TKAFTER Protocol

- Interventional Research with Minimal Risk and Constraints -

Registration number: No. 2019-A00929-48
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"Chronic pain and functional prognosis after total knee replacement (TKR): continuous regional analgesia via femoral triangle catheter versus tissue infiltration as part of an enhanced recovery after surgery (ERAS) program"

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SIGNATURE PAGE

SIGNATURE OF THE SPONSOR

The sponsor undertakes to conduct this study in accordance with all legislative and regulatory provisions applicable to the research and in accordance with the protocol.		
Name and position of the signing representative: **Managing Director, CHD Vendée** **Mr. Francis SAINT-HUBERT**	**Date:**	**Signature:**

SIGNATURE OF INVESTIGATORS

I have read all the pages of the clinical trial protocol sponsored by CHD Vendée. I confirm that it contains all the information necessary to conduct the trial. I undertake to conduct the trial in accordance with the protocol and the terms and conditions set out therein. I undertake to conduct the trial in accordance with:

- the principles of the "Declaration of Helsinki,"
- the rules and recommendations of international (ICH) and French (rules of good clinical practice for biomedical research involving on medicinal products for human use)
- European regulations and/or national legislation and regulations relating to clinical trials,

I also undertake to ensure that investigators and other qualified members of my team have access to this protocol and to the documents relating to the conduct of the trial so that they can work in accordance with the provisions contained in these documents.

Coordinating Investigator	**Name:**	**Date:**	**Signature:**
Principal Investigator	**Name and institution:**	**Date:**	**Signature:**

LIST OF ABBREVIATIONS

NSAID	Nonsteroidal anti-inflammatory drug
MA	Marketing Authorization
ANSM	French National Agency for Medicines and Health Products Safety Health
APAIS	Amsterdam Preoperative Anxiety and Information Scale
ARC	Clinical Research Associate (monitor)
ASA	American Society of Anesthesiologists
BNP	Peripheral Nerve Blocks
BTF	Femoral Triangle Block
CKD-EPI	Chronic Kidney Disease - Epidemiology Collaboration
CNIL	French Data Protection Authority
CPP	Committee for the Protection of Individuals
CRF	Case Report Form (observation log)
CSP	Public Health Code
CTCAE	Common Terminology Criteria for Adverse Event
DCPC	Chronic Post-Surgical Pain
DM	Medical Device
DN4	Neuropathic pain (4 questions)
eCRF	Electronic Case Report Form
EI	Adverse Event
SAE	Serious Adverse Event
EII	Unexpected Adverse Effect
EvI	Adverse Event
EvIG	Serious Adverse Event
EN	Numerical Scale
EQ 5D	EuroQol 5D
EVA	Visual Analog Scale
HAS	French National Authority for Health
ICH	International Conference on Harmonization (International Conference on Harmonization)
IDE	State-certified nurse
IPACK	Infiltration between Popliteal Artery and Capsule of the Knee
IT	Tissue Infiltration
IV	Intravenous
KTTF	Femoral Triangle Catheter
MR	CNIL Reference Methodology
NFS	Complete Blood Count
NVPO	Postoperative Nausea and Vomiting
PCA	Patient-Controlled Analgesia
PTG	Total Knee Replacement
RAAC	Enhanced Recovery After Surgery
RCP	Summary of Product Characteristics
RIRCM	Minimal Risk and Burden Interventional Research
SSPI	Post-Interventional Monitoring Room
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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INTRODUCTION

The prevalence of chronic postoperative pain (CPP) after knee replacement (KR), defined as pain greater than or equal to 4/10 on the visual analog scale (VAS) after the third postoperative month, is recognized as being high, with an average of **20%** (ranging from 7% to 45%) (1-7).

These DCPCs, when present, are associated with a poor long-term functional prognosis for the joint and a reduced quality of life for patients. Numerous pre-, peri-, and post-operative predictive factors for these DCPCs have been identified in recent years. The most common post-operative risk factor found in the literature is the intensity of early pain (1-3).

Treatment protocols for this early postoperative pain are currently and predominantly multimodal in nature, combining systemic analgesics (paracetamol, NSAIDs, morphine derivatives) and local anesthetics, administered either as **peripheral nerve blocks (PNBs) (**continuous or single injection) or as **tissue infiltration (TI)** performed by the surgeon (14-22) during the procedure.
Very few of these techniques have been evaluated for their ability to reduce the incidence of PCSD. Drugs with anti-hyperalgesic properties such as ketamine or nefopam have been shown to be of no benefit (6), except in reducing the proportion of neuropathic pain. To date, only continuous femoral nerve block has shown any benefit over IT in reducing the incidence of CPPS (8,19).

The main objective of this study is to show that a multimodal analgesia protocol based on continuous regional analgesia via a femoral triangle catheter (FTTC) could reduce the incidence of chronic postoperative pain (CPP) compared to a protocol based on tissue infiltration (TI).

1. JUSTIFICATION FOR THE STUDY

1.1. POSITIONING OF THE RESEARCH

According to the Haute Autorité de Santé (HAS), 70,000 total knee replacements (TKR) are performed each year in France, the vast majority for primary osteoarthritis. The main purpose of joint replacement is to reduce long-term pain and provide functional benefits.

Although this procedure is common, it is associated with **intense postoperative pain**, the management of which is a major challenge. Optimal management of early analgesia improves patient comfort, allows patients to start walking again sooner, prevents stiffness, reduces the length of hospital stays, and may also reduce **the incidence of chronic post-surgical pain (CPPS).** Technical advances in this area in recent years, particularly in terms of dynamic analgesia, have led to the development of the concept of enhanced recovery after surgery (ERAS).

However, there is currently considerable disparity among teams regarding these RAAC analgesia protocols, which are often multimodal in nature, combining systemic analgesics (paracetamol, NSAIDs, morphine derivatives) with local anesthetics, administered either as **peripheral nerve blocks (PNBs) (**continuous or single injection) or as **tissue infiltration (TI)** performed by the surgeon (14-22) during the procedure. The latter technique is currently the most widely used among teams, mainly because it is simple to perform and inexpensive.

Among the PNB techniques, the femoral triangle block (FTB) (related to the adductor canal) has gradually replaced the femoral nerve block in recent years: this is because, with a comparable analgesic effect, it better preserves quadriceps motor function and therefore allows active mobilization, enabling a faster return to walking (8-13). However, as it does not cover the posterior part of the knee in terms of analgesia, this block is very often combined with a posterior infiltration, which is now performed more reliably under ultrasound guidance (IPACK – Infiltration between Popliteal Artery and Capsule of the Knee) (23,24).

