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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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2
3 29 **ABSTRACT**

4 30 **Introduction:** Treatment of acute stroke has drastically changed in the last 10 years.
5
6 31 Endovascular therapy is now the standard of care for patients with a stroke caused by a
7
8 32 large vessel occlusion in the anterior circulation. The impact of the type of anaesthesia
9
10 33 (general anaesthesia or conscious sedation) during endovascular therapy on the outcome of
11
12 34 the patients is still a matter of debate. Previous studies are mostly retrospective and/or
13
14 35 focused on the early post-procedure outcome and/or without blood pressure goals and/or
15
16 36 single-centre small size studies. We therefore designed a multicentre study hypothesizing
17
18 37 that conscious sedation is associated with a better functional outcome 3 months after
19
20 38 endovascular therapy for the treatment of stroke compared with general anaesthesia.
21

22 39
23
24 40 **Methods/analysis:** The GASS trial is a randomised, parallel, single-blind, multicentre study
25
26 41 of 350 patients undergoing endovascular therapy for the treatment of stroke. Patients will be
27
28 42 randomly allocated to receive either a general anaesthesia or a conscious sedation. The
29
30 43 primary outcome measure is the modified Rankin score assessed 3 months after the
31
32 44 treatment. Data will be analysed on the intention-to-treat principle.
33

34 45
35
36 46 **Ethics/dissemination:** The GASS trial has been approved by an independent ethics
37
38 47 committee for all study centres. Participant recruitment begins in September 2016. Results
39
40 48 will be published in international peer-reviewed medical journals.
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43
44 50 **Trial registration number:** The trial is registered at ClinicalTrials.gov (Identifier: NCT
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46 51 02822144)
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3 52 **Strengths and limitations of this study**

- 4
5 53 • GASS trial is the first randomised, parallel, single-blind, multicentre study comparing the
6
7 54 effects of general anaesthesia and conscious sedation during endovascular therapy for
8
9 55 stroke and focused on the functional outcome of the patients 3 months after the
10
11 56 treatment.
- 12
13 57 • The multicentre design, broad inclusion criteria, large sample size (350 patients) and
14
15 58 follow-up will support external validity.
- 16
17 59 • Limitations: The study does not include a systemic CT-scan after the endovascular
18
19 60 treatment. The sizing of the stroke is also not part of the study as it is newly
20
21 61 implemented technology. It was not part of the routine care at the time of the design of
22
23 62 the study.
- 24
25 63

64 INTRODUCTION

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

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

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2
3 92 tested as a secondary endpoint, was better in the GA group. Finally, a meta-analysis
4
5 93 analysing the pooled data of 7 trials (14) reported that worse outcomes at 3 months were
6
7 94 associated with GA. However, the choice to treat a patient with or without GA was not
8
9 95 randomized in the trials included in this meta-analysis (14).

10
11 96 So far, no study has assessed the clinical outcome 3 months after the stroke treatment
12
13 97 comparing GA and CS using standardized anaesthetic protocols and tight haemodynamic
14
15 98 control.

16
17 99 Therefore, we designed a RCT comparing GA and CS during endovascular treatment for
18
19 100 acute stroke. Both GA and CS protocols will be standardized and the control of arterial blood
20
21 101 pressure too. We hypothesized that CS will be associated with a better clinical outcome
22
23 102 measured with the modified Rankin score (mRS) 3 months after the procedure.

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25 103

104 **METHODS AND ANALYSIS**

105 **Trial design**

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

111

112 **Participant eligibility and consent**

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

116

117 Inclusion criteria

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

123 Non-inclusion criteria

- 124 1. Pregnant or breast-feeding women
- 125 2. Patients already intubated and mechanical ventilated before inclusion in the study
- 126 3. Intracerebral haemorrhage associated with the ischemic stroke
- 127 4. Contra-indications to conscious sedation: Glasgow coma scale inferior to 8, agitation
128 not allowing the patient to stay still during the procedure, deglutition disorders
- 129 5. Contra-indications to succinylcholine: hyperkalaemia, allergy
- 130 6. Body mass index superior to 35kg/m²
- 131 7. Contra-indication to general anaesthesia

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3 132 8. Contra-indication to one of the anaesthetic drugs
4
5 133 9. Uncontrolled hypotension,
6
7 134 10. Life-threatening comorbidity
8
9 135 11. Adults legally protected (under judicial protection, guardianship, or supervision),
10
11 136 persons deprived of their liberty
12
13 137

14 138 **Allocation and blinding**

16 139 Patients will be randomised in two groups (general anaesthesia group and conscious
17
18 140 sedation group). Randomisation will be done by investigators as close as possible to the
19
20 141 endovascular therapy. Each patient will be given a unique randomisation number (patient
21
22 142 code). Randomization will be stratified on the centre, the National Institute of Health Stroke
23
24 143 Score (NIHSS \leq or $>$ 14) and the administration or not of IV thrombolysis. The primary
25
26 144 evaluation criterion will be assessed blinded to the randomisation group. During the study
27
28 145 period, outcome assessors will be kept blind to the randomisation group. Research nurses
29
30 146 evaluating the outcomes 3 months after the treatment will not participate to the anaesthesia
31
32 147 and will not be aware of the randomisation group. They will be blind to the treatment. The
33
34 148 anaesthesiologist, the nurse anaesthesiologist, the neuroradiologist and the neurologist will
35
36 149 not be blinded. They will not participate in the assessment of the patients at any time.
37
38 150 At each participating centre, data will be collected and entered into the electronic web-based
39
40 151 case report form (eCRF) by trial or clinical trained personal (clinical research associate),
41
42 152 blinded to the allocation group, under the supervision of the trial site investigators.
43

44 153

46 154 **Interventions**

48 155 All included patients will be allocated to one of the following two study groups:

- 50 156 • **General anaesthesia group:** patients will receive a standardised anaesthesia
51
52 157 protocol with remifentanil
53
54 158 • **Conscious sedation group:** patients will receive a standard conscious sedation with
55
56 159 remifentanil
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4 161 *Standardized general anaesthesia will include:* Induction: Etomidate (0.25 – 0.4 mg/kg) and
5
6 162 succinylcholine (1 mg/kg) and maintenance: TCI propofol (maximum target: 4 microg/ml),
7
8 163 TCI remifentanil (0.5-4 ng/ml) and curares as needed.

9
10 164 *Standardized conscious sedation will include:* TCI remifentanil (maximum target 2 ng/ml),
11
12 165 local anaesthesia with lidocaine 10 mg/ml (maximum 10 ml). Oxygen will be administered
13
14 166 only if $SPO_2 \leq 96\%$. Respiratory rate and capnography will be monitored.

15
16 167 Conscious sedation can be converted into a general anaesthesia in the following situations:

- 17
18 168
- 19 169 • Agitation or restlessness not allowing the endovascular therapy
 - 20 170 • Vomiting not allowing the endovascular therapy
 - 21 171 • Glasgow coma scale < 8 and /or deglutition disorders
 - 22 172 • Severe hypoxemia with $SPO_2 < 96\%$ with oxygen delivered with a high concentration
23 173 mask (10 l/min maximum)
 - 24 174 • Respiratory depression with respiratory rate > 35 /min and/or clinical signs of
25 175 respiratory exhaustion

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31 176 In both groups:

32
33 177 intraoperative dose changes will be left to the anaesthesiologist in charge of the patient if
34
35 178 necessary, IV norepinephrine will be administered in order to maintain blood pressure (BP)
36
37 179 within the recommended range: systolic blood pressure (SBP) between 140 and 185 mmHg;
38
39 180 diastolic blood pressure (DBP) < 110 mmHg. A drop of more than 25% of the mean blood
40
41 181 pressure (MBP) will also be avoided. Norepinephrine will be administered in a dedicated
42
43 182 intravenous line and diluted at 250 microg/ml.

44
45 183 Decisions about all other aspects of patient care will be performed according to the expertise
46
47 184 of the staff at each centre and to routine clinical practice to minimize interference with the
48
49 185 trial intervention. Three months after the thrombectomy, patients will consult with a
50
51 186 neurologist.

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55 188 **Outcome measures**

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3 189 Primary outcome measure

4 190 The primary outcome measure will be the neurological outcome assessed with the modified
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6 191 Rankin score 3 months (15) after the endovascular therapy. Success will be considered as a
7
8 192 modified Rankin score ≤ 2 . The modified Rankin score (mRS) will be assessed by trained
9
10 193 research nurse blinded to the randomisation group.

11
12 194 An additional exploratory analysis of the primary endpoint will be performed to assess
13
14 195 treatments effects according to baseline NIHSS (\leq or $>$ 14) and the administration or not of IV
15
16 196 thrombolysis.
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19
20 198 Secondary outcomes measures

- 21
22 199
- 23 • Time between the beginning of the clinical symptoms and the last angiography
 - 24 200 • Time between the arrival of the patient and the beginning of the endovascular therapy
 - 25 (time of puncture)
 - 26 201
 - 27 • Quality of the recanalization after the endovascular treatment evaluated by the
 - 28 202 neuroradiologist (not blinded). A good quality recanalization corresponds to a 2b or 3
 - 29 203 modified treatment in cerebral ischemia scale (TICI) (16)
 - 30 204
 - 31 • NIHSS score at Day 1 (day after the endovascular treatment) and Day 7 (or the day
 - 32 205 the patient leaves the hospital if scheduled before D7) (17)
 - 33 206
 - 34 207 • Complications during the procedure (dissection, rupture of the artery, thrombus in
 - 35 208 another territory)
 - 36 209
 - 37 • Mortality rate 3 months after the endovascular treatment
 - 38 210
 - 39 • Number of hypo- or hypertension events during the procedure and the first 24 hours
 - 40 211 after the procedure (hypotension defined as SBP $<$ 140 mmHg or a drop of the MBP
 - 41 212 of 40% or more, hypertension defined as SBP $>$ 185 mmHg or DBP $>$ 110 mmHg)
 - 42 213
 - 43 • Number of patients who received norepinephrine
 - 44 214
 - 45 • Number of conversion of conscious sedation to general anaesthesia
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216 **Statistical analysis**

217 Statistical analysis will be performed on all randomized and evaluated patients (intention to
218 treat analysis). It will be performed with SAS software (SAS Institute, Cary, NC, USA) in the
219 Methodology/Biometrics department of the Inserm 1414 Clinical Investigation Centre of
220 Rennes. A first overall descriptive analysis and analysis by group will be performed. This
221 consists of separate estimates, numbers and percentages for qualitative variables, means,
222 standard error, medians and interquartile intervals for quantitative variables. The normal
223 feature of the distribution of quantitative variables will be checked. Student's t test or a Mann-
224 Whitney test if necessary will be used to compare quantitative variables, and a Chi² or
225 Fisher's exact test if necessary will be used to compare qualitative variables between two
226 groups at inclusion. The primary endpoint will be compared between the two groups with the
227 Chi² test. Two interim analyses after inclusion of 1/3 and 2/3 of the patients, and one final
228 analysis are planned. Stopping rules will use the alpha spending function with the O'Brien-
229 Fleming boundary. The cumulative values of alpha for each analysis are: 0.00021 at the first
230 analysis, 0.01202 at the second analysis and 0.04626 at the final analysis (nTerim, V1.1,
231 Statistical solutions Ltd, Cork, Ireland). The trial will be stopped early if the significance of the
232 Chi² test is below these alpha values. For the analysis of the other endpoints, the same
233 strategy as for baseline comparisons will be used. Continuous endpoints repeatedly
234 measured during the study will be compared using a repeated measure two-way (time, group)
235 analysis of variance. For all these analyses, adjustments can be made in case of
236 heterogeneity at inclusion. Except for the interim analyses, a p value <0.05 will be
237 considered as significant for all analyses.

