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GASS Trial study protocol: a multicentre, single-blind, randomised clinical trial comparing general anaesthesia and sedation during intra-arterial treatment for stroke.

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Title: GASS Trial study protocol: a multicentre, single-blind, randomised clinical trial comparing general anaesthesia and sedation during intra-arterial treatment for stroke.

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ABSTRACT

Introduction: Treatment of acute stroke has drastically changed in the last 10 years. Endovascular therapy is now the standard of care for patients with a stroke caused by a large vessel occlusion in the anterior circulation. The impact of the type of anaesthesia (general anaesthesia or conscious sedation) during endovascular therapy on the outcome of the patients is still a matter of debate. Previous studies are mostly retrospective and/or focused on the early post-procedure outcome and/or without blood pressure goals and/or single-centre small size studies. We therefore designed a multicentre study hypothesizing that conscious sedation is associated with a better functional outcome 3 months after endovascular therapy for the treatment of stroke compared with general anaesthesia.

Methods/analysis: The GASS trial is a randomised, parallel, single-blind, multicentre study of 350 patients undergoing endovascular therapy for the treatment of stroke. Patients will be randomly allocated to receive either a general anaesthesia or a conscious sedation. The primary outcome measure is the modified Rankin score assessed 3 months after the treatment. Data will be analysed on the intention-to-treat principle.

Ethics/dissemination: The GASS trial has been approved by an independent ethics committee for all study centres. Participant recruitment begins in September 2016. Results will be published in international peer-reviewed medical journals.

Trial registration number: The trial is registered at ClinicalTrials.gov (Identifier: NCT 02822144**)**

Strengths and limitations of this study

- GASS trial is the first randomised, parallel, single-blind, multicentre study comparing the effects of general anaesthesia and conscious sedation during endovascular therapy for stroke and focused on the functional outcome of the patients 3 months after the treatment.
- The multicentre design, broad inclusion criteria, large sample size (350 patients) and follow-up will support external validity.
- Limitations: The study does not include a systemic CT-scan after the endovascular treatment. The sizing of the stroke is also not part of the study as it is newly implemented technology. It was not part of the routine care at the time of the design of the study.

INTRODUCTION

The treatment of acute stroke has been recently transformed with the publication of RCTs showing the benefit of endovascular therapy when compare with the medical treatment in terms of functional outcome (1-4). Endovascular therapy in addition to the medical treatment is now the standard of care for selected patients who had a stroke caused by a large vessel occlusion in the anterior circulation. All studies have highlighted that the rapidity of the treatment is an essential factor for a good outcome. The other important factor is the haemodynamic conditions during the procedure because instability can worsen the clinical outcome (5,6). A retrospective study concluded that a change of even 10% in mean arterial pressure almost quadrupled the risk for poor outcomes (7).

In this context, the best anaesthetic strategy during the endovascular treatment has not been yet defined. Indeed, the choice between general anaesthesia (GA) and conscious sedation (CS) remains unclear. While allowing immobility, cerebral protection and airway control, GA can delay the endovascular treatment. On the other hand, CS is more rapid, allows neurological assessment during the procedure but the thrombectomy can be more difficult for the neuroradiologist because of patients' movements. In terms of haemodynamic stability, retrospective studies reported results favouring CS (8-10). However, these studies did not focus on the anaesthetic protocol and the intra-procedure haemodynamic. Anaesthetic protocols were not standardized. The first randomized controlled trial (RCT) on the subject was published in 2016 (11). This monocentric study did not find any benefit of CS over GA in terms of outcome 24 hours and 3 months after the treatment. However, functional outcome at 3 months was only a secondary outcome and the anaesthesia protocol was not detailed. Moreover, the design allowed patients in the CS group to receive analgesics and/or sedatives if necessary, which could then transform a CS into a light GA. Löwhagen et al (12) did also not show any difference between the two anaesthetic technics using a well-described anaesthesia protocol. However, the study included only 80 patients and was monocentric. The most recent study (13) using an identical design with infarct growth as the primary endpoint reported no differences between CS and GA. Clinical outcome at 90 days,

tested as a secondary endpoint, was better in the GA group. Finally, a meta-analysis analysing the pooled data of 7 trials (14) reported that worse outcomes at 3 months were associated with GA. However, the choice to treat a patient with or without GA was not randomized in the trials included in this meta-analysis (14).

So far, no study has assessed the clinical outcome 3 months after the stroke treatment comparing GA and CS using standardized anaesthetic protocols and tight haemodynamic control.

Therefore, we designed a RCT comparing GA and CS during endovascular treatment for acute stroke. Both GA and CS protocols will be standardized and the control of arterial blood pressure too. We hypothesized that CS will be associated with a better clinical outcome measured with the modified Rankin score (mRS) 3 months after the procedure.

METHODS AND ANALYSIS

Trial design

The GASS study is an investigator initiated, national, multicentre, randomised, simple-blind, parallel-group clinical trial with concealed allocation of patients scheduled to undergo endovascular therapy for stroke 1:1 to receive either a general anaesthesia protocol or a conscious sedation protocol. The trial will be conducted in four university and non-university centres. It started in September 2016 and will continue for a total of 36 months.

Participant eligibility and consent

Trial site investigators will identify consecutive eligible patients from the listed criteria. Eligible patients or a family member when appropriate will receive written and oral information and will be included after investigators have obtained informed written consent.

Inclusion criteria

1. Adult (18 years or older) patients admitted to the participating centre
2. Occlusion of a large vessel in the anterior cerebral circulation
3. Undergoing endovascular therapy for stroke
4. Benefiting from the health insurance system
5. Signed informed consent from the patient or their legally next of kin

Non-inclusion criteria

1. Pregnant or breast-feeding women
2. Patients already intubated and mechanical ventilated before inclusion in the study
3. Intracerebral haemorrhage associated with the ischemic stroke
4. Contra-indications to conscious sedation: Glasgow coma scale inferior to 8, agitation not allowing the patient to stay still during the procedure, deglutition disorders
5. Contra-indications to succinylcholine: hyperkalaemia, allergy
6. Body mass index superior to 35kg/m^2
7. Contra-indication to general anaesthesia

8. Contra-indication to one of the anaesthetic drugs
9. Uncontrolled hypotension,
10. Life-threatening comorbidity
11. Adults legally protected (under judicial protection, guardianship, or supervision), persons deprived of their liberty

Allocation and blinding

Patients will be randomised in two groups (general anaesthesia group and conscious sedation group). Randomisation will be done by investigators as close as possible to the endovascular therapy. Each patient will be given a unique randomisation number (patient code). Randomization will be stratified on the centre, the National Institute of Health Stroke Score (NIHSS ≤ or > 14) and the administration or not of IV thrombolysis. The primary evaluation criterion will be assessed blinded to the randomisation group. During the study period, outcome assessors will be kept blind to the randomisation group. Research nurses evaluating the outcomes 3 months after the treatment will not participate to the anaesthesia and will not be aware of the randomisation group. They will be blind to the treatment. The anaesthesiologist, the nurse anaesthesiologist, the neuroradiologist and the neurologist will not be blinded. They will not participate in the assessment of the patients at any time.

At each participating centre, data will be collected and entered into the electronic web-based case report form (eCRF) by trial or clinical trained personal (clinical research associate), blinded to the allocation group, under the supervision of the trial site investigators.

Interventions

All included patients will be allocated to one of the following two study groups:

- **General anaesthesia group:** patients will receive a standardised anaesthesia protocol with remifentanil
- **Conscious sedation group:** patients will receive a standard conscious sedation with remifentanil

Standardized general anaesthesia will include: Induction: Etomidate (0.25 – 0.4 mg/kg) and succinylcholine (1 mg/kg) and maintenance: TCI propofol (maximum target: 4 microg/ml), TCI remifentanil (0.5-4 ng/ml) and curares as needed**.**

Standardized conscious sedation will include: TCI remifentanil (maximum target 2 ng/ml), local anaesthesia with lidocaine 10 mg/ml (maximum 10 ml). Oxygen will be administered only if $SPO_2 \leq 96\%$. Respiratory rate and capnography will be monitored.