The prevalence of DCPC after TEPT, defined as pain greater than or equal to 4/10 on the visual analog scale (VAS) after the third month, averages **20%**, with extremes ranging from 7 to 45% (1-7). Apart from the type of population studied, this wide variability can be explained by the type of perioperative care, which can vary greatly from one institution to another, **particularly in terms of analgesia (**IV morphine-based PCA, infiltrations, blocks (single or continuous injection)). When present, these DCPCs are associated with a poor long-term joint function prognosis and an impaired quality of life for patients. Numerous pre-, peri-, and post-operative predictive factors for these DCPCs have been identified in recent years. The most common postoperative risk factor found in the literature is the intensity of early pain. Conversely, certain factors related to anesthetic management are considered protective, such as the use of prolonged regional analgesia or the use of drugs such as ketamine.

Among these analgesia techniques, very few have been evaluated for their ability to reduce the incidence of CPCD. Drugs with antihyperalgesic properties such as ketamine or nefopam have proven to be of no benefit in the context of TEP (6), except for

reducing the proportion of neuropathic pain. In two studies (8,19), continuous femoral block has shown benefits compared to IT. To date, to our knowledge, continuous femoral triangle block (KTTF) has never been evaluated in this regard.

At a time when RAAC is being implemented, and probably due to the wide variety of protocols, very few teams adopting a RAAC protocol have so far sought to document their patients' chronic pain rates and long-term joint prognosis, with the focus mainly on the early postoperative period, with the aim of minimizing the length of stay or even offering outpatient care in some centers.

The objective of this multicenter study is therefore to compare two analgesia techniques aimed at reducing motor block and facilitating ambulation after TKR, namely continuous regional analgesia via **femoral triangle catheter (FTTC)** and **tissue infiltration (TI)**, in terms of chronic pain rates at 3 months.

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1.2. BENEFITS AND RISKS FOR PEOPLE PEOPLE PARTICIPATING IN RESEARCH

1.2.1. Benefits

1.2.1.1. Individual benefit

The expected benefits of analgesia using local anesthetics (KTTF such as IT) in the perioperative management of a patient undergoing TKA are:

- less use of morphine derivatives during surgery, thereby improving the quality of recovery
- a significant reduction in post-operative pain and in the consumption of analgesics, particularly morphine derivatives, in the post-operative period, as well as a reduction in the occurrence of adverse effects associated with these drugs
- a reduction in the incidence of postoperative nausea and vomiting linked to the reduction in the use of morphine derivatives
- better preservation of quadriceps motor function, which is already naturally reduced by a mechanism of shock related to the surgical procedure itself

- earlier resumption of independent walking with effective locking of the operated joint
-Faster rehabilitation and recovery after surgery

The expected benefits of KTTF compared to IT are:
- longer duration of analgesia
- lower incidence of chronic pain

1.2.1.2. Collective benefit

The use of local analgesia in the postoperative period following TKA is one way of reducing the length of hospital stays as part of a rapid rehabilitation policy, thereby reducing the costs associated with hospitalization.

1.2.2. Risks

1.2.2.1. Individual risks

Related to the procedure for placing a perineural catheter:

- Persistent nerve damage discovered incidentally:
  - Traumatic due to the needle used to insert the catheter or due to intraneural injection
  - Ischemic due to compressive hematoma related to vascular breach

Related to the perineural catheter:

- Very mild pain when the catheter is removed
- Catheter infection, suspected in the event of fever (>38°C) or signs of inflammation around the puncture site. This risk is very low due to the catheterization duration not exceeding 48 hours.
- Risk of falls due to unlocking of the knee on the operated side: this risk is particularly present to a lesser degree with KTTF, which has less impact on quadriceps motor function. This risk is prevented by the usual prophylactic measures of monitoring and informing patients, carried out by the state-registered nurses (IDE) and physiotherapists of the department, who are the only ones authorized to allow patients to walk with crutches or a walker after testing their quadriceps muscle strength. Getting up without a splint is only done with minimal locking force. Otherwise, the patient is first fitted with a locking splint to keep the knee extended before being helped to stand up and walk.
- Catheter occlusion leading to premature catheter removal
- Leakage of ropivacaine at the puncture site leading to premature removal of the catheter
- Risk of displacement (untimely movement of the patient)/ineffectiveness

Related to the infiltration technique:

- Performed intraoperatively, therefore no additional pain, but risk of infection difficult to separate from that of the procedure
- Risk of skin necrosis, very rare, due to skin vasoconstriction linked to the presence of adrenaline

Related to ropivacaine (mainly related to the risk of overdose)
Ropivacaine is administered in both arms, but at different doses; thus, the risks are increased in the IT group (compared to the KTTF group) due to the use of higher doses of ropivacaine.

Local anesthetics can cause adverse effects that are generally minor and transient: digestive effects such as nausea and vomiting are reported in less than 5% of patients, although the causality remains uncertain (anxiety related to the procedure may cause such effects).

The adverse effects of these drugs are mainly related to overdose, with toxicity primarily affecting the nervous and cardiorespiratory systems.

- Overdose
  - Minor risks: tinnitus, dysgeusia, logorrhea, sometimes preceding signs of severe overdose.
  - Severe overdose: convulsions, bradycardia, ventricular arrhythmias (tachycardia, fibrillation), cardiac arrest. This risk is often linked to accidental intravascular injection or plasma resorption of a toxic dose.
- The risk of developing an allergy/hypersensitivity to ropivacaine is very rare. The risk of allergy is further minimized by the absence of preservatives in the commercial solution used.

All expected adverse events associated with the use of ropivacaine are listed in the vigilance section and detailed in the current version of the SPC.

These complications usually resolve favorably after symptomatic treatment, but a fatal outcome cannot be ruled out.

The risks associated with the procedure and the placement of an ECP, as well as with the usual associated treatments (analgesics, antibiotics, rehabilitation equipment, etc.) are present in both arms and are identical to those observed outside the study; these risks are presented in the vigilance section.

1.2.2.2. Collective risk

No collective risk is expected from the conduct of this study. There is no change in management outside of randomization.

1.2.3. Benefit/risk balance

The research manager classifies this study as **a low-risk, low-burden interventional study** (RIRCM), since:

✓ All procedures are performed in the usual manner *(blood sampling, interventions, etc.)* and are defined in the decree of April 12, 2018, issued by the ministry.

The research does not focus on techniques or strategies that are either innovative or obsolete.

All patient care will be identical to usual practice. In particular, the discharge date will be decided by the physician in charge of the patient, independently of the study, and will be recorded in the patient file and the research eCRF.

Consequently, the specific implementation procedures in the research represent negligible constraints for the person participating in the research. (Article R 1121-3 of the Public Health Code (CSP), Decree No. 2006-477 of April 26, 2006)

The research manager shall therefore submit the study protocol to the Committee for the Protection of Persons (CPP) Est IV in accordance with Article L 1121-1 of the Public Health Code (CSP) as resulting from Laws No. 2004-806 of August 9, 2004, and No. 2006-450 of April 18, 2006, relating to public health policy.