238

239 **Missing values**

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

242

243 **Sample size estimation**

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3 244 A previous study reported 30% of the patients with a mRS score ≤ 2 after endovascular
4 245 therapy under general anaesthesia (18). We aim to show an increase of patients with a good
5 246 prognostic (defined as mRS ≤ 2) up to 45% after endovascular treatment under conscious
6 247 sedation. Therefore, 166 patients per group will be needed to have 80% power, at a two-
7 248 sided alpha level of 0.05. A total of 350 patients will be included to take into account non-
8 249 evaluable patients and drop outs.
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251 **Data Registration**

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18 252 Data will be entered into the web- based electronic case report form (eCRF) by trial or clinical
19 253 personnel under the supervision of the trial site investigators at each participating centre.
20 254 From the eCRF the trial database will be established. Data collection will be monitored by
21 255 trained research coordinators.
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257 The following data will be registered:

258 Baseline characteristics at randomisation:

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

266 Intraoperative data:

267 Time of arterial puncture, time of recanalization, TICl score (16), doses of norepinephrine,
268 intraoperative complications (hypotension defined as SBP < 140 mmHg or a drop of the MBP
269 of 40% or more, hypertension defined as SBP> 185 mmHg or DBP > 110 mmHg) necessity
270 to convert the conscious sedation onto a general anaesthesia.
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3 272 Postoperative data:

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5 273 The following data will be collected:

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7 274 • NIHSS day 1 and Day 7 or the day the patient leaves the hospital if before Day 7
8
9 275 • Necessity of noradrenaline during the first 2 hours after the endovascular treatment
10
11 276 • Hypo-or hypertension events as defined above during first 24 hours
12
13 277 • Death until the final call for mRS (3 months after the procedure)
14
15 278 • mRS 3 months after the procedure during a telephone interview (19).
16

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19 280 **Patient withdrawal**

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21 281 A participant who no longer agrees to participate in the clinical trial can withdraw the
22
23 282 informed consent at any time without need of further explanation. Participants who will
24
25 283 withdraw from the study will be followed up, according to routine clinical practice in each
26
27 284 participating centre. In order to conduct intention-to-treat analyses with as little missing data
28
29 285 as possible, the investigator may ask the participant which aspects of the trial he/she wishes
30
31 286 to withdraw from (participation in the remaining follow-up assessments, use of already
32
33 287 collected data). Whenever possible, the participant will be asked for permission to obtain
34
35 288 data for the primary outcome measure. All randomised patients will be reported, and all data
36
37 289 available with consent will be used in the analyses. If appropriate, missing data will be
38
39 290 handled in accordance with multiple imputation procedures if missing data are greater than
40
41 291 5%.
42

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45 293 **Safety**

46
47 294 Every serious adverse event related to the studied treatment or not, expected or unexpected,
48
49 295 will be reported within 24 hours by the investigator to the sponsor on a "Serious adverse
50
51 296 event" form on which will be indicated the date of occurrence, criterion of severity, intensity,
52
53 297 relationship with the treatment (or the study) evaluated, and the outcome. The period in
54
55 298 which serious adverse events should be reported begins from the day of the written informed
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3 299 consent to the end of the follow-up (day of the evaluation of mRS 3 to 4 months after the
4
5 300 procedure). Whenever a serious adverse event persists at the end of the study, the
6
7 301 investigator will follow the patient until the event is considered resolved. The following events:
8
9 302 hypo- or hypertension will be recorded as study endpoints criterion in the case report form. In
10
11 303 order to avoid collection duplication, they will not be reported on the “adverse event” page of
12
13 304 the case report form. As planned in the study, they will be analysed at the time of interim
14
15 305 analyses (two interim analyses after inclusion of 1/3 and 2/3 of the patients) which will permit
16
17 306 to show potential difference between the two groups during the study.

18
19 307 In addition, serious adverse events will be submitted to the data monitoring and safety
20
21 308 committee (DMSC). The DMSC is independent of the trial investigators and will perform an
22
23 309 ongoing review of safety parameters and overall study conduct. The DMSC is comprised of a
24
25 310 neurologist, an anaesthesiologist, a neuroradiologist, a pharmacologist and a methodologist.
26
27 311 The DMSC will be responsible for safeguarding the interests of trial participants, assessing
28
29 312 the safety and efficacy of the interventions during the trial, and for monitoring the overall
30
31 313 conduct of the clinical trial. To contribute to enhancing the integrity of the trial, the DMSC
32
33 314 may also formulate recommendations relating to the recruitment/retention of participants,
34
35 315 their management, improving adherence to protocol-specified regimens and retention of
36
37 316 participants, and the procedures for data management and quality control.
38
39 317 Recommendations for pausing or stopping the study will be made by the DMSC in case of
40
41 318 serious adverse reactions and suspected unexpected serious adverse reaction.

42
43 319 All adverse events for which the investigator or the sponsor considers that a causal
44
45 320 relationship with the investigational medicinal products can be reasonably considered, will be
46
47 321 considered as suspected adverse reactions. If they are unexpected, they are qualified as
48
49 322 being Suspected Unexpected SAR (SUSAR) and will be notified in a report by the sponsor to
50
51 323 Eudravigilance (European pharmacovigilance database) and to local regulatory agency
52
53 324 within the regulatory time periods for reporting: Immediate declaration if seriousness criteria
54
55 325 is death or life-threatening condition, declaration within 15 days for other seriousness criteria.

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3 327 **Data handling and retention**

4 328 Data will be handled according to French law. All original records (including consent forms,
5
6 329 reports of suspected unexpected serious adverse reactions and relevant correspondences)
7
8 330 will be archived at trial sites for 15 years. The clean trial database file will be anonymised and
9
10 331 maintained for 15 years.

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14 333 **Patient and public involvement**

15
16 334 Patient and public were not involved in any of the phases of this study

17
18 335

19
20 336 **ETHICS AND DISSEMINATION**

21
22 337

23
24 338 **Ethical and legislative approvals**

25
26 339 GASS trial was approved by the French National Safety and Drug Agency (Agence Nationale
27
28 340 de Sécurité du Médicament (September 8th, 2016). By June 13th, 2016, the study has been
29
30 341 approved for all centres by a central ethics committee (Comité de Protection des Personnes
31
32 342 de Poitiers). The GASS trial is registered in the European Clinical Trials Database (EudraCT
33
34 343 2016-000795-25) and at ClinicalTrials.gov with the trial identification number NCT02822144.
35
36 344 Trial methods and results will be reported according to the Consolidated Standards of
37
38 345 Reporting Trials (CONSORT) 2010 guidelines (20).

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42 347 **Publication plan**

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44 348 Scientific presentations and reports corresponding to the study will be written under the
45
46 349 responsibility of the coordinating investigator of the study with the agreement of the principal
47
48 350 investigators and the methodologist. The co-authors of the report and of publications will be
49
50 351 the investigators and clinicians involved, on a pro rata basis of their contribution in the study,
51
52 352 as well as the biostatistician and associated researchers. All trial sites will be acknowledged,
53
54 353 and all investigators at these sites will appear with their names under 'the GASS

1
2
3 354 investigators' in an Appendix to the final manuscript. Rules on publication will follow
4
5 355 international recommendations (21).

6
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8
9 357 **Conclusion**

10 358 The GASS trial is the first randomised, parallel, single-blind, multicentre study evaluating the
11
12 359 effect the type of anaesthesia on the functional outcome 3 months after endovascular
13
14 360 therapy for stroke. The results of GASS will give strong data to help choosing the best type of
15
16 361 sedation during endovascular therapy for stroke.
17

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19 362

20 363 **Contributors:** Axelle Maurice (AM) contributed to the conception and design of the research
21
22 364 protocol and wrote the research protocol. Helene Beloeil (HB) provided critical input
23
24 365 pertaining to the design of the trial interventions and procedures. AM wrote the first draft of
25
26 366 the protocol and HB this manuscript. Bruno Laviolle (BL) designed the study and its statistical
27
28 367 analysis plan. All authors (AM, JCF, TR, JMD, AS, BL, HB) critically revised and modified the
29
30 368 protocol and the article. They all approved the final version to be published.
31

32
33 369

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35
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37
38 372 The funding sources had no role in the trial design, trial conduct, data handling, data analysis
39
40 373 or writing and publication of the manuscript.
41

42
43 374

44 375 **Sponsor:** CHU de Rennes, Direction de la recherché Clinique, 2 avenue Henri Le Guilloux,
45
46 376 35033 Rennes Cedex, France. The sponsor had no role in the trial design, trial conduct, data
47
48 377 handling, data analysis or writing and publication of the manuscript.
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54 380 **Competing interests:** None

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382 **References**

- 383 1- Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, et al. MR
384 CLEAN Investigators. A randomized trial of intra-arterial treatment for acute
385 ischemic stroke. *N Engl J Med*. 2015; 372:11-20.
- 386 2- Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, et al. ESCAPE Trial
387 Investigators. Randomized Assessment of Rapid Endovascular Treatment of
388 Ischemic Stroke. *N Engl J Med*. 2015; 372:1019-30.
- 389 3- Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, and al. EXTEND-IA
390 Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging
391 selection. *N Engl J Med*. 2015; 372:1009-18.
- 392 4- Nogueira RG, Smith WS, Sung G, et al. Effect of time to reperfusion on clinical
393 outcome of anterior circulation strokes treated with thrombectomy: pooled
394 analysis of the MERCI and Multi MERCI trials. *Stroke*. 2011; 42: 3144–9.
- 395 5- Davis MJ, Menon BK, Baghirzada LB, Campos-Herrera CR, Goyal M, Hill MD,
396 Archer DP; Calgary Stroke Program. Aesthetic management and outcome in
397 patients during endovascular therapy for acute stroke. *Anesthesiology*.
398 2012;116:396-405.
- 399 6- Löwhagen Hendén P, Rentzos A, Karlsson JE, Rosengren L, Sundeman H,
400 Reinsfelt B, Ricksten SE. Hypotension During Endovascular Treatment of
401 Ischemic Stroke Is a Risk Factor for Poor Neurological Outcome. *Stroke*. 2015;
402 46:2678-2680.
- 403 7- Whalin MK, Halenda KM, Haussen DC, Rebello LC, Frankel MR, Gershon RY,
404 Nogueira RG. Even Small Decreases in Blood Pressure during Conscious
405 Sedation Affect Clinical Outcome after Stroke Thrombectomy: An Analysis of
406 Hemodynamic Thresholds. *AJNR Am J Neuroradiol*. 2017;38:294-298.
- 407 8- Berkhemer OA, van den Berg LA, Fransen PS, Beumer D, Yoo AJ, Lingsma HF,
408 Schonewille WJ, van den Berg R, Wermer MJ, Boiten J, Lycklama À Nijeholt GJ,
409 Nederkoorn PJ, Hollmann MW, van Zwam WH, van der Lugt A, van
410 Oostenbrugge RJ, Majoie CB, Dippel DW, Roos YB; MR CLEAN investigators.
411 The effect of anaesthetic management during intra-arterial therapy for acute
412 stroke in MR CLEAN. *Neurology*. 2016 ;87:656-64.
- 413 9- Abou-Chebl A, Yeatts SD, Yan B, Cockroft K, Goyal M, Jovin T, Khatri P, Meyers
414 P, Spilker J, Sugg R, Wartenberg KE, Tomsick T, Broderick J, Hill MD. Impact of
415 General Anesthesia on Safety and Outcomes in the Endovascular Arm of
416 interventional Management of Stroke (IMS) III Trial. *Stroke*. 2015;46:2142-8.

