**Satistical Analysis Plan**

| | |
|---|---|
| Date | 15 Jan 2026 |
| SAP version Number | V1.0 |
| Protocol version | V13.0 |
| Trial Statistician | Jean-François HAMEL |
| Data Manager | |
| SAP Authors | Jean-François HAMEL<br>Sigismond LASOCKI |

**SAP Signatures**

**SAP Version Number being approved: 1.0**

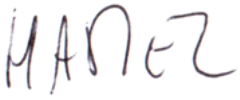
I give my approval for the attached SAP entitled MiVAR Trial dated 2025

Trial Statistician

Name: Jean-François HAMEL

Signature:

Date: 15/01/2026



Chief Investigator

Name: Sigismond LASOCKI

Signature:

Date: 15/01/2026

## Abbreviations and Definitions

| | |
|---|---|
| aASAH | aneurysmal subarachnoid hemorrhage |
| CTA | Computed Tomography Angiography |
| DAAH90 | number of days alive and at home at day 90 |
| DCI | delayed cerebral ischemia |
| DSMB | Data Safety Monitoring Board |
| EQ-5D- 5L | EuroQOL Quality of Life Scale 5-Dimension 5-Level |
| eSAE | expected Serious Adverse Events |
| GOSE | Glasgow Outcome Scale Extended |
| IV | intravenous |
| MCID | minimal clinically important difference |
| MRI | magnetic resonance imaging |
| mRS | modified Rankin Scale |
| RCT | randomized controlled trial |
| SAP | statistical analytic plan |
| SFAR | Société Française d'Anesthésie Réanimation |
| uSAE | unexpected Serious Adverse Events |
| TCD | transcranial Doppler |
| VAS | visual analogue scale |
| WFNS | World Federation of Neurological Surgeons |

# 1 Section 1: Introduction

## 1.1 Background and Rationale

Aneurysmal subarachnoid hemorrhage (aSAH) is relatively frequent, accounting for 5% of strokes, and affects a relatively young population. The most frequent complication of aSAH is arterial vasospasm, with an estimated incidence in the literature as high as 70%. Vasospasm is responsible for delayed cerebral ischemia (DCI) which in turn is responsible for severe morbidity (neurological deficit, neuro psychiatric disorders...), poor quality of life (institutionalization, inability to return to work ...) and increased mortality. Treatment with intravenous (IV) milrinone, an arterial vasodilator, has been proposed, but no randomised controlled trial (RCT) exist. We hypothesized that an IV infusion of milrinone will improve the neurological recovery of patients with vasospasm following aneurysmal aSAH at 3 months. In collaboration with the ATLANREA group and the SFAR research network, we are conducting a multicenter, double blinded RCT to evaluate the effect of IV milrinone infusion compared to placebo on 3-months functional neurologic outcome, in patients with proven vasospasm on a computed tomographic angiography (CTA), following acute aSAH.

## 1.2 Objectives

### *1.2.1 Primary objective*

The primary objective of this study is to evaluate the effect of intravenous milrinone infusion, as compared with placebo, on functional neurological outcomes at 3 months in patients with arterial vasospasm following acute aSAH.

### *1.2.2 Secondary objectives:*

To evaluate the effect of IV milrinone vs placebo on a) 3 and 6 months overall function; b) 3- and 6-months quality of life, c) mortality.

### *1.2.3 Tertiary objectives:*

To evaluate the effect of IV milrinone vs placebo on the intensive care unit (ICU) and hospital length of stays, on angiographic success at D7 and D14 (if available), on cerebral necrotic volume assess by magnetic resonance imaging (MRI) between 3 and 6 months following aSAH (if available) and on adverse events.

# 2 Section 2: Study Methods

## 2.1 Trial Design

MiVAR is a multi-center, double blinded, randomized, placebo-controlled trial that compares the effect of IV milrinone vs placebo (saline), started within 6 hours of the vasospasm confirmation using an computed tomography angiography (CTA), on 3-months function outcomes, in patients with cerebral vasospasm following aSAH.

