The Statistical Analysis Plan of the REVDOU Study

This Statistical Analysis Plan (SAP) was written according to the guidelines proposed by Yuan et al. [1] and by Gamble et al. [2] for randomized clinical trials.

1. SAP versions, dates and reasons for revision

Version #1: September 25th, 2025.

2. Trial registration number

NCT07181434 (Clinical Trials Number).

3. Study title

Impact of virtual reality on patient's pain during endovascular surgery for lower limbs revascularization under sedated local anesthesia: a randomized controlled study.

4. SAP contributors with roles and responsibilities

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5. Background and rationale of study

The prevalence of peripheral arterial disease (PAD) increases with age. In France, 1 million people are affected by this disease. Endovascular procedures can be performed to prevent complications and/or sequelae (relapse, loss of function of the affected limb, amputation, death), but also to relieve pain. This is a minimally invasive procedure most often performed under local anesthesia (LA) with sometimes the administration of sedatives (morphine and analgesics) to relieve pain and reduce anxiety related to the procedure.

Local anesthesia causes discomfort related to the operating environment (low temperature, harsh lighting, noise, supine position, arms at the side of the body, cold, hard, narrow table), impacting the patient's cooperation and making the procedure difficult, with the need to multiply X-ray images, to reinject potentially nephrotoxic contrast products. It can lead to stopping the procedure with serious consequences (postponement, persistence or even worsening of pain, amputation, death).

Non-drug methods such as virtual reality (VR) are increasingly being used as an alternative to general anesthesia and excessive opioid use. VR has been shown to be effective in managing pain and anxiety during various medical, surgical, and endovascular procedures. Its high graphic quality allows patient immersion; hypnotic speech and relaxing elements capture the patient's attention; breathing exercises help manage stress; relaxing music provides a soothing atmosphere. This support ensures better mental and physical comfort by reducing pain and anxiety.

We hypothesize that VR could reduce pain during endovascular surgery for lower limbs revascularization.

6. Study type

This is a superiority, prospective, individual randomized, open-label and monocentric study.

7. Objectives and related endpoints (units and calculations used to derive outcomes)

7.1. Primary objective

The primary objective is to assess the impact of VR on the patient's pain during endovascular surgery for lower limbs revascularization under local anesthesia.

The primary outcome is the maximal intensity pain felt by the patient during the surgery. It will be assessed at the end of the surgery by a 0-10 numerical rating scale (NRS) with 0 anchored for "no pain" and 10 anchored for "worst imaginable pain".

7.2. Secondary objectives

The secondary objectives are to compare the following outcomes:

- The anxiety difference before and after the surgery. Anxiety will be assessed by a 0-10 NRS with 0 anchored for "no anxiety" and 10 anchored for "maximal imaginable anxiety".
- The patient's comfort felt during the surgery, which will be assessed at the end of the surgery by a 0-10 NRS with 0 anchored for "very uncomfortable" and 10 anchored for "very comfortable".
- The evolution of the vitals parameters: systolic blood pressure (in mmHg), diastolic blood pressure (in mmHg), heart rate (in beats per minute), respiratory rate (in breaths per minute) during the procedure.
- The standardized dose (in mL/kg) of local anesthetic products (lidocaine), the standardized dose (in mg/kg) of morphine products (remifentanil and morphine), and the standardized dose (in mg/kg) of analgesic products. Each total dose will be standardized with patient's weight.
- The total dose of X-ray irradiation assessed by the dose area product (in $mGy.cm^2$).
- The volume of contrast products delivered (in mL).
- The difference between the duration of the surgery estimated by the patient and the real duration of the surgery (in minutes).
- The proportion of successful surgery (total revascularization of the artery declared by the surgeon).

In the experimental group (with VR), we will describe the acceptability of the VR mask during the procedure, and the patient's satisfaction about their VR experience (0-10 NRS with 10 anchored for "absolutely satisfied").

8. Inclusion criteria

- Patient with PAD (peripheral arterial disease), going to benefit from revascularization of the lower limbs by endovascular surgery, scheduled, under local anesthesia associated with sedation.
- Adult patient (≥ 18 years).
- Patient understanding and speaking French language.
- Patient benefiting from a Social Security system or benefiting from it through a third party.
- Free subject, without tutorship or curatorship.
- Free consent given by the patient.