2. OBJECTIVES AND EVALUATION CRITERIA

2.1. OBJECTIVE AND MAIN EVALUATION CRITERION

2.1.1. Main objective

The main objective of this study is to show that a multimodal analgesia protocol based on continuous regional analgesia via a femoral triangle catheter (FTTC) could reduce the incidence of chronic postoperative pain (CPP) compared to a protocol based on tissue infiltration (TI).

2.1.2. Primary endpoint

EN pain on walking greater than or equal to 4 three months after surgery.

2.2. SECONDARY OBJECTIVES AND EVALUATION CRITERIA

2.2.1. Secondary objectives

The secondary objectives of this study are to compare the following in each group:

1. the evolution of DCPC at rest;
2. the evolution of DCPC during mobilization (walking effort);
3. the neuropathic nature of these chronic pains during the study;
4. the functional prognosis for the joints;
5. the improvement in quality of life in the medium and long term;
6. the time to complete patient independence;
7. the consumption of analgesic medications targeting pain in the operated knee in the medium and long term.

2.2.2. Secondary evaluation criteria

1. EN pain at rest at inclusion, hospital discharge, 1 month, 3 months, 6 months, and 1 year post-op;
2. EN pain when walking at inclusion, discharge from hospital, 1 month, 6 months, and 1 year post-op;
3. Scores obtained on the simplified DN4 questionnaire at inclusion, hospital discharge, 1 month, 3 months, 6 months, and 1 year post-op;
4. Scores obtained for the WOMAC index at inclusion, 1 month, 3 months, 6 months, and 1 year post-operatively;
5. Scores obtained on the EQ-5D-5L questionnaires at inclusion, at M3 and 1 year post-operatively;

6. Time to resumption of independent walking **without a splint (locking achieved) in** postoperative period;
7. Recording of medication use at inclusion, 1 month, 3 months, and 1 year post-op.

3. STUDY POPULATION

3.1. DESCRIPTION OF THE POPULATION

This study is intended for patients undergoing surgery for PTG at the centers participating in the study. Recruitment will be carried out prospectively during the anesthesia consultation.

Inclusion period: 30 months Follow-up
period: 12 months
Total duration of the study: 42 months

The study plans to include 440 patients with the aim of obtaining **420 randomized patients**. Inclusion will stop when the potential number of randomized patients is reached.

3.2. INCLUSION CRITERIA

Patients with the following characteristics will be eligible for inclusion:

- Adult patient;
- Unilateral tricompartmental knee replacement for knee osteoarthritis;
- ASA score between I and III;
- Scheduled non-septic surgery;
- PTG scheduled for one of the first three days of the week (Monday to Wednesday inclusive) in order to benefit from consistent post-operative physical therapy;
- Able to understand the protocol;
- Having agreed to participate in the study and having given express verbal consent;
- Affiliated with a social security system;
- Eligible for treatment under the protocol.

3.3. EXCLUSION CRITERIA

- Age≥ 86 years old;
- BMI > 35;
- PTG revision;
- Chronic pain in the operated knee;
- Vascular surgery on the femoral vessels on the operated side;
- Suspected diffuse polyalgic syndrome (fibromyalgia);
- Documented neuropathy of the lower limb;
- Infection localized at the catheter insertion site (femoral triangle);
- Known allergy to ropivacaine;
- Severe renal impairment (clearance – CKD-EPI formula – creatinine <50 mL/min) and/or severe hepatic impairment (prothrombin blood level <50%);
- Inflammatory rheumatic disease (rheumatoid arthritis, ankylosing spondylitis);
- Patients undergoing immunosuppressive treatment or systemic corticosteroid therapy;

- Daily use of level II or III analgesics for more than one month prior to surgery;
- Known intolerance to level III analgesics;
- Allergy or contraindications to standard perioperative and postoperative treatments (paracetamol, NSAIDs);
- Patients who participated in the study for the contralateral knee;
- Patients who are uncooperative or do not understand French, difficulties in understanding and assessing pain scores (EN), preoperative cognitive dysfunction making questioning unreliable;
- Patients under guardianship, conservatorship, or deprived of liberty;
- Patients already enrolled in another interventional clinical trial (category 1);
- Pregnant or breastfeeding women, or women of childbearing age who refuse to use effective contraception;
- Refusal to participate;
- Inability to understand the protocol and its requirements, and/or to give express oral consent.

4. STUDY DESIGN AND PROCEDURE

4.1. STUDY SCHEDULE

The TKAFTER study will be explained and proposed to the patient during the anesthesia consultation (inclusion visit from D-30 to D-1).
An information letter will then be sent to them. (See Appendix 4)

The patient's express verbal consent must be obtained between this consultation and no later than the day of randomization.

Randomization must be carried out prior to the procedure for reasons related to the organization of the surgical schedule (time required to insert the catheter for the KTTF group or to inform the surgeon for the IT group).

- In the KTTF group, the catheter will be placed approximately 1 to 1.5 hours before the procedure so that the first injection of ropivacaine can be administered and its clinical efficacy tested and verified after 30 to 45 minutes.

The clinical effectiveness of the catheter will be assessed by *testing* sensitivity on the inner side of the leg according to the following scale:

Sensitivity rating: S0 to S2
S0= **Complete** anesthesia (touch+ prick), S1= Perception of touch but **not cold or prick**, S2 = **Normal** sensitivity

A sensitivity rating of S2 indicating clinical ineffectiveness will result in repositioning of the catheter.

- In the IT group, tissue infiltration will be performed intraoperatively by the surgeon using the technique described in section 4.4.1 (Description and justification of the treatment regimen).

In both groups, the patient will undergo **ultrasound-guided infiltration of the posterior capsule** (**IPACK**) to achieve analgesia of the posterior part of the knee joint (blocking of the sensory nerve branches originating from the popliteal plexus) according to the technique described in section 4.4.1 (Description and justification of the treatment regimen).

