BMJ Open

# Direct transfer to angiosuite for patients with severe acute stroke treated with thrombectomy: the multicenter randomized DIRECT ANGIO trial protocol



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-040522 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 22-May-2020 |





| | |
|---|---|
| Complete List of Authors: | Riou-Comte, Nolwenn<br>Zhu, François<br>CHERIFI, Aboubaker; CHU Nancy, INSERM CIC-IT 1433<br>Richard, Sébastien<br>Nace, Lionel<br>Audibert, Gérard; CHRU Nancy, Hôpital Central, Service d'Anesthésie-Réanimation<br>ACHIT, Hamza; Centre Hospitalier Universitaire de Nancy, CIC-1433 Epidémiologie clinique,<br>Costalat , Vincent ; Centre Hospitalier Universitaire de Montpellier,<br>Arquizan, Caroline<br>Beaufils, Olivier<br>Consoli, Arturo; Azienda Ospedaliero Universitaria Careggi, Neuroradiology; Hopital Foch, Neuroradiology<br>Lapergue, Bertrand<br>Loeb, Thomas<br>Rouchaud, Aymeric<br>Macian, Francisco<br>Cailloce, Dominique<br>Biondi, Alessandra<br>Moulin, Thierry<br>Desmettre, Thibaut; University of Franche Comté, Emergency<br>Marnat, Gaultier<br>Sibon, Igor; CHU Bordeaux,<br>Combes, Xavier<br>Lebedinsky, Ariel<br>Vuillemet, Francis<br>Kempf, Nicolas<br>Pierot, Laurent<br>Moulin, Solene<br>Lemmel, Philippe<br>Mazighi, Mikael<br>Blanc, Raphael<br>Sabben, Candice<br>Schluck, Eric<br>Bracard, Serge<br>Anxionnat, René<br>Guillemin, Francis<br>HOSSU, Gabriela; CHU Nancy, INSERM U1254; CHU Nancy, CIC-IT 1433 |

| | |
|---|---|
| | Gory, Benjamin; Hôpital Central, Neuroradiology |
| Keywords: | Interventional radiology < RADIOLOGY & IMAGING, STROKE MEDICINE, Clinical trials < THERAPEUTICS |
| | |

*I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.*

*The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.*

*Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.*

# Direct transfer to angiosuite for patients with severe acute stroke treated with thrombectomy: the multicenter randomized DIRECT ANGIO trial protocol

Nolwenn Riou-Comte,[1] François Zhu,[2] Aboubaker Cherifi,[3] Sébastien Richard,[1,4] Lionel Nace,[5] Gérard Audibert,[6] Hamza Achit,[7] Vincent Costalat,[8] Caroline Arquizan,[9] Olivier Beaufils,[10] Arturo Consoli,[11] Bertrand Lapergue,[12] Thomas Loeb,[13] Aymeric Rouchaud,[14] Francisco Macian-Montoro[15], Dominique Cailloce,[16] Alessandra Biondi,[17] Thierry Moulin,[18] Thibaut Desmettre,[19] Gaultier Marnat,[20] Igor Sibon,[21] Xavier Combes,[22] Pablo A. Lebedinsky,[23] Francis Vuillemet,[24] Nicolas Kempf,[25] Laurent Pierot,[26] Solène Moulin,[27] Philippe Lemmel,[28] Mikael Mazighi,[29] Raphaël Blanc,[29] Candice Sabben,[30] Eric Schlück,[31] Serge Bracard,[2,3] René Anxionnat,[2,3] Francis Guillemin,[5] Gabriela Hossu,[3] Benjamin Gory,[2,3] on behalf of the DIRECT ANGIO Investigators*

[1] Université de Lorraine, CHRU-Nancy, Department of Neurology, Stroke Unit, F-54000, Nancy, France.

[2] Université de Lorraine, CHRU-Nancy, Department of Diagnostic and Therapeutic Neuroradiology, F-54000 Nancy, France.

[3] CIC 1433 Technological Innovation, Nancy University Hospital, Université de Lorraine, Nancy, France.

[4] CIC 1433 Plurithematic, Nancy University Hospital, Université de Lorraine, Nancy, France.

[5] Université de Lorraine, CHRU-Nancy, Emergency and Reanimation Department, F-54000, Nancy, France.

[6] Université de Lorraine, CHRU-Nancy, Department of Anesthesiology and Critical Care Medicine, F-54000 Nancy, France.

[7] CIC 1433 Clinical Epidemiology, Nancy University Hospital, Université de Lorraine, Nancy, France.

[8] Department of Neuroradiology, CHRU Gui de Chauliac, Montpellier, France.

[9] Department of Neurology, CHRU Gui de Chauliac, Montpellier, France.

[10] Department of Emergency, CHRU Gui de Chauliac, Montpellier, France.

[11] Department of Diagnostic and Interventional Neuroradiology, Foch Hospital, Versailles Saint-Quentin en Yvelines University, Suresnes, France.

[12] Department of Neurology, Stroke Unit, Foch Hospital, Versailles Saint-Quentin en Yvelines University, Suresnes, France.

[13] Emergency Medical Services (SAMU) 92, Raymond Poincaré Hospital, Garches, France.

[14] Department of Interventional Neuroradiology, CHU Dupuytren, Limoges, France.

[15] Department of Neurology, Stroke Unit, CHU Dupuytren, Limoges, France.

[16] SAMU/SMUR, CHU Dupuytren, Limoges, France.

[17] Department of Neuroradiology and Endovascular Therapy, Besançon University Hospital, Besancon, France.

[18] Department of Neurology, Stroke Unit, Besançon University Hospital, Besancon, France.

[19] Department of Emergency, Besançon University Hospital, Besançon, France.

[20] Department of Neuroradiology, University Hospital of Bordeaux, Bordeaux, France.

[21] Department of Neurology, Stroke Center, University Hospital of Bordeaux, Bordeaux, France.

[22] Department of Emergency, University Hospital of Bordeaux, Bordeaux, France.

[23] Department of Interventional Neuroradiology, Hospital of Colmar, Colmar, France.

[24] Department of Neurology, Stroke Unit, Hospital of Colmar, Colmar, France.

[25] Department of Emergency, Hospital of Colmar, Colmar, France.

[26] Department of Neuroradiology, Université Reims Champagne-Ardenne, Hospital Maison-Blanche, CHU de Reims, Reims, France.

[27] Department of Neurology, Stroke Unit, Université Reims Champagne-Ardenne, Hospital Maison-Blanche, CHU de Reims, Reims, France.

[28] SAMU/SMUR, CHU Reims, Reims, France.

[29] Department of Interventional Neuroradiology, Rothschild Foundation Hospital, Paris, France.

[30] Department of Neurology, Stroke Unit, Rothschild Foundation Hospital, Paris, France.

[31] Department of Neurology, Stroke Unit, Mulhouse, France.

**Correspondence to**

Dr Benjamin Gory, CHRU Nancy, Service de Neuroradiologie Diagnostique et Thérapeutique, Nancy 54035, France ; benjagory@gmail.com

**Cover title:** DIRECT ANGIO Trial Protocol

**Word count:** 4988

**Itemized list of tables and figures:**

**Figure 1.** CONSORT diagram of the DIRECT ANGIO trial illustrating the randomization and flow of patients in the study.