### *2.1.1 Trial interventions*

Eligible patients are randomly assigned to receive either milrinone or placebo within 6 hours after confirmation of the vasospasm diagnosis on a CTA. Study medications are prepared by unblinded nurses or pharmacists not involved in patients care. The study drugs are diluted according to the patient's body weight, so that infusion rates are identical in the two groups for all patients (i.e. an infusion rate of 10 ml per hour corresponds to 0.1 µg/kg/min of milrinone). Milrinone and saline solution are identical in appearance, thereby ensuring blinding of patients, nurses, physicians and outcome assessors.

- **Milrinone group**: milrinone is administered intravenously as a bolus of 0.1 mg/kg over 30 minutes followed by a continuous infusion at a rate of 1 µg/kg/min. In the absence of improvement, the infusion rate may be increased to 1.5 µg/kg/min.
- **Placebo group**: placebo (normal saline) is administered intravenously at the same infusion rate as milrinone.
- **Both groups**: in both groups, induced hypertension with norepinephrine is recommended, along with maintenance of normovolemia. Oral nimodipine is also recommended through D21 after aSAH. Persistence of vasospasm should be assessed at least twice daily by clinical evaluation and/or transcranial doppler (TCD)

examination. In absence of improvement, arteriography for mechanical and/or pharmacological dilatation is recommended.

Duration of treatments

- Study frug weaning is initiated after 48 hours of infusion, with gradual dose tapering in decrement of 0.5 µg/kg/min steps), once vasospasm is controlled. Study medication is discontinued after 7 days in absence of effect on the D7 CTA or on D14.

## 2.2 Randomization

Randomization is performed using a web-based system (Clinsight® software). Patients are randomly assigned in a 1:1 ratio to one of the two groups using a minimization algorithm based on three determinants: study site, initial World Federation of Neurological Surgeons (WFNS) grade ([1 or 2] vs [3 to 5], higher scores being indicative of more severe aSAH), state of consciousness at the time of vasospasm diagnosis (conscious vs unconscious, including patients under sedation).

## 2.3 Sample Size

We estimated that the rate of favorable neurological outcomes (defined as a mRS ≤2) at 3 months in patients with vasospasm following acute aSAH without milrinone infusion is approximately 35%. (This percentage was estimated based on the analysis of data extacted from the ATLANREA database, including 436 patients in 3 years, ClinicalTrials.gov - identifiant : NCT02714387) The proportion of favorable outcomes reported in case series of patients with vasospasm treated with milrinone is between 50 and 60%. For our sample size calculation, we thus hypothesized a percentage of favorable outcomes at 3 months of 35 and 50% respectively in the control and milrinone group. Considering a two sided test and a type I and type II error rates of 5 and 20%, the sample size required is 340 (170 patients in each group). Considering a 5% proportion of withdrawals, we planned to include 360 patients, and increased this number to 370 to compensate for patients included but not randomized because of early withdrawal.

## 2.4 Timing of final analysis

Six months after completing the trial enrollment (corresponding to the follow-up of the last patients included), the database will be monitored, cleaned, verified and locked. The publication of this SAP will occur prior to the database lock. Final analysis will commence once the final lock has been confirmed by the principal investigator. Unblinding will only occur once the primary and secondary analyses are complete.

## 2.5 Timing of outcome assessment

### *2.5.1 Primary outcome:*

a) Modified Rankin Scale (mRS) score [3 months]

### *2.5.2 Secondary outcomes:*

a) Modified Rankin Scale (mRS) score [6 months]; Glasgow Outcome Scale Extended (GOSE) [3 & 6 months]
b) EuroQOL Quality of Life Scale 5-Dimension 5-Level (EQ-5D-5L) [6 months]
c) Mortality [in hospital and 6 months]

### *2.5.3 Tertiary outcomes:*

a) ICU and hospital length of stays [in hospital]
b) Angiographic success on CTA [D7 and D14 (if available)]
c) Number of therapeutic arteriography [D14]
d) Cerebral necrotic volume assess by magnetic resonance imaging (MRI) between 3 and 6 months following aSAH [6 months]
e) Adverse events [study medication infusion, maximum 14 days]

# 3 Section 3: Statistical Principles

## 3.1 Confidence Intervals and P-values

The statistical uncertainty of all estimates will be expressed as two-sided 95% confidence intervals. A p-value will only be reported for all the primary and secondary outcomes. A p-value <0.05 will be considered significant.

