

Anaesthesiological Routine Care for Thrombectomy In Cerebral Ischaemia

(ARCTIC-I):

An International Prospective Observational Study

Study protocol

Version 1.0 of 28 September 2020
ClinicalTrials.gov Identifier: NCT04522856



Sponsor/Funder

European Society of Anaesthesiology
and Intensive Care
24, Rue des Comédiens
BE-1000 Brussels, Belgium
Phone: +32 2 743 3290
Fax: +32 2 743 3298
E-mail 1: research@esaic.org
E-mail 2: ARCTIC-I@esaic.org

Chief Investigator

Dr. med. Andreas Ranft, Senior Physician
Klinik für Anaesthesiologie und Intensivmedizin
Klinikum rechts der Isar, Technische Universität München
Ismaninger Str. 22
D-81675 München, Germany
Phone +49 89 4140 9632
Fax +49 89 4140 4886
E-mail: andreas.ranft@tum.de

Legal note: Access to research documents

The information contained in this document is confidential and the property of the European Society of Anaesthesiology and Intensive Care (address as above). The information may not be transmitted, reproduced, published, or disclosed to others than the applicable competent research ethical boards and regulatory authorities without prior written authorization from the sponsor except to the extent necessary to obtain informed consent from those who will participate in the study.

Table of Contents

1	Title Page.....	1
2	Protocol Synopsis	4
3	Roles and Responsibilities	5
3.1	Chief Investigator	5
3.2	Steering Committee	5
3.3	Sponsorship, Funding and Support	5
4	Scientific Background	6
4.1	State of Research.....	6
4.2	Rationale for the Project	6
5	Objectives.....	6
5.1	Main Objective	6
5.2	Secondary Objectives	7
6	End points.....	7
6.1	Primary Endpoint.....	7
6.2	Secondary Endpoints.....	7
7	Study Population	7
7.1	In- and Exclusion Criteria.....	8
7.2	Sample Size Calculation.....	8
7.3	Screening and Patient Inclusion	8
8	Conduct of the Study.....	8
8.1	International Multicentre Approach	8
8.1.1	Local Principal Investigators (PI).....	8
8.1.2	National Coordinators (NC)	9
8.2	Participant Information and Informed Consent.....	9
8.3	Data Sources.....	10
8.4	Data to be Collected	10
8.5	Schedule for the Individual Participant	10
8.6	End of Data Collection	10
8.7	Study Workflow in Overview	10
9	Risk-Benefit-Assessment	11
9.1	Individual Patient’s Benefit	11
9.2	Study-Associated Risk.....	11

9.3	Ethical justifiability	12
9.4	Insurance	12
10	Planned Analyses.....	12
10.1	Main Analysis.....	12
10.2	Handling of Missing Data.....	12
10.3	Subgroup Analysis	12
11	Data Management and Data Protection	12
11.1	Data Recording, Storage, Transfer, Archiving, and Protection.....	13
11.2	Pseudonymization	13
11.3	Withdrawal, Deletion of Data.....	14
12	Publication Policy	14
12.1	Dissemination of Results and Authorship Rules.....	14
12.2	Nested Substudies.....	15
12.3	Secondary Analyses, Data Sharing	15
13	Literature.....	15
14	List of appendices.....	16
15	Protocol Changes.....	16
15.1	Rights and obligations	16
15.2	History of protocol changes	17
16	Protocol Signature Sheet.....	18

Abbreviations (in alphabetical order)

AIS-LVO	Acute Ischaemic Stroke due to Large Vessel Occlusion
CTN	Clinical Trial Network
eCRF	Electronic Case Report Form
ESAIC	European Society of Anaesthesiology and Intensive Care
ET	Endovascular Thrombectomy
GCP	Good Clinical Practice
IC	Informed Consent
IRB	Institutional Review Board
mRS	modified Rankin Scale
NC	National Coordinator
PI	Principal Investigator (on site)
SOP	Standard Operating Procedure

2 Protocol Synopsis

Chief Investigator	Dr. med. Andreas Ranft, DESA, Senior Physician Klinikum rechts der Isar, Technische Universität München E-mail: andreas.ranft@tum.de
Study Title	Anaesthesiological Routine Care for Thrombectomy in Cerebral Ischaemia: An International Prospective Observational Study
Acronym, NCT ID	ARCTIC-I, NCT04522856
Protocol Version	Version 1.0, 28 September 2020
Design	International Prospective Observational Study
Background	Endovascular thrombectomy is the standard of care for acute ischaemic stroke due to large-vessel occlusion. Current guidelines for periprocedural anaesthesiological care lack detailed information.
Main Objective	To determine how anaesthesiologists support endovascular thrombectomy with regard to anaesthetic technique, choice of substances, haemodynamic management, and ventilation. With a multivariate analysis, we will look for the factors of anaesthetic management that are independently correlated with a good or bad outcome.
Secondary Objectives	To find factors that predict failure of sedation with need of conversion to general anaesthesia. To describe which patients are successfully extubated at the end of the procedure.
Primary Endpoint	Functional outcome at 90 days expressed as modified Rankin Scale (mRS), dichotomized into good (mRS ≤ 2) versus poor (mRS > 2) outcome
Secondary Endpoints	Functional outcome at 90 days using the full ordinal mRS Mortality at 90 days Extent of reperfusion Duration to arterial puncture and to reperfusion Frequency of conversion from sedation to general anaesthesia Ratio of patients breathing spontaneously before transfer from angio suite
Inclusion Criteria	Endovascular thrombectomy involving anaesthesia care
Exclusion Criteria	In-hospital onset of stroke Inclusion in an interventional study concerning the anaesthesia protocol Age under 18 years
Study assessment	Patients or their relatives will be contacted by telephone 90 days after the stroke for a structured interview which will take less than five minutes
Participants	Following sample size estimation, we plan to enrol at least 5,000 patients
Centres	We intend to involve about 100 centres
Project Duration	Inclusion period for each centre: 6 months, follow-up: 3 months Duration of the entire trial: 4 years
Statistical Considerations	Multivariable regression models will be computed to produce prediction models and to investigate prognostic and predictive factors associated with treatment and with the primary and secondary endpoints. Sensitivity analyses: Parametric and nonparametric models used in personalized medicine.