**Table 1.** DIRECT ANGIO inclusion and exclusion criteria.

**Strengths and limitations of this study**

- DIRECT ANGIO trial is the first multicenter randomized clinical trial to directly comparing direct angiosuite transfert (DAT) versus standard management for highly suspected patients with anterior circulation large vessel occlusion ischemic stroke.
- DIRECT ANGIO aims to provide further evidence of the clinical benefit of DAT, as well as socioeconomic positive impact for the global health system.
- The multicenter setting and large pragmatic inclusions criteria compatible with current clinical practice and recommendations will allow external validity.
- Primary outcome measure will allow evaluation of functional independence at 90 days. Secondary outcomes will measure different important aspects of care, especially the safety and medico-economic impact.

## ABSTRACT

**Introduction** Mechanical thrombectomy (MT) increases functional independence in acute ischemic stroke patients with anterior circulation large vessel occlusion (LVO), and the probability to achieve functional independence decreases 20% for each 1 hour delay to reperfusion. Therefore, we aim to investigate whether direct angiosuite transfer (DAT) is superior to standard imaging/emergency department-based management in achieving 90-day functional independence in patients presenting with an acute severe neurological at pre hospital stage deficit likely due to LVO requiring emergent treatment with MT.

**Methods and analysis** DIRECT ANGIO (Effect of DIRECT transfert to ANGIOsuite on functional outcome in patient with severe acute stroke treated with thrombectomy: the randomized DIRECT ANGIO Trial) trial is an investigator-initiated, multicenter, prospective, randomized, open-label, blinded endpoint (PROBE) study. Eligibility requires a patient ≤75 years, pre-stroke modified Rankin Scale (mRS) 0-2, presenting an acute severe neurological deficit and admitted within 5 hours of symptoms onset in an endovascular-capable center. A total of 208 patients are randomly allocated in a 1:1 ratio to DAT or standard management before hospital admission. The primary outcome is the rate of patients achieving a functional independence, assessed as mRS 0-2 at 90 days. Secondary endpoints include patients presenting confirmed LVO, patients eligible to intravenous thrombolysis alone, patients with intracerebral hemorrhage and stroke-mimics, intra-hospital time metrics, early neurological improvement (reduction in National Institutes of Health Stroke Scale by ≥8 points or reaching 0-1 at 24 hours), and mRS overall distribution at 90 days and 12 months. Safety outcomes are death and intracerebral hemorrhage transformation. Medico-economics analyses include health-related quality of life, and costs utility assessment.

**Ethics and dissemination** The DIRECT ANGIO trial was approved by an independent ethics committee. Study began in April 2020. Results will be published in an international peer-reviewed medical journal.

**Trial registration number** NCT03969511.

# INTRODUCTION

## Background and rationale

Strokes remain a large cause of death and disability, and prevalence of large vessel occlusion (LVO) among patients with suspected acute ischemic stroke ranged from 13% to 52%, with overall prevalence of 30.0%.[1] Mechanical thrombectomy (MT) has become the standard of care for reperfusion therapies in acute LVO strokes,[2] and is strongly dependent on time with 20% decreased probability of functional independence for each 1 hour delay to reperfusion.[3] HERMES meta-analysis demonstrated that prognosis is directly related to combined ischemic core volume with age and expected imaging-to-reperfusion time after successful reperfusion.[4] While the stroke network reorganization reduced symptoms-to-needle time and increased accessibility to endovascular-capable centers, it is currently crucial to achieve fast triage and initiation of endovascular therapy. To date, patients with a suspected stroke are firstly admitted in the radiology/emergency department and secondary transfer to the angiosuite for MT if LVO is confirmed. This approach results in a prolonged delays in delivering definitive therapy in the setting of LVO, whereas the angiosuite has imaging facilities to rule out intracranial hemorrhage (ICH) and confirm proximal arterial occlusion (Conebeam CT [CBCT] and Conebeam CT-angiography [CBCT-A]), and therefore the ability to triage patients. Retrospective studies reported a clinical benefit of a direct angiosuite transfer (DAT) of stroke patients.[5-7] The aim of DIRECT ANGIO (Effect of DIRECT transfert to ANGIOsuite on functional outcome in patient with severe acute stroke treated with thrombectomy: the randomized DIRECT ANGIO Trial) trial is to compare the effectiveness and safety of DAT versus conventional management in patients presenting acute severe neurological deficit at pre hospital stage and thus due to LVO eligible to MT.

## Objectives

Primary objective

The primary objective of the study is to determine whether DAT compared to conventional management is associated with improved 90-day functional independence in patients presenting with pre hospital acute severe neurological deficit likely to require treatment with MT. Functional independence is defined as am mRS score 0-2 at 90 days.

Secondary objectives

The study will also explore the feasibility, efficacy and safety of DAT, as well as cost-utility assessment.

## Trial design

DIRECT ANGIO trial is a prospective, multicenter, randomized, open-label, blinded-endpoint (PROBE), two-arms, clinical trial to compare the effectiveness and safety of DAT compared to standard management in acute pre hospital severe deficit suspected to LVO.

## CONSORT diagram

Figure 1 shows the shows the Consolidated Standards of Reporting Trials (CONSORT) diagram of the DIRECT ANGIO trial.[8]

## METHODS AND ANALYSIS

### Participants, interventions and outcomes

This manuscript was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines.[9]

### Study setting

The DIRECT ANGIO trial takes place in 10 comprehensive stroke centers in France (Nancy, Besançon, Colmar, Strasbourg, Reims, Paris Fondation Adolphe de Rothschild, Suresnes Foch, Montpellier, Limoges, Bordeaux).

### Eligibility criteria

Inclusion criteria

Adult patients ≤75 year-old, pre-stroke modified Rankin Scale [mRS] score 0-2, with acute severe neurological deficit at pre hospital stage and directly admitted at an endovascular-capable center within 5 hours of symptoms onset and who meet all eligibility criteria is considered for study enrolment. Secondary transfer patients are not eligible in the trial. As the study objective is to target a completely autonomous population that can be assumed to have neither cognitive problems, nor a history of stroke age was limited to 75 years old. **Table 1** lists the inclusion and exclusion criteria.

As of the phone call from the emergency rescue service, inclusion and exclusion criteria are checked and then the patient randomize during the hospital travel (before admission). Oral informed consent will be sought via telephone conversations from patient or from their relatives. Emergency consent procedure may be considered if consent is not possible by the subject or a proxy. Written informed consent for continuation will be then collect as soon as possible, within 3 months.