STUDY TIMELINE

Actions	Inclusion: D-30 *(Anesthesia consultation)* to D-1	D *(Surgery)*	SSPI	Hospitalization	Discharge from hospital	Post-op M1 *(telephone contact)*	M3 post-op *(Consultation with surgeon)*	M6 post-op *(telephone contact)*	M12 post-op *(Consultation with Surgeon)*
						+/- 1 week	*- 1 week/ + 15 days*	*+/-15 days*	*+/- 1 month*
Patient information	X								
Informed consent (verbal)	X								
Randomization	X								
Clinical data[1]	X								
Biological assessment (Hematocrit)	X*	X *(D-7)**			X				
Collection of data relating to the procedure[2]		X							
Pain assessment (EN) at rest	X		X *(arrival+ discharge)*		X	X	X	X	X
Pain assessment (EN) while walking (flat terrain – 5 minutes)	X			X *(D1, D2)****	X	X	X	X	X
Simplified DN4 questionnaire	X				X	X*(mail)*	X	X*(mail)*	X
WOMAC index	X					X*(mail)*	X	X*(mail)*	X
EQ-5D-5L questionnaire	X						X		X
APAIS questionnaire	X								
Medication use[3]	X					X	X		X
30-meter walk test	X				X		X		X
Distance between heel and resting surface (supine position)		X *(pre- and post-KT)*	X *(discharge)*	X *(D1, D2)*	X				
Degree of joint flexion	X				X		X		X
Adverse events *(Special situations/New developments)*		X	X	X	X	X			

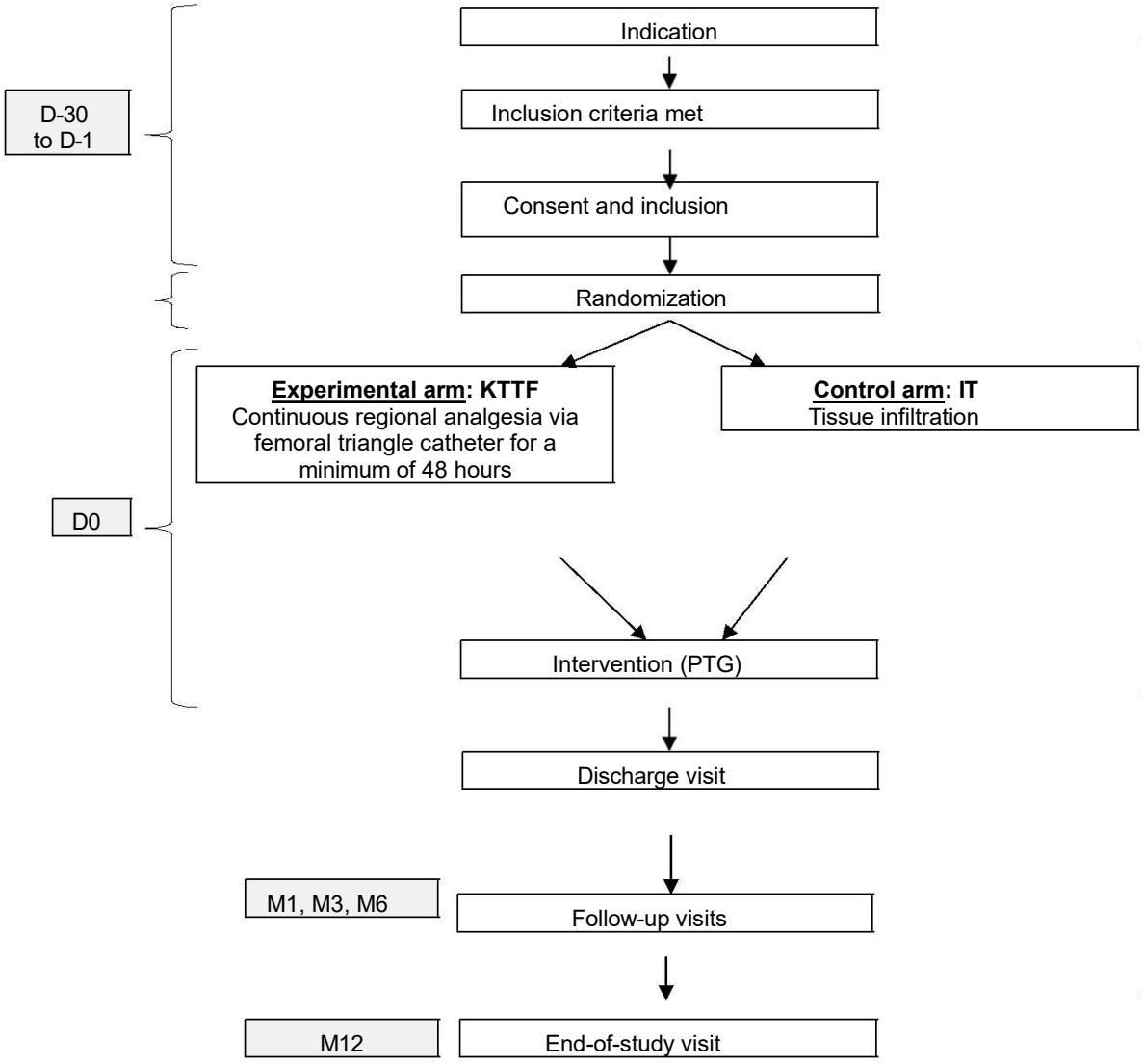
[1] Age, sex, height, weight, BMI, ASA score
[2] Date of procedure, side of procedure, duration of procedure, tourniquet, drainage, cryotherapy splint
[3] Paracetamol, gabapentinoids, antidepressants, NSAIDs, level II analgesics, level III analgesics (and associated dose only for level III analgesics at inclusion, M3 and M12)
* Hematocrit measured during the anesthesia consultation. For patients receiving blood conservation therapy (EPO and/or iron): hematocrit closest to the procedure in addition to that measured during the anesthesia consultation
** Last blood test performed before discharge from hospital
*** EN in motion (walking or arthromotor)

4.2. GENERAL RESEARCH METHODOLOGY

The research has the following characteristics:

- Type of research: Interventional Research with Minimal Risk and Constraints (IRMC)
- Comparative
- Multicenter
    - Center 01 - CHD Vendée
    - Center 02 - Cesson Sévigné Polyclinic
    - Center 03 - Diaconesses Croix Saint Simon Hospital Group
    - Center 04 - Victor Pauchet Clinic
    - Center 05 - Béthune Beuvry Hospital Center
- Prospective
- Controlled
- Randomized
- Single-blind

4.3. STUDY DESIGN



4.4. DESCRIPTION AND JUSTIFICATION OF THE TREATMENT PLAN

4.4.1. Preoperative period

Prior to surgery: Randomization

Experimental group (KTTF): Ultrasound-guided placement (6-13 MHz linear probe) of a perineural KTTF inserted 3 cm into the paravascular space under the sartorius muscle (puncture point 12-15 cm below the inguinal fold)

→ Initial bolus of 10 mL (11) of 0.2% ropivacaine into the KT

Control group (IT): In order to comply with the blind concept, skin fixation with a Steristrip of a fictitious epidural catheter on the side of the operated knee at the same puncture point 12 cm below the inguinal fold (visually mimicking a catheter in the femoral triangle) with an occlusive dressing
NB: tissue infiltration performed secondarily intraoperatively by the surgeon (see section 4.4.2)

For both groups:
Preoperative ultrasound-guided infiltration of the posterior capsule (IPACK) (needle in the ultrasound plane, 2-5 MHz curved probe) as a single injection via the medial route at the popliteal fossa using a short bevel needle (80 or 100 mm) and injection of 40 ml of 0.2% ropivacaine + 200 µg adrenaline (5 µg/mL).