Conscious sedation can be converted into a general anaesthesia in the following situations:

- Agitation or restlessness not allowing the endovascular therapy
- Vomiting not allowing the endovascular therapy
- Glasgow coma scale < 8 and /or deglutition disorders
- Severe hypoxemia with SPO_2 < 96 % with oxygen delivered with a high concentration mask (10 l/min maximum)
- Respiratory depression with respiratory rate > 35 /min and/or clinical signs of respiratory exhaustion

In both groups:

intraoperative dose changes will be left to the anaesthesiologist in charge of the patient if necessary, IV norepinephrine will be administered in order to maintain blood pressure (BP) within the recommended range: systolic blood pressure (SBP) between 140 and 185 mmHg; diastolic blood pressure (DBP) < 110 mmHg. A drop of more than 25% of the mean blood pressure (MBP) will also be avoided. Norepinephrine will be administered in a dedicated intravenous line and diluted at 250 microg/ml.

Decisions about all other aspects of patient care will be performed according to the expertise of the staff at each centre and to routine clinical practice to minimize interference with the trial intervention. Three months after the thrombectomy, patients will consult with a neurologist.

Outcome measures

Primary outcome measure

The primary outcome measure will be the neurological outcome assessed with the modified Rankin score 3 months (15) after the endovascular therapy. Success will be considered as a modified Rankin score ≤ 2. The modified Rankin score (mRS) will be assessed by trained research nurse blinded to the randomisation group.

An additional exploratory analysis of the primary endpoint will be performed to assess treatments effects according to baseline NIHSS (≤ or > 14) and the administration or not of IV thrombolysis.

Secondary outcomes measures

- Time between the beginning of the clinical symptoms and the last angiography
- Time between the arrival of the patient and the beginning of the endovascular therapy (time of punction)
- Quality of the recanalization after the endovascular treatment evaluated by the neuroradiologist (not blinded). A good quality recanalization corresponds to a 2b or 3 modified treatment in cerebral ischemia scale (TICI) (16)
- NIHSS score at Day 1 (day after the endovascular treatment) and Day 7 (or the day the patient leaves the hospital if scheduled before D7) (17)
- Complications during the procedure (dissection, rupture of the artery, thrombus in another territory)
- Mortality rate 3 months after the endovascular treatment
- Number of hypo- or hypertension events during the procedure and the first 24 hours after the procedure (hypotension defined as SBP < 140 mmHg or a drop of the MBP of 40% or more, hypertension defined as SBP> 185 mmHg or DBP > 110 mmHg)
- Number of patients who received norepinephrine
- Number of conversion of conscious sedation to general anaesthesia

Statistical analysis

Statistical analysis will be performed on all randomized and evaluated patients (intention to treat analysis). It will be performed with SAS software (SAS Institute, Cary, NC, USA) in the Methodology/Biometrics department of the Inserm 1414 Clinical Investigation Centre of Rennes. A first overall descriptive analysis and analysis by group will be performed. This consists of separate estimates, numbers and percentages for qualitative variables, means, standard error, medians and interquartile intervals for quantitative variables. The normal feature of the distribution of quantitative variables will be checked. Student's t test or a Mann-Whitney test if necessary will be used to compare quantitative variables, and a Chi^2 or Fisher's exact test if necessary will be used to compare qualitative variables between two groups at inclusion. The primary endpoint will be compared between the two groups with the Chi^2 test. Two interim analyses after inclusion of 1/3 and 2/3 of the patients, and one final analysis are planned. Stopping rules will use the alpha spending function with the O'Brien-Fleming boundary. The cumulative values of alpha for each analysis are: 0.00021 at the first analysis, 0.01202 at the second analysis and 0.04626 at the final analysis (nTerim, V1.1, Statistical solutions Ltd, Cork, Ireland). The trial will be stopped early if the significance of the Chi^2 test is below these alpha values. For the analysis of the other endpoints, the same strategy as for baseline comparisons will be used. Continuous endpoints repeatedly measured during the study will be compared using a repeated measure two-way (time, group) analysis of variance. For all these analyses, adjustments can be made in case of heterogeneity at inclusion. Except for the interim analyses, a p value <0.05 will be considered as significant for all analyses.

Missing values

Missing data will not be replaced. Mixed models can be used in analysis of repeated data to avoid deleting subjects with any missing values.

Sample size estimation

A previous study reported 30% of the patients with a mRS score ≤ 2 after endovascular therapy under general anaesthesia (18). We aim to show an increase of patients with a good prognostic (defined as mRS ≤ 2) up to 45% after endovascular treatment under conscious sedation. Therefore, 166 patients per group will be needed to have 80% power, at a two-sided alpha level of 0.05. A total of 350 patients will be included to take into account non-evaluable patients and drop outs.

Data Registration

Data will be entered into the web- based electronic case report form (eCRF) by trial or clinical personnel under the supervision of the trial site investigators at each participating centre. From the eCRF the trial database will be established. Data collection will be monitored by trained research coordinators.

The following data will be registered:

Baseline characteristics at randomisation:

Demographic data (age, height, weight, gender and body mass index); American Society of Anaesthesiologists (ASA) physical status; significant comorbidities (cardio-vascular, respiratory, neurologic , psychiatric and /or abdominal disease, cancer, preoperative chemotherapy or radiotherapy), NIHSS score, time of arrival at the hospital, time of the beginning of the symptoms, time of the cerebral angiography or MRI, localisation of the stroke, IV fibrinolysis if applicable, creatinine clearance, haemostasis (PT and ACT if available).

Intraoperative data:

Time of arterial puncture, time of recanalization, TICI score (16), doses of norepinephrine, intraoperative complications (hypotension defined as SBP < 140 mmHg or a drop of the MBP of 40% or more, hypertension defined as SBP> 185 mmHg or DBP > 110 mmHg) necessity to convert the conscious sedation onto a general anaesthesia.

Postoperative data:

The following data will be collected:

- NIHSS day 1 and Day 7 or the day the patient leaves the hospital if before Day 7
- Necessity of noradrenaline during the first 2 hours after the endovascular treatment
- Hypo-or hypertension events as defined above during first 24 hours
- Death until the final call for mRS (3 months after the procedure)
- mRS 3 months after the procedure during a telephone interview (19).

Patient withdrawal

A participant who no longer agrees to participate in the clinical trial can withdraw the informed consent at any time without need of further explanation. Participants who will withdraw from the study will be followed up, according to routine clinical practice in each participating centre. In order to conduct intention-to-treat analyses with as little missing data as possible, the investigator may ask the participant which aspects of the trial he/she wishes to withdraw from (participation in the remaining follow-up assessments, use of already collected data). Whenever possible, the participant will be asked for permission to obtain data for the primary outcome measure. All randomised patients will be reported, and all data available with consent will be used in the analyses. If appropriate, missing data will be handled in accordance with multiple imputation procedures if missing data are greater than 5%.

Safety

Every serious adverse event related to the studied treatment or not, expected or unexpected, will be reported within 24 hours by the investigator to the sponsor on a “Serious adverse event” form on which will be indicated the date of occurrence, criterion of severity, intensity, relationship with the treatment (or the study) evaluated, and the outcome. The period in which serious adverse events should be reported begins from the day of the written informed

consent to the end of the follow-up (day of the evaluation of mRS 3 to 4 months after the procedure). Whenever a serious adverse event persists at the end of the study, the investigator will follow the patient until the event is considered resolved. The following events: hypo- or hypertension will be recorded as study endpoints criterion in the case report form. In order to avoid collection duplication, they will not be reported on the "adverse event" page of the case report form. As planned in the study, they will be analysed at the time of interim analyses (two interim analyses after inclusion of 1/3 and 2/3 of the patients) which will permit to show potential difference between the two groups during the study.

