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GENicular nerve block in KNEE arthroplasty

(The GENKNEE Trial)

A randomized, multiple-blind, placebo-controlled study investigating the effect of preoperative genicular nerve block on postoperative pain in primary total knee arthroplasty

Norway 2025

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1. STUDY SYNOPSIS

Study Synopsis for Study: The GENKNEE trial

Topic	Details
Protocol Title:	GENicular nerve block in KNEE arthroplasty (The GENKNEE Trial): A randomized, multiple-blind, placebo-controlled study investigating the effect of preoperative genicular nerve block on postoperative pain in primary total knee arthroplasty
Study Type:	Clinical
Indication:	Compare the effect of preoperative genicular nerve block (GNB) and placebo for pain control in patients assigned for unilateral primary total knee arthroplasty (TKA). TKA is a common procedure and despite advances in surgical technique and perioperative care, postoperative pain management remains a challenge. Traditional approaches such as systemic non-steroid anti-inflammatory drugs and opioids, spinal analgesia and nerve blocks are used, but have limitations. GNB has demonstrated efficacy in managing chronic knee pain, but the role as preoperative analgesic technique remains under-investigated.
Hypothesis Statement:	The hypothesis to be tested is that, in patients undergoing primary unilateral TKA, preoperative GNB is superior to placebo in reducing postoperative pain intensity during ambulation 24 hours after surgery, as measured by the Numeric Rating Scale (NRS) for pain.
Study Objectives:	Questionnaires: NRS for pain at rest and ambulation, Tegner activity score, The Knee Injury and Osteoarthritis Outcome Score, Forgotten Joint Score, EQ-5D-5L, cumulative opioid consumption, NRS for nausea and vomiting, confusion assessment and 4-point sedation scale. Mobility: activPAL4™ measures. Socio-economic: direct and indirect healthcare costs and quality-adjusted life years. Radiology: radiograph of the knee.

Study Synopsis for Study: The GENKNEE trial

Topic	Details
	The primary endpoint is the difference in NRS for pain during ambulation 24 hours after unilateral primary TKA between the 2 groups (GNB and placebo).
Study Design:	A prospective randomized, multiple-blind, placebo-controlled superiority trial with 2 treatment arms (GNB and placebo).
Duration of Study:	Approximately 24 months inclusion and 3 months follow-up. In total 27 months.
Follow-up Period:	3 months.
Study Location:	Nordmøre and Romsdal Hospital (SNR).
Number of Subjects:	70 patients
Study Population:	Inclusion: men and women aged 18-80 years undergoing unilateral primary TKA due to osteoarthritis in spinal anesthesia, ASA physical status II-IV and able to provide written informed consent. Exclusion: Age < 18 or > 80 years, ASA physical status IV, allergy to local anaesthetics, revision surgery, chronic opioid use (> 3 months), coagulopathy, cognitive impairment, inability to comply with study procedures and patients scheduled for day care surgery.
Treatment Groups:	2 treatment groups with 35 patients in each group.
Visit Schedule:	1 week (± 1 day), 1 month (± 1 week) and 3 months (± 2 weeks) after surgery.
Safety Assessments:	If any unforeseen complication outside normal clinical practice occurs, the sponsor representative will be contacted as soon as possible. During each follow up, there will be a case report form regarding complications and safety.
Overview of Statistics:	Continuous variables will be analysed using Student's t-test or Mann-Whitney U test as appropriate. Categorical variables will be analysed using chi-square or Fisher’s exact test. Linear mixed model analysis will assess repeated pain scores over time.

Study Synopsis for Study: The GENKNEE trial

Topic	Details
	Multivariable regressions may be used to adjust for potential confounders. Statistical significance level is set to 5%.
Sample Size:	A reduction of 1.0 points on the NRS for pain is considered the minimal clinically important difference in postoperative pain management following TKA. Assuming a standard deviation of 1.4 to detect a between-group difference with 80% power and a two-sided alpha level of 0.05, a sample size of 32 patients per group is required. To account for an anticipated 10% dropout rate, a total of 70 participants (35 in each group) will be recruited.
Interim Analysis:	No interim analysis will be done.
Monitoring Plan:	Not required.
Study Stopping Rules:	Inclusion of 70 patients.
End of Study:	The end of this study is 3 months after the last included patient.
Estimated Cost of Study:	Outside standard clinical practice, cost are related to purchase and maintenance of 15 activity monitors (activPAL4™ measures), 2 USB Hubs & charging stations and 1 dedicated computer.
Operational Risk Analysis:	Inability to include 70 patients in 24 months years or drop-outs. May prolong the inclusion period.
Study Target Dates:	See table below.