3 Roles and Responsibilities

3.1 Chief Investigator

Dr. med. Andreas Ranft, Senior Physician
Klinik für Anaesthesiologie und Intensivmedizin
Klinikum rechts der Isar, Technische Universität München
Ismaninger Str. 22, 81675 München – Germany
E-mail: andreas.ranft@tum.de Phone +49 89 4140 9632

3.2 Steering Committee

Dr. med. Andreas Ranft, Chief Investigator, address as above

Prof. Dr. med. Gerhard Schneider, Chair
Klinik für Anaesthesiologie und Intensivmedizin
Klinikum rechts der Isar, Technische Universität München
Ismaninger Str. 22, 81675 München – Germany
E-mail: gerhard.schneider@tum.de Phone +49 89 4140 4291

PD Dr. med. Nicolai Goettel, Senior Physician
Department of Anesthesia, Surgical Intensive Care,
Prehospital Emergency Medicine and Pain Therapy
University Hospital Basel
Spitalstrasse 21, CH-4031 Basel – Switzerland
E-mail: nicolai.goettel@usb.ch Phone: +41 61 556 5228

Dr. Francesca Rapido, Praticien Hospitalier des Hôpitaux
Département d'anesthésie-réanimation pôle Neurosciences Tête et Cou
CHU MONTPELLIER - Gui de Chauliac
80 avenue Augustin Fliche, 34295 MONTPELLIER Cedex 5 – France
E-mail: f-rapido@chu-montpellier.fr Phone : +33 6 72 18 47 20 or +33 7 88 01 45 97

Prof. Dr. med. Jens Meier, Chair
Department of Anesthesiology and Intensive Care
Kepler University Clinic Linz
Krankenhausstr. 9, A-4021 Linz – Austria
E-mail: jens.meier@kepleruniklinikum.at Phone +43 5 7680 83 2158

Dipl.-Stat. PD Dr. Alexander Hapfelmeier, Study statistician for ARCTIC-I
Institut für Medizinische Informatik, Statistik und Epidemiologie
Klinikum rechts der Isar, Technische Universität München
Ismaninger Str. 22, 81675 München – Deutschland
E-mail: alexander.hapfelmeier@tum.de Phone +49 89 4140 4340

The SC members declare not to have any conflicts of interest (a declaration of conflict of interest will be signed by each SC member and kept by the sponsor).

3.3 Sponsorship, Funding and Support

ARCTIC-I is sponsored by a grant from the European Society of Anaesthesiology and Intensive Care (ESAIC) Clinical Trial Network (CTN). ESAIC's CTN provides an infrastructure for clinical research in the

fields of Anaesthesia, Pain, Intensive Care and Emergency Medicine by transnational collaborative studies. No other institution or industrial company is or will be involved in planning or conducting the ARCTIC-I study. However, the submission for national or local peer-reviewed grants to fund national or local implementation of the study is allowed conditional on prior written authorization from the sponsor and the SC.

ESAIC's CTN can be contacted via: Saman Sepehr and Pierre Harlet, study coordinators
Research Department
European Society of Anaesthesiology and Intensive Care
24, Rue des Comédiens – BE-1000 Brussels, Belgium
Tel: +32 2 226 6 633, Fax: +32 2 743 32 98
E-mail #1: research@esaic.org; E-mail #2: ARCTIC-I@esaic.org

4 Scientific Background

According to the World Health Organization, strokes are globally the second most common cause of death and one of the leading causes of acquired disabilities.¹ In Europe, the age-standardized incidence of stroke ranges from about 100 to 300/100,000 per year, with one-month case-fatality rates between 13 and 35 %.² For acute ischaemic stroke due to large-vessel occlusion (AIS-LVO), which represent some 30 % of strokes,³ endovascular thrombectomy (ET) in addition to systemic thrombolysis has been proven clinically effective⁴ and is now the standard of care.⁵

4.1 State of Research

For ET, some patients imperatively require general anaesthesia with intubation and controlled ventilation because of severe agitation, reduced consciousness, loss of airway protective reflexes, or impaired respiratory function. For example, posterior vessel occlusion is frequently associated with these conditions.⁶ On the other hand, symptoms might be so slight that patients manage to cooperate and lie still. In between, there are patients with preserved airway protective reflexes and stable respiration who need sedation to establish adequate conditions for the intervention.⁷ In these cases, ET can be done under sedation with preserved spontaneous ventilation as well as under general anaesthesia with endotracheal intubation and controlled mechanical ventilation.⁸