### Interventions

Experimental arm (DAT approach)

Upon arrival in angiosuite and after rapid neurological examination (using National Institutes of Health Stroke Scale [NIHSS] and mRS scores) and blood sample, the patient undergoes CBCT in order to exclude non-ischemic stroke and CBCT-A to confirm LVO (tandem, intracranial internal carotid artery, M1 or proximal M2 segment of the middle cerebral artery, basilar artery or P1 segment of the posterior cerebral artery). Several managements can be performed:

1. Whatever the NIHSS score at admission, patients with no ICH and with LVO were treated with MT and, if eligible, with intravenous recombinant tissue plasminogen activator (IV rt-PA) as soon as possible. A low Alberta Stroke Program Early CT Scale (ASPECTS) or low collateral score was not an exclusion criterion for MT.
2. Patients with no ICH and with a distal vessel occlusion were treated with IV rt-PA alone, if eligible.
3. Patients with no ICH and with no arterial occlusion were started on IV rt-PA, if eligible, and received an additional stroke imaging (MRI or CT) to decide on further treatment.
4. Patients with an ICH and no occlusion were treated as per institutional standards.
5. Patients with an ICH and LVO were treated with MT after an individualized case discussion between neurologist, neuroradiologist and patient or his/her proxy.

However, the subject will remain in the intention-to-treat population.

Control Arm (conventional approach)

Arrival is in the imaging/emergency department and after neurological examination and blood sample, patient undergoes stroke imaging (multimodal MRI or CT). After LVO confirmation, patient is treated with IV rt-PA, if eligible, and transfer to angiosuite for MT as soon as possible. In the setting of no LVO, patients are treated according to as per institutional standards.

**Clinical assessment**

Baseline characteristics include pre-stroke mRS score, symptoms, and intra-hospital time metrics. Neurological deficit is assessed using the NIHSS score at baseline, after 24 (±6) hours, at 5-7 days (or discharge if earlier), and at 90 (±15) days. At 90 (±15) days and 12 (±1) months, outcome assessment is also comprise the mRS score and health-related quality of life (EQ-5D-5L).

**Imaging protocol**

In the standard management group, baseline imaging (multimodal MRI or CT) and in the DAT group (CBCT and CBCT-A) is performed. Baseline imaging, angiographic imaging before, and at the end of endovascular procedure as well as follow-up imaging at 24 (±6) hours for ICH are assessed by an independent core laboratory. The core laboratory evaluate the findings on the baseline imaging for the ASPECTS (range 0 to 10, with 1 point subtracted for any evidence of early ischemic change in each defined region on the CT scan or diffusion-weighted imaging sequence),[10] baseline vessel imaging (CT angiogram or MR angiogram) for the location of the occlusion. The core laboratory assessed also angiographic outcomes on digital subtraction angiography, using the modified Thrombolysis in Cerebral Infarction (mTICI) score, which ranges from 0 (no reperfusion) to 3 (complete reperfusion).[11] Radiological outcome measures will be centrally analyzed, blinded to treatment allocation.

**Outcomes**

Primary outcome

The proportion of patients with functional independence defined as mRS 0-2 at 90 (±15) days between DAT and conventional admission in patients ≤75 year-old presenting an acute severe neurological deficit at pre hospital stage probably related to LVO stroke and directly admitted at an endovascular-capable center within 5 hours of onset.

Secondary outcomes

1. Secondary feasibility endpoints:
   - Rate and site of the confirmed LVO.
   - Intra-hospital time metrics (admission to imaging/needle/puncture/reperfusion, imaging to puncture/reperfusion, and puncture to reperfusion).
2. Secondary efficacy endpoints:
   - Quality of reperfusion according to the mTICI score.
   - Procedural complications (embolus in a new territory, perforation and dissection).
   - Clinical status with the NIHSS score at 24 (±6) hours, 5-7 days (or discharge if earlier), 90 (±15) days.
   - Blinded 12 (±1)-month mRS score.
3. Secondary safety endpoints:
   - Rate of patients eligible to IV rt-PA alone.
   - Rate of ICH.
   - Rate of stroke mimics
   - Rate of patients requiring secondary stroke imaging.
   - Rate of intracerebral hemorrhagic transformation of ischemic stroke according to the European Cooperative Acute Stroke Study III classification (12).
   - Rate of mortality at 90 (±15) days and 12 (±1) months
   - Rate of decompressive hemicraniectomy.
4. Cost-utility assessment include health-related quality of life assessment at 90 (±15) days and 12 (±1) months and assessment of costs from the time of randomization to the 12-month follow-up:
   - Costs of hospitalization.
   - Institutionalized living.
   - Outpatient care.
   - Informal care provided by relatives.
   - Cost of lost productivity.

**Recruitment**

Patients are expected to be included during a 30 months period starting in april 2020.

2016–2017: Protocol, approvals from ethics committee (CPP IDF I) and the French Medicine Agency (Agence Nationale de Sécurité du Médicament et des produits de santé, ANSM); trial tool development (online case report form (CRF) and randomisation system).

2020-2023: Inclusion of patients.

2023-2024: cleaning and closure of the database, data analyses, writing of the manuscript and submission for publication.

**Trial status**

The current protocol is 2.0. Study started enrolment in 27th april 2020. To date (14h May 2020), 0 patients have been randomised in the study.

**Patient and public involvement**

Patients will not be invited to comment on study design or conduction of the trial.

## METHODS: ASSIGNMENT OF INTERVENTIONS

**Allocation and sequence generation**

After inclusion and before arrival, patients are randomized in two arms using a web-based centralized system with a 1:1 ratio to either DAT or standard management **(Figure 1)**. The randomization sequence is provided by an independent statistician (who did not take part in assessing the patients at any point in the study) using computer-generated random numbers. The randomization sequence is implemented in the electronic case report form system to ensure a centralized real-time randomization procedure. Subjects are enrolled and randomized by emergency physicians, neurologists or neuroradiologists.

**Blinding**

For the primary outcome, a centralized certified clinical research nurse from the trial center, who will be unaware of the treatment group assignments, records the mRS at 90 days and 1 year by telephone with the patient, proxy, or health care provider.[8,9] All neuroimaging readings including determination of the ASPECTS score, arterial occlusion site, clot burden score, and hemorrhagic transformation are performed by the imaging core laboratory, which is also blinded to procedure allocation.

## METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

**Data collection and management**

The entire study is conducted using eCRFs, where all clinical data on enrolled subjects are entered (single-keyed) by the site personnel. The eCRF was developed using CleanWeb (Tentelemed) software. The essential data necessary for monitoring the primary and secondary endpoints are identified and managed at regular intervals throughout the trial. Data are monitored by members of the CIC 1433 Technological

Innovation of Nancy University Hospital using the predefined rules and queries are automatically edited. Lastly, overall automated monitoring is performed by the data manager after completion of data entry. In cases of discrepancies, queries can be edited to resolve the problems encountered.

**Patient withdrawal**

Evaluated procedure is tested during the management of endovascular thrombectomy. Nevertheless, participant can withdraw consent at any time without need for further explanation. Data will be destroyed and a new patient will be randomized for the complete sample size.

**Statistical methods**

Sample size estimation

Based on the literature,[2,5-7] we expect a 90-day mRS 0-2 rate of 30% in the control arm. We assume that DAT approach (intervention arm) will be associated with an absolute increase of 20% (corresponding to a 90-day mRS 0-2 rate of 50%) due to 1 hour delay to reperfusion reduction. To detect this effect size, with a two-sided test at the 0.05 level of significance, and a power of 80%, 93 subjects per arm will be required. To account for an anticipated rate of 10% drop-out (i.e. patients lost to follow-up and without LVO), we planned to include a total of 208 subjects (104 per arm).