Milestone	Study Timeline: Target Date (Month/Year)
First Patient In (FPI)	June 2026
Last Patient In (LPI)	June 2028
Last Patient Out (LPO)	September 2028
Database Lock (DBL)	December 2028
First Look (FL)	January 2029
CSR Completed	April 2029

Appendix 1: Budget Components

The study budget may be prepared in any format; the following lists the minimal components required. The more detailed the budget, the easier it will be to evaluate. Estimates should be reliably estimated within ± 5% of the final study expenses.

- Supplies: 15 activPAL4™ activity measurements with 2 charging docks and 1 computer
- Institutional Fees: Included in the abovementioned.

Appendix 2: Study Activities

Tests and Assessments	Inclusion	Intervention	24 hours	1 week	1 month	3 months
Medical History	X		X	X	X	X
Analgetic consumption	X		X	X	X	X
Physical Examination	X		X	X	X	X
Questionnaires	X		X	X	X	X
Informed consent	X					
Radiograph	X		X			X
Randomization and intervention		X				
Activity measurements			X	X		X
Adverse Events		Monitor and record throughout the study				

2. SHORT SUMMARY

Total knee arthroplasty (TKA) is a common procedure and despite advances in surgical technique and perioperative care, postoperative pain management remains a challenge. Traditional approaches such as systemic non-steroid anti-inflammatory drugs and opioids, spinal analgesia and peripheral nerve blocks are used, but have limitations. Genicular nerve block **(**GNB) has demonstrated efficacy in managing chronic knee pain, but the role as preoperative analgesic technique remains under-investigated. In this study, the effect of preoperative GNB and placebo for pain control in patients assigned for unilateral primary TKA are compared.

3. INTRODUCTION

3.1. Background

Total knee arthroplasty (TKA) is a procedure intended to relieve pain and improve function in patients with advanced knee osteoarthritis (OA) [1]. TKA are one of the most commonly performed procedures globally [2, 3], and only in Norway, 8 000 TKAs are performed annually [4]. In the coming decades, the burden of knee OA is expected to increase substantially due to an aging population, the obesity epidemic, sedentary lifestyles and inactivity, combined with increased life expectancy [5]. Studies predict a global increase in knee OA with 50% [6], which will most likely lead to an increasing number of TKAs. Despite advancements in surgical technique and perioperative care, postoperative pain management remains a challenge [7]. Future surgical innovations on knee OA treatment are adopting outpatient TKA, but poorly controlled postoperative pain can delay mobilization, prolong hospitalization, and lead to chronic pain and opioid dependency [8].

Traditional analgesic approaches such as systemic opioids, spinal analgesia, and peripheral nerve blocks (e.g., femoral or adductor canal block) are routinely used but have limitations. Femoral nerve blocks may cause quadriceps weakness, hindering early mobilization [9], whereas adductor canal blocks provide limited analgesia for posterior knee pain [10]. Perioperative local infiltration analgesia (LIA) of the joint capsule has been demonstrated to be an effective component of multimodal pain management in TKA, providing significant reductions in postoperative pain and opioid requirements, while facilitating early mobilization and recovery [11].

Recently, genicular nerve block (GNB), an ultrasound-guided technique targeting the sensory branches around the knee, has emerged as a promising option [12]. This minimally invasive pain management procedure involves injecting a local anesthetic around the genicular nerves that supply sensation to the knee joint and include the superior medial, superior lateral, and inferior medial genicular nerves.

GNB has demonstrated efficacy in managing chronic knee pain due to OA and following TKA [13]. The role of GNB in the acute postoperative setting, particularly as a preoperative analgesic technique in TKA, remains under-investigated. To our knowledge, only one study has compared preoperative GNB with placebo in TKA but only reported short term effects

[14]. There is lacking evidence on whether GNB improves rehabilitation and return to activity, and functional outcome measures with follow-up period beyond the first postoperative days are missing. Further, none has evaluated health economic measures for preoperative GNB in TKA. Due to an aging population, the obesity epidemic, sedentary lifestyles and inactivity, combined with increased life expectancy, the socio-economic burden of knee OA and TKA is expected to increase substantially in the coming decades [5].

The significance of the research project within the discipline and its originality is marked by the preemptive use, as unlike typical nerve blocks administered postoperatively, this trial explores its effectiveness when given preoperatively to "prepare" the joint against nociceptive input. Further, the multiple-blind design minimizes bias, enhancing the reliability of the findings, whereas **c**omparing GNB to a placebo injection helps determine the true analgesic effect and rule out placebo-induced pain reduction. Lastly, the project focus on long-term outcomes and not only acute pain relief, assessing functional outcomes**,** rehabilitation milestones**,** and opioid consumption over time.