4.2 Rationale for the Project

ET is a safe and effective intervention for selected patients with AIS-LVO. While more and more patients are receiving this treatment, there are many open questions concerning anaesthesiological management of the patient during the intervention.⁹ Although current guidelines give gross recommendations,⁶ detailed information, like on choice of technique or drugs, are missing.¹⁰

The present study is intended to describe the variation of routine clinical practice for anaesthesiological care during ET. In the collected data characterising the patients' pre-stroke state of health, the vascular accident itself, periprocedural management and physiology, we will look for the factors of anesthetic management that are independently correlated with a good or bad functional outcome after 90 days.

5 Objectives

5.1 Main Objective

ARCTIC-I aims to describe international differences in anaesthesia care for ET. Based on these data, we want to develop recommendations for anaesthesiological support of ET concerning anaesthetic technique, substances, as well as management of haemodynamics, oxygenation, and ventilation in order to optimise patients' functional outcome three months after the stroke.

5.2 Secondary Objectives

We will seek factors that predict failing sedation with the need for conversion to general anaesthesia and controlled mechanical ventilation. Moreover, we will report which patients are successfully extubated at the end of the procedure.

6 End points

6.1 Primary Endpoint

The proportion of patients able to live independently 3 months after their stroke is the primary endpoint. This corresponds to a modified Rankin scale (mRS) ≤ 2 (see table below). The value on the mRS will be determined in a validated structured telephone interview¹¹ with the patient or a relative or a follow-up visit 90 days after ET (range, 80 to 105 days) according to a flow chart that is contained in the data collection form (Appendix 9B).

TABLE: MODIFIED RANKIN SCALE (adapted from Kasner¹²).

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

6.2 Secondary Endpoints

The following secondary endpoints will be used (cf. data collection form, Appendix 9B).

- From the day of the intervention (day 0):
 - Duration from patient's arrival in angiography suite to arterial puncture (for ET)
 - Duration from arterial puncture to reperfusion (or, in case of futility, last attempt of clot removal)
 - Extent of reperfusion after ET (as graded by interventionalist using an ordinal score)
 - Frequency of conversion from sedation to general anaesthesia: proportion of patients primarily treated awake or with sedation that were subsequently intubated
 - Ratio of patients breathing spontaneously without endotracheal tube or supraglottic airway device before transfer from the angio suite
- At 90 days after the intervention (range, 80 to 105 days):
 - Functional outcome at 90 days using the full ordinal mRS (without dichotomization)
 - Mortality at 90 days (equivalent to frequency of mRS 6 at 90 days)

7 Study Population

The target population consists of patients undergoing emergency ET for treatment of AIS-LVO. The planned minimum sample size is 5,000 patients. Eligibility criteria are as follows.

7.1 In- and Exclusion Criteria

- Inclusion criterion: ET involving anaesthesia care
- Exclusion criteria:
 - In-hospital onset of stroke
 - Inclusion in an interventional study concerning the anaesthesia protocol
 - Age under 18 years

7.2 Sample Size Calculation

A number of 10 observations per parameter of a multivariable model has been recommended for consistent estimation.¹³ With a binary outcome this rule refers to the number of observations in the less frequent outcome class. Considering the subgroup of posterior circulation strokes, which represent approximately 20% of cerebral large vessel occlusions,¹⁴ the overall sample size, which is expected to lie within the range of 5,000-10,000 patients for the given recruitment period of 1.5 years, reduces to 1,000-2,000 patients. With a binary outcome representing a rare event, for example occurring in 5 % of the patients, there would be 50-100 events observed. This results in $50/10 = 5$ to $100/10 = 10$ parameters for estimation, which is already a limiting factor against the background of >10 predictor variables and the additional interaction effects that should be simultaneously investigated in a multivariable model. Therefore 5,000 patients overall is a minimal sample size needed for the planned analyses. However, sample sizes up to 10,000 patients can be pursued to extend the multiplicity of the model and to thereby increase the information gain.

7.3 Screening and Patient Inclusion

Any patient who has undergone ET with anaesthesia care (using either standby, sedation or general anaesthesia) for out-of-hospital stroke is a candidate for enrolment in ARCTIC-I. In- and exclusion criteria are detailed above (section 7.1). In order to gauge the proportion of patients that were included, a list of all eligible patients (screening list) has to be kept and updated in every centre (Appendix 7).

8 Conduct of the Study

8.1 International Multicentre Approach

Any hospital that performs ET routinely involving anaesthesia care is welcome to contribute as a study centre. Centres can register online via the 'call for centres form' on the ESAIC website. After participating in the pre-study enquiry (cf. Appendix 3), approval of the protocol (including all appendices) must be sought from the institutional review board (IRB). As soon as documentation of approval (Appendix 4) has reached ESAIC, the centre can determine the beginning of the inclusion period (at the earliest in the fourth quarter of 2020, cf. Appendix 2). The minimum length of the enrolment phase (interval 'first patient in to last patient in') per centre is six months but can be prolonged up to nine months.

