Agency, and the Research Ethics Committee (EU CT no. 2022-502,502-32-00; 29-03-2023). All enrolled patients must provide written informed consent for participation in compliance with national regulations. Updates on trial progress are available at www.perisafe.dk.

The detailed SAP is finalized before the last patient is randomly assigned and data collection is completed. It was approved by the steering committee on April 29, 2025. All analysis for the primary publication of the PERISAFE trial will be conducted in accordance with this plan.

2.2 | Randomization, Stratification and Blinding

Randomization is performed by an investigator or trained project staff in the orthopedic or anaesthesiology department using the clinical trial management software REDCap (www.redcap.regionsjaelland.dk). Patients are randomized in a 1:1 ratio with block sizes unknown to the investigators. The Copenhagen Trial Unit, Copenhagen, Denmark, has generated a computer-based allocation sequence stratified by site. The Capital Region Pharmacy is responsible for packaging and labeling the trial medication according to allocation numbers and distributing it to participating sites.

Patients, clinicians, trial personnel, outcome assessors, data managers, manuscript authors, and statisticians remain blinded to trial treatment allocation throughout the trial.

2.3 | Outcome Measures

2.3.1 | Primary Outcome

The primary outcome is a composite of one or more of the following events within 90 days postoperatively: death, acute myocardial infarction, stroke, pulmonary embolism, deep venous thrombosis, renal failure, major bleeding, re-operation, gastrointestinal ulcer, or readmission.

2.3.2 | Secondary Outcomes

- Hospital-free days within 90-days postoperatively.

- A composite outcome of ibuprofen related adverse reactions based on eight-day postoperative diary: pain or discomfort from the epigastrium, reflux, and diarrhea.

- A composite outcome of opioid-related adverse reactions based on eight-day postoperative diary: nausea, vomiting,

constipation, sedation, headache, mood changes, mouth dryness.

- Health related quality of life assessed using the European Quality of Life (EuroQol)—EQ-VAS [19, 20] at 90-days postoperatively.

2.3.3 | Explorative Outcomes

- Postoperative pain levels, analgesic treatment, and opioid consumption based on an eight-day postoperative diary and a questionnaire 14 days and 90 days postoperatively.

Each individual component of the primary and secondary composite outcome will also be reported separately (Table 1) please view Tables 2 and 3.

The primary outcome and health-related quality of life via EQ-5D-5L are collected after one year, alongside pain levels and analgesic treatment. These will be published in a separate publication using the methodology outlined in this statistical analysis plan. Please see the Supporting Information for definitions for each of the components and for registered variables during one year follow-up.

The composite outcome of ibuprofen and opioid-related adverse reactions will be reported as one or more of the defined outcomes and as the total number of outcomes in each group. Please view Tables 3 and 4 alongside Supporting Information for further information.

Health related quality of life will be reported as EQ-VAS for both groups in the manuscript. Information regarding each domain of the 5 dimensions 5-level questionnaire (EQ-5D-5L) will be reported in a table in Supporting Information. Please view Supporting Information for elaboration of the EQ-5D-5L domains and levels. We will use the Danish value set to calculate the EQ-5D-5L index value set for the Danish population [20].

2.4 | Sample Size

The primary outcome sample size calculation is based on data from a large Danish cohort study [21] with 36,935 total hip and knee arthroplasty procedures, a large Danish registry study [22] of 7449 patients undergoing mixed surgical procedures, and a randomized clinical trial (the PANSAID trial [4] with 556 patients undergoing total hip arthroplasties) using data from patients receiving ibuprofen for postoperative analgesia.

With the composite primary outcome of 10 items, it is therefore reasonable to expect a proportion of serious adverse events of 8% in the ibuprofen group.

Accepting a risk of type II error of 20%, a risk of type I error of 5%, using a power of 80%, and a proportion of serious adverse events in the ibuprofen group of 8%, we will need 2902 (1451 in each group) patients to detect or discard an effect corresponding to a relative risk reduction of 33% in the placebo group.

Due to trial medication being delivered in chunks of 24, the total number of patients will be 2904.