9. Non-inclusion criteria

- Patient with a contraindication for VR mask (mono or binocular blindness, epilepsy, migraines, psychiatric disorders, pacemaker, hearing aids, defibrillator, recent lesions to the eyes, face or scalp preventing comfortable use of VR).
- Patient with presumed VR mask intolerance (sensitivity to nausea in cars, history of balance or eye diseases).
- Bad previous experience with a VR.
- Patient with regional anesthesia.
- Protected population, namely persons deprived of liberty by a judiciary or administrative decision, pregnant women, sick persons in vital emergency.

10. Post-randomization exclusion criteria

- Consent withdrawal.

11. Definition of the two compared groups

- The experimental group is defined by usual care with the addition of VR mask during surgery. The nurse will present and install the VR mask on the patient before the beginning of the surgery. In case of VR intolerance, the mask will be removed.
- The control group is defined by usual care (no VR mask).

12. Randomization details

Subjects will be randomized to one of two study groups with a 1:1 allocation using a secure web-based random-number generator, using random block sizes.

13. Sample size calculation

Lier et al. [3] exhibited a standardized mean difference of 0.62 for the acute/procedural pain felt by the patient with the use of VR against no VR, which correspond to a medium effect size. Considering a two-sided type I error of 5%, a power of 80% and a 5% rate of missing data (missing outcomes, consent withdrawal, etc.), we need to include 90 patients (45 in each group).

Sample size was obtained with the following calculator: Soper, D.S. (2025). A-priori Sample Size Calculator for Student t-Tests [Software]. Available from https://www.danielsoper.com/statcalc

14. Interim analysis (timing, person, adjustment of the significance level)

No interim analysis was planned.

15. Guidelines for an early stop of the study

The study may be prematurely suspended in the event of unexpected adverse events. On the same token, in the event of unexpected developments or new information and showing that the objectives of the study or the clinical program are unlikely to be reached, the sponsor may be persuaded to prematurely suspend the study.

No statistical discontinuation criteria have been drawn up.

16. Timing of final analysis

- Inclusion period: 18 months.
- Follow-up duration: 1 day.

- Data base locking period: 3 months.
- Data analyses period: 6 months.

17. Timing for assessing each collected parameter

	Inclusion Day 0		
	Before the surgery	During surgery	After the surgery
Informed consent	X		
Randomization	X		
Demographical data	X		
Clinical exam (weight, height, PAD characteristics)	X		
Medical history, comorbidities, current treatments	X		
Vital parameters (SBP, DBP, HR, RR)	X	X Every 15 minutes	X
Anxiety NRS	X		X
Pain NRS	X		X
Comfort NRS			X
Surgical procedure data[1]			X
Duration of the surgery estimated by the patient			X
VR Satisfaction NRS (experimental group only)			X