4.4.2. Intraoperative period

Antibiotic prophylaxis (cefazolin 2 g or dalacin 900 mg in case of allergy)
+ Tranexamic acid 30mg/kg
+ Dexamethasone 12 mg
+ General anesthesia or spinal anesthesia (0.5% hyperbaric bupivacaine or 0.5% isobaric levobupivacaine)
NB: No nitrous oxide, ketamine, or nefopam

- Paracetamol 1g+ Ketoprofen 100mg in intraoperative infusion

Control group (IT) only: Tissue infiltration performed in two stages by the surgeon during the procedure, using a total of 80ml of ropivacaine 0.2% + adrenaline 400µg (5µg/mL)

-First stage (40mL): after implants in the anterior compartment in the suprapatellar region and the quadriceps tendon

-2nd time (40mL): in the periarticular tissues

4.4.3. SSPI

Experimental group (KTTF) only:

→ **Second systematic bolus of 10mL of 0.2% ropivacaine upon arrival in the PACU, then**
connection to KT in place of a programmable electronic pump with 0.2% ropivacaine
200mL according to the following program: continuous flow rate of 3mL/h, bolus of 10mL, 60-minute lockout, maintained in place for at least 48 hours

For both groups:
On arrival and departure from the PACU:

- Assess the intensity (EN) of the patient's pain at rest

If EN at rest≥ 4 (moderate to severe pain): begin IV morphine titration (morphine, oxycodone) as follows: 3mg IVD/5' (2mg in patients >80 years old) until EN pain is <4
NB: Discontinue this titration in the event of sedation making the patient difficult to awaken with verbal stimulation or in the event of a respiratory rate <10/min

- If **nausea/vomiting** occurs during the SSPI period: ondansetron 4 mg IV

4.4.4. Postoperative period

Systemic analgesia with paracetamol 1 g x 4/day+ Ketoprofen 100 mg LP x 2/day starting 4 hours post-op as standard

If EN ≥ 4: oral administration of Oxynorm® 10 mg every 4 to 6 hours (5 mg if weight <60 kg) Rescue

analgesia: If EN remains ≥ 6 for a prolonged period despite Oxynorm® peros:
Administration of Oxynorm® in SSPI using an IV titration method to achieve a resting EN < 4 and oral relay with Oxycontin 10 mg LP morning and evening or even IV PCA if insufficient

H4:
- Oral refeeding
- Ondansetron 4 mg IV if postoperative nausea and vomiting (PONV)

D1:
- Removal of drains according to surgical prescription (D1 or D2)
- Removal of peripheral venous line if blood count is normal
- Possible removal of urinary catheter (if postoperative urinary retention)
- Ondansetron 4 mg IV if PONV

D2:
- Removal of perineural KT in the afternoon (KT left in place for at least 48 hours)
- Ondansetron 4 mg IV if NVPO

4.5. DESCRIPTION OF THE ASSESSMENT AND OF DATA COLLECTED

For ethical reasons, we deliberately chose not to use the **double-blind** method, which would have required:

- On the one hand, the insertion of a placebo catheter (i.e., infused with isotonic saline solution) for the IT (Tissue Infiltration) group, a procedure that we considered to have an unfavorable risk/benefit ratio.

- On the other hand, a placebo infiltration (performed with isotonic saline solution) for the KTTF (femoral triangle catheter) group, a procedure that would have been difficult to perform in the operating room, a source of potential unintentional deviations from the protocol and, moreover, generating potentially iatrogenic tumescence of the joint.

We therefore decided to preserve the single-blind aspect by not informing the patient of the randomization arm and by placing a **dummy catheter simply stuck to the skin** during anesthesia **for patients in the IT group**. This procedure was performed at the beginning of the operation without the patient's knowledge (after placing a drape covering the lower part of the body).

- **Numerical Scale (NS):** performed by the physical therapist or registered nurse
Self-assessment scale used to quantify the patient's pain on a virtual scale ranging from 0 (no pain) to 10 (maximum pain imaginable)

- **ASA** *(American Society of Anesthesiologists)* **score**: calculated by the anesthesiologist Scale used in anesthesiology to classify patients into 6 categories:
  1) Healthy patient
  2) Patient with moderate impairment of a major function
  3) Patient with severe impairment of a major function that does not result in disability
  4) Patient with severe impairment of a major function, which is disabling and life-threatening
  5) Dying patient
  6) Patient declared brain dead whose organs are being harvested for transplantation

- **Simplified DN4 questionnaire** *(Neuropathic pain in 4 questions)*: completed by the nurse Questionnaire used to diagnose neuropathic pain.
This questionnaire consists of 4 questions representing 10 items to be checked:
  - The nurse interviews the patient and completes the questionnaire.
  - For each item, the patient must answer "yes" or "no."
  - At the end of the questionnaire, the practitioner counts the answers, 1 for each "yes" and 0 for each "no."
  - The sum obtained gives the patient's score, out of 10

→ If the score is greater than or equal to 4/10, the test is positive.

- **WOMAC** *(Western Ontario and McMaster Universities Osteoarthritis Index)* **score:** performed by the nurse
Index enabling functional assessment of coxarthrosis and/or gonarthrosis.
For each item, the patient must answer each question using a scale from 0 to 4. The score is calculated by adding up the results for each question.

The higher the score, the greater the functional impact of coxarthrosis and/or gonarthrosis.

- **EQ-5D-5L** *(EuroQol-5D)* **questionnaire**: completed by the nurse.

Questionnaire to assess the impact of health status on quality of life according to five dimensions:

1) Mobility
2) Personal autonomy
3) Daily activities
4) Pain/discomfort
5) Anxiety/depression

Each item has 5 response levels.

- **APAIS questionnaire** *(Amsterdam Preoperative Anxiety and Information Scale)*: completed by the nurse

Scale used to assess the patient's preoperative anxiety. Each item is rated from 1 (none) to 5 (extreme).
To obtain the anxiety score, the scores obtained for items 1, 2, 4, and 5 are added together. Subjects are considered anxious when they have a score strictly greater than 11 for the sum obtained for these four items.

Items 3 and 6 measure the desire for information. To obtain the desire for information score, the scores obtained for these two items are added together. A score of 2 to 4 would imply a "refusal of information," a score between 5 and 7 would imply a "moderate desire for information," and a score above 7 would imply an "eager desire for information."

4.6. IDENTIFICATION OF ALL SOURCE DATA NOT INCLUDED IN THE MEDICAL RECORD

- Numerical scale (pain at rest and when walking)
- 30-meter walking test
- Degree of joint flexion
- Flessum
- DN4 questionnaire
- WOMAC index
- EQ-5D-5L questionnaire
- Medication use
- APAIS questionnaire
- Heel-to-ground distance
- Expected events with an impact on the protocol objective (accidental withdrawal, catheter occlusion, etc.)
- Special situations and new developments

4.7. RULES FOR DISCONTINUING A PERSON'S PARTICIPATION

4.7.1. Criteria for premature discontinuation of a person's participation in the research

Any patient included in the protocol who no longer wishes to participate will be withdrawn from the study prematurely as soon as they express their request, before the results are published.