3.2. Purpose of this study

Local anesthesia is routinely used in clinical practice for effective pain management; however, this study will specifically focus on the method of sensory nerve block around the knee as a preoperative analgesic technique.

The purpose of this study is to evaluate whether a preoperative GNB reduces postoperative pain intensity and opioid consumption after primary TKA compared to placebo. Furthermore, this study will assess physical activity and long-term functional outcome scores and include health economic outcomes to evaluate the potential cost-effectiveness of preoperative GNB compared to placebo in primary TKA.

4. RESEARCH DESIGN

A prospective randomized, multiple-blind, placebo-controlled superiority trial with 2 treatment arms (GNB and placebo).

The study will be conducted at Nordmøre and Romsdal Hospital. The sponsor of the study is Helse Møre and Romsdal Hospital Trust (HMR-HT), with sponsor representative research group leader Tommy Frøseth Aae at HMR-HT.

Inclusion, intervention and follow-up of the patients will be done at the orthopedic clinic at Nordmøre and Romsdal Hospital. Figure 1 outlines the study overview.

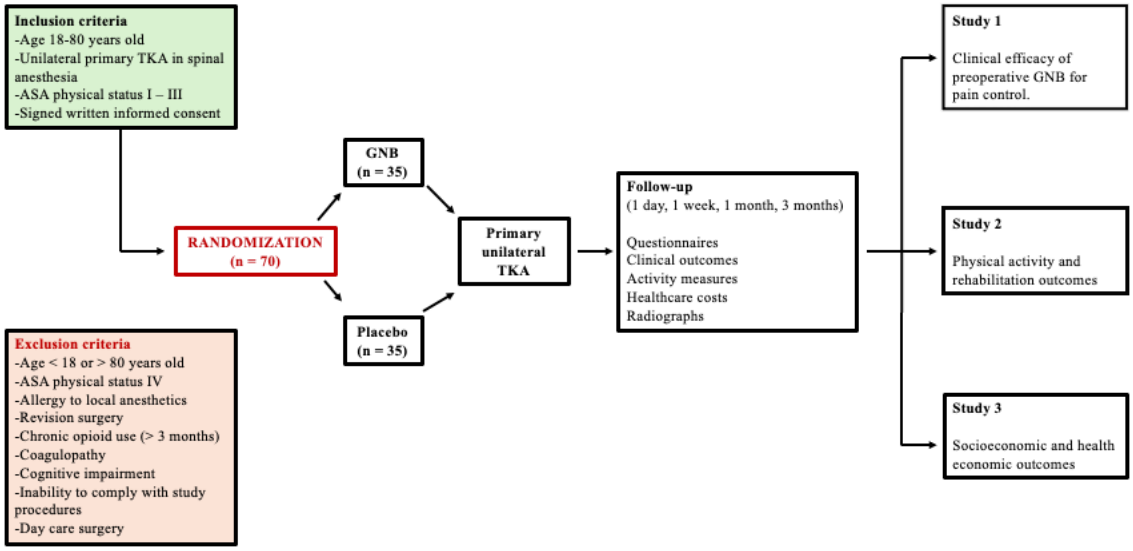

Figure 1: Flow chart of the project. TKA – total knee arthroplasty, ASA – American Society of Anesthesiologists, n – numbers, GNB – genicular nerve block.

5. MATERIALS AND METHODS

5.1. Participants

The study will include a total of 70 patients, both men and women, aged 18 to 80 years referred to the orthopedic outpatient clinic at Nordmøre and Romsdal Hospital (SNR). Inclusion criteria are patients with symptomatic knee OA scheduled for primary TKA. All patients will be evaluated both clinically and radiologically prior to inclusion and must have radiographic evidence of osteoarthritis grade II–IV according to the Kellgren–Lawrence classification system [1]. Eligible patients must also meet the American Society of Anesthesiologists (ASA) Physical Status grade I–III (REF), be able to provide written informed consent, and undergo surgery under spinal anesthesia.

Exclusion criteria include patients younger than 18 or older than 80 years, an ASA physical status IV or known allergy to local anesthetics. Patients referred for revision surgery will be excluded, as well as patients with chronic opioid use (> 3 months), coagulopathy, cognitive impairment, inability to comply with study procedures and patients scheduled for day care surgery.

Excluded patients or patients declining participation in the trial or withdrawing will receive appropriate treatment according to the standard of care.