2.5 | General Analytic Principle

All analyzes will be performed on the modified intention-to-treat (mITT) population as well as the per-protocol population (PP). The mITT population is defined as all randomized patients who undergo surgery. The primary conclusion of the trial will be based upon mITT analysis of the primary outcome. The PP population is defined as the mITT population excluding patients having one or more major protocol violations during the intervention period. Major protocol violations are defined as:

- Patients who did not receive any of the allocated trial medication.
- Patients who withdrew from the trial intervention, not allowing the use of their registered data.

2.6 | Statistical Analysis

2.6.1 | Analysis of Dichotomous Data

Dichotomized outcomes will be presented as proportions of patients in each group experiencing the event, along with the risk ratio and risk difference, both reported with 95% confidence intervals. Dichotomous outcomes will be analyzed using mixed effects generalized linear models with a log link, 'site' as a random intercept, and an exchangeable covariance matrix.

2.6.2 | Analysis of Count Data

Count data will be presented as medians, interquartile ranges or just ranges when appropriate. Count data will be analyzed using van Elteren test stratified by 'site' and presented with the median of differences and 95% confidence intervals according to the Hodges-Lehmann estimator [23].

2.6.3 | Analysis of Continuous Data

Continuous outcomes will be presented as means and standard deviations for each group along with 95% confidence interval for both the group means and the mean difference between the groups. Continuous outcome will be analyzed using mixed effect linear regression, with 'site' as a random intercept, and an exchangeable covariance matrix.

2.6.4 | Analysis Using Win-Ratio

The primary outcome, a composite of 10 items, will be analyzed using a win-ratio approach as an exploratory analysis [24]. The patients will be unmatched, meaning all patients in the intervention group will be compared with all patients of the placebo

TABLE 1 | Characteristics of intention-to-treat population.

Baseline characteristics	Ibuprofen ($N = 1452$)	Placebo ($N = 1452$)
Age, years	Median (IQR)	Median (IQR)
Female sex, no. (%)	No. (%)	No. (%)
American society of anaesthesiologist score, no. (%)		
1	No. (%)	No. (%)
2	No. (%)	No. (%)
3	No. (%)	No. (%)
4	No. (%)	No. (%)
Height, cm	Median (IQR)	Median (IQR)
Weight, kg	Median (IQR)	Median (IQR)
Body mass index, kg/m^2	Median (IQR)	Median (IQR)
Diabetes, no/yes	No. (%)	No. (%)
Type 1, no/yes	No. (%)	No. (%)
Type 2, no/yes	No. (%)	No. (%)
Treatment with insulin, no/yes	No. (%)	No. (%)
Preoperative medication		
Use of NSAID, no use/daily use	No. (%)	No. (%)
Use of opioids, no use/daily use	No. (%)	No. (%)
• Equivalent morphine daily dose (mg)	Median (IQR)	Median (IQR)
Use of diuretics, no use/daily use	No. (%)	No. (%)
Use of ACE-inhibitors, no use/daily use	No. (%)	No. (%)
Use of Angiotensin-II-receptor antagonists, no use/daily use	No. (%)	No. (%)
Use of oral anticoagulants, no use/daily use	No. (%)	No. (%)
Use of oral thrombocyte inhibitors, no use/daily use	No. (%)	No. (%)
Use of proton pump inhibitor, no use/daily use	No. (%)	No. (%)
Surgical characteristics		
Type of surgery	No. (%)	No. (%)
• Total hip arthroplasty		
◦ Uncemented		
◦ Hybrid		
◦ Cemented		
• Total knee arthroplasty		
◦ Uncemented		
◦ Hybrid		
◦ Cemented		
• Unicompartmental knee arthroplasty		
◦ Uncemented		
◦ Cemented		
Laterality, right/left/bilateral	No. (%)	No. (%)
Type of anaesthesia (general anaesthesia/spinal anaesthesia/spinal anaesthesia converted to general anaesthesia)	No. (%)	No. (%)
Administration of peripheral nerve blockade, no/yes	No. (%)	No. (%)

TABLE 2 | Proportion of individual serious adverse events in the composite primary outcome.