8.1.1 Local Principal Investigators (PI)

Local PI will provide leadership for the study in their institution and have the following responsibilities:

- Ensure all relevant regulatory/ethical approvals are in place for their institution
- Ensure adequate training of all relevant staff prior to data collection
- Supervise enrolment and data collection until follow-up assessment
- Ensure timely data entry into online database and data cleaning queries
- Communicate with ESAIC and the relevant National Coordinators during all steps
- Maintain and update their investigator's site file according to the recommendation of the ICH-GCP Guidelines E6(R2).

The local PI is ultimately responsible for the integrity of data collection. By signing the data on the electronic case report form (eCRF), the local PI confirms the data integrity.

8.1.2 National Coordinators (NC)

NC are appointed by ESAIC and the SC to lead the study within individual countries. Often, NC will simultaneously be PI at their centre. NC are responsible for:

- Identification of eligible centres in their country and recruitment of local PI
- Assistance in the translation of required study documents
- Ensuring that all necessary regulatory approvals are in place prior to start of patient inclusion
- Assisting and training the local PI and monitoring the conduct of the study according to good clinical practice (GCP)
- Support of communication between ESAIC headquarters and the PI in his/her country throughout the study including data cleaning

Translations of the Appendices (esp. App. 6A, 6B, 6C, and 6D) into the national languages should be sent to ESAIC for validation prior to submission to the IRB.

8.2 Participant Information and Informed Consent

Every patient enrolled (alternatively their legal representatives) will be provided with the study information (Appendix 6A, but also contained in 6B, 6C, and 6D). In brief, this leaflet will

- explain our motivation to carry out ARCTIC-I
- detail which data will be collected
- announce the study-related telephone interview three months after stroke
- describe that personal identities will be replaced by a subject code (pseudonymization)
- assure that the key linking the subject code with personal identities (and phone numbers) will be protected and kept locked on site
- state that ESAIC will only receive fully pseudonymized data (for explanation, cf. section 11.2)

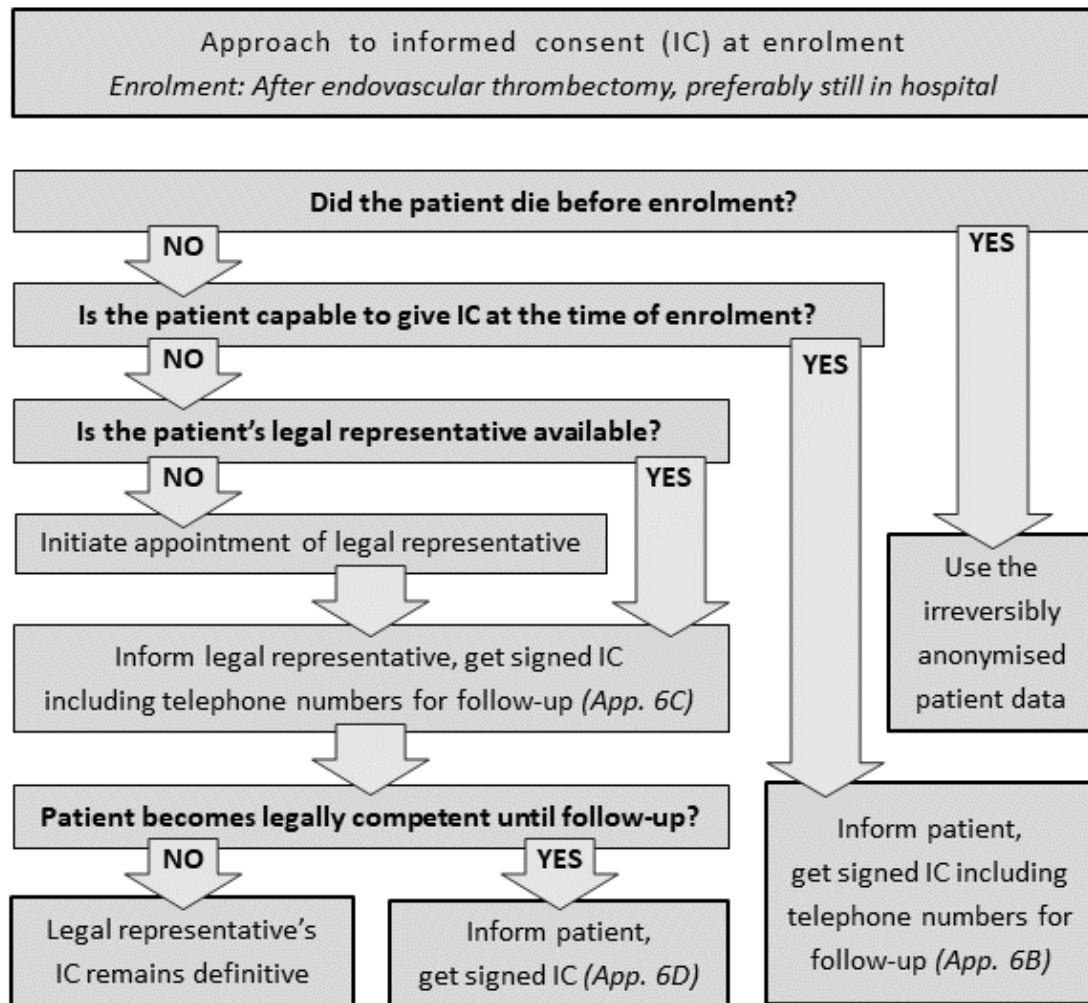
For regulatory assessment of ARCTIC-I by the appropriate regulatory authorities, we anticipate the following two approaches:

- individual patient consent may be **required** or
- individual patient consent may be **waived**.