5.2. Randomization and blinding

Patients will be allocated to either GNB or placebo using eFORSK, which is a platform-independent ICT solution [15]. This solution assists clinical researchers at Helse Midt-Norge with setting up randomization of study participants in research projects and collecting data from study participants in an efficient and secure manner.
The randomization will be done digitally with eFORSK by a research collaborator working at Nordmøre and Romsdal Hospital, but is not involved in the study, to secure blinding. Block randomization with variable block sizes will be applied and stratified by sex and alignment technique (e.g. mechanical or inverse kinematic). The randomization process occurs prior to preoperative analgesics.
The study is designed as a multiple blinded study. As long as the trial lasts, patients will not verbally nor written be informed which intervention is given to them. When patients are completing the questionnaires during follow-ups, the case report forms will not contain any information of the given treatment. The anesthesiologist performing the intervention (GNB or placebo) will be blinded as the hospital pharmacy (or colleague) will prepare the mixture of injection with the same appearance. All involved health care personnel will be blinded throughout the study period, as will the statistician.

5.3. Preoperative management

All patients will receive a standard preoperative combination consisting of:

- Oral preoperative analgesics (1 hour before start of surgery)
    - Paracetamol; 1.5 g tablet for patients < 70 kg, 2.0 g tablet for patients > 70 kg
    - Non-steroidal anti-inflammatory (Etorikoksib); 90 mg tablet for patients < 70 kg, 120 mg tablet for patients > 70 kg
    - Dexametasone; 16 mg tablet for patients < 70 kg, 20 mg tablet for patients > 70 kg
- Spinal anesthesia; 2.5-3.0 mL bupivacaine 5 mg/mL
- Femoral triangle block; 10 mL 5 mg/mL ropivacaine

5.4. Intervention

Furthermore, patients will receive an ultrasound-guided injection according to randomization before surgery. The ultrasound-guided injection will be performed as a sterile procedure by an experienced anesthesiologist trained in the method. The ultrasound machine used for the intervention is General Electric Healthcare Venue Go (Chicago, Illinois, United States) with L4-20t or C2-9 probes. A 50 or 80 mm 22G block needle will be used.

Group A (Intervention): Ultrasound-guided GNB with 5 mL of 5 mg/mL ropivacaine at the superolateral genicular nerve (SLGN), superomedial genicular nerve (SMGN), and the inferomedial genicular nerve (IMGN) with a total volume of 15 mL.

Group B (Control): Identical procedure using 5 mL of 0.9% normal saline at the same anatomical landmarks (SLGN, SMGN and IMGN) with a total volume of 15 mL.

SLGN: The Ultrasound transducer is placed over the lateral femoral epicondyle, in a coronal orientation and is moved proximally to identify the metaphysis of the bone. Between the deep fascia of the vastus lateralis and femur the superolateral genicular artery may be seen. The needle tip is advanced to the side of the artery. If the artery cannot be accessed, the needle is advanced until it is in contact with the femoral bone. After satisfactory needle position, 5 mL of 5 mg/mL ropivacaine or 5 mL of 0.9% normal saline will slowly be injected. Spread of local anesthetic will be documented.
SMGN: The Ultrasound transducer is placed over the medial femoral epicondyle, in a coronal orientation and is moved proximally to identify the metaphysis of the bone. Between the deep fascia of the vastus medialis and femur the superomedial genicular artery may be seen. The needle tip is advanced to the side of the artery. If the artery cannot be accessed, the needle is advanced until it is in contact with the femoral bone. After satisfactory needle position, 5 mL of 5 mg/mL ropivacaine or 5 mL of 0.9% normal saline will slowly be injected. Spread of local anesthetic will be documented.
IMGN: The Ultrasound transducer is placed over the medial condyle of the tibia, in a coronal orientation and is moved distally to identify the metaphysis of the bone. The inferomedial genicular artery can be seen beneath the medial collateral ligament. The needle tip is advanced to the side of the artery. If the artery cannot be accessed, the needle is advanced until it is in contact with the femoral bone. After satisfactory needle position, 5 mL of 5 mg/mL ropivacaine or 5 mL of 0.9% normal saline will slowly be injected. Spread of local anesthetic will be documented.

5.4. Operative procedure

All TKA surgeries will be performed by an experienced orthopedic surgeon with the respective implants. A medial para-patellar approach with the patella slided or everted. Tourniquet at 250 mmHg will be used during cementing, and implants will be used according

to preoperative planning. The surgeon will infiltrate the posterior and anterior joint capsule with a combination of 100 mL ropivacaine 2mg/ml, 1 mL fentanyl 50 mcg/mL and 0.5 mL adrenalin 1 mg/mL before wound closure.

5.5. Intraoperative management

If patients request sedation, propofol will be administered using a target-controlled infusion system, adjusted to maintain a plasma concentration of 1 to 1.5 micrograms per millilitre – a light sedation level typically used for monitored anesthesia care or mild sedation (not full general anesthesia). At the conclusion of surgery, the propofol will be discontinued and patients transported to postoperative ward.