In addition, serious adverse events will be submitted to the data monitoring and safety committee (DMSC). The DMSC is independent of the trial investigators and will perform an ongoing review of safety parameters and overall study conduct. The DMSC is comprised of a neurologist, an anaesthesiologist, a neuroradiologist, a pharmacologist and a methodologist. The DMSC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control. Recommendations for pausing or stopping the study will be made by the DMSC in case of serious adverse reactions and suspected unexpected serious adverse reaction.

All adverse events for which the investigator or the sponsor considers that a causal relationship with the investigational medicinal products can be reasonably considered, will be considered as suspected adverse reactions. If they are unexpected, they are qualified as being Suspected Unexpected SAR (SUSAR) and will be notified in a report by the sponsor to Eudravigilance (European pharmacovigilance database) and to local regulatory agency within the regulatory time periods for reporting: Immediate declaration if seriousness criteria is death or life-threatening condition, declaration within 15 days for other seriousness criteria.

Data handling and retention

Data will be handled according to French law. All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years.

Patient and public involvement

Patient and public were not involved in any of the phases of this study

ETHICS AND DISSEMINATION

Ethical and legislative approvals

GASS trial was approved by the French National Safety and Drug Agency (Agence Nationale de Sécurité du Médicament (September 8th, 2016). By June 13th, 2016, the study has been approved for all centres by a central ethics committee (Comité de Protection des Personnes de Poitiers). The GASS trial is registered in the European Clinical Trials Database (EudraCT 2016-000795-25) and at ClinicalTrials.gov with the trial identification number NCT02822144. Trial methods and results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines (20).

Publication plan

Scientific presentations and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study with the agreement of the principal investigators and the methodologist. The co-authors of the report and of publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. All trial sites will be acknowledged, and all investigators at these sites will appear with their names under 'the GASS

investigators' in an Appendix to the final manuscript. Rules on publication will follow international recommendations (21).

Conclusion

The GASS trial is the first randomised, parallel, single-blind, multicentre study evaluating the effect the type of anaesthesia on the functional outcome 3 months after endovascular therapy for stroke. The results of GASS will give strong data to help choosing the best type of sedation during endovascular therapy for stroke.

Contributors: Axelle Maurice (AM) contributed to the conception and design of the research protocol and wrote the research protocol. Helene Beloeil (HB) provided critical input pertaining to the design of the trial interventions and procedures. AM wrote the first draft of the protocol and HB this manuscript. Bruno Laviolle (BL) designed the study and its statistical analysis plan. All authors (AM, JCF, TR, JMD, AS, BL, HB) critically revised and modified the protocol and the article. They all approved the final version to be published.

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The funding sources had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

Sponsor: CHU de Rennes, Direction de la recherché Clinique, 2 avenue Henri Le Guilloux, 35033 Rennes Cedex, France. The sponsor had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

Competing interests: None

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Page 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Page 2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Pages 4&5
	2b	Specific objectives or hypotheses	Page 5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Page 6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	Page 6
	4b	Settings and locations where the data were collected	Page 6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Pages 7&8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Page 9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	Page 11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Page 10
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Page 7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Page 7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Page 7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Page 7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Page 7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Page 10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Page 10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	Page 2
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Page 15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

GASS Trial study protocol: a multicentre, single-blind, randomised clinical trial comparing general anaesthesia and sedation during intra-arterial treatment for stroke.

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Title: GASS Trial study protocol: a multicentre, single-blind, randomised clinical trial comparing general anaesthesia and sedation during intra-arterial treatment for stroke.

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ABSTRACT

Introduction: Treatment of acute stroke has drastically changed in the last 10 years. Endovascular therapy is now the standard of care for patients with a stroke caused by a large vessel occlusion in the anterior circulation. The impact of the type of anaesthesia (general anaesthesia or conscious sedation) during endovascular therapy on the outcome of the patients is still a matter of debate. Previous studies are mostly retrospective and/or focused on the early post-procedure outcome and/or without blood pressure goals and/or single-centre small size studies. We therefore designed a multicentre study hypothesizing that conscious sedation is associated with a better functional outcome 3 months after endovascular therapy for the treatment of stroke compared with general anaesthesia.

Methods/analysis: The GASS trial is a randomised, parallel, single-blind, multicentre study of 350 patients undergoing endovascular therapy for the treatment of stroke. Patients will be randomly allocated to receive either a general anaesthesia or a conscious sedation. The primary outcome measure is the modified Rankin score assessed 3 months after the treatment. Data will be analysed on the intention-to-treat principle.

Ethics/dissemination: The GASS trial has been approved by an independent ethics committee for all study centres. Participant recruitment begins in September 2016. Results will be published in international peer-reviewed medical journals.

Trial registration number: The trial is registered at ClinicalTrials.gov (Identifier: NCT 02822144**)**

Strengths and limitations of this study

- GASS trial is the first randomised, parallel, single-blind, multicentre study comparing the effects of general anaesthesia and conscious sedation during endovascular therapy for stroke and focused on the functional outcome of the patients 3 months after the treatment.
- The multicentre design, broad inclusion criteria, large sample size (350 patients) and follow-up will support external validity.
- Limitations: The study does not include a systemic CT-scan after the endovascular treatment. The sizing of the stroke is also not part of the study as it is newly implemented technology. It was not part of the routine care at the time of the design of the study.

INTRODUCTION

The treatment of acute stroke has been recently transformed with the publication of RCTs showing the benefit of endovascular therapy when compare with the medical treatment in terms of functional outcome (1-4). Endovascular therapy in addition to the medical treatment is now the standard of care for selected patients who had a stroke caused by a large vessel occlusion in the anterior circulation. All studies have highlighted that the rapidity of the treatment is an essential factor for a good outcome. The other important factor is the haemodynamic conditions during the procedure because instability can worsen the clinical outcome (5,6). A retrospective study concluded that a change of even 10% in mean arterial pressure almost quadrupled the risk for poor outcomes (7).

In this context, the best anaesthetic strategy during the endovascular treatment has not been yet defined. Indeed, the choice between general anaesthesia (GA) and conscious sedation (CS) remains unclear. While allowing immobility, cerebral protection and airway control, GA can delay the endovascular treatment. On the other hand, CS is more rapid, allows neurological assessment during the procedure but the thrombectomy can be more difficult for the neuroradiologist because of patients' movements. In terms of haemodynamic stability, retrospective studies reported results favouring CS (8-10). However, these studies did not focus on the anaesthetic protocol and the intra-procedure haemodynamic. Anaesthetic protocols were not standardized. The first randomized controlled trial (RCT) on the subject was published in 2016 (11). This monocentric study did not find any benefit of CS over GA in terms of outcome 24 hours and 3 months after the treatment. However, functional outcome at 3 months was only a secondary outcome and the anaesthesia protocol was not detailed. Moreover, the design allowed patients in the CS group to receive analgesics and/or sedatives if necessary, which could then transform a CS into a light GA. Löwhagen et al (12) did also not show any difference between the two anaesthetic technics using a well-described anaesthesia protocol. However, the study included only 90 patients and was monocentric. The most recent study (13) using an identical design with infarct growth as the primary endpoint reported no differences between CS and GA. Clinical outcome at 90 days, tested as a secondary endpoint,

was better in the GA group. Finally, a meta-analysis analysing the pooled data of 7 trials (14) reported that worse outcomes at 3 months were associated with GA. However, the choice to treat a patient with or without GA was not randomized in the trials included in this meta-analysis (14).