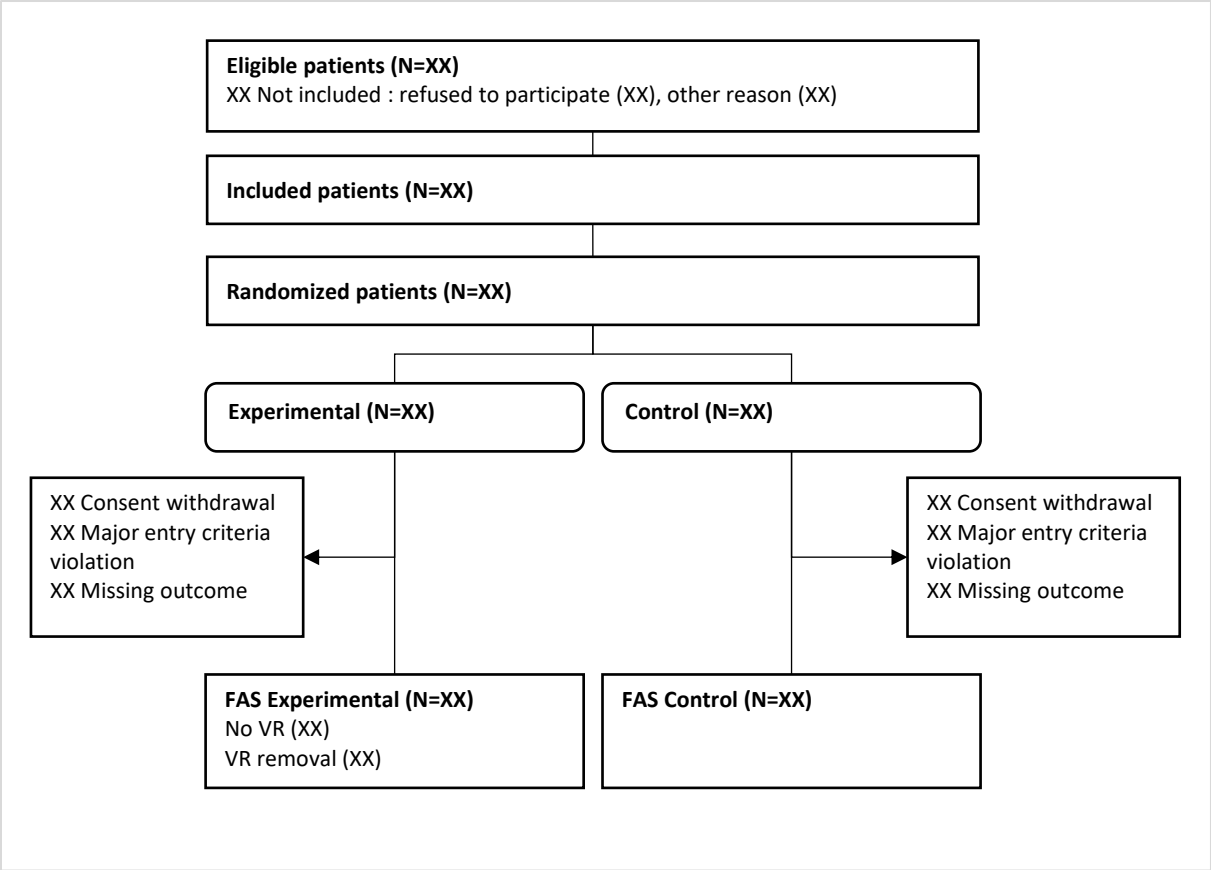
PAD: peripheral arterial disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, RR: respiratory rate, VR: virtual reality, NRS: Numerical Rating Scale.

[1]Surgical procedure data: duration of the surgery, doses of anesthetic, analgesic, and morphine products, dose area product, volume of contrast products delivered, success of the surgery.

18. Reporting the representativity of the studied population

A flowchart will be decomposed according to the following sets. The effectives and the related differences in-between two consecutive sets will be reported. The causes of the related differences will also be listed.

- The screened set. The patients having given an oral consent.
- The full analysis set (FAS). The patients who were randomized, excluding participants who:
    - failed to meet major entry criteria [4] (including patients with post-randomization consent withdrawal), or
    - have no data post-randomization, or
    - have missing primary outcome.



19. Withdrawals and follow-up data

Patients may be withdrawn early from the clinical investigation for several reasons, including but not limited to consent withdrawal or medical decision. The investigator will document the reasons for premature study discontinuation. The withdrawals will be exhaustively described in the flowchart.

20. Definition of the studied population

All the analyses will be performed based on the full analysis set. Patients who have withdrawn their consent prior to randomization will be replaced. If a patient withdraws consent, he/she will be asked for permission to use data obtained prior to withdrawal and to collect the primary outcome. If this is achieved, the patient will be included in the final analyses. If the patient declines, all data from that patient will be destroyed (except for safety data) and a new patient will be randomized.

21. Level of statistical significance (p-values, confidence intervals, one- or two-sided)

For the primary and secondary objectives, statistical significances will be achieved for p-values < 5% by using two-sided alternative hypotheses and two-sided 95% confidence intervals.

22. Plan and rationale for controlling the type I error (multiplicity of tests)

We will not consider the inflation of the type I error. The level of the proof will be the higher for the primary outcome. The statistical analyses related the secondary outcomes will be consider as exploratory results with a risk of false positive.

23. Sub-group analyses and/or tests of interactions

No sub-group analyses are planned.

24. Description of baseline patient characteristics

Demographic variables and other baseline characteristics will be summarized for the full analysis set.

The mean, the standard deviation and the number of missing values will be presented for each arm and marginally for the following variables: age (years), body mass index (kg/m²), pre-operative systolic blood pressure (mmHg), pre-operative diastolic blood pressure (mmHg), pre-operative heart rate (beats per minute), pre-operative respiratory rate (breaths per minute), anxiety NRS (0-10), pain NRS (0-10).