4.7.2. Procedures for premature termination of a person's participation in the research

A patient's withdrawal from the study will not affect their usual care for their condition.
For information on how data from individuals who have withdrawn prematurely from the study will be used, please refer to the statistics section.

4.7.3. Criteria for stopping part or all of the research (excluding biostatistical considerations)

Part or all of the study may be permanently or temporarily halted by decision of the ANSM, the CPP, or the study sponsor.

In all cases: Written confirmation will be sent to the study's coordinating investigator (specifying the reasons for premature termination) and to the principal investigator at the centers concerned.

5. DATA MANAGEMENT AND STATISTICS

5.1. COLLECTION AND PROCESSING OF STUDY DATA

5.1.1. Data collection

An electronic case report form (eCRF) will be created for each patient. All information required by the protocol must be provided in the eCRF. It must include the data necessary to confirm compliance with the protocol and all data necessary for statistical analysis; it must allow for the detection of major deviations from the protocol.

The persons responsible for completing the eCRF (investigator, CRA, etc.) must be defined and identified in the table of delegated responsibilities for each center (kept in the investigator's binder).

5.1.2. Data coding

By signing this protocol, the principal investigator and all co-investigators undertake to keep the identities of the patients who participated in the study confidential.

The transmission of an individual's data for research purposes will therefore only be possible subject to the application of a coding system; the presentation of research results must exclude any direct or indirect identification.

Patients will be identified according to the order in which they are enrolled, using a number automatically assigned by the Clinsight software (eCRF) followed by the patient's initials (first letter of first name + first letter of last name).

This code will be the only information that will appear on the eCRF form and will enable the eCRF to be linked to the patient retrospectively.
The investigator is also required to code patient data on all documents in their possession (imaging reports, laboratory reports, etc.) that are attached to the eCRF.

A correspondence table will be set up at each center. This table will be kept in a secure location by the center's principal investigator and will contain the patient code and their personal data so that the patient file can be traced in the event of missing or incorrect data. No clinical data will be collected in these correspondence tables.

5.1.3. Data processing

Clinical data will be collected using a database and data entry forms modeled on the observation log, in accordance with the protocol and current regulations.
The structure of the database and data entry screens will be approved by the research manager.

5.2. *STATISTICS*

Statistical analysis manager:

Lucie Planche
Vendée Departmental Hospital Clinical Research
Unit lucie.planche@chd-vendee.fr

Software
The analyses will be performed using SAS v.9.4 software.

5.2.1. Description of methods planned planned, including the schedule for planned interim analyses

All variables will be described globally and by group. The description will include the numbers and percentages of modalities for qualitative variables and the minimum, maximum, mean, standard deviation, and median for quantitative variables.

Primary endpoint

The primary endpoint is defined as the presence of pain when walking≥ 4 to M3.

The primary endpoint will be analyzed using a generalized linear regression model taking into account the random effect center criterion. In each group, the presence of walking pain ≥ 4 at M3 will be estimated with a 95% confidence interval.

Secondary criteria

Change in DCPC at rest
The change in DCPC at rest will be estimated and compared using a mixed linear model that takes into account baseline data and the random center effect. The group effect, time effect, and time-group interaction will be evaluated.

Change in DCPCs during mobilization (walking effort)
The change in DCPCs during mobilization will be estimated and compared using a mixed linear model that takes into account baseline data and the random center effect. The group effect, time effect, and time-group interaction will be evaluated.

Neuropathic pain
Neuropathic pain will be assessed using the DN4 questionnaire. A score ≥ 4/10 indicates neuropathic pain. This criterion will be analyzed using a generalized linear regression model taking into account the random center criterion. In each group, the presence of neuropathic pain will be estimated with a 95% confidence interval.

Joint function prognosis
The joint function prognosis will be assessed using the total WOMAC index score at inclusion, 3 months, and 1 year. The change in the total WOMAC index score will be estimated and compared using a mixed linear model that takes into account baseline data and the random center effect. The group effect, time effect, and time-group interaction will be evaluated.

Quality of life
The score obtained on the EQ-5D-5L questionnaire will be estimated and compared using a mixed linear model taking into account baseline data and the random center effect. The group effect, time effect, and time-group interaction will be evaluated.

Patient autonomy time
The time to resumption of independent walking without a splint will be assessed graphically and using the Kaplan-Meier method, and compared between the two groups using a Logrank test.

Consumption of analgesic medications
For each treatment studied, the number and percentage of patients who took at least one dose of the treatment in the three days prior to the visit will be presented. The consumption of each treatment will be compared using a generalized linear regression model taking into account the random center criterion.

5.2.2. Statistical justification for the number of inclusions

The calculation of the number of subjects is based on the primary criterion, which corresponds to the percentage of patients with walking pain greater than or equal to 4 on a numerical scale measured 3 months after the intervention.

The prevalence of chronic postoperative pain (CPPS) after knee replacement (KR) after the third postoperative month is recognized as being high, with an average of 20% (ranging from 7% to 45%) (1-7). Recent data from the literature show that local regional analgesia may reduce CPSP (7,8).

In view of these data (7), we consider that a difference of 10% can be considered clinically relevant.

With an alpha risk of 5% and a power of 80%, 398 patients are required. In order to guarantee the power of the study, 5% additional patients will be randomized, for a total of 420 patients.

5.2.3. Expected statistical significance level

The alpha risk is set at 5%.

5.2.4. Statistical criteria for stopping the research

NA

5.2.5. Method for accounting for missing, unused, or invalid data

All missing data and the reasons for their absence will be described in each group.

For the analysis of the primary endpoint, missing data will be imputed as a failure, i.e., walking pain greater than or equal to 4 at the 3-month assessment.

For the analysis of secondary endpoints, no imputation will be performed.

5.2.6. Management of changes to the initial strategy analysis plan

NA

5.2.7. Selection of individuals to be included in the analyses

The main analysis will be performed on the modified intention-to-treat (mITT) population, i.e., all randomized patients who received the intervention.
A complementary analysis will be performed on the Per Protocol (PP) population, including randomized patients for whom no major deviations from the protocol were observed.
A data review meeting will be organized to review and define whether each deviation is a major criterion or not.

5.2.8. Randomization

Randomization will be stratified by center. It will be performed according to a 1:1 ratio and will be carried out in blocks.

Randomization will be performed using Ennov Clinical by connecting to the website: https://nantes-lrsy.ennov.com.
The connection will be made using a login, password, and study number provided by the data manager of the Research Unit at La Roche sur Yon Hospital. The following information must be provided:

- First initial of surname,
- First initial of first name,
- Month and year of birth,
- Compliance with inclusion and exclusion criteria (yes/no),

Randomization will be performed by the investigator after confirmation of eligibility for inclusion in the study. The inclusion number will be assigned automatically during randomization. A confirmation email will be sent to the person who performed the randomization and to all persons concerned.