So far, no study has assessed the clinical outcome 3 months after the stroke treatment comparing GA and CS using standardized anaesthetic protocols and tight haemodynamic control. Indeed, in previous studies (11,12,13), the anaesthesia protocol was either not standardized or the doses not given, the blood pressure was controlled with vasoactives drugs as different as dopamine and norepinephrine in the same study and the clinical outcome 3 months after the stroke was not the primary objective of one study (13). The recently published post hoc analysis of the Siesta trial (15) reported no association between heamodynamic variations and NIHSS change after 24 hours."

Therefore, we designed a RCT comparing GA and CS during endovascular treatment for acute stroke. Both GA and CS protocols will be standardized and the control of arterial blood pressure too. We hypothesized that CS will be associated with a better clinical outcome measured with the modified Rankin score (mRS) 3 months after the procedure. The Gass study is the first multicentric RCT including a detailed anaesthesia protocol with a tight haemodynamic control, comparing GA and CS during EVT and evaluating the functional outcome at 3 months.

METHODS AND ANALYSIS

Trial design

The GASS study is an investigator initiated, national, multicentre, randomised, simple-blind, parallel-group clinical trial with concealed allocation of patients scheduled to undergo endovascular therapy for stroke 1:1 to receive either a general anaesthesia protocol or a conscious sedation protocol. The trial will be conducted in four university and non-university centres. It started in September 2016 and will continue for a total of 36 months.

Participant eligibility and consent

Trial site investigators will identify consecutive eligible patients from the listed criteria. Eligible patients or a family member when appropriate will receive written and oral information and will be included after investigators have obtained informed written consent.

Inclusion criteria

1. Adult (18 years or older) patients admitted to the participating centre
2. Occlusion of a large vessel in the anterior cerebral circulation
3. Undergoing endovascular therapy for stroke
4. Benefiting from the health insurance system
5. Signed informed consent from the patient or their legally next of kin

Non-inclusion criteria

1. Pregnant or breast-feeding women
2. Patients already intubated and mechanical ventilated before inclusion in the study
3. Intracerebral haemorrhage associated with the ischemic stroke
4. Contra-indications to conscious sedation: Glasgow coma scale inferior to 8, agitation not allowing the patient to stay still during the procedure, deglutition disorders
5. Contra-indications to succinylcholine: hyperkalaemia, allergy
6. Body mass index superior to 35kg/m^2
7. Allergy to one of the anaesthetic drugs

8. Uncontrolled hypotension,
9. Life-threatening comorbidity
10. Adults legally protected (under judicial protection, guardianship, or supervision), persons deprived of their liberty

Allocation and blinding

Patients will be randomised in two groups (general anaesthesia group and conscious sedation group). Randomisation will be done by investigators as close as possible to the endovascular therapy. Each patient will be given a unique randomisation number (patient code). Randomization will be stratified on the centre, the National Institute of Health Stroke Score (NIHSS ≤ or > 14) and the administration or not of IV thrombolysis. The primary evaluation criterion will be assessed blinded to the randomisation group. During the study period, outcome assessors will be kept blind to the randomisation group. Research nurses evaluating the outcomes 3 months after the treatment will not participate to the anaesthesia and will not be aware of the randomisation group. They will be blind to the treatment. The anaesthesiologist, the nurse anaesthesiologist, the neuroradiologist and the neurologist will not be blinded. They will not participate in the assessment of the patients at any time.

At each participating centre, data will be collected and entered into the electronic web-based case report form (eCRF) by trial or clinical trained personal (clinical research associate), blinded to the allocation group, under the supervision of the trial site investigators.

Interventions

All included patients will be allocated to one of the following two study groups:

- **General anaesthesia group:** patients will receive a standardised anaesthesia protocol with remifentanil
- **Conscious sedation group:** patients will receive a standard conscious sedation with remifentanil

Standardized general anaesthesia will include: Induction: Etomidate (0.25 – 0.4 mg/kg) and succinylcholine (1 mg/kg) and maintenance: TCI propofol (maximum target: 4 microg/ml), TCI remifentanil (0.5-4 ng/ml) and curares as needed.

Standardized conscious sedation will include: TCI remifentanil (maximum target 2 ng/ml), local anaesthesia with lidocaine 10 mg/ml (maximum 10 ml). Oxygen will be administered only if $SPO_2 \leq 96\%$. Respiratory rate and capnography will be monitored.

Conscious sedation can be converted into a general anaesthesia in the following situations:

- Agitation or restlessness not allowing the endovascular therapy
- Vomiting not allowing the endovascular therapy
- Glasgow coma scale < 8 and /or deglutition disorders
- Severe hypoxemia with SPO_2 < 96 % with oxygen delivered with a high concentration mask (10 l/min maximum)
- Respiratory depression with respiratory rate > 35 /min and/or clinical signs of respiratory exhaustion

In both groups:

intraoperative dose changes will be left to the anaesthesiologist in charge of the patient if necessary, IV norepinephrine will be administered in order to maintain blood pressure (BP) within the recommended range: systolic blood pressure (SBP) between 140 and 185 mmHg; diastolic blood pressure (DBP) < 110 mmHg. A drop of more than 25% of the mean blood pressure (MBP) will also be avoided. Norepinephrine will be administered in a dedicated intravenous line and diluted at 250 microg/ml.

A systematic immediate post-EVT Cone-beal CT scan wiil be performed for all patients.

Decisions about all other aspects of patient care will be performed according to the expertise of the staff at each centre and to routine clinical practice to minimize interference with the trial intervention. Three months after the thrombectomy, patients will consult with a neurologist.

Outcome measures

Primary outcome measure

The primary outcome measure will be the neurological outcome assessed with the modified Rankin score 3 months (16) after the endovascular therapy. Success will be considered as a modified Rankin score ≤ 2. The modified Rankin score (mRS) will be assessed by trained research nurse blinded to the randomisation group.

An additional exploratory analysis of the primary endpoint will be performed to assess treatments effects according to baseline NIHSS (≤ or > 14) and the administration or not of IV thrombolysis.

Secondary outcomes measures

- Time between the beginning of the clinical symptoms and the last angiography
- Time between the arrival of the patient at the stroke center and the beginning of the endovascular therapy (time of punction)
- Quality of the recanalization after the endovascular treatment evaluated by the neuroradiologist (not blinded). A good quality recanalization corresponds to a 2b or 3 modified treatment in cerebral ischemia scale (mTICI) (17)
- NIHSS score at Day 1 (day after the endovascular treatment) and Day 7 (or the day the patient leaves the hospital if scheduled before D7) (18)
- Complications during the procedure (dissection, rupture of the artery, thrombus in another territory)
- Mortality rate 3 months after the endovascular treatment
- Number of hypo- or hypertension events during the procedure and the first 24 hours after the procedure (hypotension defined as SBP < 140 mmHg or a drop of the MBP of 40% or more, hypertension defined as SBP> 185 mmHg or DBP > 110 mmHg)
- Number of patients who received norepinephrine
- Number of conversion of conscious sedation to general anaesthesia

Statistical analysis

Statistical analysis will be performed on all randomized and evaluated patients (intention to treat analysis). It will be performed with SAS software (SAS Institute, Cary, NC, USA) in the Methodology/Biometrics department of the Inserm 1414 Clinical Investigation Centre of Rennes. A first overall descriptive analysis and analysis by group will be performed. This consists of separate estimates, numbers and percentages for qualitative variables, means, standard error, medians and interquartile intervals for quantitative variables. The normal feature of the distribution of quantitative variables will be checked. Student's t test or a Mann-Whitney test if necessary will be used to compare quantitative variables, and a Chi^2 or Fisher's exact test if necessary will be used to compare qualitative variables between two groups at inclusion. The primary endpoint will be compared between the two groups with the Chi^2 test. Two interim analyses after inclusion of 1/3 and 2/3 of the patients, and one final analysis are planned. Stopping rules will use the alpha spending function with the O'Brien-Fleming boundary. The cumulative values of alpha for each analysis are: 0.00021 at the first analysis, 0.01202 at the second analysis and 0.04626 at the final analysis (nTerim, V1.1, Statistical solutions Ltd, Cork, Ireland). The trial will be stopped early if the significance of the Chi^2 test is below these alpha values. For the analysis of the other endpoints, the same strategy as for baseline comparisons will be used. Continuous endpoints repeatedly measured during the study will be compared using a repeated measure two-way (time, group) analysis of variance. For all these analyses, adjustments can be made in case of heterogeneity at inclusion. Except for the interim analyses, a p value <0.05 will be considered as significant for all analyses.