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51
52
53
54
55
56
57
58
59
60

- 417 10- Bekelis K, Missios S, MacKenzie TA, Tjoumakaris S, Jabbour P. Anesthesia
418 Technique and Outcomes of Mechanical Thrombectomy in Patients with Acute
419 Ischemic Stroke. *Stroke* 2017 ;48:361-366.
- 420 11- Schönenberger S, Uhlmann L, Hacke W, Schieber S, Mundiyanapurath S,
421 Purruicker JC, Nagel S, Klose C, Pfaff J, Bendszus M, Ringleb PA, Kieser M,
422 Möhlenbruch MA, Bösel J. Effect of Conscious Sedation vs General Anesthesia
423 on Early Neurological Improvement Among Patients with Ischemic Stroke
424 Undergoing Endovascular Thrombectomy: A Randomized Clinical Trial. *JAMA*.
425 2016;316 :1986-1996.
- 426 12- Löwhagen Henden P, Rentzos A, Karlsson JE, Rosengren L, Leiram B, et al.
427 General anaesthesia versus conscious sedation for endovascular treatment of
428 acute ischaemic stroke : the anstroke trial (anaesthesia during stroke). *Stroke*
429 2017 ; 48 : 1601-1607.
- 430 13- Simonsen CZ, Yoo AJ, Sørensen LH, Juul N, Johnsen SP, Andersen G,
431 Rasmussen M. Effect of General Anesthesia and Conscious Sedation During
432 Endovascular Therapy on Infarct Growth and Clinical Outcomes in Acute Ischemic
433 Stroke: A Randomized Clinical Trial *JAMA Neurol*. 2018 ;75(470-477).
- 434 14- Campbell BCV, van Zwam WH, Menon BK, Dippel DWJ, Demchuk AM, Bracad S
435 et al. Effect of general anaesthesia on functional outcome in patients with anterior
436 circulation ischaemic stroke having endovascular thrombectomy versus standard
437 of care: a meta-analysis of individual patient data. *Lancet neurol* 2018; 17:47-53.
- 438 15- Banks JL, Marotta CA. Outcomes Validity and Reliability of the Modified Rankin
439 Scale: Implications for Stroke Clinical Trials. A Literature Review and Synthesis.
440 *Stroke*. 2007; 38:1091-1096.
- 441 16- Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, et al.
442 Cerebral Angiographic Revascularization Grading (CARG) Collaborators; STIR
443 Revascularization working group; STIR Thrombolysis in Cerebral Infarction (TICI)
444 Task Force. Recommendations on angiographic revascularization grading
445 standards for acute ischemic stroke: a consensus statement. *Stroke*.
446 2013 ;44:2650-2663.
- 447 17- Brott T, Adams HP, Olinger CP, Marler JR, Barsan WG, Biller J, SpilkerJ, Holleran
448 R, Eberle R, Hertzberg V, Rorick M, Moomaw CJ, Walker M. Measurements of
449 acute cerebral infarction: a clinical examination scale. *Stroke*. 1989; 20:864–870.
- 450 18- Abou-Chebl A, Lin R, Hussain MS, Jovin TG, Levy EI, Liebeskind DS, et al.
451 Conscious sedation versus general anaesthesia during endovascular therapy for

- 1
2
3 452 acute anterior circulation stroke: preliminary results from a retrospective,
4 453 multicentre study. *Stroke*. 2010; 41:1175-79.
5
6 454 19- Bruno A, Akinwuntan AE, Lin C, Close B, Davis K, Baute V et al. Simplified
7 455 modified rankin scale questionnaire. Reproducibility over the telephone and
8 validation with quality of life. *Stroke* 2011; 42:2276-9.
9 456
10 457 20- Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated
11 guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
12 458
13 459 21- International Committee of Medical Journal E. Uniform requirements for
14 manuscripts submitted to biomedical journals. *The New England journal of*
15 460 *medicine* 1997;336(4):309-15
16 461
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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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024249.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Nov-2018
Complete List of Authors:	Maurice, Axelle; CHU Rennes, Pôle Anesthésie et Réanimation, Inserm, NuMeCan, CIC 1414 and Université de Rennes 1 Ferré, Jean-Christophe; CHU Rennes, Department of Neuroradiology Ronzière, Thomas; CHU Rennes, Department of Neurology Devys, Jean-Michel; Service d'Anesthésie-Réanimation, Fondation Ophtalmologique Adolphe de Rothschild 25, rue Manin, F-75019 Paris, France Subileau, Aurelie; Service d'anesthésie réanimation, CHRU La Cavale Blanche, Boulevard T.Prigent, F-29200 Brest, france Laffon, Marc; Service d'anesthésie réanimation 1 , CHU hôpital Bretonneau, 2 boulevard Tonnellé, F-37044 Tours, France Laviolle, Bruno; CHU Rennes, Clinical Pharmacology department and Inserm CIC 1414, Université de Rennes 1 beloel, helene; CHU Rennes, Pôle Anesthésie et Réanimation, Inserm, NuMeCan, CIC 1414 and Université de Rennes 1,
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Neurology, Radiology and imaging
Keywords:	Stroke < NEUROLOGY, endovascular therapy, Anaesthesia in neurology < ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Neurology < INTERNAL MEDICINE, RADIOLOGY & IMAGING

SCHOLARONE™
Manuscripts

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3 1 **Title:** GASS Trial study protocol: a multicentre, single-blind, randomised clinical trial comparing
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5 2 general anaesthesia and sedation during intra-arterial treatment for stroke.
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9 4 **Authors:** Axelle Maurice¹, Jean-Christophe Ferré², Thomas Ronziere³, Jean-Michel Devys
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11 5 ⁴, Aurelie Subileau⁵, Marc Laffon⁶, Bruno Laviolle⁷, Helene Beloeil¹, on behalf of the SFAR
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3 **29 ABSTRACT**
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5 **30 Introduction:** Treatment of acute stroke has drastically changed in the last 10 years.
6
7 **31** Endovascular therapy is now the standard of care for patients with a stroke caused by a large
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9 **32** vessel occlusion in the anterior circulation. The impact of the type of anaesthesia (general
10
11 **33** anaesthesia or conscious sedation) during endovascular therapy on the outcome of the
12
13 **34** patients is still a matter of debate. Previous studies are mostly retrospective and/or focused on
14
15 **35** the early post-procedure outcome and/or without blood pressure goals and/or single-centre
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17 **36** small size studies. We therefore designed a multicentre study hypothesizing that conscious
18
19 **37** sedation is associated with a better functional outcome 3 months after endovascular therapy
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21 **38** for the treatment of stroke compared with general anaesthesia.
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26 **40 Methods/analysis:** The GASS trial is a randomised, parallel, single-blind, multicentre study of
27
28 **41** 350 patients undergoing endovascular therapy for the treatment of stroke. Patients will be
29
30 **42** randomly allocated to receive either a general anaesthesia or a conscious sedation. The
31
32 **43** primary outcome measure is the modified Rankin score assessed 3 months after the treatment.
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34 **44** Data will be analysed on the intention-to-treat principle.
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39 **46 Ethics/dissemination:** The GASS trial has been approved by an independent ethics
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41 **47** committee for all study centres. Participant recruitment begins in September 2016. Results will
42
43 **48** be published in international peer-reviewed medical journals.
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47 **50 Trial registration number:** The trial is registered at ClinicalTrials.gov (Identifier: NCT
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49 **51** 02822144)
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3 52 **Strengths and limitations of this study**
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- 5 53 • GASS trial is the first randomised, parallel, single-blind, multicentre study comparing the
6 effects of general anaesthesia and conscious sedation during endovascular therapy for
7 54 stroke and focused on the functional outcome of the patients 3 months after the treatment.
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11 56 • The multicentre design, broad inclusion criteria, large sample size (350 patients) and
12 follow-up will support external validity.
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16 58 • Limitations: The study does not include a systemic CT-scan after the endovascular
17 treatment. The sizing of the stroke is also not part of the study as it is newly implemented
18 59 technology. It was not part of the routine care at the time of the design of the study.
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62 INTRODUCTION

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

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

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3 90 was better in the GA group. Finally, a meta-analysis analysing the pooled data of 7 trials (14)
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5 91 reported that worse outcomes at 3 months were associated with GA. However, the choice to
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7 92 treat a patient with or without GA was not randomized in the trials included in this meta-analysis
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9 93 (14).

10
11 94 So far, no study has assessed the clinical outcome 3 months after the stroke treatment
12
13 95 comparing GA and CS using standardized anaesthetic protocols and tight haemodynamic
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15 96 control. Indeed, in previous studies (11,12,13), the anaesthesia protocol was either not
16
17 97 standardized or the doses not given, the blood pressure was controlled with vasoactives drugs
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19 98 as different as dopamine and norepinephrine in the same study and the clinical outcome 3
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21 99 months after the stroke was not the primary objective of one study (13). The recently published
22
23 100 post hoc analysis of the Siesta trial (15) reported no association between haemodynamic
24
25 101 variations and NIHSS change after 24 hours.”

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28 102 Therefore, we designed a RCT comparing GA and CS during endovascular treatment for acute
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30 103 stroke. Both GA and CS protocols will be standardized and the control of arterial blood
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32 104 pressure too. We hypothesized that CS will be associated with a better clinical outcome
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34 105 measured with the modified Rankin score (mRS) 3 months after the procedure. The Gass
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36 106 study is the first multicentric RCT including a detailed anaesthesia protocol with a tight
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38 107 haemodynamic control, comparing GA and CS during EVT and evaluating the functional
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40 108 outcome at 3 months.

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110 **METHODS AND ANALYSIS**

111 **Trial design**

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

117

118 **Participant eligibility and consent**

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

122

123 Inclusion criteria

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

129 Non-inclusion criteria

- 130 1. Pregnant or breast-feeding women
- 131 2. Patients already intubated and mechanical ventilated before inclusion in the study
- 132 3. Intracerebral haemorrhage associated with the ischemic stroke
- 133 4. Contra-indications to conscious sedation: Glasgow coma scale inferior to 8, agitation
134 not allowing the patient to stay still during the procedure, deglutition disorders
- 135 5. Contra-indications to succinylcholine: hyperkalaemia, allergy
- 136 6. Body mass index superior to 35kg/m²
- 137 7. Allergy to one of the anaesthetic drugs

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3 138 8. Uncontrolled hypotension,
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5 139 9. Life-threatening comorbidity
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7 140 10. Adults legally protected (under judicial protection, guardianship, or supervision),
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9 141 persons deprived of their liberty
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11 142

143 **Allocation and blinding**

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

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

158

159 **Interventions**

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

- 161 • **General anaesthesia group:** patients will receive a standardised anaesthesia protocol
162 with remifentanyl
- 163 • **Conscious sedation group:** patients will receive a standard conscious sedation with
164 remifentanyl

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3 166 *Standardized general anaesthesia will include:* Induction: Etomidate (0.25 – 0.4 mg/kg) and
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5 167 succinylcholine (1 mg/kg) and maintenance: TCI propofol (maximum target: 4 microg/ml), TCI
6
7 168 remifentanil (0.5-4 ng/ml) and curares as needed.

9 169 *Standardized conscious sedation will include:* TCI remifentanil (maximum target 2 ng/ml), local
10
11 170 anaesthesia with lidocaine 10 mg/ml (maximum 10 ml). Oxygen will be administered only if
12
13 171 $SPO_2 \leq 96\%$. Respiratory rate and capnography will be monitored.

15 172 Conscious sedation can be converted into a general anaesthesia in the following situations:

- 17 173
- 18 173 • Agitation or restlessness not allowing the endovascular therapy
 - 19 174 • Vomiting not allowing the endovascular therapy
 - 20 174
 - 21 175 • Glasgow coma scale < 8 and /or deglutition disorders
 - 22 175
 - 23 176 • Severe hypoxemia with $SPO_2 < 96\%$ with oxygen delivered with a high concentration
 - 24 177 mask (10 l/min maximum)
 - 25 177
 - 26 178 • Respiratory depression with respiratory rate > 35 /min and/or clinical signs of
 - 27 179 respiratory exhaustion
 - 28 179

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31 181 In both groups:

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33 182 intraoperative dose changes will be left to the anaesthesiologist in charge of the patient if
34
35 183 necessary, IV norepinephrine will be administered in order to maintain blood pressure (BP)
36
37 184 within the recommended range: systolic blood pressure (SBP) between 140 and 185 mmHg;
38
39 185 diastolic blood pressure (DBP) < 110 mmHg. A drop of more than 25% of the mean blood
40
41 186 pressure (MBP) will also be avoided. Norepinephrine will be administered in a dedicated
42
43 187 intravenous line and diluted at 250 microg/ml.