Primary outcome	Ibuprofen (N)	Placebo (N)	Adjusted absolute risk difference (95% CI)	Adjusted relative risk (95% CI)
One or more of composite outcome	No/total no. (%)	No/total no. (%)		
Death	No/total no. (%)	No/total no. (%)		
Acute myocardial infarction	No/total no. (%)	No/total no. (%)		
Stroke	No/total no. (%)	No/total no. (%)		
Pulmonary embolism	No/total no. (%)	No/total no. (%)		
Deep venous thrombosis	No/total no. (%)	No/total no. (%)		
Renal failure	No/total no. (%)	No/total no. (%)		
Major bleeding	No/total no. (%)	No/total no. (%)		
Re-operation	No/total no. (%)	No/total no. (%)		
Gastrointestinal ulcer	No/total no. (%)	No/total no. (%)		
Readmission	No/total no. (%)	No/total no. (%)		
Total no. of events	No/total no. (%)	No/total no. (%)		

Note: All analyzes are adjusted for stratification: trial site.

TABLE 3 | Absolute numbers of adverse reactions of ibuprofen during intervention period (postoperative day 0–7).

Adverse reactions of ibuprofen	Ibuprofen (N)	Placebo (N)	Adjusted absolute risk difference (95% CI)	Adjusted relative risk (95% CI)
One or more of composite outcome	No/total no. (%)	No/total no. (%)		
Pain or discomfort from the epigastrium	No/total no. (%)	No/total no. (%)		
Reflux	No/total no. (%)	No/total no. (%)		
Diarrhea	No/total no. (%)	No/total no. (%)		
Total no. of events	No/total no. (%)	No/total no. (%)		

Note: All analyzes are adjusted for stratification: trial site.

TABLE 4 | Absolute numbers of adverse reactions of opioid during intervention period (postoperative day 0–7).

Adverse reactions of opioid	Ibuprofen (N)	Placebo (N)	Adjusted absolute risk difference (95% CI)	Adjusted relative risk (95% CI)
One or more of composite outcome	No/total no. (%)	No/total no. (%)		
Nausea	No/total no. (%)	No/total no. (%)		
Vomiting	No/total no. (%)	No/total no. (%)		
Constipation	No/total no. (%)	No/total no. (%)		
Sedation	No/total no. (%)	No/total no. (%)		
Headache	No/total no. (%)	No/total no. (%)		
Mood changes	No/total no. (%)	No/total no. (%)		
Mouth dryness	No/total no. (%)	No/total no. (%)		
Total no. of events	No/total no. (%)	No/total no. (%)		

group ($1452 \times 1452 = 2{,}108{,}304$) unmatched pairs classified into 20 categories of the composite outcome [24].

Items of the primary outcome are ranked hierarchical: death; acute myocardial infarction; stroke; pulmonary embolism; deep venous thrombosis; renal failure; major bleeding; re-operation; gastrointestinal ulcer; readmission during 90-days follow-up.

Win ratio is the odds that the intervention of ibuprofen wins for any randomly chosen patient pair in the placebo group. A win ratio, therefore, describes the ratio of the proportion of win pairs to the proportion of losses, and a win ratio with a lower 95% confidence limit above 1 indicates that ibuprofen is worse than placebo.

Further, win difference (%wins − %losses) will be calculated in order to quantify the absolute and relative risk of the win ratio [25].

2.6.5 | Handling of Missing Data

Missing data and assessment of underlying statistical assumption will follow the recommendations of Jakobsen et al. [26].

2.7 | Assessment of Underlying Statistical Assumptions

We will systematically assess the underlying statistical assumptions for all statistical analyzes [27]. For *all* regression analyzes, both primary and secondary, we will test for major interactions between each covariate and the intervention variable. When assessing for major interactions, we will, in turn, include each possible first-order interaction between included covariates and the intervention variable. For each combination, we will test if the interaction term is significant and assess the effect size. We will only consider evidence of an interaction if the interaction is statistically significant following a Bonferroni adjusted threshold (0.05 divided by number of possible interactions), and if the interaction shows a clinically important effect. If a significant interaction is detected, we will consider both presenting an analysis separate for each site and an overall analysis including the interaction term in the model [27].