Missing values

Missing data will not be replaced. Mixed models can be used in analysis of repeated data to avoid deleting subjects with any missing values.

Sample size estimation

A previous study reported 30% of the patients with a mRS score ≤ 2 after endovascular therapy under general anaesthesia (19). We aim to show an increase of patients with a good prognostic

(defined as mRS ≤ 2) up to 45% after endovascular treatment under conscious sedation. Therefore, 166 patients per group will be needed to have 80% power, at a two-sided alpha level of 0.05. A total of 350 patients will be included to take into account non-evaluable patients and drop outs.

Data Registration

Data will be entered into the web- based electronic case report form (eCRF) by trial or clinical personnel under the supervision of the trial site investigators at each participating centre. From the eCRF the trial database will be established. Data collection will be monitored by trained research coordinators.

The following data will be registered:

Baseline characteristics at randomisation:

Demographic data (age, height, weight, gender and body mass index); American Society of Anaesthesiologists (ASA) physical status; significant comorbidities (cardio-vascular, respiratory, neurologic , psychiatric and /or abdominal disease, cancer, preoperative chemotherapy or radiotherapy), NIHSS score, time of arrival at the hospital, time of the beginning of the symptoms, time of the cerebral angiography or MRI (meaning time of first image for diagnosis) , time between the first contact of the patient with the anaesthesiologist and the induction of anaesthesia (GA or CS),localisation of the stroke, IV fibrinolysis if applicable, creatinine clearance, haemostasis (PT and ACT if available).

Intraoperative data:

Time of arterial puncture, time of recanalization, mTICI score (16), doses of norepinephrine, intraoperative complications (hypotension defined as SBP < 140 mmHg or a drop of the MBP of 40% or more, hypertension defined as SBP> 185 mmHg or DBP > 110 mmHg) necessity to convert the conscious sedation onto a general anaesthesia, duration of anaesthesia and procedure, procedure related complications (distal embolization in a different territory, intramural arterial dissection, arterial perforation, access-site complications leading to surgery).

Postoperative data:

The following data will be collected:

- NIHSS day 1 and Day 7 or the day the patient leaves the hospital if before Day 7
- Necessity of noradrenaline during the first 2 hours after the endovascular treatment
- Hypo-or hypertension events as defined above during first 24 hours
- Bradycardie with atropine treatment during first 24 hours
- Hospitalization in intensive care unit
- Number of hours of invasive ventilation
- Pneumonia
- Death until the final call for mRS (3 months after the procedure)
- mRS 3 months after the procedure during a telephone interview (20).

Patient withdrawal

A participant who no longer agrees to participate in the clinical trial can withdraw the informed consent at any time without need of further explanation. Participants who will withdraw from the study will be followed up, according to routine clinical practice in each participating centre. In order to conduct intention-to-treat analyses with as little missing data as possible, the investigator may ask the participant which aspects of the trial he/she wishes to withdraw from (participation in the remaining follow-up assessments, use of already collected data). Whenever possible, the participant will be asked for permission to obtain data for the primary outcome measure. All randomised patients will be reported, and all data available with consent will be used in the analyses. If appropriate, missing data will be handled in accordance with multiple imputation procedures if missing data are greater than 5%.

Safety

Every serious adverse event related to the studied treatment or not, expected or unexpected,

will be reported within 24 hours by the investigator to the sponsor on a “Serious adverse event” form on which will be indicated the date of occurrence, criterion of severity, intensity, relationship with the treatment (or the study) evaluated, and the outcome. The period in which serious adverse events should be reported begins from the day of the written informed consent to the end of the follow-up (day of the evaluation of mRS 3 to 4 months after the procedure). Whenever a serious adverse event persists at the end of the study, the investigator will follow the patient until the event is considered resolved. The following events: hypo- or hypertension will be recorded as study endpoints criterion in the case report form. In order to avoid collection duplication, they will not be reported on the “adverse event” page of the case report form. As planned in the study, they will be analysed at the time of interim analyses (two interim analyses after inclusion of 1/3 and 2/3 of the patients) which will permit to show potential difference between the two groups during the study.

In addition, serious adverse events will be submitted to the data monitoring and safety committee (DMSC). The DMSC is independent of the trial investigators and will perform an ongoing review of safety parameters and overall study conduct. The DMSC is comprised of a neurologist, an anaesthesiologist, a neuroradiologist, a pharmacologist and a methodologist. The DMSC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control. Recommendations for pausing or stopping the study will be made by the DMSC in case of serious adverse reactions and suspected unexpected serious adverse reaction.

All adverse events for which the investigator or the sponsor considers that a causal relationship with the investigational medicinal products can be reasonably considered, will be considered as suspected adverse reactions. If they are unexpected, they are qualified as being Suspected Unexpected SAR (SUSAR) and will be notified in a report by the sponsor to Eudravigilance

(European pharmacovigilance database) and to local regulatory agency within the regulatory time periods for reporting: Immediate declaration if seriousness criteria is death or life-threatening condition, declaration within 15 days for other seriousness criteria.

Data handling and retention

Data will be handled according to French law. All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years.

Patient and public involvement

Patient and public were not involved in any of the phases of this study

ETHICS AND DISSEMINATION

Ethical and legislative approvals

GASS trial was approved by the French National Safety and Drug Agency (Agence Nationale de Sécurité du Médicament (September 8th, 2016). By June 13th, 2016, the study has been approved for all centres by a central ethics committee (Comité de Protection des Personnes de Poitiers). The GASS trial is registered in the European Clinical Trials Database (EudraCT 2016-000795-25) and at ClinicalTrials.gov with the trial identification number NCT02822144. Trial methods and results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines (21).

Publication plan

Scientific presentations and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study with the agreement of the principal investigators and the methodologist. The co-authors of the report and of publications will be

the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. All trial sites will be acknowledged, and all investigators at these sites will appear with their names under 'the GASS investigators' in an Appendix to the final manuscript. Rules on publication will follow international recommendations (22).

Contributors: Axelle Maurice (AM) contributed to the conception and design of the research protocol and wrote the research protocol. Helene Beloeil (HB) provided critical input pertaining to the design of the trial interventions and procedures. AM wrote the first draft of the protocol and HB this manuscript. Bruno Laviolle (BL) designed the study and its statistical analysis plan. All authors (AM, JCF, TR, JMD, AS, BL, HB) critically revised and modified the protocol and the article. They all approved the final version to be published.

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Competing interests: None

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21- Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.