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45 188 A systematic immediate post-EVT Cone-beal CT scan will be performed for all patients

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47 189 Decisions about all other aspects of patient care will be performed according to the expertise
48
49 190 of the staff at each centre and to routine clinical practice to minimize interference with the trial
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51 191 intervention. Three months after the thrombectomy, patients will consult with a neurologist.

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54 193 **Outcome measures**

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56 194 Primary outcome measure

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3 195 The primary outcome measure will be the neurological outcome assessed with the modified
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5 196 Rankin score 3 months (16) after the endovascular therapy. Success will be considered as a
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7 197 modified Rankin score ≤ 2 . The modified Rankin score (mRS) will be assessed by trained
8
9 198 research nurse blinded to the randomisation group.

11 199 An additional exploratory analysis of the primary endpoint will be performed to assess
12
13 200 treatments effects according to baseline NIHSS (\leq or > 14) and the administration or not of IV
14
15 201 thrombolysis.

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20 203 Secondary outcomes measures

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22 204 • Time between the beginning of the clinical symptoms and the last angiography
23
24 205 • Time between the arrival of the patient at the stroke center and the beginning of the
25
26 206 endovascular therapy (time of puncture)
27
28 207 • Quality of the recanalization after the endovascular treatment evaluated by the
29
30 208 neuroradiologist (not blinded). A good quality recanalization corresponds to a 2b or 3
31
32 209 modified treatment in cerebral ischemia scale (mTICI) (17)
33
34 210 • NIHSS score at Day 1 (day after the endovascular treatment) and Day 7 (or the day
35
36 211 the patient leaves the hospital if scheduled before D7) (18)
37
38 212 • Complications during the procedure (dissection, rupture of the artery, thrombus in
39
40 213 another territory)
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42 214 • Mortality rate 3 months after the endovascular treatment
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44 215 • Number of hypo- or hypertension events during the procedure and the first 24 hours
45
46 216 after the procedure (hypotension defined as SBP < 140 mmHg or a drop of the MBP of
47
48 217 40% or more, hypertension defined as SBP > 185 mmHg or DBP > 110 mmHg)
49
50 218 • Number of patients who received norepinephrine
51
52 219 • Number of conversion of conscious sedation to general anaesthesia
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58 221 **Statistical analysis**
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3 222 Statistical analysis will be performed on all randomized and evaluated patients (intention to
4
5 223 treat analysis). It will be performed with SAS software (SAS Institute, Cary, NC, USA) in the
6
7 224 Methodology/Biometrics department of the Inserm 1414 Clinical Investigation Centre of
8
9 225 Rennes. A first overall descriptive analysis and analysis by group will be performed. This
10
11 226 consists of separate estimates, numbers and percentages for qualitative variables, means,
12
13 227 standard error, medians and interquartile intervals for quantitative variables. The normal
14
15 228 feature of the distribution of quantitative variables will be checked. Student's t test or a Mann-
16
17 229 Whitney test if necessary will be used to compare quantitative variables, and a Chi² or Fisher's
18
19 230 exact test if necessary will be used to compare qualitative variables between two groups at
20
21 231 inclusion. The primary endpoint will be compared between the two groups with the Chi² test.
22
23 232 Two interim analyses after inclusion of 1/3 and 2/3 of the patients, and one final analysis are
24
25 233 planned. Stopping rules will use the alpha spending function with the O'Brien-Fleming
26
27 234 boundary. The cumulative values of alpha for each analysis are: 0.00021 at the first analysis,
28
29 235 0.01202 at the second analysis and 0.04626 at the final analysis (nTerim, V1.1, Statistical
30
31 236 solutions Ltd, Cork, Ireland). The trial will be stopped early if the significance of the Chi² test is
32
33 237 below these alpha values. For the analysis of the other endpoints, the same strategy as for
34
35 238 baseline comparisons will be used. Continuous endpoints repeatedly measured during the
36
37 239 study will be compared using a repeated measure two-way (time, group) analysis of variance.
38
39 240 For all these analyses, adjustments can be made in case of heterogeneity at inclusion. Except
40
41 241 for the interim analyses, a p value <0.05 will be considered as significant for all analyses.
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243 **Missing values**

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

246

247 **Sample size estimation**

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

1
2
3 250 (defined as mRS \leq 2) up to 45% after endovascular treatment under conscious sedation.
4
5 251 Therefore, 166 patients per group will be needed to have 80% power, at a two-sided alpha
6
7 252 level of 0.05. A total of 350 patients will be included to take into account non-evaluable patients
8
9 253 and drop outs.
10

11 254

13 255 **Data Registration**

15 256 Data will be entered into the web- based electronic case report form (eCRF) by trial or clinical
16
17 257 personnel under the supervision of the trial site investigators at each participating centre. From
18
19 258 the eCRF the trial database will be established. Data collection will be monitored by trained
20
21 259 research coordinators.
22

23 260

24
25
26 261 The following data will be registered:

27 262 Baseline characteristics at randomisation:

28
29
30 263 Demographic data (age, height, weight, gender and body mass index); American Society of
31
32 264 Anaesthesiologists (ASA) physical status; significant comorbidities (cardio-vascular,
33
34 265 respiratory, neurologic , psychiatric and /or abdominal disease, cancer, preoperative
35
36 266 chemotherapy or radiotherapy), NIHSS score, time of arrival at the hospital, time of the
37
38 267 beginning of the symptoms, time of the cerebral angiography or MRI (meaning time of first
39
40 268 image for diagnosis) , time between the first contact of the patient with the anaesthesiologist
41
42 269 and the induction of anaesthesia (GA or CS),localisation of the stroke, IV fibrinolysis if
43
44 270 applicable, creatinine clearance, haemostasis (PT and ACT if available).
45

46 271 Intraoperative data:

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49 272 Time of arterial puncture, time of recanalization, mTICI score (16), doses of norepinephrine,
50
51 273 intraoperative complications (hypotension defined as SBP < 140 mmHg or a drop of the MBP
52
53 274 of 40% or more, hypertension defined as SBP> 185 mmHg or DBP > 110 mmHg) necessity to
54
55 275 convert the conscious sedation onto a general anaesthesia, duration of anaesthesia and
56
57 276 procedure, procedure related complications (distal embolization in a different territory,
58
59 277 intramural arterial dissection, arterial perforation, access-site complications leading to surgery).
60

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5 279 Postoperative data:
6

7 280 The following data will be collected:
8

- 9 281 • NIHSS day 1 and Day 7 or the day the patient leaves the hospital if before Day 7
- 10 282 • Necessity of noradrenaline during the first 2 hours after the endovascular treatment
- 11 283 • Hypo-or hypertension events as defined above during first 24 hours
- 12 284 • Bradycardie with atropine treatment during first 24 hours
- 13 285 • Hospitalization in intensive care unit
- 14 286 • Number of hours of invasive ventilation
- 15 287 • Pneumonia
- 16 288 • Death until the final call for mRS (3 months after the procedure)
- 17 289 • mRS 3 months after the procedure during a telephone interview (20).
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31 291 **Patient withdrawal**
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33 292 A participant who no longer agrees to participate in the clinical trial can withdraw the informed
34 293 consent at any time without need of further explanation. Participants who will withdraw from
35 294 the study will be followed up, according to routine clinical practice in each participating centre.
36 295 In order to conduct intention-to-treat analyses with as little missing data as possible, the
37 296 investigator may ask the participant which aspects of the trial he/she wishes to withdraw from
38 297 (participation in the remaining follow-up assessments, use of already collected data).
39 298 Whenever possible, the participant will be asked for permission to obtain data for the primary
40 299 outcome measure. All randomised patients will be reported, and all data available with consent
41 300 will be used in the analyses. If appropriate, missing data will be handled in accordance with
42 301 multiple imputation procedures if missing data are greater than 5%.
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56 303 **Safety**
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58 304 Every serious adverse event related to the studied treatment or not, expected or unexpected,
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3 305 will be reported within 24 hours by the investigator to the sponsor on a "Serious adverse event"
4
5 306 form on which will be indicated the date of occurrence, criterion of severity, intensity,
6
7 307 relationship with the treatment (or the study) evaluated, and the outcome. The period in which
8
9 308 serious adverse events should be reported begins from the day of the written informed consent
10
11 309 to the end of the follow-up (day of the evaluation of mRS 3 to 4 months after the procedure).
12
13 310 Whenever a serious adverse event persists at the end of the study, the investigator will follow
14
15 311 the patient until the event is considered resolved. The following events: hypo- or hypertension
16
17 312 will be recorded as study endpoints criterion in the case report form. In order to avoid collection
18
19 313 duplication, they will not be reported on the "adverse event" page of the case report form. As
20
21 314 planned in the study, they will be analysed at the time of interim analyses (two interim analyses
22
23 315 after inclusion of 1/3 and 2/3 of the patients) which will permit to show potential difference
24
25 316 between the two groups during the study.
26
27 317 In addition, serious adverse events will be submitted to the data monitoring and safety
28
29 318 committee (DMSC). The DMSC is independent of the trial investigators and will perform an
30
31 319 ongoing review of safety parameters and overall study conduct. The DMSC is comprised of a
32
33 320 neurologist, an anaesthesiologist, a neuroradiologist, a pharmacologist and a methodologist.
34
35 321 The DMSC will be responsible for safeguarding the interests of trial participants, assessing the
36
37 322 safety and efficacy of the interventions during the trial, and for monitoring the overall conduct
38
39 323 of the clinical trial. To contribute to enhancing the integrity of the trial, the DMSC may also
40
41 324 formulate recommendations relating to the recruitment/retention of participants, their
42
43 325 management, improving adherence to protocol-specified regimens and retention of
44
45 326 participants, and the procedures for data management and quality control. Recommendations
46
47 327 for pausing or stopping the study will be made by the DMSC in case of serious adverse
48
49 328 reactions and suspected unexpected serious adverse reaction.
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51 329 All adverse events for which the investigator or the sponsor considers that a causal relationship
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53 330 with the investigational medicinal products can be reasonably considered, will be considered
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55 331 as suspected adverse reactions. If they are unexpected, they are qualified as being Suspected
56
57 332 Unexpected SAR (SUSAR) and will be notified in a report by the sponsor to Eudravigilance
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3 333 (European pharmacovigilance database) and to local regulatory agency within the regulatory
4
5 334 time periods for reporting: Immediate declaration if seriousness criteria is death or life-
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7 335 threatening condition, declaration within 15 days for other seriousness criteria.
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11 337 **Data handling and retention**

13 338 Data will be handled according to French law. All original records (including consent forms,
14
15 339 reports of suspected unexpected serious adverse reactions and relevant correspondences)
16
17 340 will be archived at trial sites for 15 years. The clean trial database file will be anonymised and
18
19 341 maintained for 15 years.
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24 343 **Patient and public involvement**

26 344 Patient and public were not involved in any of the phases of this study
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28 345

30 346 **ETHICS AND DISSEMINATION**

31 347

34 348 **Ethical and legislative approvals**

36 349 GASS trial was approved by the French National Safety and Drug Agency (Agence Nationale
37
38 de Sécurité du Médicament (September 8th, 2016). By June 13th, 2016, the study has been
39 350 approved for all centres by a central ethics committee (Comité de Protection des Personnes
40
41 351 de Poitiers). The GASS trial is registered in the European Clinical Trials Database (EudraCT
42
43 352 2016-000795-25) and at ClinicalTrials.gov with the trial identification number NCT02822144.
44
45 353 Trial methods and results will be reported according to the Consolidated Standards of
46
47 354 Reporting Trials (CONSORT) 2010 guidelines (21).
48
49 355

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53 357 **Publication plan**

55 358 Scientific presentations and reports corresponding to the study will be written under the
56
57 359 responsibility of the coordinating investigator of the study with the agreement of the principal
58
59 360 investigators and the methodologist. The co-authors of the report and of publications will be

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2
3 361 the investigators and clinicians involved, on a pro rata basis of their contribution in the study,
4
5 362 as well as the biostatistician and associated researchers. All trial sites will be acknowledged,
6
7 363 and all investigators at these sites will appear with their names under ‘the GASS investigators’
8
9 364 in an Appendix to the final manuscript. Rules on publication will follow international
10
11 365 recommendations (22).