Interim analysis

One interim analysis is planned once 50% of patients have been included, for the study to be stopped early owing either to compelling evidence of efficacy (using a pre-specified Haybittle–Peto efficacy boundary with an alpha level of 0.001) or of futility. The independent data and safety monitoring board (DSMB) could recommend stopping the study if prolongation of the trial clearly compromises patient safety (in case of serious adverse reactions (SARs) or suspected unexpected serious adverse reactions (SUSARs)). The steering committee will be responsible to continue, hold or stop the study based on the DSMB recommendations.

Statistical analyses

Statistical analyses will be carried out independently by the CIC 1433 Technological Innovation of Nancy University hospital under the responsibility of Professor Jacques Felblinger, where statisticians and investigators will be aware of the treatment group allocation. Baseline characteristics will be described for each treatment group; categorical variables will be expressed as frequencies and percentages and quantitative variables will be expressed as means ± standard deviation or medians (interquartile range) for non-Gaussian distribution. Normality of distributions will be assessed graphically and by using the Shapiro-Wilk test. No formal statistical comparisons of baseline characteristics will be done; clinical importance of any imbalance will be noted. All analyses will be performed using all randomized participants based on their original group of randomization, according to the intention-to-treat principle. The intention to treat analysis will analyze all included patients and patients will be analyzed according to the randomization scheme. This analysis will include all patients with LVO but also with ICH, stroke mimics, ischemic stroke without LVO

at admission, independently of receiving MT or not. A per protocol analysis will be considered only for primary endpoint as a secondary analysis. Per protocol population will include all randomized patients excluding those without LVO strokes. Furthermore, the costs avoided analysis will take into account a cost-difference between the two randomization arms at 12 (±1) months and will extrapolate this difference over an expected lifetime using a Markov model. The cost-utility analysis will be also performed with health-related quality of life estimated with EQ-5D-5L questionnaire. The CONSORT statement recommendations will be applied for drafting the final report.

## METHODS: MONITORING

### Data monitoring

Before the start of the study, neurological and neuroradiological medical and paramedical teams are trained at each site for the study protocol by study coordinators. Physicians are in charge of patient screening and inclusion. Data will be collected in a web-based eCRF by trial personnel. Each centre will only have access to site-specific data. Each patient will receive a unique trial identification number. Only the investigators and research team will have access to any protected health information of study participants and any study data.

Data monitoring and quality control will be conducted in each center after the first 10 inclusions then after the next 20 inclusions and at the end of the study by official representatives of the study promoter (Department of Clinical Research and Innovation, Nancy University Hospital). Data will be handled according to the French law. All originals records (including consent forms, reports of SUSARs and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years. Only the principal investigators and the statistician will have access to the final dataset.

### Harms

Every adverse event that could be related to the trial will be reported to the trial coordinating center. According to the French law, all suspected serious adverse events will be reported to the ANSM. The DSMB will also be informed. DSMB is independent from the trial investigators and will perform an ongoing review of safety parameters and study conduct. The members of the DSMB are not participants of the DIRECT ANGIO consortium and not involved in the clinical trial. The DSMB is composed by one neuroradiologist, one pharmacovigilance specialist and one methodologist, who are not participating in the study and are not affiliated with the sponsor and who have skills and expertise in clinical neuroscience and clinical research. The DSMB will be responsible for safeguarding the interests of trial participants, assessing the safety of the interventions during the trial and for monitoring the overall conduct of the trial. DSMB could also formulate recommendations related to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control. No formal criteria are set to stop the study. However, recommendations for pausing or

stopping the study could be made by DSMB in case of SARs and SUSAR. The scientific committee will be responsible for promptly reviewing the DSMB recommendations and to decide whether to continue, hold or stop the study, and to determine whether amendments to the protocol are needed.

## ETHICS AND DISSEMINATION

Any change to eligibility criteria, outcomes and analyses will be communicated to investigators, the ethics committee and the ANSM to obtain their approval.

### Consent or assent

Whenever possible to include the patient, written inform consent will be searched. Nevertheless, related to neurological injury and emergency, the patient may be unable to provide written informed consent. In this case, written informed consent could be obtained from the patient next of kin if immediately available. Otherwise, an emergency consent procedure is used with investigator signature countersigned by an independent physician. As soon as possible after recovery, written informed consent from

### Study organization and funding

DIRECT ANGIO is a French-funded, investigator-initiated and conducted clinical trial. Coordination and project management will be provided by Prof. Benjamin Gory (Department of Diagnostic and Therapeutic Neuroradiology, University Hospital Nancy, France). The study is sponsored by Centre Hospitalier Regional Universitaire (CHRU) Nancy. DIRECT ANGIO is registred at ClinicalTrials.gov (ClinicalTrials.gov Identifier NCT03969511).

## DISCUSSION

Few studies evaluated the impact of DAT in the management of suspected LVO stroke patients, especially in the setting of primary admission. DIRECT ANGIO is a French PROBE, two-arm randomized trial comparing DAT versus standard management for patients with acute severe neurological deficit before hospital admission and thus suspected to anterior circulation LVO eligible to MT. Randomization is performed before hospital admission and within 5 hours of onset. Primary endpoint is the 90-day functional independence. The study will provide efficacy and safety data as well as socioeconomic evidence for the DAT management for patients with acute severe stroke.

### Collaborators

**CHRU Nancy:** Benjamin Gory, Isabelle Costa, Serge Bracard, René Anxionnat, Marc Braun, Anne-Laure Derelle, Romain Tonnelet, Liang Liao, François Zhu, Emmanuelle Schmitt, Sophie Planel, Sébastien Richard, Lisa Humbertjean, Gioia Mione, Jean-Christophe Lacour, Nolwenn Riou-Comte, Gabriela Hossu, Marine Beaumont, Mitchelle Bailang, Gérard Audibert, Marie Reitter, Agnès Masson, Lionel Alb, Adriana Tabarna, Marcela Voicu, Iona Podar, Madalina Brezeanu.

**CHU Besançon:** Alessandra Biondi, Giovanni Vitale, Fortunato Di Caterino, Guillaume Charbonnier, Panagiotis Primikiris, Thierry Moulin, Elisabeth de Bustos Medeiros, Benjamin Bouamra, Louise Bonnet, Fabrice Vuillier, Thibaut Desmettre

**CH Colmar:** Pablo A. Lebedinsky, Mariano Musacchio, Frederico Bolognini, Francis Vuillemet, Nicolas Kempf,

**CH Mulhouse:** Eric Schlück, Mathilde Goudot, Alessandro Laporta.

**CHU Reims:** Sébastien Soize, Solène Moulin, Laurent Pierot, Pierre-François Manceau, Maher Sahnoun, Christophe Gelmini, Nathalie Caucheteux, Vi Tuan Hua, Isabelle Serre, Mickaël Hoang.