2.7.1 | Assessment of Underlying Statistical Assumption for Dichotomous Outcomes

We will assess overdispersion by examining whether the deviance divided by the degrees of freedom is significantly larger than one. Overdispersion occurs when the observed variability (statical dispersion) in the data set is greater than expected under the given statistical model. If this is present, we will consider using a maximum likelihood estimate of the dispersion parameter to adjust for excess variability.

2.7.2 | Assessment of Underlying Statistical Assumption for Linear Regression

We will visually inspect quantile-quantile plots of the residuals to assess if these are normally distributed and use residuals

plotted against covariates and fitted values to assess the homogeneity of variance. If the plots show deviations from the model assumptions, we will consider transformation of data, e.g., using log transformation or square root and/or use robust standard errors [27] to improve the model fit for linear regression.

2.7.3 | Trial Profile

A Consolidated Standards of Reporting of Randomized Trials (CONSORT) diagram will display the flow of trial participants [28]. The CONSORT diagram will present the number of patients fulfilling inclusion criteria, the number of excluded patients with reasons for exclusion, and the number of patients included in the mITT and PP analyzes.

2.7.4 | Pre-Planned Test of Interaction of Subgroups

Test of interaction will be performed on the primary and secondary outcomes based on the patient characteristics at baseline:

- Type of surgery (total hip arthroplasty or total knee arthroplasty or unicompartmental knee arthroplasty).
- Age (≤ 69 vs. ≥ 70 years).
- Sex (female vs. male).
- Preoperative use of NSAIDs, including type of NSAID.

2.8 | Data Monitoring and Safety Committee

A data monitoring safety committee (DMSC) is established and consists of two clinicians, one with statistical experience. The DMSC will oversee the trial and is responsible for safeguarding the interests of trial patients. For further information, please view the protocol article for the PERISAFE trial [16].

2.9 | Statistical Reports

Blinded data on all outcomes will be independently analyzed by two statisticians. Two independent statistical reports will be sent to the principal investigator and will be shared with the steering committee and author group. If any discrepancies arise between the two primary statistical reports, the possible reason will be identified, and the steering committee will decide which is the most correct result. A final statistical report will be prepared and will contain all three statistical reports.

3 | Discussion

The PERISAFE trial is expected to provide high quality data on the adverse effects associated with ibuprofen treatment after primary hip and knee arthroplasty surgery. By adhering to a strict methodology, we aim to generate results with low risks of bias and perform a pragmatic study with high external validity. We expect our trial to provide important

information for future treatment of ibuprofen for hip and knee arthroplasties.

3.1 | Strengths

The statistical plan describes the principles of the analysis and secures that the risk of data-driven analyzes is reduced. It enables the reproduction of trial results and preserves transparency. The statistical methods are systematically used and validated methods. Two independent blinded statisticians will improve objectivity and ensure the quality of data by translating them into interpretable and usable final trial results for clinicians.

3.2 | Limitations

The true incidence of serious adverse events of short-term treatment with ibuprofen after major orthopedic surgery is unknown. Though the power calculation is thoroughly discussed, the study may be underpowered.

The composite outcome may not show the risk of the individual components, and the relevance of the individual components likely differs between participants. Consequently, each component will also be shown in the main article and analyzed using win-ratio.

3.3 | Trial Status

The study included the first patient in April 2023 and is expected to complete enrolment in May 2025. As of April 28, 2889 patients have been enrolled in the PERISAFE trial.

Author Contributions

C.C.W.L. drafted the manuscript in close collaboration with J.C.J., O.M., T.H.L. and D.H.P. M.O., A.K., T.J., N.A.P., T.T., B.K.G., T.B., P.B.H., C.R., M.Y., S.B.E., A.S.N.T., J.S., K.S.G., K.T., K.H.W.L., S.B., C.V., M.L.L., and S.O. made substantial contributions to the development of the protocol and this manuscript. All authors have read and approved the final manuscript and are members of the steering committee. D.H.P. is sponsor and C.C.W.L. is coordinating investigator.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.