22- International Committee of Medical Journal E. Uniform requirements for manuscripts submitted to biomedical journals. The New England journal of medicine 1997;336(4):309-15

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Page 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Page 2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Pages 4&5
	2b	Specific objectives or hypotheses	Page 5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Page 6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	Page 6
	4b	Settings and locations where the data were collected	Page 6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Pages 7&8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Page 9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	Page 11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Page 10
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Page 7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Page 7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Page 7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Page 7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Page 7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Page 10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Page 10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	Page 2
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Page 15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry page 2
	2b	All items from the World Health Organization Trial Registration Data Set NA
Protocol version	3	Date and version identifier NA
Funding	4	Sources and types of financial, material, and other support page 15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors page 1
	5b	Name and contact information for the trial sponsor page 15-16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities page 15-16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) page 13
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention page 4-5
	6b	Explanation for choice of comparators page 4-5
Objectives	7	Specific objectives or hypotheses page 5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) page 6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained page 6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) page 6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered page 7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) page 8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial page 8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended page 9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) page 9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations page 10-11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size page 10-11

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions page 7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned page 7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions page 7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how page 7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol page11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols page 11-12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol page 14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol page 10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) page 10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) page 10

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed page 11 & 13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial page 13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct page 13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor page 13

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval already done page 14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) page 14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) page 7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial page 14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site page 16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators page 14-15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions page 14-15
	31b	Authorship eligibility guidelines and any intended use of professional writers page 14-15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

GASS Trial study protocol: a multicentre, single-blind, randomised clinical trial comparing general anaesthesia and sedation during intra-arterial treatment for stroke.

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Title: GASS Trial study protocol: a multicentre, single-blind, randomised clinical trial comparing general anaesthesia and sedation during intra-arterial treatment for stroke.

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ABSTRACT

Introduction: Treatment of acute stroke has drastically changed in the last 10 years. Endovascular therapy is now the standard of care for patients with a stroke caused by a large vessel occlusion in the anterior circulation. The impact of the type of anaesthesia (general anaesthesia or conscious sedation) during endovascular therapy on the outcome of the patients is still a matter of debate. Previous studies are mostly retrospective and/or focused on the early post-procedure outcome and/or without blood pressure goals and/or single-centre small size studies. We therefore designed a multicentre study hypothesizing that conscious sedation is associated with a better functional outcome 3 months after endovascular therapy for the treatment of stroke compared with general anaesthesia.

Methods/analysis: The GASS trial is a randomised, parallel, single-blind, multicentre study of 350 patients undergoing endovascular therapy for the treatment of stroke. Patients will be randomly allocated to receive either a general anaesthesia or a conscious sedation. The primary outcome measure is the modified Rankin score assessed 3 months after the treatment. Data will be analysed on the intention-to-treat principle.

Ethics/dissemination: The GASS trial has been approved by an independent ethics committee for all study centres. Participant recruitment begins in September 2016. Results will be published in international peer-reviewed medical journals.

Trial registration number: The trial is registered at ClinicalTrials.gov (Identifier: NCT 02822144**)**

Strengths and limitations of this study

- GASS trial is a randomised, parallel, single-blind, multicentre study comparing the effects of general anaesthesia and conscious sedation during endovascular therapy for stroke.
- GASS trial is focused on the functional outcome of the patients 3 months after the treatment.
- The multicentre design, broad inclusion criteria, large sample size (350 patients) and follow-up will support external validity.
- The study does not include a systemic CT-scan after the endovascular treatment.
- The sizing of the stroke is also not part of the study as it is newly implemented technology.

INTRODUCTION

The treatment of acute stroke has been recently transformed with the publication of RCTs showing the benefit of endovascular therapy when compare with the medical treatment in terms of functional outcome (1-4). Endovascular therapy in addition to the medical treatment is now the standard of care for selected patients who had a stroke caused by a large vessel occlusion in the anterior circulation. All studies have highlighted that the rapidity of the treatment is an essential factor for a good outcome. The other important factor is the haemodynamic conditions during the procedure because instability can worsen the clinical outcome (5,6). A retrospective study concluded that a change of even 10% in mean arterial pressure almost quadrupled the risk for poor outcomes (7).

In this context, the best anaesthetic strategy during the endovascular treatment has not been yet defined. Indeed, the choice between general anaesthesia (GA) and conscious sedation (CS) remains unclear. While allowing immobility, cerebral protection and airway control, GA can delay the endovascular treatment. On the other hand, CS is more rapid, allows neurological assessment during the procedure but the thrombectomy can be more difficult for the neuroradiologist because of patients' movements. In terms of haemodynamic stability, retrospective studies reported results favouring CS (8-10). However, these studies did not focus on the anaesthetic protocol and the intra-procedure haemodynamic. Anaesthetic protocols were not standardized. The first randomized controlled trial (RCT) on the subject was published in 2016 (11). This monocentric study did not find any benefit of CS over GA in terms of outcome 24 hours and 3 months after the treatment. However, functional outcome at 3 months was only a secondary outcome and the anaesthesia protocol was not detailed. Moreover, the design allowed patients in the CS group to receive analgesics and/or sedatives if necessary, which could then transform a CS into a light GA. Löwhagen et al (12) did also not show any difference between the two anaesthetic technics using a well-described anaesthesia protocol. However, the study included only 90 patients and was monocentric. The most recent study (13) using an identical design with infarct growth as the primary endpoint reported no differences between CS and GA. Clinical outcome at 90 days, tested as a secondary endpoint,

was better in the GA group. Finally, a meta-analysis analysing the pooled data of 7 trials (14) reported that worse outcomes at 3 months were associated with GA. However, the choice to treat a patient with or without GA was not randomized in the trials included in this meta-analysis (14).

So far, few studies has assessed the clinical outcome 3 months after the stroke treatment comparing GA and CS using standardized anaesthetic protocols and tight haemodynamic control. Indeed, in previous studies (11,12,13), the anaesthesia protocol was either not standardized or the doses not given, the blood pressure was controlled with vasoactives drugs as different as dopamine and norepinephrine in the same study and the clinical outcome 3 months after the stroke was not the primary objective of one study (13). The recently published post hoc analysis of the Siesta trial (15) and the GOLIATH trial (16) reported no association between heamodynamic variations and NIHSS change after 24 hours."

Therefore, we designed a RCT comparing GA and CS during endovascular treatment for acute stroke. Both GA and CS protocols will be standardized and the control of arterial blood pressure too. We hypothesized that CS will be associated with a better clinical outcome measured with the modified Rankin score (mRS) 3 months after the procedure. The Gass study is the first multicentric RCT including a detailed anaesthesia protocol with a tight haemodynamic control, comparing GA and CS during EVT and evaluating the functional outcome at 3 months.

METHODS AND ANALYSIS

Trial design

The GASS study is an investigator initiated, national, multicentre, randomised, simple-blind, parallel-group clinical trial with concealed allocation of patients scheduled to undergo endovascular therapy for stroke 1:1 to receive either a general anaesthesia protocol or a conscious sedation protocol. The trial will be conducted in four university and non-university centres. It started in September 2016 and will continue for a total of 36 months.

Participant eligibility and consent

Trial site investigators will identify consecutive eligible patients from the listed criteria. Eligible patients or a family member when appropriate will receive written and oral information and will be included after investigators have obtained informed written consent.