**CHU Bordeaux:** Catherine Pradeau, Gaultier Marnat, Florent Gariel, Xavier Barreau, Jérôme Berge, Louis Veunac, Patrice Menegon, Igor Sibon, Ludovic Lucas, Stéphane Olindo, Pauline Renou, Sharmila Sagnier, Mathilde Poli, Sabrina Debruxelles, Jean-Marc Mene, Musa Sesay.

**CHU Montpellier:** Vincent Costalat, Caroline Arquizan, Cyril Dargazanli, Grégory Gascou, Pierre-Henri Lefèvre, Imad Derraz, Carlos Riquelme, Nicolas Gaillard, Isabelle Mourand, Lucas Corti.

**Fondation Adolphe de Rothschild:** Michel Piotin, Raphael Blanc, Hocine Redjem, Simon Escalard, Jean-Philippe Desilles, Gabriele Ciccio, Stanislas Smajda, Mikael Mazighi, Mikael Obadia, Candice Sabben, Ovide Corabianu, Thomas de Broucker, Didier Smadja, Sonia Alamowitch, Olivier Ille, Eric Manchon, Pierre-Yves Garcia, Guillaume Taylor, Malek Ben Maacha.

**Hôpital Foch:** Adrien Wang, Serge Evrard, Maya.tchikviladze, Nadia Ajili, Bertrand Lapergue, David Weisenburger, Lucas Gorza, Oguzhan Coskun, Arturo Consoli, Federico Di Maria, Georges Rodesh, Morgan Leguen, Julie Gratieux, Fernando Pico, Haja Rakotoharinandrasana, Philippe Tassan, Roxanna Poll, Sylvie Marinier.

**CHU Limoges:** Aymerci Rouchaud, Suzana Saleme, Charbel Mounayer, Francisco Macian-Montoro, Dominique Cailloce.

**Contributors** NRC, AC, SR, LN, FG, GH and BG are members of DIRECT ANGIO scientific committee and contributed to the conception and design of the research protocol. NRC, AC, SR and BG provided critical skills concerning trial interventions and procedures. NRC and BG wrote the first version of the protocol. BG wrote this manuscript. GH designed the statistical analysis plan. NRC, FZ, AC, SR, FG, GH and BG are involved in acquisition, analysis and interpretation of the data. All authors revised the final protocol and approved his submission.

**Funding** DIRECT ANGIO trial was supported by funding from French Ministry of Health (Programme Hospitalier de Recherche Clinique Inter Régional (PHRC IR 2018) and from the university hospital of Nancy (PI: Benjamin Gory. Funding amount: 295 990 euros).

**Disclaimer** The funder had no role in study design, study conduction, writing or submitting the manuscript.

***Competing interests*** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Acknowledgments** DIRECT ANGIO boards and institutions: DSMB, CHRU Nancy, CIC-IT, CIC-EC, DRI.

**Patient consent for publication** Not required.

**Ethics approval** The DIRECT ANGIO study is conducted in accordance with the Declaration of Helsinki. The trial was approved by the ethics committee CPP IDF I on 27 September 2019 (approval number 2019-A01454-53) and ANSM on 26 September 2019 (approval number 2019-092600159).

## REFERENCES

1. Waqas M, Rai AT, Vakharia K, *et al*. Effect of definition and methods on estimates of prevalence of large vessel occlusion in acute ischemic stroke: a systematic review and meta-analysis. *J Neurointerv Surg* 2020;12:260-5.

2. Bracard S, Ducrocq X, Mas JL, *et al*. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol* 2016;15:1138-47.

3. Saver JL, Goyal M, van der Lugt A, *et al*. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA* 2016;316:1279-88.

4. Campbell BCV, Majoie CBLM, Albers GW, *et al*. Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. *Lancet Neurol* 2019;18:46-55.

5. Psychogios MN, Behme D, Schregel K, *et al*. One-stop management of acute stroke patients: minimizing door-to-reperfusion times. *Stroke* 2017;48:3152-5.

6. Ribo M, Boned S, Rubiera M, *et al*. Direct transfer to angiosuite to reduce door-to-puncture time in thrombectomy for acute stroke. *J Neurointerventional Surg* 2018;10:221-4.

7. Jadhav AP, Kenmuir CL, Aghaebrahim A, *et al*. Interfacility transfer directly to the neuroangiography suite in acute ischemic stroke patients undergoing thrombectomy. *Stroke* 2017;48:1884-9.

8. Schulz KF, Altman DG, Moher D, et al. Statement: updated guidelines for reporting parallel group randomised trials. Bmj 2010;2010.

9. Chan A-W, Tetzlaff JM, Gotzsche PC, et al. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;346:e7586.

10. van Swieten JC, Koudstaal PJ, Visser MC, *et al*. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604-7.

11. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.

12. Barber PA, Demchuk AM, Zhang J, *et al*. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. *Lancet* 2000;355:1670-4. [Erratum, Lancet 2000;355:2170.]

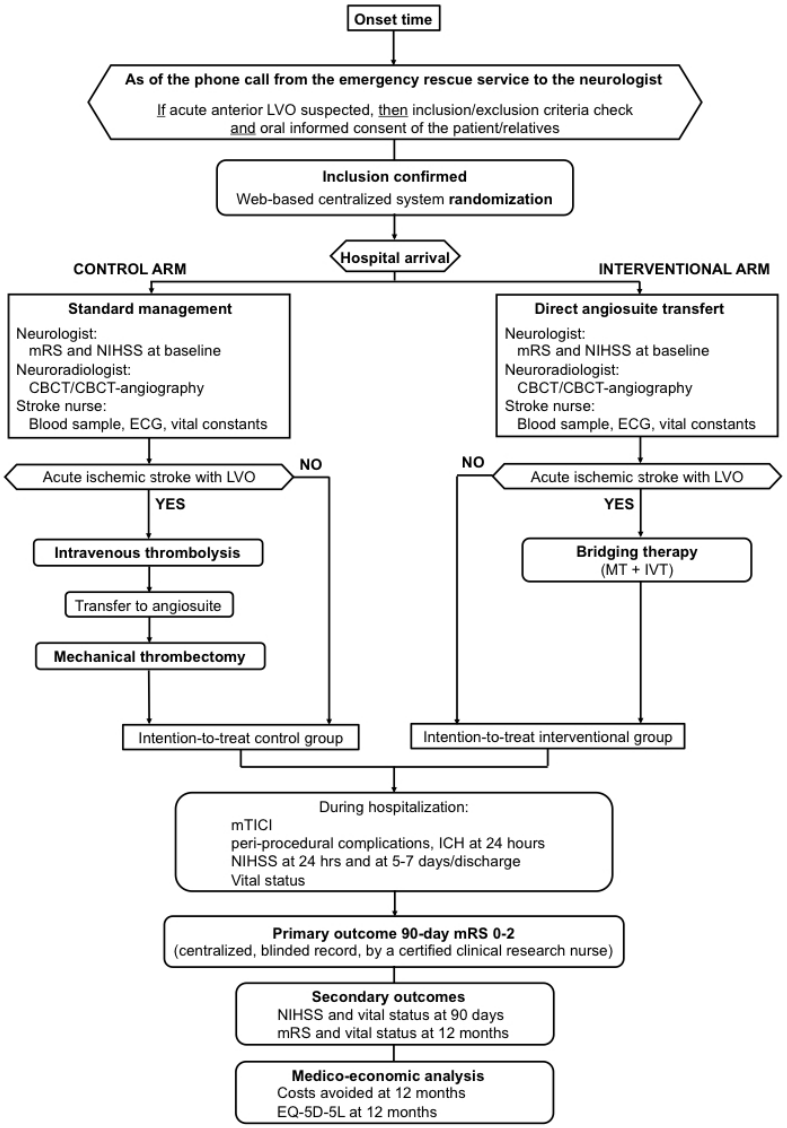
13. Zaidat OO, Yoo AJ, Khatri P, *et al*. Cerebral Angiographic Revascularization Grading (CARG) Collaborators; STIR Revascularization working group; STIR Thrombolysis in Cerebral Infarction (TICI) Task Force. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke* 2013;44:2650-63.

14. Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317-29.

**Table 1.** DIRECT ANGIO inclusion and exclusion criteria

| Inclusion | Exclusion |
|---|---|
| ✓ Adult ≤75 years<br>✓ Pre-stroke mRS 0-2<br>✓ Acute severe neurological deficit defined as:<br>• Hemiplegia/paresis<br>and<br>• ≥1 cortical symptom (apahsia, hemianospia, unilateral neglect, and/or gaze deviation)<br>✓ Projected last seen well time to hospital admission ≤5 hours<br>✓ Patients directly admitted to an endovascular-capable center<br>✓ Immediate availability of the angiosuite and endovascular treatment team at the admission<br>✓ Affiliation to / beneficiary of a social regime | ✓ Severe allergy to contrast agents<br>✓ Pregnant or breastfeeding women<br>✓ Consent refusal or opposition of the relatives<br>✓ Under legal protection<br>✓ Any terminal illness such that patient would not be expected to survive more than 90 days |

**Figure 1.** CONSORT diagram of the DIRECT ANGIO trial illustrating the randomization and flow of patients in the study. AOL, arterial occlusive lesion; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ECG, electrocardiogram; MT, mechanical thrombectomy; IVT, intravenous thrombolysis; mTICI, modified Thrombolysis In Cerebral Infarction; EVT, endovascular treatment; ICH, intracerebral hemorrhage; EQ-5D-5L, 5 dimensions and 5 levels EuroQol questionnaire.




254x375mm (72 x 72 DPI)

BMJ Open

# Direct transfer to angiosuite for patients with severe acute stroke treated with thrombectomy: the multicenter randomized DIRECT ANGIO trial protocol



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-040522.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 01-Sep-2020 |





| | |
|---|---|
| Complete List of Authors: | Riou-Comte, Nolwenn; CHRU de Nancy, Neurology, Stroke Unit<br>Zhu, François; CHRU de Nancy, Neuroradiology<br>CHERIFI, Aboubaker; CHU Nancy, INSERM CIC-IT 1433<br>Richard, Sébastien; CHRU de Nancy, Neurology, Stroke Unit<br>Nace, Lionel; CHRU de Nancy, Urgences<br>Audibert, Gérard; CHRU Nancy, Hôpital Central, Service d'Anesthésie-Réanimation<br>ACHIT, Hamza; Centre Hospitalier Universitaire de Nancy, CIC-1433 Epidémiologie clinique,<br>Costalat , Vincent ; Centre Hospitalier Universitaire de Montpellier,<br>Arquizan, Caroline; CHU Montpellier, Neurology, Stroke Unit<br>Beaufils, Olivier; CHU Montpellier, Urgences<br>Consoli, Arturo; Azienda Ospedaliero Universitaria Careggi, Neuroradiology; Hopital Foch, Neuroradiology<br>Lapergue, Bertrand; Hôpital Foch, Neurology, Stroke Unit<br>Loeb, Thomas; APHP, SAMU 92<br>Rouchaud, Aymeric; CHU Limoges, Interventional Neuroradiology<br>Macian, Francisco; CHU Limoges, Neurology, Stroke Unit<br>Cailloce, Dominique; CHU Limoges, SAMU<br>Biondi, Alessandra; CHU Besancon, Neuroradiology<br>Moulin, Thierry; CHU Besancon, Neurology, Stroke Unit<br>Desmettre, Thibaut; University of Franche Comté, Emergency<br>Marnat, Gaultier; CHU de Bordeaux, Neuroradiology<br>Sibon, Igor; CHU Bordeaux, Neurology, Stroke Unit<br>Combes, Xavier; CHU de Bordeaux, Anesthesiology<br>Lebedinsky, Ariel; CH Colmar, Neuroradiology<br>Vuillemet, Francis; CH Colmar, Neurology, Stroke Unit<br>Kempf, Nicolas; CH Colmar, SAMU<br>Pierot, Laurent; CHU Reims, Neuroradiology<br>Moulin, Solene; CHU Reims, Neurology, Stroke Unit<br>Lemmel, Philippe; CHU Reims, Urgences<br>Mazighi, Mikael; Fondation Rothschild, Interventional Neuroradiology<br>Blanc, Raphael; Fondation Rothschild, Interventional Neuroradiology<br>Sabben, Candice ; Fondation Rothschild, Neurology, Stroke Unit<br>Schluck, Eric; CH Mulhouse, Neurology, Stroke Unit<br>Bracard, Serge; CHRU de Nancy, Neuroradiology<br>Anxionnat, René; CHRU de Nancy, Neuroradiology<br>Guillemin, Francis; CHRU de Nancy, CIC EC<br>HOSSU, Gabriela; CHU Nancy, INSERM U1254; CHU Nancy, CIC-IT 1433 |

| | |
|---|---|
| | Gory, Benjamin; Hôpital Central, Neuroradiology |
| Primary Subject Heading: | Neurology |
| Secondary Subject Heading: | Radiology and imaging, Emergency medicine |
| Keywords: | Interventional radiology < RADIOLOGY & IMAGING, STROKE MEDICINE, Clinical trials < THERAPEUTICS |
| | |

*I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.*

*The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.*

*Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.*

# Direct transfer to angiosuite for patients with severe acute stroke treated with thrombectomy: the multicenter randomized DIRECT ANGIO trial protocol

Nolwenn Riou-Comte,[1] François Zhu,[2] Aboubaker Cherifi,[3] Sébastien Richard,[1,4] Lionel Nace,[5] Gérard Audibert,[6] Hamza Achit,[7] Vincent Costalat,[8] Caroline Arquizan,[9] Olivier Beaufils,[10] Arturo Consoli,[11] Bertrand Lapergue,[12] Thomas Loeb,[13] Aymeric Rouchaud,[14] Francisco Macian,[15] Dominique Cailloce,[16] Alessandra Biondi,[17] Thierry Moulin,[18] Thibaut Desmettre,[19] Gaultier Marnat,[20] Igor Sibon,[21] Xavier Combes,[22] Ariel P. Lebedinsky,[23] Francis Vuillemet,[24] Nicolas Kempf,[25] Laurent Pierot,[26] Solène Moulin,[27] Philippe Lemmel,[28] Mikael Mazighi,[29] Raphaël Blanc,[29] Candice Sabben,[30] Eric Schlück,[31] Serge Bracard,[2,3] René Anxionnat,[2,3] Francis Guillemin,[5] Gabriela Hossu,[3] Benjamin Gory,[2,3] on behalf of the DIRECT ANGIO Investigators*

[1] Université de Lorraine, CHRU-Nancy, Department of Neurology, Stroke Unit, F-54000, Nancy, France.