The randomization list will be drawn up by the statistician at the CHD Research Unit in La Roche sur Yon. An explanatory guide to randomization will be available online at Ennov Clinical.

6. VIGILANCE AND MANAGEMENT OF ADVERSE EVENTS

6.1. DEFINITIONS

Vigilance	This refers to the monitoring of drugs, medical devices, and other health products. It also involves preventing the risk of adverse effects resulting from their use, whether the risk is potential or proven.
Adverse events (AE)	Any harmful event occurring in a person participating in research involving human subjects, whether or not this event is related to the research or the product to which the research relates.
Intensity of Adverse Events (AE)	The severity of adverse events will be rated according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 classification 1 – Mild 2 – Moderate 3 – Severe or medically significant but not immediately life-threatening 4 – Life-threatening 5 – Death related to EI
Adverse events (AE)	An adverse event occurring in a person participating in research involving human subjects, when this event is related to the research or the product being researched.
Serious adverse effects/events (SAE)/(SAE)	Any adverse effect/event that: * results in death, * is life-threatening, * causes temporary or permanent disability or incapacity, * requires or prolongs hospitalization of the patient, * causes a congenital or neonatal abnormality, * is medically significant
Unexpected adverse effects (UEA)	Any adverse effect whose nature, severity, or progression does not correspond to the information relating to the products, procedures, and methods used during the research.
New information	Any new data that could lead to a reassessment of the benefits and risks of the research or the product being researched, to changes in the use of this product, in the conduct of the research, or in the documents relating to the research, or to the suspension, interruption, or modification of the research protocol or similar research. For trials involving the first administration or use of a health product in people who do not have any medical conditions: any serious adverse effect. serious adverse event.
Abuse	Intentional, persistent, or sporadic excessive use of a drug that is accompanied by harmful physical or psychological reactions.

Overdose	Administration of a quantity of medication, given in a single dose or cumulatively, that exceeds the maximum recommended dose according to the product's compliance or usage guidelines. Clinical judgment should always be applied. (actual overdose: due to an excessively large gross quantity) /relative overdose: due to predisposing factors in the patient, such as renal failure, hypoalbuminemia, etc.)
Misuse or off-label use	A situation where the product is intentionally used in a manner that does not comply with the product's specifications for use (e.g., route of administration/dosage or indication different from those listed in the reference document).
Medication error medication error (ME)	Corresponds to any proven (or potential) omission or unintentional action that occurred during the care process, *in the circuit (from manufacture to administration)* involving a product that may cause a risk or adverse event for the patient. The risk of error or potential error concerns situations where the error did not occur, was intercepted but could have occurred

6.2. LIST OF EXPECTED AES

Within the framework of this protocol, the expected adverse events are:

Expected adverse events related to prosthetic surgery (PTG):

- Postoperative pain
- Postoperative bleeding causing hemarthrosis or hematoma
- Postoperative anemia due to intraoperative and postoperative blood loss
- Delayed healing at the surgical suture site
- Joint stiffness due to prosthesis dysfunction
- Injury to the infrapatellar branch of the saphenous nerve secondary to the surgical approach, causing peripatellar sensory deficit that is sometimes persistent
- Infection of the surgical site: early sepsis on PTG
- Implantation syndrome (intraoperative embolic migration of bone debris from femoral reaming and fibrin-blood clots)
- Deep vein thrombosis or even pulmonary embolism
- Intraoperative injury to the fibular component of the sciatic nerve, causing paralysis of the foot elevators
- Intraoperative injury to the popliteal artery

Prosthesis-related complications:

- Infection due to contamination
- Fracture
- Dysfunction
- Loosening
- Intolerance – allergy to the material

EvI Related to the administration procedure:

In the arm KTTF

- Related to the puncture (preoperative catheter placement):
    - Unpleasant sensation or even pain during the puncture procedure, despite the administration of a temporary and non-serious subcutaneous injection of 1% lidocaine (5 ml)
    - Bruising, bleeding at the puncture site

- Related to perineural puncture:
    - Neurogenic pain (like an electric shock) in the event of nerve puncture, immediately reversible upon removal of the needle
    - Risk of persistent secondary nerve damage (traumatic damage caused by the needle used to insert the catheter or by intraneural injection, ischemic damage caused by compressive hematoma related to vascular rupture)

- Related to perineural analgesia:
    - Unpleasant tingling sensation or loss of sensation throughout the anesthetized area

- Related to the perineural catheter:
    - Very mild, fleeting pain when the catheter is removed.
    - Risk of infection
    - Risk of falling due to failure of the knee to unlock by extension of the femoral nerve
    - Risk of displacement (unexpected movement by the patient)
    - Ineffectiveness
    - Catheter occlusion leading to premature catheter removal
    - Leakage of ropivacaine at the puncture site leading to premature removal of the catheter

In the IT arm:

- Risk of infection
- Increased risk of vascular passage of ropivacaine with clinical manifestations of overdose
- Risk of skin necrosis, very rare, due to skin vasoconstriction in the infiltrated area, linked to the presence of adrenaline

<u>EI Related to ropivacaine in both arms</u>:

Local anesthetics can cause adverse effects that are generally minor and transient: digestive effects such as nausea and vomiting are reported in less than 5% of patients, although causality remains uncertain (anxiety related to the procedure may cause such effects).

AEs are mainly related to overdose, with toxicity primarily affecting the nervous and cardiorespiratory systems.

- Overdose
    - Minor risks: tinnitus, dysgeusia, logorrhea, sometimes preceding signs of severe overdose
    - Severe overdose: convulsions, bradycardia, ventricular arrhythmias (tachycardia, fibrillation), cardiac arrest. This risk is often linked to accidental intravascular injection or plasma resorption of a toxic dose.

- The risk of allergy/hypersensitivity related to ropivacaine is very rare. The risk of allergy is further minimized by the absence of preservatives in the commercial solution used.

All expected adverse events associated with the use of ropivacaine are listed in the vigilance section and detailed in the current version of the SPC.

AEs related to other treatments
In the usual context of PTG surgery, ancillary treatments may be administered, such as analgesics, antibiotics, filling solutions, transfusions, but also medical devices (MD) such as canes, walking aids, etc., depending on the clinical situation.
It is impossible to provide an exhaustive list of potentially used drugs, but these treatments are prescribed within the framework of marketing authorization or professional recommendations. Thus, the expected AEs associated with these treatments correspond to the AEs listed in the respective SPCs for drugs or in the package inserts or user manuals for MDs.

6.3. MANAGEMENT OF ADVERSE EVENTS

6.3.1. Collection of EvI/EI

In the context of this research involving minimal risks and constraints, the protocol does not involve any changes to the usual care of patients.