Inclusion criteria

1. Adult (18 years or older) patients admitted to the participating centre
2. Occlusion of a large vessel in the anterior cerebral circulation
3. Undergoing endovascular therapy for stroke
4. Benefiting from the health insurance system
5. Signed informed consent from the patient or their legally next of kin

Non-inclusion criteria

1. Pregnant or breast-feeding women
2. Patients already intubated and mechanical ventilated before inclusion in the study
3. Intracerebral haemorrhage associated with the ischemic stroke
4. Contra-indications to conscious sedation: Glasgow coma scale inferior to 8, agitation not allowing the patient to stay still during the procedure, deglutition disorders
5. Contra-indications to succinylcholine: hyperkalaemia, allergy
6. Body mass index superior to 35kg/m^2
7. Allergy to one of the anaesthetic drugs

8. Uncontrolled hypotension,
9. Life-threatening comorbidity
10. Adults legally protected (under judicial protection, guardianship, or supervision), persons deprived of their liberty
11. patients who could not walk prior stroke

Allocation and blinding

Patients will be randomised in two groups (general anaesthesia group and conscious sedation group). Randomisation will be done by investigators as close as possible to the endovascular therapy. Each patient will be given a unique randomisation number (patient code). Randomization will be stratified on the centre, the National Institute of Health Stroke Score (NIHSS ≤ or > 14) and the administration or not of IV thrombolysis. The primary evaluation criterion will be assessed blinded to the randomisation group. During the study period, outcome assessors will be kept blind to the randomisation group. Research nurses evaluating the outcomes 3 months after the treatment will not participate to the anaesthesia and will not be aware of the randomisation group. They will be blind to the treatment. The anaesthesiologist, the nurse anaesthesiologist, the neuroradiologist and the neurologist will not be blinded. They will not participate in the assessment of the patients at any time.

At each participating centre, data will be collected and entered into the electronic web-based case report form (eCRF) by trial or clinical trained personal (clinical research associate), blinded to the allocation group, under the supervision of the trial site investigators.

Interventions

All included patients will be allocated to one of the following two study groups:

- **General anaesthesia group:** patients will receive a standardised anaesthesia protocol with remifentanil
- **Conscious sedation group:** patients will receive a standard conscious sedation with remifentanil

Standardized general anaesthesia will include: Induction: Etomidate (0.25 – 0.4 mg/kg) and succinylcholine (1 mg/kg) and maintenance: TCI propofol (maximum target: 4 microg/ml), TCI remifentanil (0.5-4 ng/ml) and curares as needed.

Standardized conscious sedation will include: TCI remifentanil (maximum target 2 ng/ml), local anaesthesia with lidocaine 10 mg/ml (maximum 10 ml). Oxygen will be administered only if $SPO_2 \leq 96\%$. Respiratory rate and capnography will be monitored.

Conscious sedation can be converted into a general anaesthesia in the following situations:

- Agitation or restlessness not allowing the endovascular therapy
- Vomiting not allowing the endovascular therapy
- Glasgow coma scale < 8 and /or deglutition disorders
- Severe hypoxemia with SPO_2 < 96 % with oxygen delivered with a high concentration mask (10 l/min maximum)
- Respiratory depression with respiratory rate > 35 /min and/or clinical signs of respiratory exhaustion

In both groups:

intraoperative dose changes will be left to the anaesthesiologist in charge of the patient if necessary, IV norepinephrine will be administered in order to maintain blood pressure (BP) within the recommended range: systolic blood pressure (SBP) between 140 and 185 mmHg; diastolic blood pressure (DBP) < 110 mmHg. A drop of more than 25% of the mean blood pressure (MBP) will also be avoided. Blood pressure will be continuously non invasively monitored. Norepinephrine will be administered in a dedicated intravenous line and diluted at 250 microg/ml. Hyperglycemia will be treated with IV insuline when necessary (target 11 mmol/L).

A systematic immediate post-EVT Cone-beal CT scan will be performed for all patients.

Decisions about all other aspects of patient care will be performed according to the expertise of the staff at each centre and to routine clinical practice to minimize interference with the trial intervention. Postoperative blood pressure targets are defined as follows: SBP < 180 mmHg,

DBP< 110 mmHg and MBP > 65 mmHg. In case of TICI 2a or lower, the objective is MBP > 75 mmHg. Norepinephrine will be used if necessary. Three months after the thrombectomy, patients will consult with a neurologist.

Outcome measures

Primary outcome measure

The primary outcome measure will be the neurological outcome assessed with the modified Rankin score 3 months (17) after the endovascular therapy. Success will be considered as a modified Rankin score ≤ 2. The modified Rankin score (mRS) will be assessed by trained research nurse blinded to the randomisation group.

An additional exploratory analysis of the primary endpoint will be performed to assess treatments effects according to baseline NIHSS (≤ or > 14) and the administration or not of IV thrombolysis.

Secondary outcomes measures

- Time between the beginning of the clinical symptoms and the last angiography
- Time between the arrival of the patient at the stroke center and the beginning of the endovascular therapy (time of punction)
- Quality of the recanalization after the endovascular treatment evaluated by the neuroradiologist (not blinded). A good quality recanalization corresponds to a 2b or 3 modified treatment in cerebral ischemia scale (mTICI) (18)
- NIHSS score at Day 1 (day after the endovascular treatment) and Day 7 (or the day the patient leaves the hospital if scheduled before D7) (19)
- Complications during the procedure (dissection, rupture of the artery, thrombus in another territory)
- Mortality rate 3 months after the endovascular treatment
- Number of hypo- or hypertension events during the procedure and the first 24 hours

after the procedure (hypotension defined as SBP < 140 mmHg or a drop of the MBP of 40% or more, hypertension defined as SBP> 185 mmHg or DBP > 110 mmHg)

- Number of patients who received norepinephrine
- Number of conversion of conscious sedation to general anaesthesia

Statistical analysis

Statistical analysis will be performed on all randomized and evaluated patients (intention to treat analysis). It will be performed with SAS software (SAS Institute, Cary, NC, USA) in the Methodology/Biometrics department of the Inserm 1414 Clinical Investigation Centre of Rennes. A first overall descriptive analysis and analysis by group will be performed. This consists of separate estimates, numbers and percentages for qualitative variables, means, standard error, medians and interquartile intervals for quantitative variables. The normal feature of the distribution of quantitative variables will be checked. Student's t test or a Mann-Whitney test if necessary will be used to compare quantitative variables, and a Chi^2 or Fisher's exact test if necessary will be used to compare qualitative variables between two groups at inclusion. The primary endpoint will be compared between the two groups with the Chi^2 test. Two interim analyses after inclusion of 1/3 and 2/3 of the patients, and one final analysis are planned. Stopping rules will use the alpha spending function with the O'Brien-Fleming boundary. The cumulative values of alpha for each analysis are: 0.00021 at the first analysis, 0.01202 at the second analysis and 0.04626 at the final analysis (nTerim, V1.1, Statistical solutions Ltd, Cork, Ireland). The trial will be stopped early if the significance of the Chi^2 test is below these alpha values. For the analysis of the other endpoints, the same strategy as for baseline comparisons will be used. Continuous endpoints repeatedly measured during the study will be compared using a repeated measure two-way (time, group) analysis of variance. For all these analyses, adjustments can be made in case of heterogeneity at inclusion. Except for the interim analyses, a p value <0.05 will be considered as significant for all analyses.

Missing values

Missing data will not be replaced. Mixed models can be used in analysis of repeated data to avoid deleting subjects with any missing values.

Sample size estimation

A previous study reported 30% of the patients with a mRS score ≤ 2 after endovascular therapy under general anaesthesia (20). We aim to show an increase of patients with a good prognostic (defined as mRS ≤ 2) up to 45% after endovascular treatment under conscious sedation. Therefore, 166 patients per group will be needed to have 80% power, at a two-sided alpha level of 0.05. A total of 350 patients will be included to take into account non-evaluable patients and drop outs.

Data Registration

Data will be entered into the web- based electronic case report form (eCRF) by trial or clinical personnel under the supervision of the trial site investigators at each participating centre. From the eCRF the trial database will be established. Data collection will be monitored by trained research coordinators.

The following data will be registered:

<u>Baseline characteristics at randomisation:</u>

Demographic data (age, height, weight, gender and body mass index); American Society of Anaesthesiologists (ASA) physical status; significant comorbidities (cardio-vascular, respiratory, neurologic , psychiatric and /or abdominal disease, cancer, preoperative chemotherapy or radiotherapy), NIHSS score, time of arrival at the hospital, time of the beginning of the symptoms, time of the cerebral angiography or MRI (meaning time of first image for diagnosis) , time between the first contact of the patient with the anaesthesiologist and the induction of anaesthesia (GA or CS),localisation of the stroke, IV fibrinolysis if applicable, creatinine clearance, haemostasis (PT and ACT if available).