## 3.2 Protocol violations

- Timing of inclusion: the patients should be included within 6 hours after the vasospasm diagnosis confirmation by CTA, which may be delayed relative to CTA acquisition, when a re-analysis by an expert is required. A delay of more than 6 hours is considered as a protocol violation and constitute an exclusion criteria.
- Study medication infusion: the study medication should be administered for at least 48 hours. However it could be suspended for several hours (in case of intolerance), without protocol violation, if the study medication is reinfused.
- Any administration of intravenous milrinone is a protocol violation, but intra-arterial use during angiography, is allowed.
- Study medication weaning is protocolized through progressive tapering of infusion rate, decrement of 5 ml/h every 24-48 hours. A quicker tapering is considered as a protocol deviation, but not a violation. Study medication may be stopped after D7 CTA, if the vasospasm did not improve at all.

## 3.3 Analysis populations

- The intent-to-treat (ITT) population includes all the randomized patients except those who withdrew consent. Patients who were lost to follow up will still be considered in the ITT population trough imputation processes, described below.
- The per-protocol population (PP) includes all patients in the ITT population without protocol violations (mainly open-label IV milrinone infusion or

definitive stop of study medication within the first 48 hours). The protocol violations will be determined before locking the database by a group of experts.

# 4 Section 4 – Trial Population

## 4.1 Eligibility

Patients hospitalized for acute aSAH will be included if a cerebral vasospasm occurred, suspected because of a clinical deterioration and/or high blood flow velocity on TCD examination and confirmed by CTA. The inclusion /randomization will be done within 6 hours after vasospasm diagnosis (i.e., when the study investigator get the information, sometimes after re-analysis of the CTA by an expert). Inclusion and exclusion criteria are presented below:

### *4.1.1 Inclusion criteria:*

- Adult patients hospitalized for aneurysmal aSAH
- First episode of vasospasm, with a diagnosis confirmed on CTA
- Delay between diagnosis of vasospasm and inclusion ≤ 6 hours
- Informed consent from the patient, a legal representative or emergency procedure

### *4.1.2 Exclusion criteria:*

- Initial Glasgow score at 3 with a bilateral mydriasis
- Moribund patient
- Contraindication to Milrinone
- Cerebral infarction in the vasospasm area already present on the CT-scanner at the time of diagnosis (lack of expected benefit of treatment in this case according to medical judgement)
- Cardiac failure requiring inotrope administration at the time of randomisation
- Uncontrolled elevated intra-cranial pressure (i.e. ICP>25 mmHg for more than 20 minutes)
- Patient with flutter or cardiac arrhythmia (atrial fibrillation) poorly tolerated

- Major metabolic disturbance (uncorrected hypokalaemia <3 mmol/L)
- Non-affiliation to French health care coverage
- Pregnant, breastfeeding or parturient woman
- Adult deprived of their liberty by judicial or administrative decision
- Adult under compulsory psychiatric care
- Adult patient protected under the law (guardianship or trusteeship)
- Inclusion in an interventional study using Milrinone, or evaluating a treatment of cerebral vasospasm or with the same primary endpoint (mRS at 3 months)

## 4.2 Withdrawal/Follow-up

When a patient is loss of follow-up their 3-month mRS will be missing. We anticipate few events that would make it impossible to measure the primary outcome, based on our cohort experience. However, in case of such missing data, imputation processes will be carried out to allow an ITT analysis. The considered imputation processes are described below.

For patients who withdraw consent, those who have not been randomized will be excluded from the analysis, but described in the CONSORT flowchart. For the patients who withdraw consent after, all the data obtained on the inclusion visit (see below) will be kept to allow the imputation process, and the safety data will be also analyzed.

## 4.3 Baseline characteristics

Baseline characteristics of randomized patients include age; sex, comorbidities, usual medication, admission ECG, hemoglobin at patient's admission, parameters of secondary brain injury (natremia min/max, body temperature min/max, mean arterial pressure min/max, ICP min/max), SAH characteristics/grade (WFNS initial score, Fisher class), Initial treatment of aneurysm (embolization and/or surgery), Consciousness at inclusion.