5.6. Post-operative management

The two treatment groups will receive identical postoperative care. The patients are admitted to the hospital for 1 day. Intravenous prophylactic antibiotics and anti-thrombotic prophylaxis will be given according to guidelines.

<u>Postoperative analgesia</u>

Pain management is standardized according to institutional protocol at SNR.

In the post operative care unit (up to 6 hours after surgery):

- Paracetamol; 1.0 g tablet, up to four times daily
- Tapentadol (Palexia); 50 mg tablet, single dose
- Oxycodone (OxyNorm) 2.5 mg intravenous or 5 mg tablet as needed for pain (NRS > 3 at rest)

At the ward and following discharge:

- Paracetamol; 1.0 g tablet, up to four times daily
- Non-steroidal anti-inflammatory (Etorikoksib); 60 mg tablet for patients < 70 kg, 90 mg tablet for patients > 70 kg, 1 time a day up to 28 days postoperatively
- Tapentadol (Palexia); 50 mg tablet, 2 times a day up to 5 days postoperatively
- Oxycodone (OxyNorm); 5 mg tablet up to six times a day as needed for pain (NRS > 3 at rest)

Following surgery, all patients will be visited by an anesthesiologist, an orthopedic surgeon and a physiotherapist to assess any complication and ensure pain control and mobilization. Occupational patients will be given a sick leave according to profession and type of work. If a patient experiences complications during treatment (such as wound problem, bleeding or infection), the patient will receive medical attention and follow-up according to the problem.

5.7. Rehabilitation protocol

Patients will be given a standard rehabilitation protocol by external physiotherapists and compliance to the program is advised for 3 to 6 months.

6. VARIABLES

6.1. Demographics

Demographic and baseline data collected at inclusion will include age, sex, height (cm), weight (kg), body mass index (BMI), social and occupational status, nationality, current medication use (including opioids), and relevant medical history, including mean pain intensity during the week prior to surgery and anxiety. In addition, potential risk factors for postoperative nausea and vomiting (PONV) will be recorded, including sex, postoperative opioid use, smoking status, history of motion sickness, and previous PONV.

6.2. Primary endpoint

Primary objective: To evaluate whether GNB provides superior pain relief during the first 24 hours postoperatively using the Numerical Rating Scale (NRS) [16]. Pain at rest and during ambulation will be measured using the NRS at 2-hour intervals while awake, once overnight, and then every 2 hours from morning until 24 hours after surgery.
Primary outcome: Difference in NRS pain scores during ambulation at 24 hours postoperatively between the GNB and placebo groups.

6.3. Secondary endpoints

A combination of self-explanatory questionnaires, clinical parameters, activity measurements, health care cost estimates and radiograph will be used as secondary endpoints. The secondary aims will be the difference between the two treatment groups at predefined times as described below. The secondary aims are:

Secondary endpoints	Description

NRS Pain Scores	NRS at rest at 2-hour intervals while awake, once overnight, and then every 2 hours from morning until 24 hours after surgery. NRS at rest + ambulation at 1 week, 1 month, and 3 months.
Cumulative opioid consumption (24h)	Consumption documented in the medical record, converted to morphine equivalents.
Postoperative nausea	NRS at 2-hour intervals while awake, once overnight, and then every 2 hours from morning until 24 hours after surgery.
Vomiting	Yes/no, 2-hour intervals while awake, once overnight, and then every 2 hours from morning until 24 hours after surgery.
4-point sedation scale	2-hour intervals while awake, once overnight, and then every 2 hours from morning until 24 hours after surgery.
Confusion	Yes/no, 2-hour intervals while awake, once overnight, and then every 2 hours from morning until 24 hours after surgery.
Cumulative opioid consumption	Self-reported (telephone/digital questionnaire) oral opioid consumption converted to morphine equivalents at 1 week, 1 month, and 3 months.
Tegner Activity Score [17]	Measured at 1 week, 1 month, and 3 months; subjective evaluation of physical activity level.
Knee Injury and Osteoarthritis Outcome Score (KOOS) [18]	Measured at 1 week, 1 month, and 3 months; assesses pain, symptoms, ADL, sport/recreation, QoL.

Forgotten Joint Score (FJS) [19]	Measured at 1 week, 1 month, and 3 months; evaluates patient adaptation to joint replacement.
EQ-5D-5L [20]	Measured at 1 week, 1 month, and 3 months; generic health status measure used in clinical evaluation.
Activity measurements	At 24h, 1 week, and 3 months post-surgery. activPAL4™ measures lying, sitting, standing, stepping.
Return to work & physical activity	Patient-reported at 3 months.
Health care costs	Direct and indirect costs up to 3 months after intervention.