The SC considers that the ideal approach is waived consent in order to minimise selection bias. This approach permits the inclusion of the largest proportion of patients. Therefore, a written exemption from informed consent (waiver) will be requested from the responsible IRB.

If considered essential by the competent institutional review board, informed consent will be sought from each patient (or their representative) and documented on the appropriate form (Appendices 6B, 6C, or 6D).

The approach to informed consent (IC) is explained in the FLOWCHART on the following page. If a patient has died before IC can be obtained, their data may be used after irreversible anonymisation.



8.3 Data Sources

The data collected at enrolment will be extracted from the patient file. At follow-up, data will be collected on the phone. Alternatively, data may be extracted from the patient file in case mRS was assessed by occasion of an outpatient follow-up visit between day 80 and 105 after ET.

8.4 Data to be Collected

Data will relate to the following fields: Past medical history, description of the stroke, blood tests, the procedure (ET), anaesthesiological care, physiology during ET. For a comprehensive list of variables, please refer to the data collection form (Appendix 9B).

8.5 Schedule for the Individual Participant

Each participant will be contacted twice:

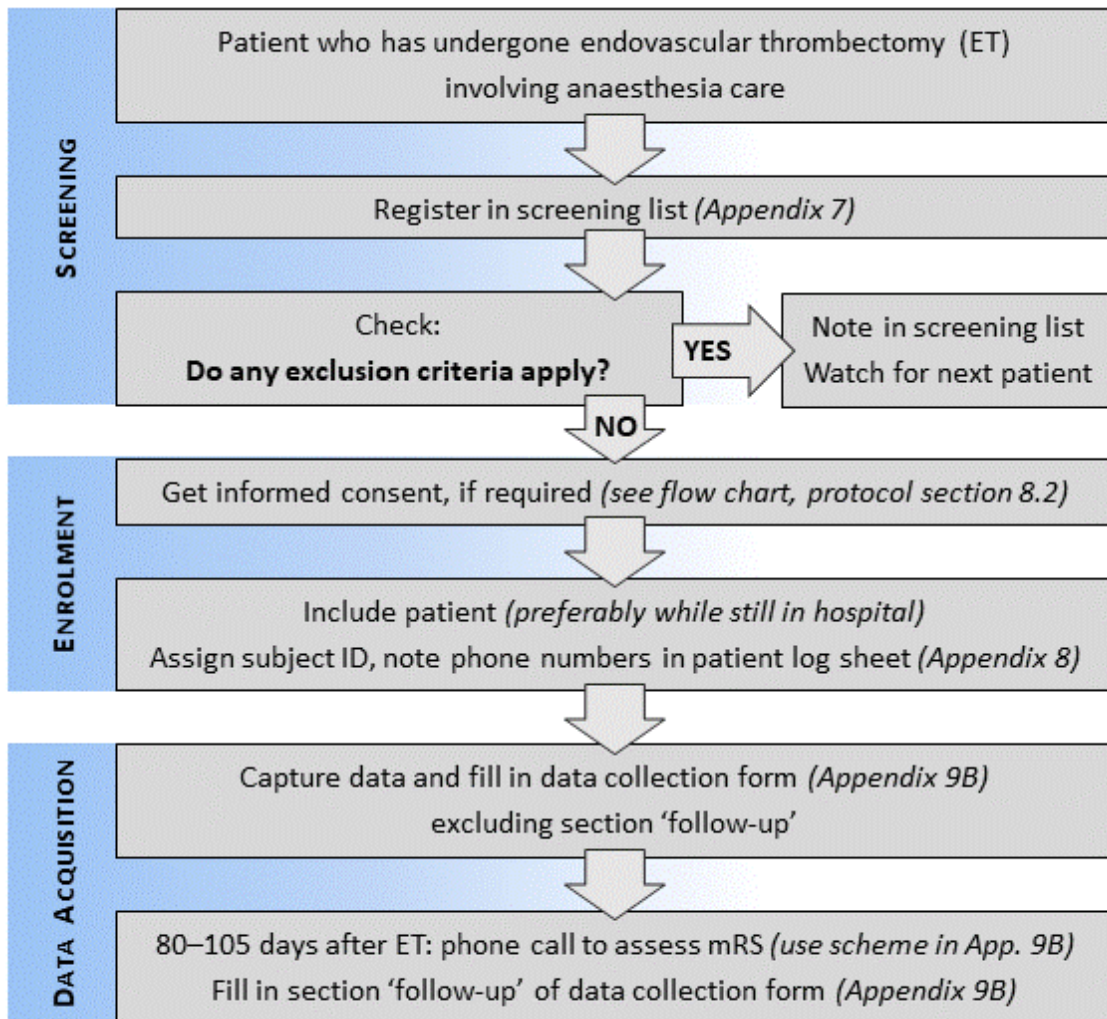
1. in person on the occasion of inclusion in the study
2. by telephone three months after the stroke to determine the functional status.