<u>Intraoperative data:</u>

Time of arterial puncture, time of recanalization, mTICI score (16), doses of norepinephrine, intraoperative complications (hypotension defined as SBP < 140 mmHg or a drop of the MBP of 40% or more, hypertension defined as SBP> 185 mmHg or DBP > 110 mmHg) necessity to convert the conscious sedation onto a general anaesthesia, duration of anaesthesia and procedure, procedure related complications (distal embolization in a different territory, intramural arterial dissection, arterial perforation, access-site complications leading to surgery).

Postoperative data:

The following data will be collected:

- Duration of invasive ventilation
- NIHSS day 1 and Day 7 or the day the patient leaves the hospital if before Day 7
- Necessity of noradrenaline during the first 2 hours after the endovascular treatment
- Hypo-or hypertension events as defined above during first 24 hours
- Bradycardie with atropine treatment during first 24 hours
- Hospitalization in intensive care unit
- Number of hours of invasive ventilation
- Pneumonia
- Death until the final call for mRS (3 months after the procedure)
- mRS 3 months after the procedure during a telephone interview (21).

Patient withdrawal

A participant who no longer agrees to participate in the clinical trial can withdraw the informed consent at any time without need of further explanation. Participants who will withdraw from the study will be followed up, according to routine clinical practice in each participating centre. In order to conduct intention-to-treat analyses with as little missing data as possible, the investigator may ask the participant which aspects of the trial he/she wishes to withdraw from (participation in the remaining follow-up assessments, use of already collected data).

Whenever possible, the participant will be asked for permission to obtain data for the primary outcome measure. All randomised patients will be reported, and all data available with consent will be used in the analyses. If appropriate, missing data will be handled in accordance with multiple imputation procedures if missing data are greater than 5%.

Safety

Every serious adverse event related to the studied treatment or not, expected or unexpected, will be reported within 24 hours by the investigator to the sponsor on a “Serious adverse event” form on which will be indicated the date of occurrence, criterion of severity, intensity, relationship with the treatment (or the study) evaluated, and the outcome. The period in which serious adverse events should be reported begins from the day of the written informed consent to the end of the follow-up (day of the evaluation of mRS 3 to 4 months after the procedure). Whenever a serious adverse event persists at the end of the study, the investigator will follow the patient until the event is considered resolved. The following events: hypo- or hypertension will be recorded as study endpoints criterion in the case report form. In order to avoid collection duplication, they will not be reported on the “adverse event” page of the case report form. As planned in the study, they will be analysed at the time of interim analyses (two interim analyses after inclusion of 1/3 and 2/3 of the patients) which will permit to show potential difference between the two groups during the study.

In addition, serious adverse events will be submitted to the data monitoring and safety committee (DMSC). The DMSC is independent of the trial investigators and will perform an ongoing review of safety parameters and overall study conduct. The DMSC is comprised of a neurologist, an anaesthesiologist, a neuroradiologist, a pharmacologist and a methodologist. The DMSC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of

participants, and the procedures for data management and quality control. Recommendations for pausing or stopping the study will be made by the DMSC in case of serious adverse reactions and suspected unexpected serious adverse reaction.

All adverse events for which the investigator or the sponsor considers that a causal relationship with the investigational medicinal products can be reasonably considered, will be considered as suspected adverse reactions. If they are unexpected, they are qualified as being Suspected Unexpected SAR (SUSAR) and will be notified in a report by the sponsor to Eudravigilance (European pharmacovigilance database) and to local regulatory agency within the regulatory time periods for reporting: Immediate declaration if seriousness criteria is death or life-threatening condition, declaration within 15 days for other seriousness criteria.

Data handling and retention

Data will be handled according to French law. All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years.

Patient and public involvement

Patient and public were not involved in any of the phases of this study

ETHICS AND DISSEMINATION

Ethical and legislative approvals

GASS trial was approved by the French National Safety and Drug Agency (Agence Nationale de Sécurité du Médicament (September 8th, 2016). By June 13th, 2016, the study has been approved for all centres by a central ethics committee (Comité de Protection des Personnes de Poitiers). The GASS trial is registered in the European Clinical Trials Database (EudraCT 2016-000795-25) and at ClinicalTrials.gov with the trial identification number NCT02822144.

Trial methods and results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines (22).

Publication plan

Scientific presentations and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study with the agreement of the principal investigators and the methodologist. The co-authors of the report and of publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. All trial sites will be acknowledged, and all investigators at these sites will appear with their names under 'the GASS investigators' in the final manuscript. Rules on publication will follow international recommendations (23).

Contributors:

Axelle Maurice (AM) as anesthetist contributed to the conception and design of the research protocol and wrote the research protocol. AM wrote the first draft of the protocol. AM critically revised and modified the protocol and the article. AM is including patients in the ongoing study in the Rennes teaching hospital. AM approved the final version to be published.

Jean-Christophe Ferré (JCF) as neuroradiologist contributed to the conception and design of the research protocol. JCF critically revised and modified the protocol and the article. JCF approved the final version to be published.

Thomas Ronziere (TR) as neurologist contributed to the conception and design of the research protocol. TR critically revised and modified the protocol and the article. TR approved the final version to be published.

Jean-Michel Devys (JMD) as anesthetist critically revised and modified the protocol and the article. JMD is including patients in the ongoing study in the Fondation Rothschild hospital in Paris. JMD approved the final version to be published.

Aurelie Subileau (AS) as anesthetist critically revised and modified the protocol and the article. AS is including patients in the ongoing study in the Brest teaching hospital. AS approved the final version to be published.

Marc Laffon (ML) as anesthetist critically revised and modified the protocol and the article. ML is including patients in the ongoing study in the Tours teaching hospital. ML approved the final version to be published.

Bruno Laviolle (BL) designed the study and its statistical analysis plan.

Helene Beloeil (HB) provided critical input pertaining to the design of the trial interventions and procedures. HB wrote this manuscript. HB is including patients in the ongoing study in the Rennes teaching hospital.

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The funding sources had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

Sponsor: CHU de Rennes, Direction de la recherché Clinique, 2 avenue Henri Le Guilloux, 35033 Rennes Cedex, France. The sponsor had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

Competing interests: None

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Page 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Page 2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Pages 4&5
	2b	Specific objectives or hypotheses	Page 5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Page 6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	Page 6
	4b	Settings and locations where the data were collected	Page 6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Pages 7&8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Page 9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	Page 11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Page 10
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Page 7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Page 7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Page 7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Page 7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Page 7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Page 10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Page 10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	Page 2
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Page 15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry page 2
	2b	All items from the World Health Organization Trial Registration Data Set NA
Protocol version	3	Date and version identifier NA
Funding	4	Sources and types of financial, material, and other support page 15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors page 1
	5b	Name and contact information for the trial sponsor page 15-16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities page 15-16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) page 13
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention page 4-5
	6b	Explanation for choice of comparators page 4-5
Objectives	7	Specific objectives or hypotheses page 5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) page 6
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained page 6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) page 6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered page 7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) page 8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial page 8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended page 9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) page 9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations page 10-11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size page 10-11
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions page 7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned page 7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions page 7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how page 7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol page11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols page 11-12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol page 14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol page 10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) page 10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) page 10

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed page 11 & 13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial page 13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct page 13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor page 13

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval already done page 14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) page 14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) page 7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial page 14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site page 16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators page 14-15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions page 14-15
	31b	Authorship eligibility guidelines and any intended use of professional writers page 14-15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.