# 5 Section 5 – Analysis

## 5.1 Outcome Definition

### *5.1.1 Primary outcome:*

The primary endpoint is the proportion of good functional outcome (defined as a modified Rankin score (mRS) ≤2) at 3 months, obtained by centralized standardized phone interview of the patient or his/her relative.

Modified Rankin Score is rated as follow:

- 0 = No symptoms,
- 1 = No significant disability. Able to carry out all usual activities, despite some symptoms,
- 2 = Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities,
- 3 = Moderate disability. Requires some help, but able to walk unassisted,
- 4 = Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted,
- 5 = Severe disability. Requires constant nursing care and attention, bedridden, incontinent,
- 6 = Death.

### *5.1.2 Secondary outcomes:*

a) Glasgow Outcome Scale Extended (GOSE) is obtained by centralized standardized phone interview of the patient or his/her relative done at 3 and 6 months. The GOSE is a global scale for functional outcome, categorized in 8 categories from 1 (death) to 8 (upper good recovery).

b) EuroQOL Quality of Life Scale 5-Dimension 5-Level (EQ-5D) is a questionnaire is conducted at baseline, 3 and 6 months. It consists of a short and simple 5-part questionnaire and a visual analogue scale (VAS). It may be self-administered, completed by interview or via a proxy respondent, and is used to value and describe health states. The questionnaire data is reported as an index value - a continuous

fractional outcome with boundaries between zero and one. Zero represents the worst health status and 1 the best. The EQ-VAS (visual analogue scale) is a self-administered visual scale in which respondents rate from 0 to 100 (worst and best state of health respectively) their perceived health-related quality of life at the time of response. In analyses including non-survivors, deceased patients will be given the lowest score. The EQ-5D will be analyzed as a variation from baseline at 3 and 6 months.

c) Mortality will be analyzed until 6 months.

### *5.1.3 Tertiary outcomes:*

a) ICU and hospital length of stays

b) Percentage of patients alive and at home at 3 and 6 months. It will also be analyzed as the number of days alive and at home at day 90 (DAAH90).

c) angiographic success will be assessed by the evaluation of vasospasm severity on inclusion, D7 and D14 (if available) CTA. Vasospasm will be quantified according to the reduction of cerebral arteries diameter evaluated on a semi-quantitative scale as: absent, light, mild, moderate or severe, (compared to the diameter measured on admission CTA).

d) Number of therapeutic arteriography

e) The volume of cerebral necrosis will be measured on magnetic resonance imaging (MRI) obtained between 3 and 6 months following aSAH

f) on adverse events evaluated until 48 hours after study medication stop.

g) The treatment tolerance will be evaluated by assessing the rate of patients with hemodynamic intolerance defined as the need for catecholamines introduction or doses increased by 50% within the first 24 hours of study medication infusion ; and of metabolic intolerance defined as the rate of patients with dysnatremia, (ie natremia<135 mmol/L or >155 mmol/L) occurring during the administration of study medication.

## 5.2 Analysis Methods

Unless otherwise specified, all analyses will be completed on the intention to treat population.

The characteristics at inclusion and the measures of patient assessments for each treatment arm will be described using percentages or means, standard deviations, medians and interquartile ranges, and compared using Khi-square tests or Student t tests for respectively categorical and continuous data. A summary of the proposed analyses is presented in Table 1.

### *5.2.1 Primary Outcome:*

*Primary analysis:*

The main statistical analysis will be performed on the intention to treat population using a binomial logistic regression model including as covariates the treatment arm and the different stratification factors for randomization (the center, the initial WFNS score dichotomized as <3 vs ≥3 and the patient's consciousness at inclusion).

*Secondary analysis:*

As a secondary analysis, we will report absolute risk reduction using a proportional odds approach, using the Brant-Wald test at the alpha level of 5%, which may be more sensitive for detecting a shift over the entire spectrum of outcome (mRS 7-point ordinal scale).

*Sensitivity analysis:*

An other model will be proposed based on the ITT population, including in addition to the covariates already considered the level of consciousness and the delay before performing angiography (within 12 hours or not), and the interactions between these two covariates and the treatment arm, to assess a possible variation in the treatment effect according to the status on these two covariates

These two models will be performed on the per-protocol population as an evaluation of the robustness of their results. In any cases, the primary analysis results will be authoritative.