8.6 End of Data Collection

The overall time window for all centres' enrolment period ends with September 2022, but might be extended until 5,000 patients are reached. – Please also see timeline (Appendix 2).

8.7 Study Workflow in Overview

The FLOWCHART on the following page shows the workflow of the study in overview.



9 Risk-Benefit-Assessment

The research project will be carried out in accordance with the study protocol and the principles enunciated in the current version of the Declaration of Helsinki by the World Medical Association and the GCP Guidelines E6(R2). Specific national and local regulatory authorities' requirements will be followed as applicable.

9.1 Individual Patient's Benefit

There is no immediate benefit for participating patients. However, ARCTIC-I will identify factors of anaesthesiological management that support a favourable outcome. The implementation of these research results carries a considerable benefit for future patients. Besides, the inclusion of patients in a study often increases the attention and performance of the treating physicians.^{15,16}

9.2 Study-Associated Risk

ARCTIC-I is an observational study to prospectively collect data from patients with AIS-LVO treated with ET. No research-related interventions are anticipated, and all patients will receive routine care according to each institution's standards. The primary study endpoint, patients' functional outcome at three months, will be assessed through a structured telephone interview.¹¹ In many hospitals, this is done routinely as part of clinical quality assurance either on the phone or during a follow-up visit in the outpatient clinic. There is no study-related procedure in ARCTIC-I that involves the patient apart

from the informed consent procedure and the phone call after three months. As such, the potential for adverse events appears too remote to require their definition, assessment, or documentation.

9.3 Ethical justifiability

Concluding from the risk-benefit assessment above, the conduct of the study is deemed justifiable.

9.4 Insurance

Insurance might be required based upon an individual agreement between local PI and the relevant institutional legal department. The ESAIC has public liability insurance in place to cover the legal liability of the ESAIC as a sponsor in the eventuality of harm to a research participant arising from the management of the research by the ESAIC. This does not affect the responsibility of a centre for any clinical negligence on the part of its staff.

10 Planned Analyses

A detailed statistical analysis plan will be written and published before end of patient recruitment (cf. timeline in Appendix 2). We will state and justify any potential deviation from this initial analysis plan in the manuscript.

10.1 Main Analysis

Multivariable regression models will be computed to produce prediction models and to investigate prognostic and predictive factors associated with treatment and with the primary and secondary endpoints. Centres will be included as clusters in the analysis, for example by use of robust Huber-White estimators of the covariance matrix or by use of random effects. Sensitivity analyses will be performed by further parametric and nonparametric models from the field of personalized medicine. In the main analyses, the full dataset will be analysed, considering the handling of missing values described below.

10.2 Handling of Missing Data

Missing data might include missing questionnaire answers, missing co-variables for the regression models, and missing follow-ups. In case of missing values, multiple imputation, conditional imputation by Random Forests or use of nonparametric models that can process missing values will be considered.

10.3 Subgroup Analysis

We plan to analyse patients with occlusions in the anterior and posterior cerebral circulation separately. These two subgroups will be addressed by including interaction effects in the statistical models.

11 Data Management and Data Protection

The sponsor is responsible for quality assurance and control systems with written standard operating procedures (SOP) to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Quality control measures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly, including written SOP for data collection and entry, automated consistency checks, and training of NC and local PI. NC, with support by the ESAIC, will be responsible for training local PI. The investigators affirm and uphold the principle of the participant's right to privacy and shall comply with applicable privacy laws. Local PI will ensure that the data is carefully entered in the eCRF and verified regularly. It will be their responsibility to conduct periodic and random checks to ensure data quality in their centre. The sponsor will make random assessments in order to confirm proper and correct data entry into the eCRF. On-site monitoring visits by the sponsor are not planned.

The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities. Any agreements made by the sponsor with the investigator/institution and any other parties involved with the study, will be in writing, as part of the protocol or in a separate agreement. No fee or financial compensation is given to PI and/or participating institutions for patient inclusion.

11.1 Data Recording, Storage, Transfer, Archiving, and Protection

The data collection forms (Appendix 9B) will be stored within a locked cabinet/office accessible to authorised personnel only in accordance with local and national regulations. The patient log sheet reporting the assigned patient identification code will be stored separately also in a locked cabinet/office in order to allow potential monitoring visits. Signed informed consent forms will be stored as just described. All study documents will be archived as required by local legislation.

Data will be collected directly from source documents into the data collection form (Appendix 9B). A copy of the original source documents will be stored in the aforementioned locked cabinet/office. From the data collection form, data will be pseudonymized and transferred to the eCRF. The eCRF are stored in a secure on-line database protected by personalised and confidential usernames and passwords. The time and individual entering the data are automatically documented. The database is hosted on servers physically located in the European Union, and data can only be transferred to servers located in member states of the European Union or in third countries whose level of personal data protection is deemed adequate by the European Commission (based on General Data Protection, EU Regulation 2016/679, Article 45).