All outcome questionnaires will be completed by the patients before surgery (pre-operative or baseline values) and at the designated follow-up appointments at 24 hours after surgery before discharge and postoperative after 1 week (± 1 days), 1 month (± 1 week) and 3 months (± 2 weeks). The assessment after 1 week and 1 months will either be by telephone interview or digital questionnaire. Radiographs will be obtained prior to inclusion, the first postoperative day and after 3 months.

7. HYPOTHESIS, STATISTICS ANALYSIS AND SAMPLE SIZE

7.1. Hypothesis for the primary aim

The hypothesis to be tested is that, in patients undergoing primary unilateral TKA, preoperative GNB is superior to placebo in reducing postoperative pain intensity during ambulation 24 hours after surgery, as measured by the NRS for pain.

7.2. Statistical analysis

Demographic and baseline characteristics will be summarized using mean and standard deviation for continuous variables with approximately normal distributions, and median with interquartile range for non-normally distributed data. Between-group comparisons will be performed using Student's *t*-test or the Mann–Whitney *U* test, as appropriate. Categorical variables will be presented as frequencies and percentages and analyzed using the chi-square test, Fisher's exact test, or rank-sum test where applicable. Repeated pain measurements over

time will be analyzed using linear mixed-effects models to account for within-patient correlations. Multivariable linear regression analyses may be applied to adjust for potential confounders.

Statistical handling of research questions

Study 1: The primary research question evaluates whether preoperative genicular nerve block (GNB) reduces postoperative pain compared with placebo. The primary endpoint is pain during ambulation 24 hours after surgery, measured using the Numeric Rating Scale (NRS). This outcome will be compared between groups using an independent-samples *t*-test or Mann–Whitney *U* test, depending on distributional assumptions. Repeated pain assessments obtained at 24 hours, 1 week, 1 month, and 3 months postoperatively will be analyzed using linear mixed-effects models with patient-level random effects. Fixed effects will include treatment group, time, and the group-by-time interaction. Secondary pain-related outcomes and patient-reported outcome measures (KOOS, Forgotten Joint Score, Tegner Activity Score, EQ-5D-5L) will be analyzed using similar mixed-model or regression-based approaches with adjustment for relevant covariates such as age, sex, and baseline pain when appropriate.

Study 2: The second research question addresses postoperative physical activity and rehabilitation. Objective activity data obtained from activPAL4 monitors will be summarized as continuous variables, including time spent sitting, standing, stepping, and total activity counts. Between-group differences in activity levels during the first postoperative week will be analyzed using linear regression or mixed-effects models for repeated daily measurements. Activity outcomes at 3 months will be assessed using between-group comparisons and adjusted regression analyses as appropriate.

Study 3: The third research question focuses on opioid consumption and health-economic outcomes. Cumulative opioid use will be converted to oral morphine equivalents and compared between groups using regression models suitable for skewed data. Health-economic analyses will be based on quality-adjusted life years (QALYs) derived from EQ-5D-5L scores in combination with prospectively collected cost data. Cost-effectiveness will be evaluated by estimating incremental cost-effectiveness ratios (ICERs), with uncertainty assessed using non-parametric bootstrapping.

Statistical significance will be defined as a two-sided p value < 0.05. All analyses will be performed using SPSS version 29.0 (IBM Corp., Armonk, NY) or Stata (StataCorp, College Station, TX).

7.3. Sample size

A reduction of 1.0 points on the NRS for pain is considered the minimal clinically important difference in postoperative pain management following TKA [21]. Assuming a standard deviation of 2.0 [21], to detect a between-group difference of 1.4 points with 80% power and a two-sided alpha level of 0.05, a sample size of 32 patients per group is required. To account for an anticipated 10% dropout rate, a total of 70 participants (35 in each group) will be recruited.

7.4 Feasibility and recruitment realism

The planned inclusion of 70 patients is considered highly feasible. Nordmøre and Romsdal Hospital performs approximately 160 primary unilateral total knee arthroplasties annually. The required recruitment rate corresponds to fewer than three patients per month over a 24-month inclusion period, representing a small proportion of the eligible population. Inclusion, intervention, and follow-up are fully integrated into standard clinical care pathways and supported by an experienced orthopedic research group with dedicated research personnel. Based on current surgical volume and previous experience with randomized clinical trials at the institution, patient inclusion is expected to progress according to plan and will most likely be completed ahead of schedule.

8. ADDITIONAL PROJECT

8.1. Cost effectiveness analysis

In addition to the prospective randomized trial, we will also conduct a treatment-cost analysis. By recording the cost of each treatment, need of sick leaves, cost of additional doctor's appointments and repeated surgery due to complications, we will estimate the cost effectiveness and not only the functional results. This will provide a necessary economic frame of reference from which to resolve treatment recommendations.