### *5.2.2 Secondary Outcomes:*

- The analysis of the mRS, the extended GOS and the EQ-5D score at 3 and 6 months will be performed considering (ordinal) proportional odds models, based on the same set of covariates.
- The ICU mortality and 6 months mortality will be analyzed using Cox models based on the same set of covariates. The validation of these models will be evaluated by analyzing Schoenfeld residuals.

### *5.2.3 Tertiary outcomes*

- The analysis of angiographic successes at day 7 and 14 will be performed considering (ordinal) proportional odds models, based on the same set of covariates
- The proportion of therapeutic arteriography between each group and the median number of arteriography will be compared.
- The analysis of hospital length of stay will be carried out by using linear regression models based on the same set of covariates.
- Patients outcomes and treatment tolerance will be analyzed using logistic models for dichotomous data (transfer to a convalescent center, patients living at home at 3 and 6 months, need to initiate or to increase the catecholamine doses by 50%, occurrence of dysnatremia), or linear regression models for continuous data (DAAH90, daily dose of catecholamines, average daily urine output).

### *5.2.4 Pre-planned sub-group analysis*

We plan exploratory subgroup analyses for the primary outcome (as described above) in the following sub-groups:
- Sex: female sex versus male sex. We hypothesize no treatment effect difference between male and female sex.
- Initial WFNS score <3 vs ≥3. We hypothesize that the treatment effect is more important in the less severe patients (WFNS <3).
- Consciousness level at inclusion: conscious vs unconscious. We hypothesize that the treatment effect is more important in the less severe patients (conscious patients).

## 5.3 Missing Data

First, every attempt will be made to retrieve the missing data. All missing data will be reported and the frequencies of these will be calculated.
A description of the patients characteristics depending on whether they have missing data or not will be proposed to distinguish missing completely at random or missing at random data.

In case of missing data, multiple imputations will be performed considering chained equations with fully conditional specification. The considered covariates included in this imputation process will include all covariates observed the ed-point evaluation (including the treatment allocation). Ten imputations will be performed for each missing data. This analysis will allow to calculate the Fraction of Missing Information (FMI), and then the Relative Efficiency (RE). If the RE $\geq$ 0.99, then the number of imputations will be considered as appropriate. If not, the number of imputations will be determined as greater than the FMI value * 100 to ensure high relative efficiency.

## 5.4 Harms

*Adverse Event Reporting*

• Expected Serious Adverse Events (eSAE). These events have been defined a priori and are being collected and reported as study outcomes and as such will not be labelled nor reported a second time as serious adverse events.

• Unexpected Serious Adverse Events (uSAE). All uSAEs are to be brought to the attention of the site PI (following site specific standard operating procedures). Causality of the uSAE should be adjudicated by the site PI. All possibly or related uSAEs are to be reported in the

Data Collection Forms (both study arms) as described in this section:

oMonitoring and reporting should begin on the first day of study intervention and continue until either:

- the uSAE has been resolved
- 48 hours post study medication stop or death whichever occurs first
- if the uSAE remains ongoing at 3 months it will be reported as such

o Supporting source documentation of all reported uSAEs must be submitted for additional and final central adjudication.

o Abnormal laboratory results do not need to be recorded unless considered by the investigator to be relevant in terms of subject or trial safety (or in relation to a serious adverse event that is being reported).

• Serious Adverse Event Reporting. All reportable unexpected SAEs must be reported to the Coordinating Centre within 24 hours of the site's knowledge of the unexpected SAE. The Study Chair and/or Study Steering Committee will review all unexpected SAE's received from the sites. If an unexpected SAE is confirmed, a document summarizing the SAE will be distributed to participating sites. Sites should follow the guidelines of their local REB with respect to the submission of SAEs that occur at the site as well as SAE Notifications.