A log (Appendix 8 – Confidential Patient Log Sheet) will be kept to record the patient name, their subject identification code and the telephone numbers for follow-up. It will be stored separately in a locked cabinet/office (accessible to authorised personnel only). Along with the Confidential Patient Identification Coversheet (Appendix 9A), it may be used to plan the follow up visits. These forms (Appendix 8 and 9A) must not be sent to the sponsor. Signed ICF (to document that written informed consent was obtained prior to enrolment) will be stored as described above. All study documents are archived in accordance with local legislation, but at least for 10 years after completion of the study.

Open direct access to all relevant study information as well as source data/documents will be permitted for purposes of monitoring, audits or inspections to the sponsor, NC, IRB, or regulatory authorities. All handling of personal data will comply with the GCP Guidelines and follow strictly the legal and national requirements of GDPR. For any additional question please contact the ESAIC Data Protection Officer at privacy@esaic.org or Rue des comédiens 24, 1000 Brussels, Belgium.

Appendix 6E (Lawfulness of processing of data – GDPR) can be used to give an overview to the patients of the processing of their data. The first part of the document details the information that can be given to the patient while the second part explains the situation to the local PI.

Appendix 12 (Data Protection Overview) is destined to any person involved in the ARCTIC-I study to have a better understanding of the data flow and data storage of the study.

11.2 Pseudonymization

The eCRF, which will not include any names, initials, dates of birth or local hospital patient numbers, is individualised by a unique subject identifier (ccc-hhh-ppp). This subject identifier is composed of

three 3-digit codes for the country (ccc), hospital (hhh), and individual patient number (ppp), respectively. The key linking patient identity and subject identifier is the Confidential Patient Logsheet (Appendix 8) which will be kept in the aforementioned locked cabinet/office. Data from patients that died before IC could be obtained must be irreversibly anonymised, i.e., their personal data will not be written in the log sheet or any other document. Data protection in the database will be guaranteed through encoding and the use of a secured database with restricted access by individual log-in and gradated user rights. Further, only encrypted data will be stored centrally.

11.3 Withdrawal, Deletion of Data

Patients who wish to withdraw from the study may do so at any point. In this case, no further data will be collected, while already collected data will be discarded. Withdrawn participants will be replaced in order to reach the projected sample size, which might necessitate extension of the inclusion period.

12 Publication Policy

12.1 Dissemination of Results and Authorship Rules

The main results of ARCTIC-I and its sub-studies will be published in peer-reviewed international medical journals and presented at Euroanaesthesia and at national meetings by members of the SC or their delegates, like NC. ESAIC will be acknowledged as sponsor in all publications and presentations. Anonymity of the participants is guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

The members of the writing group, the SC and the 'ARCTIC-I Investigators' will be authors of the publications derived from ARCTIC-I. When submitting a manuscript, the corresponding author will specify the individuals' names being part of the ARCTIC-I Investigators. Both the names of the writing group (authors) and the names of the ARCTIC-I Investigators (collaborators) will be trackable via PubMed.

**Anaesthesiological Routine Care for Thrombectomy
in Cerebral Ischaemia (ARCTIC-I):
A multicentre prospective observational study**

Author One, Author Two, Author Three, Author Four, Author Five, Author Six,
Author Seven, Author Eight, Author Nine, Author Eleven, Author Twelve, Author
Thirteen, Author Fourteen, ..., and the ARCTIC-I Investigators.

ARCTIC-I Investigators: All contributing collaborators are listed in the supplement.
Funding: European Society of Anaesthesiology and Intensive Care.

The number of collaborators and authors will be determined according to the following rules:

# of complete datasets	10 to 24	25 to 49	50 to 74	75 to 99	100 to 124	125 to 149	150 to 174	175 to 199	200 to 224	225 to 249	250 & more
# of collaborators	1	2	2	3	3	4	4	5	5	6	6
# of authors	0	0	1	1	2	2	3	3	4	4	5

Decisive for the count of patients is that they were correctly included, followed until day 90, and completely documented in the eCRF. The local PI will be asked to submit names of staff actively involved from their institution in the end of study reporting form (Appendix 11). Besides, each person who has supported the study on site according to the task delegation form (Appendix 5) will receive a certificate from ESAIC for their contribution to ARCTIC-I.

12.2 Nested Substudies

Local or national nested cohorts addressing additional questions, i.e. issues not addressed in ARCTIC-I, and collecting additional data while sharing part of the variables collected for ARCTIC-I, are allowed under the following conditions: nomination of a separate sponsor (i.e., other than the ESAIC), separate ethical approval, separate informed consent, independent data management, and approval of the study proposal by the SC. The publication of the main results of ARCTIC-I will precede publication of any nested substudy.

12.3 Secondary Analyses, Data Sharing

After publication of the pooled results, centres will be allowed to use their own anonymised data for local presentation and publication (except for duplicate data publication). The anonymised pooled dataset may be available for secondary analyses upon specific request to the SC in form of a detailed study proposal. The final approval of these potential secondary analyses rests with the SC. Prior to journal submission, any paper originating from the pooled data will be reviewed by the SC that is also entitled to require revisions. Requests for data sharing for individual-level meta-analyses shall be addressed to the sponsor and the SC. The sponsor of the study (ESAIC CTN) can use anonymised pooled data for internal analyses and educational purposes.