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18 368 **Contributors:** Axelle Maurice (AM) contributed to the conception and design of the research
19
20 369 protocol and wrote the research protocol. Helene Beloeil (HB) provided critical input pertaining
21
22 370 to the design of the trial interventions and procedures. AM wrote the first draft of the protocol
23
24 371 and HB this manuscript. Bruno Laviolle (BL) designed the study and its statistical analysis plan.
25
26 372 All authors (AM, JCF, TR, JMD, AS, BL, HB) critically revised and modified the protocol and
27
28 373 the article. They all approved the final version to be published.

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30 374

31
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33
34 376 Hospitalier de Recherché Clinique Inter regional (PHRCI 2015).

35
36 377 The funding sources had no role in the trial design, trial conduct, data handling, data analysis
37
38 378 or writing and publication of the manuscript.

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40 379

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43 380 **Sponsor:** CHU de Rennes, Direction de la recherché Clinique, 2 avenue Henri Le Guilloux,
44
45 381 35033 Rennes Cedex, France. The sponsor had no role in the trial design, trial conduct, data
46
47 382 handling, data analysis or writing and publication of the manuscript.

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53 385 **Competing interests:** None

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57 387 **References**

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- 1- Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, et al. MR CLEAN Investigators. A randomized trial of intra-arterial treatment for acute ischemic stroke. *N Engl J Med*. 2015; 372:11-20.
- 2- Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, et al. ESCAPE Trial Investigators. Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke. *N Engl J Med*. 2015; 372:1019-30.
- 3- Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, and al. EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015; 372:1009-18.
- 4- Nogueira RG, Smith WS, Sung G, et al. Effect of time to reperfusion on clinical outcome of anterior circulation strokes treated with thrombectomy: pooled analysis of the MERCI and Multi MERCI trials. *Stroke*. 2011; 42: 3144–9.
- 5- Davis MJ, Menon BK, Baghirzada LB, Campos-Herrera CR, Goyal M, Hill MD, Archer DP; Calgary Stroke Program. Aesthetic management and outcome in patients during endovascular therapy for acute stroke. *Anesthesiology*. 2012;116:396-405.
- 6- Löwhagen Hendén P, Rentzos A, Karlsson JE, Rosengren L, Sundeman H, Reinsfelt B, Ricksten SE. Hypotension During Endovascular Treatment of Ischemic Stroke Is a Risk Factor for Poor Neurological Outcome. *Stroke*. 2015; 46:2678-2680.
- 7- Whalin MK, Halenda KM, Hauszen DC, Rebello LC, Frankel MR, Gershon RY, Nogueira RG. Even Small Decreases in Blood Pressure during Conscious Sedation Affect Clinical Outcome after Stroke Thrombectomy: An Analysis of Hemodynamic Thresholds. *AJNR Am J Neuroradiol*. 2017;38:294-298.
- 8- Berkhemer OA, van den Berg LA, Fransen PS, Beumer D, Yoo AJ, Lingsma HF, Schonewille WJ, van den Berg R, Wermer MJ, Boiten J, Lycklama À Nijeholt GJ, Nederkoorn PJ, Hollmann MW, van Zwam WH, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW, Roos YB; MR CLEAN investigators. The effect of anaesthetic management during intra-arterial therapy for acute stroke in MR CLEAN. *Neurology*. 2016 ;87:656-64.
- 9- Abou-Chebl A, Yeatts SD, Yan B, Cockroft K, Goyal M, Jovin T, Khatri P, Meyers P, Spilker J, Sugg R, Wartenberg KE, Tomsick T, Broderick J, Hill MD. Impact of General Anesthesia on Safety and Outcomes in the Endovascular Arm of interventional Management of Stroke (IMS) III Trial. *Stroke*. 2015;46:2142-8.
- 10- Bekelis K, Missios S, MacKenzie TA, Tjoumakaris S, Jabbour P. Anesthesia Technique and Outcomes of Mechanical Thrombectomy in Patients with Acute Ischemic Stroke. *Stroke* 2017 ;48:361-366.

- 1
2
3 424 11- Schönenberger S, Uhlmann L, Hacke W, Schieber S, Mundiyanapurath S,
4 425 Purrucker JC, Nagel S, Klose C, Pfaff J, Bendszus M, Ringleb PA, Kieser M,
5 426 Möhlenbruch MA, Bösel J. Effect of Conscious Sedation vs General Anesthesia on
6 427 Early Neurological Improvement Among Patients with Ischemic Stroke Undergoing
7 428 Endovascular Thrombectomy: A Randomized Clinical Trial. JAMA.
8 429 2016;316 :1986-1996.
- 12 430 12- Löwhagen Henden P, Rentzos A, Karlsson JE, Rosengren L, Leiram B, et al.
13 431 General anaesthesia versus conscious sedation for endovascular treatment of
14 432 acute ischaemic stroke : the anstroke trial (anaesthesia during stroke). Stroke 2017 ;
15 433 48 : 1601-1607.
- 19 434 13- Simonsen CZ, Yoo AJ, Sørensen LH, Juul N, Johnsen SP, Andersen G,
20 435 Rasmussen M. Effect of General Anesthesia and Conscious Sedation During
21 436 Endovascular Therapy on Infarct Growth and Clinical Outcomes in Acute Ischemic
22 437 Stroke: A Randomized Clinical Trial JAMA Neurol. 2018 ;75(470-477).
- 25 438 14- Campbell BCV, van Zwam WH, Menon BK, Dippel DWJ, Demchuk AM, Bracad S
26 439 et al. Effect of general anaesthesia on functional outcome in patients with anterior
27 440 circulation ischaemic stroke having endovascular thrombectomy versus standard
28 441 of care: a meta-analysis of individual patient data. Lancet neurol 2018; 17:47-53.
- 32 442 15- Schönenberger S, Uhlmann L, Ungerer M, Pfaff J, Nagel S, Kose C, et al.
33 443 Association of blood pressure with short-and long-term functional outcome after
34 444 stroke thrombectomy: post hoc analysis of the siest trial. Stroke 2018; 49: 1451-
35 445 1456.
- 38 446 16- Banks JL, Marotta CA. Outcomes Validity and Reliability of the Modified Rankin
39 447 Scale: Implications for Stroke Clinical Trials. A Literature Review and Synthesis.
40 448 Stroke. 2007; 38:1091-1096.
- 43 449 17- Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, et al. Cerebral
44 450 Angiographic Revascularization Grading (CARG) Collaborators; STIR
45 451 Revascularization working group; STIR Thrombolysis in Cerebral Infarction (TICI)
46 452 Task Force. Recommendations on angiographic revascularization grading
47 453 standards for acute ischemic stroke: a consensus statement. Stroke.
48 454 2013 ;44:2650-2663.
- 52 455 18- Brott T, Adams HP, Olinger CP, Marler JR, Barsan WG, Biller J, SpilkerJ, Holleran
53 456 R, Eberle R, Hertzberg V, Rorick M, Moomaw CJ, Walker M. Measurements of
54 457 acute cerebral infarction: a clinical examination scale. Stroke. 1989; 20:864–870.
- 57 458 19- Abou-Chebl A, Lin R, Hussain MS, Jovin TG, Levy EI, Liebeskind DS, et al.
58 459 Conscious sedation versus general anaesthesia during endovascular therapy for
59 459
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2
3 460 acute anterior circulation stroke: preliminary results from a retrospective,
4 461 multicentre study. Stroke. 2010; 41:1175-79.
5
6 462 20- Bruno A, Akinwuntan AE, Lin C, Close B, Davis K, Baute V et al. Simplified modified
7
8 463 rankin scale questionnaire. Reproducibility over the telephone and validation with
9
10 464 quality of life. Stroke 2011; 42:2276-9.
11 465 21- Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated
12
13 466 guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
14 467 22- International Committee of Medical Journal E. Uniform requirements for
15
16 468 manuscripts submitted to biomedical journals. The New England journal of
17
18 469 medicine 1997;336(4):309-15
19
20
21
22
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24
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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.



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

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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:

1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions page 7
8			
9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned page 7
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions page 7
17			
18			
19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how page 7
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial
26			
27			

Methods: Data collection, management, and analysis

28			
29			
30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol page 11-12
36			
37			
38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols page 11-12
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44			range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol page 14
46			
47			
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods		Reference to where other details of the statistical analysis plan can be
50			found, if not in the protocol page 10
51			
52		20b	Methods for any additional analyses (eg, subgroup and adjusted
53			analyses) page 10
54			
55		20c	Definition of analysis population relating to protocol non-adherence
56			(eg, as randomised analysis), and any statistical methods to handle
57			missing data (eg, multiple imputation) page 10
58			
59			
60			

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

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| 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 |

16 Appendices

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- | | | |
|-------------------------------|----|--|
| 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 |

25 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
26 Explanation & Elaboration for important clarification on the items. Amendments to the
27 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
28 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)"
29 license.
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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024249.R2
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Date Submitted by the Author:	08-Feb-2019
Complete List of Authors:	Maurice, Axelle; CHU Rennes, Pôle Anesthésie et Réanimation, Inserm, NuMeCan, CIC 1414 and Université de Rennes 1 Ferré, Jean-Christophe; CHU Rennes, Department of Neuroradiology Ronzière, Thomas; CHU Rennes, Department of Neurology Devys, Jean-Michel; Service d'Anesthésie-Réanimation, Fondation Ophtalmologique Adolphe de Rothschild 25, rue Manin, F-75019 Paris, France Subileau, Aurelie; Service d'anesthésie réanimation, CHRU La Cavale Blanche, Boulevard T.Prigent, F-29200 Brest, france Laffon, Marc; Service d'anesthésie réanimation 1 , CHU hôpital Bretonneau, 2 boulevard Tonnellé, F-37044 Tours, France Laviolle, Bruno; CHU Rennes, Clinical Pharmacology department and Inserm CIC 1414, Université de Rennes 1 beloel, helene; CHU Rennes, Pôle Anesthésie et Réanimation, Inserm, NuMeCan, CIC 1414 and Université de Rennes 1,
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Neurology, Radiology and imaging
Keywords:	Stroke < NEUROLOGY, endovascular therapy, Anaesthesia in neurology < ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Neurology < INTERNAL MEDICINE, RADIOLOGY & IMAGING

SCHOLARONE™
Manuscripts

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3 1 **Title:** GASS Trial study protocol: a multicentre, single-blind, randomised clinical trial comparing
4
5 2 general anaesthesia and sedation during intra-arterial treatment for stroke.
6
7 3

8
9 4 **Authors:** Axelle Maurice¹, Jean-Christophe Ferré², Thomas Ronziere³, Jean-Michel Devys
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11 5 ⁴, Aurelie Subileau⁵, Marc Laffon⁶, Bruno Laviolle⁷, Helene Beloeil¹, on behalf of the SFAR
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13 6 research network
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2
3 **29 ABSTRACT**
4

5 **30 Introduction:** Treatment of acute stroke has drastically changed in the last 10 years.
6
7 **31** Endovascular therapy is now the standard of care for patients with a stroke caused by a large
8
9 **32** vessel occlusion in the anterior circulation. The impact of the type of anaesthesia (general
10
11 **33** anaesthesia or conscious sedation) during endovascular therapy on the outcome of the
12
13 **34** patients is still a matter of debate. Previous studies are mostly retrospective and/or focused on
14
15 **35** the early post-procedure outcome and/or without blood pressure goals and/or single-centre
16
17 **36** small size studies. We therefore designed a multicentre study hypothesizing that conscious
18
19 **37** sedation is associated with a better functional outcome 3 months after endovascular therapy
20
21 **38** for the treatment of stroke compared with general anaesthesia.
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25
26 **40 Methods/analysis:** The GASS trial is a randomised, parallel, single-blind, multicentre study of
27
28 **41** 350 patients undergoing endovascular therapy for the treatment of stroke. Patients will be
29
30 **42** randomly allocated to receive either a general anaesthesia or a conscious sedation. The
31
32 **43** primary outcome measure is the modified Rankin score assessed 3 months after the treatment.
33
34 **44** Data will be analysed on the intention-to-treat principle.
35
36

37 **45**
38
39 **46 Ethics/dissemination:** The GASS trial has been approved by an independent ethics
40
41 **47** committee for all study centres. Participant recruitment begins in September 2016. Results will
42
43 **48** be published in international peer-reviewed medical journals.
44
45

46
47 **50 Trial registration number:** The trial is registered at ClinicalTrials.gov (Identifier: NCT
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49 **51** 02822144)
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3 52 **Strengths and limitations of this study**
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- 5 53 • GASS trial is a randomised, parallel, single-blind, multicentre study comparing the effects
6
7 54 of general anaesthesia and conscious sedation during endovascular therapy for stroke.
8
9 55 • GASS trial is focused on the functional outcome of the patients 3 months after the
10
11 56 treatment.
12
13 57 • The multicentre design, broad inclusion criteria, large sample size (350 patients) and
14
15 58 follow-up will support external validity.
16
17 59 • The study does not include a systemic CT-scan after the endovascular treatment.
18
19 60 • The sizing of the stroke is also not part of the study as it is newly implemented technology.
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62 INTRODUCTION

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

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

1
2
3 90 was better in the GA group. Finally, a meta-analysis analysing the pooled data of 7 trials (14)
4
5 91 reported that worse outcomes at 3 months were associated with GA. However, the choice to
6
7 92 treat a patient with or without GA was not randomized in the trials included in this meta-analysis
8
9 93 (14).