To assess the cost-effectiveness of the two treatments we need to estimate both health outcome and costs. The health outcome will be measured by means of EQ-5D-5L, which is recommended for use in cost-effectiveness analyses by the Washington Panel on Cost Effectiveness in Health and Medicine [22], and by the International Society for

Pharmacoeconomics and Outcomes Research task force on good clinical practices: Randomized Clinical Trial-Cost-Effectiveness Analysis [23].

Costs will include costs in the health care sector and production loss. Further, use of other health care services (home care services, rehabilitation and institution) will be registered for both groups. Standard methods in economic evaluation will be applied, and cost-effectiveness will be calculated by means of the incremental cost-effectiveness ratio, defined by the cost per incremental quality-adjusted life year (QALY) [24]. Further uncertainty will be displayed by applying the bootstrap method with 1000 replications to illustrate the variation in the patient population with regard to incremental health gain and cost.

Cost-Utility Analysis:
A cost-utility analysis will be conducted from a healthcare payer perspective. The primary outcome will be the Incremental Cost-Effectiveness Ratio (ICER). The ICER is a measure used in health economics to assess the cost-effectiveness of a new intervention compared to existing standard of care and will be calculated using the formula:

ICER = (Cost GNB – Cost Placebo) / (QALY GNB – QALY Placebo)

The cost GNB and Placebo are the total healthcare costs per patient in each group, whereas QALY GNB and Placebo represent the quality-adjusted life years gained per patient over a 3-month period.

Cost and outcome data will be collected prospectively and analyzed using non-parametric bootstrapping to assess uncertainty in the ICER. This analysis will help determine whether preoperative GNB is not only clinically beneficial but also economically viable as a standard component of perioperative care in primary TKA.

9. INSTITUTIONS AND RESPONSIBLE INVESTIGATORS

9.1. Institutions

The project is designed as an interregional collaboration involving two key Norwegian health regions: Helse Midt-Norge and Helse Sør-Øst**.** Participating institutions include:

- **Helse Midt-Norge:** Nordmøre and Romsdal Hospital, St. Olavs Hospital and Norwegian University of Science and Technology (NTNU).
- **Helse Sør-Øst:** Oslo University Hospital – Rikshospitalet and University of Oslo (UiO).

This structured collaboration is fully aligned with regional development plans, which prioritize active engagement in research initiatives. Inclusion, intervention, and follow-up for the clinical trial will take place at Nordmøre and Romsdal Hospital, which conducted 163 primary unilateral TKAs in 2024.

This project is firmly anchored within OrtoForsk-KSU, the orthopedic research group at Helse Møre and Romsdal Hospital Trust (HMR-HT)**.** OrtoForsk-KSU brings substantial expertise in conducting clinical TKA studies and health economic evaluations, supported by a robust and well-established research infrastructure. This includes access to a statistician and a specialized research nurse/coordinator, ensuring high-quality data management and streamlined clinical follow-up. The project will be led by the sponsor representative, who is also the research group leader at OrtoForsk-KSU, providing leadership and alignment with both clinical and scientific objectives.

9.2. Responsible investigators

The project reflects a multidisciplinary scope and is organized to ensure rigorous project management and adherence to clinical trial protocols.

10. USER INVOLVEMENT

User involvement is integral to healthcare research, reflecting the principles of the WHO's 1978 Declaration, which emphasizes the right and responsibility of individuals to participate in the planning and implementation of their healthcare. Active collaboration between healthcare professionals, researchers, and patients enhances study design, recruitment, and dissemination, aligning research priorities with patient needs. This approach is particularly relevant in OA research, where patients often prioritize practical interventions like TKA, education, and self-management, contrasting with traditional research focuses.
User involvement is a key aspect of this project, ensuring that patient perspectives are integrated into study design and implementation. The project has received strong support from the Kristiansund Rheumatism Association and the user committee at HMR-HT reflecting

patient trust and commitment to the study's goals. This involvement aims to optimize recruitment strategies, enhance patient-centered approaches, and address potential barriers to participation from the outset.

11. ETHICS

The study will follow the CONSORT guidelines and will be performed in full compliance with ethical principles outlined in the Declaration of Helsinki, the ICH Good Clinical Practice (GCP) standards, and applicable national regulatory and data protection frameworks. Ethical approval will be obtained from the Regional Ethics Committee, the local Data Access Committee, and the data protection officer at HMR-HT. The trial will be registered at clinicaltrials.gov and helseforsk.no, in line with CONSORT guidelines. The Directorate for Medical Products has confirmed that no application is required (ref. no: 25/06627-13).