13 Literature

1. Johnston SC, Mendis S, Mathers CD. Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modelling. *Lancet Neurol.* 2009;8(4):345-354. doi:10.1016/S1474-4422(09)70023-7
2. Béjot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. *Press Medicale.* 2016;45(12):e391-e398. doi:10.1016/j.lpm.2016.10.003
3. Beumer D, Mulder MJHL, Saiedie G, et al. Occurrence of intracranial large vessel occlusion in consecutive, non-referred patients with acute ischemic stroke. *Neurovascular Imaging.* 2016;2(11):1-6. doi:10.1186/s40809-016-0022-5
4. Goyal M, Menon BK, Van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet.* 2016;387(10029):1723-1731. doi:10.1016/S0140-6736(16)00163-X
5. Wahlgren N, Moreira T, Michel P, et al. Mechanical thrombectomy in acute ischemic stroke: Consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. *Int J Stroke.* 2016;11(1):134-147. doi:10.1177/1747493015609778
6. Talke PO, Sharma D, Heyer EJ, Bergese SD, Blackham KA, Stevens RD. Society for Neuroscience in Anesthesiology and Critical Care Expert consensus statement: anesthetic management of endovascular treatment for acute ischemic stroke. *J Neurosurg Anesthesiol.* 2014;26(2):95-108. doi:10.1097/ANA.0000000000000042
7. Davis MJ, Menon BK, Baghirzada LB, et al. Anesthetic management and outcome in patients during endovascular therapy for acute stroke. *Anesthesiology.* 2012;116(2):396-405. doi:10.1097/ALN.0b013e318242a5d2
8. Schönenberger S, Hendén PL, Simonsen CZ, et al. Association of General Anesthesia vs Procedural Sedation With Functional Outcome Among Patients With Acute Ischemic Stroke Undergoing Thrombectomy. *JAMA.* 2019;322(13):1283. doi:10.1001/jama.2019.11455

9. Venema AM, Uyttenboogaart M, Absalom AR. Land of confusion: anaesthetic management during thrombectomy for acute ischaemic stroke. *Br J Anaesth.* 2019;122(3):300-304. doi:10.1016/j.bja.2018.12.004
10. Hindman BJ, Dexter F. Anesthetic Management of Emergency Endovascular Thrombectomy for Acute Ischemic Stroke, Part 2: Integrating and Applying Observational Reports and Randomized Clinical Trials. *Anesth Analg.* 2019;128(4):706-7017. doi:10.1213/ANE.0000000000004045
11. Bruno A, Akinwuntan AE, Lin C, et al. Simplified modified Rankin scale questionnaire: reproducibility over the telephone and validation with quality of life. *Stroke.* 2011;42(8):2276-2279. doi:10.1161/STROKEAHA.111.613273
12. Kasner SE. Clinical interpretation and use of stroke scales. *Lancet Neurol.* 2006;5(7):603-612. doi:10.1016/S1474-4422(06)70495-1
13. Harrell FEJ. *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis.* Springer International Publishing Switzerland 2015; 2015. doi:10.1007/978-3-319-19425-7_3
14. Nouh A, Remke S, Ruland S. Ischemic posterior circulation stroke: a review of anatomy, clinical presentations, diagnosis, and current management. *Front Neurol.* 2014;5(30). doi:10.3389/fneur.2014.00030
15. Kaptchuk TJ. Powerful placebo: The dark side of the randomised controlled trial. *Lancet.* 1998;351(9117):1722-1725. doi:10.1016/S0140-6736(97)10111-8
16. Gale EAM. The Hawthorne studies - A fable for our times? *Q J Med.* 2004;97(7):439-449. doi:10.1093/qjmed/hch070

14 List of appendices

Appendix 1	Synopsis (identical to protocol section 1.1)
Appendix 2	Timeline
Appendix 3	Invitation to pre-study survey
Appendix 4	Approval documentation coversheet
Appendix 5	Task delegation form
Appendix 6A	Patient information only (in case of waiver)
Appendix 6B	Patient information and informed consent form
Appendix 6C	Legal representative's information and informed consent form
Appendix 6D	Patient information and retroactive informed consent form
Appendix 6E	Lawfulness of processing data
Appendix 7	Screening list
Appendix 8	Confidential patient log sheet
Appendix 9A	Confidential patient identification coversheet
Appendix 9B	Data collection form ('paper CRF')
Appendix 10	Glossary to data collection form
Appendix 11	End of study reporting form
Appendix 12	Data protection overview

15 Protocol Changes

15.1 Rights and obligations

Only the SC is entitled to amend the protocol. NC and local PI will receive notification of changes and will be required to submit amendments locally. Subsequently, documentation of the amendments' approval will be provided to the sponsor. Substantial amendments of the protocol will only be implemented after approval by the responsible IRB. All non-substantial amendments like administrative changes will be communicated to the IRB as necessary by the PI.

15.2 History of protocol changes

The protocol hasn't been changed so far.

16 Protocol Signature Sheet

Chief Investigator

(Place, Date)

(Name, Signature)

Sponsor

(Place, Date)

(Name, Signature)

Local Principal Investigator

(Centre)

(Place, Date)

(Name, Signature)