The effectives, the percentages of patients in each category and the number of missing values will be presented for each arm and marginally for the following categorical variables: gender (male/female), Rutherford AOMI grade (0/I/II/III/IV), Rutherford AOMI classification (0/1/2/3/4/5/6), persistent and recurrent decubitus pain (yes/no), trophic disorders (yes/no), cold member (yes/no), sensory disorders (yes/no), motor deficits (yes/no), arterial hypertension (yes/no), diabetes mellitus (yes/no), dyslipidemia (yes/no), kidney failure (yes/no), dialysis (yes/no), ischemic cardiomyopathy (yes/no), heart failure (yes/no), respiratory failure (yes/no), stroke or transient ischemic attack history (yes/no), current antiplatelet medication (yes/no), current analgesic medication (yes/no), current anxiolytic medication (yes/no), current diabetes treatment (yes/no), current morphine medication (yes/no).

No p-value will be reported. The balance diagnostics of baseline covariates between the two arms will be achieved by estimating standardized differences [5]. Unbalances will be considered for values higher than 10%.

Underlined covariates are baseline potential risk factors for outcomes and analyses will be adjusted on these factors (section 26).

25. Description of the outcomes

The outcomes of the patients will be compared for the full analysis set. Because the percentage of missing data on the outcomes is expected low, complete case analyses will be performed.

The mean, the standard deviation and the number of missing values will be presented for each treatment arm and marginally for the following numeric outcomes:

- Systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate (repeated outcomes).
- Maximal pain NRS, anxiety NRS difference (before and after surgery), patient's comfort NRS, standardized doses of local anesthetic products, of morphine products and of analgesic products, dose area product, total volume of contrast products delivered, surgery duration difference (real duration and patient's estimation).

Student t-test will be performed to obtain the p-values.

The effectives, the percentages of patients in each category and the numbers of missing values will be presented for each arm and marginally for the binary outcome (successful surgery). Pearson's Chi2 test will be performed to obtain the p-value. Only when at least one theoretical effective under the null assumption will be lower than 5, a Fisher exact test.

In the experimental group (with VR), we will describe the number of patients who removed the VR headset (and the reason) before the end of the surgical procedure and we will present the mean and the standard deviation of the patient's satisfaction about their VR experience.

26. Adjustments and estimands

Adjusted analyses on the risk factors of the outcome may increase power and give correct type I error rates [6]. We will use the G-computation to estimate the average treatment effect (ATE). The following analyses will be performed for the full analysis set.

Firstly, we will estimate the outcome models. The lasso regularization [7] will be used to select the variables considered in the model, among the potential risk factors highlighted in the section 24. The penalty parameters will by estimated by minimizing the 20-fold cross-validation mean square errors.

The repeated numeric outcomes will be analysed with a mixed linear regression adjusted with their pre-operative value, where time is considered as fixed effect and patient as random intercept (interaction between time and randomization group will be tested and considered in the model if appropriate). The other numeric outcomes will be analysed with a linear regression. The binary outcome will be analysed with a logistic regression.

Secondly, based on the outcome models, we will predict the outcomes if all participants were assigned to the intervention arm and then if all participants were assigned to the control arm. For each outcome, the ATE will be the difference between the two means of the individual predictions (difference of the means for the numeric outcomes and the differences of the proportions for the binary outcome).

To avoid the exclusion of patients with missing values on the baseline predictors, multivariate imputation by chained equations will be performed 20 times. For each complete sample, 1,000 bootstrap samples will be generated. The confidence intervals of the ATE estimations will be non-parametrically from the 20,000 resulted samples [8]. Among the 20,000 samples, the number and percentage of occurrence of each predictor will be reported to illustrate their relative importance.

27. The assumptions of the statistical methods, and alternative methods if they are false

There is no reason to suppose that the missing values of the baseline predictors will not be missing at random in such a randomized clinical trial. Therefore, the only assumption is the good specification of the outcome models.

We will use B-splines with AIC minimization to evaluate the respect of the linearity or log-linearity assumptions for the linear or logistic models, respectively. If it does not hold, B-splines will be used to relax this assumption.

28. References

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