10
11 94 So far, few studies has assessed the clinical outcome 3 months after the stroke treatment
12
13 95 comparing GA and CS using standardized anaesthetic protocols and tight haemodynamic
14
15 96 control. Indeed, in previous studies (11,12,13), the anaesthesia protocol was either not
16
17 97 standardized or the doses not given, the blood pressure was controlled with vasoactives drugs
18
19 98 as different as dopamine and norepinephrine in the same study and the clinical outcome 3
20
21 99 months after the stroke was not the primary objective of one study (13). The recently published
22
23 100 post hoc analysis of the Siesta trial (15) and the GOLIATH trial (16) reported no association
24
25 101 between heamodynamic variations and NIHSS change after 24 hours.”

26
27 102 Therefore, we designed a RCT comparing GA and CS during endovascular treatment for acute
28
29 103 stroke. Both GA and CS protocols will be standardized and the control of arterial blood
30
31 104 pressure too. We hypothesized that CS will be associated with a better clinical outcome
32
33 105 measured with the modified Rankin score (mRS) 3 months after the procedure. The Gass
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35 106 study is the first multicentric RCT including a detailed anaesthesia protocol with a tight
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37 107 haemodynamic control, comparing GA and CS during EVT and evaluating the functional
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39 108 outcome at 3 months.

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110 **METHODS AND ANALYSIS**

111 **Trial design**

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

118 **Participant eligibility and consent**

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

123 Inclusion criteria

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

129 Non-inclusion criteria

- 130 1. Pregnant or breast-feeding women
- 131 2. Patients already intubated and mechanical ventilated before inclusion in the study
- 132 3. Intracerebral haemorrhage associated with the ischemic stroke
- 133 4. Contra-indications to conscious sedation: Glasgow coma scale inferior to 8, agitation
134 not allowing the patient to stay still during the procedure, deglutition disorders
- 135 5. Contra-indications to succinylcholine: hyperkalaemia, allergy
- 136 6. Body mass index superior to 35kg/m²
- 137 7. Allergy to one of the anaesthetic drugs

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3 138 8. Uncontrolled hypotension,
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5 139 9. Life-threatening comorbidity
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7 140 10. Adults legally protected (under judicial protection, guardianship, or supervision),
8
9 141 persons deprived of their liberty
10
11 142 11. patients who could not walk prior stroke
12
13 143

144 **Allocation and blinding**

145 Patients will be randomised in two groups (general anaesthesia group and conscious sedation
146 group). Randomisation will be done by investigators as close as possible to the endovascular
147 therapy. Each patient will be given a unique randomisation number (patient code).
148 Randomization will be stratified on the centre, the National Institute of Health Stroke Score
149 (NIHSS \leq or $>$ 14) and the administration or not of IV thrombolysis. The primary evaluation
150 criterion will be assessed blinded to the randomisation group. During the study period, outcome
151 assessors will be kept blind to the randomisation group. Research nurses evaluating the
152 outcomes 3 months after the treatment will not participate to the anaesthesia and will not be
153 aware of the randomisation group. They will be blind to the treatment. The anaesthesiologist,
154 the nurse anaesthesiologist, the neuroradiologist and the neurologist will not be blinded. They
155 will not participate in the assessment of the patients at any time.
156 At each participating centre, data will be collected and entered into the electronic web-based
157 case report form (eCRF) by trial or clinical trained personal (clinical research associate),
158 blinded to the allocation group, under the supervision of the trial site investigators.

159

160 **Interventions**

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

- 162 • **General anaesthesia group:** patients will receive a standardised anaesthesia protocol
163 with remifentanyl
- 164 • **Conscious sedation group:** patients will receive a standard conscious sedation with
165 remifentanyl

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5 167 *Standardized general anaesthesia will include:* Induction: Etomidate (0.25 – 0.4 mg/kg) and
6
7 168 succinylcholine (1 mg/kg) and maintenance: TCI propofol (maximum target: 4 microg/ml), TCI
8
9 169 remifentanil (0.5-4 ng/ml) and curares as needed.

10
11 170 *Standardized conscious sedation will include:* TCI remifentanil (maximum target 2 ng/ml), local
12
13 171 anaesthesia with lidocaine 10 mg/ml (maximum 10 ml). Oxygen will be administered only if
14
15 172 $SPO_2 \leq 96\%$. Respiratory rate and capnography will be monitored.

16
17
18 173 Conscious sedation can be converted into a general anaesthesia in the following situations:

- 19
20 174
- 21 175 • Agitation or restlessness not allowing the endovascular therapy
 - 22 176 • Vomiting not allowing the endovascular therapy
 - 23 177 • Glasgow coma scale < 8 and /or deglutition disorders
 - 24 178 • Severe hypoxemia with $SPO_2 < 96\%$ with oxygen delivered with a high concentration
25 179 mask (10 l/min maximum)
 - 26 178 • Respiratory depression with respiratory rate > 35 /min and/or clinical signs of
27 179 respiratory exhaustion
- 28 179
29 180
30 181

31 181
32
33 182 In both groups:

34
35 183 intraoperative dose changes will be left to the anaesthesiologist in charge of the patient if
36
37 184 necessary, IV norepinephrine will be administered in order to maintain blood pressure (BP)
38
39 185 within the recommended range: systolic blood pressure (SBP) between 140 and 185 mmHg;
40
41 186 diastolic blood pressure (DBP) < 110 mmHg. A drop of more than 25% of the mean blood
42
43 187 pressure (MBP) will also be avoided. Blood pressure will be continuously non invasively
44
45 188 monitored. Norepinephrine will be administered in a dedicated intravenous line and diluted at
46
47 189 250 microg/ml. Hyperglycemia will be treated with IV insuline when necessary (target 11
48
49 190 mmol/L).

50
51
52 191 A systematic immediate post-EVT Cone-beal CT scan will be performed for all patients.

53
54 192 Decisions about all other aspects of patient care will be performed according to the expertise
55
56 193 of the staff at each centre and to routine clinical practice to minimize interference with the trial
57
58 194 intervention. Postoperative blood pressure targets are defined as follows: SBP < 180 mmHg

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2
3 195 DBP < 110 mmHg and MBP > 65 mmHg. In case of TICI 2a or lower, the objective is MBP >
4
5 196 75 mmHg. Norepinephrine will be used if necessary. Three months after the thrombectomy,
6
7 197 patients will consult with a neurologist.
8

9 198

11 199 **Outcome measures**

13 200 Primary outcome measure

15 201 The primary outcome measure will be the neurological outcome assessed with the modified
16
17 202 Rankin score 3 months (17) after the endovascular therapy. Success will be considered as a
18
19 203 modified Rankin score ≤ 2 . The modified Rankin score (mRS) will be assessed by trained
20
21 204 research nurse blinded to the randomisation group.
22
23

24 205 An additional exploratory analysis of the primary endpoint will be performed to assess
25
26 206 treatments effects according to baseline NIHSS (\leq or $>$ 14) and the administration or not of IV
27
28 207 thrombolysis.
29

30 208

32 209 Secondary outcomes measures

- 34 210 • Time between the beginning of the clinical symptoms and the last angiography
- 35
36 211 • Time between the arrival of the patient at the stroke center and the beginning of the
37
38 212 endovascular therapy (time of puncture)
- 39
40 213 • Quality of the recanalization after the endovascular treatment evaluated by the
41
42 214 neuroradiologist (not blinded). A good quality recanalization corresponds to a 2b or 3
43
44 215 modified treatment in cerebral ischemia scale (mTICI) (18)
- 45
46 216 • NIHSS score at Day 1 (day after the endovascular treatment) and Day 7 (or the day
47
48 217 the patient leaves the hospital if scheduled before D7) (19)
- 49
50 218 • Complications during the procedure (dissection, rupture of the artery, thrombus in
51
52 219 another territory)
- 53
54 220 • Mortality rate 3 months after the endovascular treatment
- 55
56 221 • Number of hypo- or hypertension events during the procedure and the first 24 hours
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3 222 after the procedure (hypotension defined as SBP < 140 mmHg or a drop of the MBP of
4
5 223 40% or more, hypertension defined as SBP > 185 mmHg or DBP > 110 mmHg)

- 6
7 224
- Number of patients who received norepinephrine
- 8
9 225
- Number of conversion of conscious sedation to general anaesthesia
- 10
11 226

12 227 **Statistical analysis**

13
14
15 228 Statistical analysis will be performed on all randomized and evaluated patients (intention to
16
17 229 treat analysis). It will be performed with SAS software (SAS Institute, Cary, NC, USA) in the
18
19 230 Methodology/Biometrics department of the Inserm 1414 Clinical Investigation Centre of
20
21 231 Rennes. A first overall descriptive analysis and analysis by group will be performed. This
22
23 232 consists of separate estimates, numbers and percentages for qualitative variables, means,
24
25 233 standard error, medians and interquartile intervals for quantitative variables. The normal
26
27 234 feature of the distribution of quantitative variables will be checked. Student's t test or a Mann-
28
29 235 Whitney test if necessary will be used to compare quantitative variables, and a Chi² or Fisher's
30
31 236 exact test if necessary will be used to compare qualitative variables between two groups at
32
33 237 inclusion. The primary endpoint will be compared between the two groups with the Chi² test.
34
35 238 Two interim analyses after inclusion of 1/3 and 2/3 of the patients, and one final analysis are
36
37 239 planned. Stopping rules will use the alpha spending function with the O'Brien-Fleming
38
39 240 boundary. The cumulative values of alpha for each analysis are: 0.00021 at the first analysis,
40
41 241 0.01202 at the second analysis and 0.04626 at the final analysis (nTerim, V1.1, Statistical
42
43 242 solutions Ltd, Cork, Ireland). The trial will be stopped early if the significance of the Chi² test is
44
45 243 below these alpha values. For the analysis of the other endpoints, the same strategy as for
46
47 244 baseline comparisons will be used. Continuous endpoints repeatedly measured during the
48
49 245 study will be compared using a repeated measure two-way (time, group) analysis of variance.
50
51 246 For all these analyses, adjustments can be made in case of heterogeneity at inclusion. Except
52
53 247 for the interim analyses, a p value <0.05 will be considered as significant for all analyses.
54
55 248

56 249 **Missing values**

1
2
3 250 Missing data will not be replaced. Mixed models can be used in analysis of repeated data to
4
5 251 avoid deleting subjects with any missing values.
6