Adverse events related to the condition being studied (PTG), its treatment, co-morbidities, and their respective treatments do not need to be reported to the sponsor, even if a severity criterion is present.

Under the investigator's responsibility, as with care, the reporting of complications is subject to regulated systems: ADRs related to drugs and medical devices are reported to pharmacovigilance and medical device vigilance systems, while procedural complications and examinations are integrated into the risk management system of the institutions, for example.

In the context of this study, which aims to evaluate the benefits of continuous regional analgesia via a catheter in the femoral triangle (KTTF) on reducing the incidence of chronic postoperative pain (DCPC) compared to a protocol based on tissue infiltration (IT) in the context of surgery to insert a total knee replacement (TKR), only the following will be collected and reported if a severity criterion exists: **complications and adverse events of techniques with a potential impact on the protocol objective.**
Thus, expected events that have an impact on the protocol objective, i.e., mechanical complications related to the catheter (during the first 48 hours after device placement) and more specifically those leading to removal, **must be recorded in the CRF and analyzed within the same time frame as the objectives**:
- Accidental removal
- Ropivacaine leakage at the puncture site
- Catheter occlusion
- Infection
- Lack of efficacy
- Displacement rendering the catheter ineffective
- Nerve damage preventing continued administration

In addition, any new developments that arise during the study, particularly those related to regional analgesia and the administration technique, must be tracked.

6.3.2. Notification of serious adverse events/unexpected serious adverse events

AEs and SAEs are reported to the appropriate vigilance systems (a copy will be kept in the patient's clinical file).

Under this protocol, new developments, special situations, and mechanical complications that may impact the study objective must be reported in the CRF and will be taken into account in the analyses scheduled according to the study timetable.

Only "new developments" must be reported to the sponsor as soon as possible after they become known so that corrective measures can be put in place. For these malfunctions, the investigator may use the report made to the regulated system, which is anonymized (patient inclusion number only).

6.3.3. Period for notification to the sponsor

The investigator is responsible for recording and reporting all AEs/IRAs, special situations, or new developments, except those previously excluded, whether expected or unexpected, occurring during the entire study:

- from the intervention (D0)
- and until visit M1

6.4. MODALITIES AND DURATION OF FOLLOW-UP OF INDIVIDUALS FOLLOWING THE OCCURRENCE OF ADVERSE EVENTS

Any event, particularly serious events, must be followed up until recovery, consolidation, or death (closed event).

7. ADMINISTRATIVE AND REGULATORY ASPECTS

7.1. RIGHT OF ACCESS TO SOURCE DATA AND DOCUMENTS

Each patient's medical data will only be disclosed to the sponsor or any person duly authorized by the sponsor, and, where applicable, to the competent health authorities, under conditions that guarantee confidentiality.
The sponsor and regulatory authorities may request direct access to the medical file to verify the procedures and/or data of the clinical trial, within the limits authorized by laws and regulations.

7.2. DATA CONFIDENTIALITY

Persons with direct access shall take all necessary precautions to ensure the confidentiality of information relating to the persons involved, in particular with regard to their identity and the results obtained.
These individuals, like the investigators themselves, are subject to professional secrecy (under the conditions defined by Articles 226-13 and 226-14 of the Penal Code).
During or at the end of the research, the data collected on the individuals involved and transmitted by the participants will be anonymized.
Under no circumstances shall the names or addresses of the individuals concerned be disclosed.
Only the first letter of the subject's surname and the first letter of their first name will be recorded, accompanied by a coded number specific to the study indicating the order of inclusion of the subjects.

7.3. COMPUTERIZED DATA AND SUBMISSION TO THE CNIL

This study falls within the scope of the "Reference Methodology" (MR-001) in accordance with the provisions of Article 54, paragraph 5, of Law No. 78-17 of January 6, 1978, revised in June 2018, relating to information technology, files, and civil liberties. The CHD Vendée de La Roche sur Yon, promoter of the study, has signed a commitment to comply with this "Reference Methodology."

7.4. MONITORING OF THE TRIAL

Monitoring will be carried out by the Promotion Department of the Research Directorate. A Clinical Research Associate (CRA) will visit each investigator site regularly to perform quality control checks on the data reported in the observation logs.

The monitoring plan is defined in consultation between the research team and the responsible institution according to the objectives of the study.

On-site monitoring visits will be organized after making an appointment with the investigator. CRAs must be able to consult the following at each site:

- the data collection notebooks for the patients included,
- the patients' medical and nursing records,
- the investigator's file.

7.5. INSPECTION/AUDIT

An inspection or audit may be conducted as part of this study. The sponsor and/or participating centers must be able to provide inspectors or auditors with access to the data.

7.6. ETHICAL CONSIDERATIONS

7.6.1. Oral informed consent

The investigator undertakes to obtain the person's free, informed, and express consent, given orally, after providing them with information about the protocol (information sheet and consent form attached). They will give them a copy of the information sheet. The person may only be included in the study after having read the information sheet and given their verbal consent, having been given time to consider the information if necessary.

A record of the patient's express oral consent will be kept in the study documents.
The patient's information and consent to participate in the research must be noted in their medical file.

7.6.2. Human Subjects Review Board

The sponsor undertakes to submit the study proposal to a Human Subjects Protection Committee (CPP) for prior approval. The information provided covers both the methods and nature of the research and the safeguards provided for patients participating in the trial.

7.7. INFORMATION TO THE COMPETENT AUTHORITIES

This protocol will be reported to the ANSM.

7.8. AMENDMENTS TO THE PROTOCOL

Requests for substantial amendments shall be submitted by the sponsor to the relevant CPP for its opinion and to the ANSM for information, in accordance with the law in force and its implementing decrees.

The amended protocol must be updated and dated.
The information forms shall be amended if necessary.

7.9. FINANCING AND INSURANCE

The sponsor shall finance the study and take out an insurance policy covering the financial consequences of its civil liability, in accordance with the regulations.

7.10. RULES RELATING TO PUBLICATION

Scientific communications and reports relating to this study shall be produced under the responsibility of the study coordinator with the agreement of the principal investigators of the participating centers.

The coordinating investigator shall draw up the list of authors.
A physician affiliated with the CHD Vendée at the time of publication must be listed as the first or last author.

The publication rules will follow international recommendations (N Engl J Med, 1997; 336:309-315).

A copy of the publication will be sent to the CHD Vendée, the study sponsor, which will necessarily be cited.

7.11. ARCHIVING OF SOURCE DATA

The investigator must retain all information relating to the study for at least 15 years after the end of the study.
At the end of the study, the investigator will receive a copy of the data for each patient at their center on a CD-ROM sent by the institution responsible for the research.

LIST OF APPENDICES

- Appendix 1: Study summary
- Appendix 2: List of data collected
- Appendix 3: Questionnaires
- Appendix 4: Patient information sheet and oral consent form