• All reportable unexpected SAEs will be described with the presentation of the main results

| | Main analysis | Sensitivity analyses for the main analyses | Additional analyses | Adjustement** |
|---|---|---|---|---|
| **Primary outcome** | | | | |
| mRS at 3 month | Log-binomial logistic regression with fixed effects for treatment and, and a random effect for center, initial WFNS (<3 or ≥3) and patient's consciousness, reported as a risk ratio with 95% CI | • Another model adjusted with level of consciousness and delay before performing arteriography (< or > 12h)<br>• Sub-group analysis<br>• Per protocol analysis†<br>• Patients without missing data | • Proportional odds analysis using the Brant-Wald test | • center,<br>• initial WFNS (<3 or ≥3)<br>• patient's consciousness at inclusion |
| **Secondary outcomes** | | | | |
| mRS at 6-months | Log-binomial logistic regression reported as a risk ratio with 95% CI | | • unadjusted model<br>• Proportional odds analysis using the Brant-Wald test | • center,<br>• initial WFNS (<3 or ≥3)<br>• patient's consciousness at inclusion |
| GOSE at 3 and 6 months | Linear logistic regression model, reported as mean difference with 95% CI | | • unadjusted model | • center,<br>• initial WFNS (<3 or ≥3)<br>• patient's consciousness at inclusion |
| EQ-5D | Linear logistic regression model, reported as mean difference with 95% CI | • Excluding deceased patient | • unadjusted model | • center,<br>• initial WFNS (<3 or ≥3)<br>• patient's consciousness at inclusion |
| Mortality hospital | Log-binomial logistic regression reported as a risk ratio with 95% CI | | • unadjusted model | • center,<br>• initial WFNS (<3 or ≥3)<br>• patient's consciousness at inclusion |
| Mortality 6 months | • Kaplan-Meier curves and Cox regression hazard ratios | | • unadjusted model | • center,<br>• initial WFNS (<3 or ≥3)<br>• patient's consciousness at inclusion |
| **Tertiary outcomes** | | | | |
| ICU and Hospital LOS | Presented as median difference with 95% CI, using quantile regression | | • median with IQR<br>• unadjusted model | • center,<br>• initial WFNS (<3 or ≥3)<br>• patient's consciousness at inclusion |
| Percentage of patients alive and at home at 3 and 6 mnths | Presented as median difference with 95% CI, using quantile regression | | • median with IQR<br>• unadjusted model | • center,<br>• initial WFNS (<3 or ≥3)<br>• patient's consciousness at inclusion |
| DAAH90 | Presented as median difference with 95% CI, using quantile regression | | • median with IQR<br>• unadjusted model | • center,<br>• initial WFNS (<3 or ≥3)<br>• patient's consciousness at inclusion |
| Angiographic success at D7 and D14 | Ordinal logistic regression model | | • unadjusted model | • center,<br>• initial WFNS (<3 or ≥3)<br>• patient's consciousness at inclusion |

| | | | | |
|---|---|---|---|---|
| Number of therapeutic angiography | Presented as median difference with 95% CI, using quantile regression | | • Median with IQR<br>• unadjusted model | • center,<br>• initial WFNS (<3 or ≥3)<br>• patient's consciousness at inclusion |
| volume of cerebral necrosis on MRI done between 3 and 6 months | Presented as median difference with 95% CI, using quantile regression | | Median with IQR | |
| Proportion of patient with hemodynamic intolerance (i.e. introduction of catechoalamine or increase of ≥50% of infusion rate) within 24 hours of study medication | Log-binomial logistic regression reported as a risk ratio with 95% CI | | • unadjusted model | • center,<br>• initial WFNS (<3 or ≥3)<br>• patient's consciousness at inclusion |
| Proportion of patients with dysnatraemia | Log-binomial logistic regression reported as a risk ratio with 95% CI | | • unadjusted model | • center,<br>• initial WFNS (<3 or ≥3)<br>• patient's consciousness at inclusion |
| Daily dose of catecholamine | Presented graphically with 95% CI, per group | | | |
| Daily minimum and maximum natremia | Presented graphically with 95% CI, per group | | | |
| Daily urine outpout | Presented graphically with 95% CI, per group | | | |

Unless otherwise stated, all analyses will be conducted on the Intention to treat population: includes all aSAH patients randomized.

** Adjustments for all listed analyses unless otherwise specified

† Per-protocol population includes the intention to treat population, but excludes those who had a protocol violation.

CI – confidence interval; DAAH – days alive at home at D90; EQ-5D- EuroQOL 5 dimensions; GOSE Glasgow outcome scale extended; ICU – Intensive Care Unit; IQR – Interquartile Range; mRS – modified Rankin Scale; WFNS – World Federation of Neurological Surgeon