Informed Consent

Participants will receive detailed verbal and written information about the study purpose, interventions, risks, benefits, follow-up, and the additional cost-effectiveness analysis. Confidentiality will be emphasized, and participants will be informed that medical records may be reviewed by authorized personnel. Participation is voluntary, with the right to withdraw at any time without consequences for future care. Patients will be given time to consider participation, and written informed consent will be obtained and stored in their electronic health records.

Safety and Oversight

Any serious or unexpected adverse events and major protocol amendments will be reported to the ethics committee and data protection authorities as required. Patients will be informed promptly if new information arises that could affect their willingness to continue.

11. QUALITY-SECURITY CONTROL/SAFE STORAGE OF SENSITIVE DATA

All data is primarily registered digitally in secure database set up by eFORSK. The Clinical research forms (CRFs) will include inclusion and exclusion criteria, the validated patient reported outcome measures scores (NRS, Tegner, KOOS, FJS, and EQ-5D-5L). Data will include baseline information such as age, sex, work status, use of medication and prior medical history. Further, data will include objective measures such as activity data and

radiographs. Access to the eFORSK platform will be given only to study personnel and log in requires either BankID or pulskort. When patients fills out the questionnaires, they will be given access to their own personal scheme using BankID.

A study nurse will continuously follow-up patients at 1 week, 1 month and 3 months. At the patient's appointment, the treating doctor or study nurse secures that the patient completes all the questionnaires. Objective measurements and any complications are recorded. Sensitive data will be anonymized. It will not be possible to identify patients in the results of the study when these are published, and data will be stored 10 years after inclusion.

12. RISK AND SAFETY ASSESSMENT

The study does not pose any major risks to the patients, as the treatment of choice in this patient population is a unilateral primary TKA. Local anesthesia is routinely used in clinical practice for effective pain management; however, this study will specifically focus on the method of sensory nerve block around the knee as a preoperative analgesic technique.

Study-specific risks:

Some patients may find it unpleasant when asked about demographic information and use of medication, especially strong analgetic. Further, some may experience pain or discomfort when the intervention is performed (GNB or placebo injection), and vasovagal reactions may occur. Infection at injection site is uncommon (< 1%) but may happen. A sterile procedure when performing intervention is mandatory and thereby minimize the risk of infection.

TKA-specific risks:

Potential risk of standard clinical practice is rare but include wound bleeding, infection, deep vein thrombosis (DVT), arthralgia, headache and joint effusion/swelling. Some might experience persistent knee pain after TKA, which may require more follow-ups and revision surgery.

If any complication occurs during intervention, surgery, postoperative management and follow-up, patients will be examined by the doctor on call and treated according to clinical guidelines. Outside the abovementioned complications, it is very unlikely that other complications will occur. If any unforeseen complication outside normal clinical practice

occurs, the sponsor representative will be contacted as soon as possible. If such an event occurs, the form “skademelding pasient” will be filled out, and the patient and family notified. There will be a CRF regarding complications and safety during the follow ups. These CRF specifically ask for any complication since last follow-up, if the complication is severe and lists all the severe complications. If a severe complication occurs, the patients will always be considered for study termination. Also, the CRF contains information about the outcome after a complication, and if the complication may have a connection with study participation.

13. COST AND FINANCING PLAN

13.1. Cost

All follow-ups up to 3 months are standard clinical practice, except the assessment after 1 week and 1 month (telephone interview or digital questionnaire). However, they will not be associated with any additional costs.

Outside standard clinical practice, the study requires 15 activity monitors (activPAL4™), 2 USB Hubs & charging stations and 1 dedicated computer.

13.2. Financing plan

The study is sought financed by research funding from Samarbeidsorganet, Helse Midt-Norge RHT or HMR-HT.

14. TIME SCHEDULE AND PUBLICATION PLAN

14.1. Time Schedule

The inclusion will start in the second quarter of 2026 and is expected due the second quarter of 2028. Follow-up is 3 months. Data collection is estimated to 3 months and data analysis is estimated to 6 months. Publication is expected 6 months after first submission.

14.2. Publication plan

The results will be published in international peer reviewed anesthesiologic and/or orthopedic journals, as well as presented to the anesthesiologic and orthopedic community at national and international scientific meetings. They will also be actively communicated to the community by using the hospital web page with publication of the studies.

The study will result in 3 publications (Figure 1):

1. A randomized, multiple-blind, controlled trial comparing genicular nerve block and placebo as preoperative pain control in unilateral primary total knee arthroplasty.
2. Does preoperative GNB result in improved objective activity levels during the first postoperative week compared to placebo following primary unilateral TKA? A comparative study.
3. Does preoperative GNB reduce postoperative opioid consumption and overall healthcare costs compared to placebo in patients undergoing primary unilateral TKA? A socio-economic study.

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