[2] Université de Lorraine, CHRU-Nancy, Department of Diagnostic and Therapeutic Neuroradiology, F-54000 Nancy, France.

[3] CIC 1433 Technological Innovation, Nancy University Hospital, Université de Lorraine, Nancy, France.

[4] CIC 1433 Plurithematic, Nancy University Hospital, Université de Lorraine, Nancy, France.

[5] Université de Lorraine, CHRU-Nancy, Emergency and Reanimation Department, F-54000, Nancy, France.

[6] Université de Lorraine, CHRU-Nancy, Department of Anesthesiology and Critical Care Medicine, F-54000 Nancy, France.

[7] CIC 1433 Clinical Epidemiology, Nancy University Hospital, Université de Lorraine, Nancy, France.

[8] Department of Neuroradiology, CHRU Gui de Chauliac, Montpellier, France.

[9] Department of Neurology, CHRU Gui de Chauliac, Montpellier, France.

[10] Department of Emergency, CHRU Gui de Chauliac, Montpellier, France.

[11] Department of Diagnostic and Interventional Neuroradiology, Foch Hospital, Versailles Saint-Quentin en Yvelines University, Suresnes, France.

[12] Department of Neurology, Stroke Unit, Foch Hospital, Versailles Saint-Quentin en Yvelines University, Suresnes, France.

[13] Emergency Medical Services (SAMU) 92, Raymond Poincaré Hospital, Garches, France.

[14] Department of Interventional Neuroradiology, CHU Dupuytren, Limoges, France.

[15] Department of Neurology, Stroke Unit, CHU Dupuytren, Limoges, France.

[16] SAMU/SMUR, CHU Dupuytren, Limoges, France.

[17] Department of Neuroradiology and Endovascular Therapy, Besançon University Hospital, Besancon, France.

[18] Department of Neurology, Stroke Unit, Besançon University Hospital, Besancon, France.

[19] Department of Emergency, Besançon University Hospital, Besançon, France.

[20] Department of Neuroradiology, University Hospital of Bordeaux, Bordeaux, France.

[21] Department of Neurology, Stroke Center, University Hospital of Bordeaux, Bordeaux, France.

[22] Department of Emergency, University Hospital of Bordeaux, Bordeaux, France.

[23] Department of Interventional Neuroradiology, Hospital of Colmar, Colmar, France.

[24] Department of Neurology, Stroke Unit, Hospital of Colmar, Colmar, France.

[25] Department of Emergency, Hospital of Colmar, Colmar, France.

[26] Department of Neuroradiology, Université Reims Champagne-Ardenne, Hospital Maison-Blanche, CHU de Reims, Reims, France.

[27] Department of Neurology, Stroke Unit, Université Reims Champagne-Ardenne, Hospital Maison-Blanche, CHU de Reims, Reims, France.

[28] SAMU/SMUR, CHU Reims, Reims, France.

[29] Department of Interventional Neuroradiology, Rothschild Foundation Hospital, Paris, France.

[30] Department of Neurology, Stroke Unit, Rothschild Foundation Hospital, Paris, France.

[31] Department of Neurology, Stroke Unit, Mulhouse, France.

**Correspondence to**

Dr Benjamin Gory, CHRU Nancy, Service de Neuroradiologie Diagnostique et Thérapeutique, Nancy 54035, France ; benjagory@gmail.com

**Cover title:** DIRECT ANGIO Trial Protocol

**Word count:** 4988

**Itemized list of tables and figures:**

**Figure 1.** CONSORT diagram of the DIRECT ANGIO trial illustrating the randomization and flow of patients in the study.

**Table 1.** DIRECT ANGIO inclusion and exclusion criteria.

## ABSTRACT

**Introduction** Mechanical thrombectomy (MT) increases functional independence in patients with acute ischemic stroke with anterior circulation large vessel occlusion (LVO), and the probability to achieve functional independence decreases 20% for each 1 hour delay to reperfusion. Therefore, we aim to investigate whether direct angiosuite transfer (DAT) is superior to standard imaging/emergency department-based management in achieving 90-day functional independence in patients presenting with an acute severe neurological deficit at pre hospital stage likely due to LVO and requiring emergent treatment with MT.

**Methods and analysis** DIRECT ANGIO (Effect of DIRECT transfert to ANGIOsuite on functional outcome in patient with severe acute stroke treated with thrombectomy: the randomized DIRECT ANGIO Trial) trial is an investigator-initiated, multicenter, prospective, randomized, open-label, blinded endpoint (PROBE) study. Eligibility requires a patient ≤75 years, pre-stroke modified Rankin Scale (mRS) 0-2, presenting an acute severe neurological deficit and admitted within 5 hours of symptoms onset in an endovascular-capable center. A total of 208 patients are randomly allocated in a 1:1 ratio to DAT or standard management before hospital admission. The primary outcome is the rate of patients achieving a functional independence, assessed as mRS 0-2 at 90 days. Secondary endpoints include patients presenting confirmed LVO, patients eligible to intravenous thrombolysis alone, patients with intracerebral hemorrhage and stroke-mimics, intra-hospital time metrics, early neurological improvement (reduction in National Institutes of Health Stroke Scale by ≥8 points or reaching 0-1 at 24 hours), and mRS overall distribution at 90 days and 12 months. Safety outcomes are death and intracerebral hemorrhage transformation. Medico-economics analyses include health-related quality of life, and costs utility assessment.

**Ethics and dissemination** The DIRECT ANGIO trial was approved by an independent ethics committee. Study began in April 2020. Results will be published in an international peer-reviewed medical journal.

**Trial registration number** NCT03969511.

**Strengths and limitations of this study**

- DIRECT ANGIO trial is the first multicenter randomized clinical trial to directly comparing direct angiosuite transfert (DAT) versus standard management for highly suspected patients with anterior circulation large vessel occlusion ischemic stroke.
- DIRECT ANGIO aims to provide further evidence of the clinical benefit of DAT, as well as socioeconomic positive impact for the global health system.
- The multicenter setting and large pragmatic inclusions criteria compatible with current clinical practice and recommendations will allow external validity.
- Primary outcome measure will allow evaluation of functional independence at 90 days. Secondary outcomes will measure the safety and medico-economic impact of DAT.