7 252

8
9 253 **Sample size estimation**

10
11 254 A previous study reported 30% of the patients with a mRS score ≤ 2 after endovascular therapy
12
13 255 under general anaesthesia (20). We aim to show an increase of patients with a good prognostic
14
15 256 (defined as mRS ≤ 2) up to 45% after endovascular treatment under conscious sedation.
16
17 257 Therefore, 166 patients per group will be needed to have 80% power, at a two-sided alpha
18
19 258 level of 0.05. A total of 350 patients will be included to take into account non-evaluable patients
20
21 259 and drop outs.
22
23

24 260

25
26 261 **Data Registration**

27
28 262 Data will be entered into the web- based electronic case report form (eCRF) by trial or clinical
29
30 263 personnel under the supervision of the trial site investigators at each participating centre. From
31
32 264 the eCRF the trial database will be established. Data collection will be monitored by trained
33
34 265 research coordinators.
35
36

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38
39 267 The following data will be registered:

40
41 268 Baseline characteristics at randomisation:

42
43 269 Demographic data (age, height, weight, gender and body mass index); American Society of
44
45 270 Anaesthesiologists (ASA) physical status; significant comorbidities (cardio-vascular,
46
47 271 respiratory, neurologic , psychiatric and /or abdominal disease, cancer, preoperative
48
49 272 chemotherapy or radiotherapy), NIHSS score, time of arrival at the hospital, time of the
50
51 273 beginning of the symptoms, time of the cerebral angiography or MRI (meaning time of first
52
53 274 image for diagnosis) , time between the first contact of the patient with the anaesthesiologist
54
55 275 and the induction of anaesthesia (GA or CS),localisation of the stroke, IV fibrinolysis if
56
57 276 applicable, creatinine clearance, haemostasis (PT and ACT if available).
58

59
60 277 Intraoperative data:

1
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3 278 Time of arterial puncture, time of recanalization, mTICI score (16), doses of norepinephrine,
4
5 279 intraoperative complications (hypotension defined as SBP < 140 mmHg or a drop of the MBP
6
7 280 of 40% or more, hypertension defined as SBP> 185 mmHg or DBP > 110 mmHg) necessity to
8
9 281 convert the conscious sedation onto a general anaesthesia, duration of anaesthesia and
10
11 282 procedure, procedure related complications (distal embolization in a different territory,
12
13 283 intramural arterial dissection, arterial perforation, access-site complications leading to surgery).
14
15
16 284

17
18 285 Postoperative data:

19
20 286 The following data will be collected:

- 21
22 287 • Duration of invasive ventilation
23
24 288 • NIHSS day 1 and Day 7 or the day the patient leaves the hospital if before Day 7
25
26 289 • Necessity of noradrenaline during the first 2 hours after the endovascular treatment
27
28 290 • Hypo- or hypertension events as defined above during first 24 hours
29
30 291 • Bradycardie with atropine treatment during first 24 hours
31
32 292 • Hospitalization in intensive care unit
33
34 293 • Number of hours of invasive ventilation
35
36 294 • Pneumonia
37
38 295 • Death until the final call for mRS (3 months after the procedure)
39
40 296 • mRS 3 months after the procedure during a telephone interview (21).
41
42
43
44 297

45
46 298 **Patient withdrawal**

47
48 299 A participant who no longer agrees to participate in the clinical trial can withdraw the informed
49
50 300 consent at any time without need of further explanation. Participants who will withdraw from
51
52 301 the study will be followed up, according to routine clinical practice in each participating centre.
53
54 302 In order to conduct intention-to-treat analyses with as little missing data as possible, the
55
56 303 investigator may ask the participant which aspects of the trial he/she wishes to withdraw from
57
58 304 (participation in the remaining follow-up assessments, use of already collected data).
59
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2
3 305 Whenever possible, the participant will be asked for permission to obtain data for the primary
4
5 306 outcome measure. All randomised patients will be reported, and all data available with consent
6
7 307 will be used in the analyses. If appropriate, missing data will be handled in accordance with
8
9 308 multiple imputation procedures if missing data are greater than 5%.

10
11 309

12 310 **Safety**

13
14
15 311 Every serious adverse event related to the studied treatment or not, expected or unexpected,
16
17 312 will be reported within 24 hours by the investigator to the sponsor on a "Serious adverse event"
18
19 313 form on which will be indicated the date of occurrence, criterion of severity, intensity,
20
21 314 relationship with the treatment (or the study) evaluated, and the outcome. The period in which
22
23 315 serious adverse events should be reported begins from the day of the written informed consent
24
25 316 to the end of the follow-up (day of the evaluation of mRS 3 to 4 months after the procedure).
26
27 317 Whenever a serious adverse event persists at the end of the study, the investigator will follow
28
29 318 the patient until the event is considered resolved. The following events: hypo- or hypertension
30
31 319 will be recorded as study endpoints criterion in the case report form. In order to avoid collection
32
33 320 duplication, they will not be reported on the "adverse event" page of the case report form. As
34
35 321 planned in the study, they will be analysed at the time of interim analyses (two interim analyses
36
37 322 after inclusion of 1/3 and 2/3 of the patients) which will permit to show potential difference
38
39 323 between the two groups during the study.

40
41
42 324 In addition, serious adverse events will be submitted to the data monitoring and safety
43
44 325 committee (DMSC). The DMSC is independent of the trial investigators and will perform an
45
46 326 ongoing review of safety parameters and overall study conduct. The DMSC is comprised of a
47
48 327 neurologist, an anaesthesiologist, a neuroradiologist, a pharmacologist and a methodologist.
49
50 328 The DMSC will be responsible for safeguarding the interests of trial participants, assessing the
51
52 329 safety and efficacy of the interventions during the trial, and for monitoring the overall conduct
53
54 330 of the clinical trial. To contribute to enhancing the integrity of the trial, the DMSC may also
55
56 331 formulate recommendations relating to the recruitment/retention of participants, their
57
58 332 management, improving adherence to protocol-specified regimens and retention of
59
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2
3 333 participants, and the procedures for data management and quality control. Recommendations
4
5 334 for pausing or stopping the study will be made by the DMSC in case of serious adverse
6
7 335 reactions and suspected unexpected serious adverse reaction.

8
9 336 All adverse events for which the investigator or the sponsor considers that a causal relationship
10
11 337 with the investigational medicinal products can be reasonably considered, will be considered
12
13 338 as suspected adverse reactions. If they are unexpected, they are qualified as being Suspected
14
15 339 Unexpected SAR (SUSAR) and will be notified in a report by the sponsor to Eudravigilance
16
17 340 (European pharmacovigilance database) and to local regulatory agency within the regulatory
18
19 341 time periods for reporting: Immediate declaration if seriousness criteria is death or life-
20
21 342 threatening condition, declaration within 15 days for other seriousness criteria.
22
23

24 343

25 26 344 **Data handling and retention**

27
28 345 Data will be handled according to French law. All original records (including consent forms,
29
30 346 reports of suspected unexpected serious adverse reactions and relevant correspondences)
31
32 347 will be archived at trial sites for 15 years. The clean trial database file will be anonymised and
33
34 348 maintained for 15 years.
35

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37 349

38 39 350 **Patient and public involvement**

40
41 351 Patient and public were not involved in any of the phases of this study
42

43 352

44 45 353 **ETHICS AND DISSEMINATION**

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47 354

48 49 355 **Ethical and legislative approvals**

50
51 356 GASS trial was approved by the French National Safety and Drug Agency (Agence Nationale
52
53 357 de Sécurité du Médicament (September 8th, 2016). By June 13th, 2016, the study has been
54
55 358 approved for all centres by a central ethics committee (Comité de Protection des Personnes
56
57 359 de Poitiers). The GASS trial is registered in the European Clinical Trials Database (EudraCT
58
59 360 2016-000795-25) and at ClinicalTrials.gov with the trial identification number NCT02822144.

1
2
3 361 Trial methods and results will be reported according to the Consolidated Standards of
4
5 362 Reporting Trials (CONSORT) 2010 guidelines (22).

6
7 363

8
9 364 **Publication plan**

10
11 365 Scientific presentations and reports corresponding to the study will be written under the
12
13 366 responsibility of the coordinating investigator of the study with the agreement of the principal
14
15 367 investigators and the methodologist. The co-authors of the report and of publications will be
16
17 368 the investigators and clinicians involved, on a pro rata basis of their contribution in the study,
18
19 369 as well as the biostatistician and associated researchers. All trial sites will be acknowledged,
20
21 370 and all investigators at these sites will appear with their names under 'the GASS investigators'
22
23 371 in the final manuscript. Rules on publication will follow international recommendations (23).

24
25 372

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27 373

28
29 374 **Contributors:**

30
31 375 Axelle Maurice (AM) as anesthetist contributed to the conception and design of the research
32
33 376 protocol and wrote the research protocol. AM wrote the first draft of the protocol. AM critically
34
35 377 revised and modified the protocol and the article. AM is including patients in the ongoing study
36
37 378 in the Rennes teaching hospital. AM approved the final version to be published.

38
39 379 Jean-Christophe Ferré (JCF) as neuroradiologist contributed to the conception and design of
40
41 380 the research protocol. JCF critically revised and modified the protocol and the article. JCF
42
43 381 approved the final version to be published.

44
45 382 Thomas Ronziere (TR) as neurologist contributed to the conception and design of the research
46
47 383 protocol. TR critically revised and modified the protocol and the article. TR approved the final
48
49 384 version to be published.

50
51 385 Jean-Michel Devys (JMD) as anesthetist critically revised and modified the protocol and the
52
53 386 article. JMD is including patients in the ongoing study in the Fondation Rothschild hospital in
54
55 387 Paris. JMD approved the final version to be published.

56
57 388

1
2
3 389 Aurelie Subileau (AS) as anesthetist critically revised and modified the protocol and the article.

4
5 390 AS is including patients in the ongoing study in the Brest teaching hospital. AS approved the
6
7 391 final version to be published.

8
9 392 Marc Laffon (ML) as anesthetist critically revised and modified the protocol and the article. ML
10
11 393 is including patients in the ongoing study in the Tours teaching hospital. ML approved the final
12
13 394 version to be published.

14
15 395 Bruno Laviolle (BL) designed the study and its statistical analysis plan.

16
17 396 Helene Beloeil (HB) provided critical input pertaining to the design of the trial interventions and
18
19 397 procedures. HB wrote this manuscript. HB is including patients in the ongoing study in the
20
21 398 Rennes teaching hospital.

22
23
24 399

25
26 400 **Funding:** GASS trial is supported by funding from French Ministry of Health (Programme
27
28 401 Hospitalier de Recherche Clinique Inter regional (PHRCI 2015).

29
30 402 The funding sources had no role in the trial design, trial conduct, data handling, data analysis
31
32 403 or writing and publication of the manuscript.

33
34
35 404

36
37 405 **Sponsor:** CHU de Rennes, Direction de la recherche Clinique, 2 avenue Henri Le Guilloux,
38
39 406 35033 Rennes Cedex, France. The sponsor had no role in the trial design, trial conduct, data
40
41 407 handling, data analysis or writing and publication of the manuscript.

42
43 408

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45 409

46
47 410 **Competing interests:** None

48
49 411

50 51 412 **References**

52
53 413 1- Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, et al. MR
54
55 414 CLEAN Investigators. A randomized trial of intra-arterial treatment for acute
56
57 415 ischemic stroke. N Engl J Med. 2015; 372:11-20.

58
59
60

- 1
2
3 416 2- Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, et al. ESCAPE Trial
4 417 Investigators. Randomized Assessment of Rapid Endovascular Treatment of
5 418 Ischemic Stroke. *N Engl J Med*. 2015; 372:1019-30.
- 6
7
8 419 3- Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, and al. EXTEND-IA
9 420 Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging
10 421 selection. *N Engl J Med*. 2015; 372:1009-18.
- 11
12
13 422 4- Nogueira RG, Smith WS, Sung G, et al. Effect of time to reperfusion on clinical
14 423 outcome of anterior circulation strokes treated with thrombectomy: pooled analysis
15 424 of the MERCI and Multi MERCI trials. *Stroke*. 2011; 42: 3144–9.
- 16
17 425 5- Davis MJ, Menon BK, Baghirzada LB, Campos-Herrera CR, Goyal M, Hill MD,
18 426 Archer DP; Calgary Stroke Program. Aesthetic management and outcome in
19 427 patients during endovascular therapy for acute stroke. *Anesthesiology*.
20 428 2012;116:396-405.
- 21
22
23
24 429 6- Löwhagen Hendén P, Rentzos A, Karlsson JE, Rosengren L, Sundeman H,
25 430 Reinsfelt B, Ricksten SE. Hypotension During Endovascular Treatment of Ischemic
26 431 Stroke Is a Risk Factor for Poor Neurological Outcome. *Stroke*. 2015; 46:2678-2680.
- 27
28
29 432 7- Whalin MK, Halenda KM, Haussen DC, Rebello LC, Frankel MR, Gershon RY,
30 433 Nogueira RG. Even Small Decreases in Blood Pressure during Conscious Sedation
31 434 Affect Clinical Outcome after Stroke Thrombectomy: An Analysis of Hemodynamic
32 435 Thresholds. *AJNR Am J Neuroradiol*. 2017;38:294-298.
- 33
34
35 436 8- Berkhemer OA, van den Berg LA, Fransen PS, Beumer D, Yoo AJ, Lingsma HF,
36 437 Schonewille WJ, van den Berg R, Wermer MJ, Boiten J, Lycklama À Nijeholt GJ,
37 438 Nederkoorn PJ, Hollmann MW, van Zwam WH, van der Lugt A, van Oostenbrugge
38 439 RJ, Majoie CB, Dippel DW, Roos YB; MR CLEAN investigators. The effect of
39 440 anaesthetic management during intra-arterial therapy for acute stroke in MR
40 441 CLEAN. *Neurology*. 2016 ;87:656-64.
- 41
42
43
44
45 442 9- Abou-Chebl A, Yeatts SD, Yan B, Cockroft K, Goyal M, Jovin T, Khatri P, Meyers
46 443 P, Spilker J, Sugg R, Wartenberg KE, Tomsick T, Broderick J, Hill MD. Impact of
47 444 General Anesthesia on Safety and Outcomes in the Endovascular Arm of
48 445 interventional Management of Stroke (IMS) III Trial. *Stroke*. 2015;46:2142-8.
- 49
50
51 446 10- Bekelis K, Missios S, MacKenzie TA, Tjoumakaris S, Jabbour P. Anesthesia
52 447 Technique and Outcomes of Mechanical Thrombectomy in Patients with Acute
53 448 Ischemic Stroke. *Stroke* 2017 ;48:361-366.
- 54
55
56 449 11- Schönenberger S, Uhlmann L, Hacke W, Schieber S, Mundiyanapurath S,
57 450 Purrucker JC, Nagel S, Klose C, Pfaff J, Bendszus M, Ringleb PA, Kieser M,
58 451 Möhlenbruch MA, Bösel J. Effect of Conscious Sedation vs General Anesthesia on
59
60

- 1
2
3 452 Early Neurological Improvement Among Patients with Ischemic Stroke Undergoing
4 453 Endovascular Thrombectomy: A Randomized Clinical Trial. JAMA.
5 454 2016;316 :1986-1996.
6
7
8 455 12- Löwhagen Henden P, Rentzos A, Karlsson JE, Rosengren L, Leiram B, et al.
9 456 General anaesthesia versus conscious sedation for endovascular treatment of
10 457 acute ischaemic stroke : the anstroke trial (anaesthesia during stroke). Stroke 2017 ;
11 458 48 : 1601-1607.
12
13
14 459 13- Simonsen CZ, Yoo AJ, Sørensen LH, Juul N, Johnsen SP, Andersen G,
15 460 Rasmussen M. Effect of General Anesthesia and Conscious Sedation During
16 461 Endovascular Therapy on Infarct Growth and Clinical Outcomes in Acute Ischemic
17 462 Stroke: A Randomized Clinical Trial JAMA Neurol. 2018 ;75(470-477).
18
19
20 463 14- Campbell BCV, van Zwam WH, Menon BK, Dippel DWJ, Demchuk AM, Bracad S
21 464 et al. Effect of general anaesthesia on functional outcome in patients with anterior
22 465 circulation ischaemic stroke having endovascular thrombectomy versus standard
23 466 of care: a meta-analysis of individual patient data. Lancet neurol 2018; 17:47-53.
24
25
26 467 15- Schönenberger S, Uhlmann L, Ungerer M, Pfaff J, Nagel S, Kose C, et al.
27 468 Association of blood pressure with short-and long-term functional outcome after
28 469 stroke thrombectomy: post hoc analysis of the siest trial. Stroke 2018; 49: 1451-
29 470 1456.
30
31
32 471 16- Rasmussen M, Espelund US, Juul N, Yoo AJ, Sorensen LH, Sorensen KE et al.
33 472 The influence of blood pressure management on neurological outcome in
34 473 endovascular therapy for acute ischaemic stroke. Br J Anaesth 2018; 120:1287-
35 474 1294.
36
37
38 475 17- Banks JL, Marotta CA. Outcomes Validity and Reliability of the Modified Rankin
39 476 Scale: Implications for Stroke Clinical Trials. A Literature Review and Synthesis.
40 477 Stroke. 2007; 38:1091-1096.
41
42
43 478 18- Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, et al. Cerebral
44 479 Angiographic Revascularization Grading (CARG) Collaborators; STIR
45 480 Revascularization working group; STIR Thrombolysis in Cerebral Infarction (TICI)
46 481 Task Force. Recommendations on angiographic revascularization grading
47 482 standards for acute ischemic stroke: a consensus statement. Stroke.
48 483 2013 ;44:2650-2663.
49
50
51 484 19- Brott T, Adams HP, Olinger CP, Marler JR, Barsan WG, Biller J, SpilkerJ, Holleran
52 485 R, Eberle R, Hertzberg V, Rorick M, Moomaw CJ, Walker M. Measurements of
53 486 acute cerebral infarction: a clinical examination scale. Stroke. 1989; 20:864–870.
54
55
56
57
58
59
60

- 1
2
3 487 20- Abou-Chebl A, Lin R, Hussain MS, Jovin TG, Levy EI, Liebeskind DS, et al.
4 488 Conscious sedation versus general anaesthesia during endovascular therapy for
5 489 acute anterior circulation stroke: preliminary results from a retrospective,
6 490 multicentre study. *Stroke*. 2010; 41:1175-79.
7
8 491 21- Bruno A, Akinwuntan AE, Lin C, Close B, Davis K, Baute V et al. Simplified modified
9 492 rankin scale questionnaire. Reproducibility over the telephone and validation with
10 493 quality of life. *Stroke* 2011; 42:2276-9.
11 494 22- Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated
12 495 guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
13 496 23- International Committee of Medical Journal E. Uniform requirements for
14 497 manuscripts submitted to biomedical journals. *The New England journal of*
15 498 *medicine* 1997;336(4):309-15
16 499



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

1
2 Trial design 8 Description of trial design including type of trial (eg, parallel group,
3 crossover, factorial, single group), allocation ratio, and framework (eg,
4 superiority, equivalence, noninferiority, exploratory) [page 6](#)
5
6
7

8 **Methods: Participants, interventions, and outcomes**

9
10 Study setting 9 Description of study settings (eg, community clinic, academic hospital)
11 and list of countries where data will be collected. Reference to where
12 list of study sites can be obtained [page 6](#)
13

14 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
15 criteria for study centres and individuals who will perform the
16 interventions (eg, surgeons, psychotherapists) [page 6](#)
17
18

19 Interventions 11a Interventions for each group with sufficient detail to allow replication,
20 including how and when they will be administered [page 7-8](#)
21

22 11b Criteria for discontinuing or modifying allocated interventions for a
23 given trial participant (eg, drug dose change in response to harms,
24 participant request, or improving/worsening disease) [page 8](#)
25

26 11c Strategies to improve adherence to intervention protocols, and any
27 procedures for monitoring adherence (eg, drug tablet return,
28 laboratory tests) [NA](#)
29
30

31 11d Relevant concomitant care and interventions that are permitted or
32 prohibited during the trial [page 8](#)
33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific
35 measurement variable (eg, systolic blood pressure), analysis metric
36 (eg, change from baseline, final value, time to event), method of
37 aggregation (eg, median, proportion), and time point for each
38 outcome. Explanation of the clinical relevance of chosen efficacy and
39 harm outcomes is strongly recommended [page 9](#)
40
41

42 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
43 timeline washouts), assessments, and visits for participants. A schematic
44 diagram is highly recommended (see Figure) [page 9](#)
45

46 Sample size 14 Estimated number of participants needed to achieve study objectives
47 and how it was determined, including clinical and statistical
48 assumptions supporting any sample size calculations [page 10-11](#)
49
50

51 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
52 target sample size [page 10-11](#)
53

54 **Methods: Assignment of interventions (for controlled trials)**

55 Allocation:
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1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions page 7
8			
9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned page 7
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions page 7
17			
18			
19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how page 7
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial
26			
27			

Methods: Data collection, management, and analysis

28			
29			
30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol page 11-12
36			
37			
38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols page 11-12
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44			range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol page 14
46			
47			
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods		Reference to where other details of the statistical analysis plan can be
50			found, if not in the protocol page 10
51			
52		20b	Methods for any additional analyses (eg, subgroup and adjusted
53			analyses) page 10
54			
55		20c	Definition of analysis population relating to protocol non-adherence
56			(eg, as randomised analysis), and any statistical methods to handle
57			missing data (eg, multiple imputation) page 10
58			
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60			

Methods: Monitoring

- 1
2
3
4 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role
5 and reporting structure; statement of whether it is independent from
6 the sponsor and competing interests; and reference to where further
7 details about its charter can be found, if not in the protocol.
8 Alternatively, an explanation of why a DMC is not needed [page 11 &](#)
9 [13](#)
10
11
12 21b Description of any interim analyses and stopping guidelines, including
13 who will have access to these interim results and make the final
14 decision to terminate the trial [page 13](#)
15
16 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and
17 spontaneously reported adverse events and other unintended effects
18 of trial interventions or trial conduct [page 13](#)
19
20
21 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and
22 whether the process will be independent from investigators and the
23 sponsor [page 13](#)
24

Ethics and dissemination

- 25
26
27 Research ethics 24 Plans for seeking research ethics committee/institutional review board
28 approval [already done page 14](#)
29
30 Protocol amendments 25 Plans for communicating important protocol modifications (eg,
31 changes to eligibility criteria, outcomes, analyses) to relevant parties
32 (eg, investigators, REC/IRBs, trial participants, trial registries, journals,
33 regulators) [page 14](#)
34
35
36 Consent or assent 26a Who will obtain informed consent or assent from potential trial
37 participants or authorised surrogates, and how (see Item 32) [page 7](#)
38
39 26b Additional consent provisions for collection and use of participant data
40 and biological specimens in ancillary studies, if applicable [NA](#)
41
42 Confidentiality 27 How personal information about potential and enrolled participants will
43 be collected, shared, and maintained in order to protect confidentiality
44 before, during, and after the trial [page 14](#)
45
46
47 Declaration of interests 28 Financial and other competing interests for principal investigators for
48 the overall trial and each study site [page 16](#)
49
50 Access to data 29 Statement of who will have access to the final trial dataset, and
51 disclosure of contractual agreements that limit such access for
52 investigators [page 14-15](#)
53
54 Ancillary and post-trial care 30 Provisions, if any, for ancillary and post-trial care, and for
55 compensation to those who suffer harm from trial participation [NA](#)
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| 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 |

15 Appendices

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| 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 |

25 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
26 Explanation & Elaboration for important clarification on the items. Amendments to the
27 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
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29 license.
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