## INTRODUCTION

### Background and rationale

Strokes remain a large cause of death and disability, and prevalence of large vessel occlusion (LVO) among patients with suspected acute ischemic stroke ranged from 13% to 52%, with overall prevalence of 30.0%.[1] Mechanical thrombectomy (MT) has become the standard of care for reperfusion therapies in acute anterior LVO strokes,[2] and is strongly dependent on time with 20% decreased probability of functional independence for each 1 hour delay to reperfusion.[3] HERMES meta-analysis demonstrated that prognosis is directly related to combined ischemic core volume with age and expected imaging-to-reperfusion time after successful reperfusion.[4] While the stroke network reorganization reduced symptoms-to-needle time and increased accessibility to endovascular-capable centers, it is currently crucial to achieve fast triage and initiation of endovascular therapy. To date, patients with a suspected stroke are firstly admitted in the radiology/emergency department and secondary transfer to the angiosuite for MT if LVO is confirmed. This approach results in prolonged delays in delivering definitive therapy in the setting of LVO, whereas the angiosuite has imaging facilities to rule out intracranial hemorrhage (ICH) and confirm proximal arterial occlusion (Conebeam CT [CBCT]), and therefore the ability to triage patients. Retrospective studies reported a clinical benefit of a direct angiosuite transfer (DAT).[5-7] The aim of DIRECT ANGIO (Effect of DIRECT transfert to ANGIOsuite on functional outcome in patient with severe acute stroke treated with thrombectomy: the randomized DIRECT ANGIO Trial) trial is to compare the effectiveness and safety of DAT versus conventional management in patients presenting an acute severe neurological deficit at pre hospital stage and thus mainly due to LVO eligible to MT.

### Objectives

Primary objective

The primary objective of the study is to determine whether DAT compared to conventional management is associated with improved 90-day functional independence in patients presenting with pre hospital acute severe neurological deficit likely to require treatment with MT. Functional independence is defined as a modified Rankin Scale (mRS) score 0-2 at 90 days.

Secondary objectives

The study will also explore the feasibility, efficacy and safety of DAT, as well as cost-utility assessment.

### Trial design

DIRECT ANGIO trial is a prospective, multicenter, randomized, open-label, blinded-endpoint (PROBE), two-arms, clinical trial to compare the effectiveness and safety of DAT compared to standard management in patients with acute pre hospital severe neurological deficit suspected to LVO of the anterior circulation.

## CONSORT diagram

Figure 1 shows the shows the Consolidated Standards of Reporting Trials (CONSORT) diagram of the DIRECT ANGIO trial.[8]

## METHODS AND ANALYSIS

### Participants, interventions and outcomes

This manuscript was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines.[9]

### Study setting

The DIRECT ANGIO trial takes place in 10 comprehensive stroke centers in France (Nancy, Besançon, Colmar, Strasbourg, Reims, Paris Fondation Adolphe de Rothschild, Suresnes Foch, Montpellier, Limoges, Bordeaux).

### Eligibility criteria

Inclusion criteria

Adult patients ≤75 year-old, pre-stroke mRS 0-2, with acute severe neurological deficit at pre hospital stage and directly admitted at an endovascular-capable center within 5 hours of symptoms onset and who meet all eligibility criteria is considered for study enrolment. Secondary transfer patients are not eligible in the trial. As the study objective is to target a completely autonomous population that can be assumed to have neither cognitive problems, nor a history of stroke age was limited to 75 years old. **Table 1** lists the inclusion and exclusion criteria.

As of the phone call from the emergency rescue service, inclusion and exclusion criteria are checked and then the patient randomize during the hospital travel (before admission). Oral informed consent will be sought via telephone conversations from patient or from their relatives. Emergency consent procedure may be considered if consent is not possible by the subject or a proxy. Written informed consent for continuation will be then collect as soon as possible, within 3 months.

### Interventions

Experimental arm (DAT approach)

Upon arrival in angiosuite and after rapid neurological examination (using National Institutes of Health Stroke Scale [NIHSS] and mRS scores) and blood sample, the patient undergoes CBCT in order to exclude non-ischemic stroke and angiogram to confirm LVO (tandem, intracranial internal carotid artery, M1 or proximal M2 segment of the middle cerebral artery, basilar artery or P1 segment of the posterior cerebral artery). Several managements can be performed:

1. Whatever the NIHSS score at admission, patients with no ICH and with LVO were treated with MT and, if eligible, with intravenous recombinant tissue plasminogen activator (IV rt-PA) as soon as possible. A low Alberta Stroke Program Early CT Scale (ASPECTS) or low collateral score was not an exclusion criterion for MT.
2. Patients with no ICH and with a distal vessel occlusion were treated with IV rt-PA alone, if eligible.
3. Patients with no ICH and with no arterial occlusion were started on IV rt-PA, if eligible, and received an additional stroke imaging (MRI or CT) to decide on further treatment.
4. Patients with an ICH and no occlusion were treated as per institutional standards.
5. Patients with an ICH and LVO were treated with MT after an individualized case discussion between neurologist, neuroradiologist and patient or his/her proxy.

However, the subject will remain in the intention-to-treat population.

Control Arm (conventional approach)

Arrival is in the imaging/emergency department and after neurological examination and blood sample, patient undergoes stroke imaging (MRI or CT). After LVO confirmation, patient is treated with IV rt-PA, if eligible, and transfer to angiosuite for MT as soon as possible. In the setting of no LVO, patients are treated according to as per institutional standards.

**Clinical assessment**

Baseline characteristics include prestroke mRS score, symptoms, and intra-hospital time metrics. Neurological deficit is assessed using the NIHSS score at baseline, after 24 (±6) hours, at 5-7 days (or discharge if earlier), and at 90 (±15) days. At 90 (±15) days and 12 (±1) months, outcome assessment is also evaluated with the mRS score and health-related quality of life (EQ-5D-5L).[10,11]

**Imaging protocol**

In the standard management group, baseline imaging (MRI or CT) and in the DAT group (CBCT and angiogram) is performed. Baseline imaging, angiographic imaging before, and at the end of endovascular procedure as well as follow-up imaging at 24 (±6) hours for ICH are assessed by an independent core laboratory. The core laboratory evaluates the findings on the baseline imaging for the ASPECTS (range 0 to 10, with 1 point subtracted for any evidence of early ischemic change in each defined region on the CT scan or diffusion-weighted imaging sequence),[12] baseline vessel imaging (CT angiogram or MR angiogram) for the location of the occlusion. The core laboratory assessed also angiographic outcomes on digital subtraction angiography, using the modified Thrombolysis in Cerebral Infarction (mTICI) score, which ranges from 0 (no reperfusion) to 3 (complete reperfusion).[13] Radiological outcome measures will be centrally analyzed, blinded to treatment allocation.

**Outcomes**

Primary outcome

The proportion of patients with functional independence defined as mRS score 0-2 at 90 (±15) days between DAT and conventional admission in patients ≤75 year-old presenting an acute severe neurological deficit at pre hospital stage and directly admitted at an endovascular-capable center within 5 hours of onset.

Secondary outcomes

1. Secondary feasibility endpoints:
   - Rate and site of LVO.
   - Intra-hospital time metrics (admission to imaging/needle/puncture/reperfusion, imaging to puncture/reperfusion, and puncture to reperfusion).
2. Secondary efficacy endpoints:
   - Quality of reperfusion according to the mTICI score.
   - Procedural complications (embolus in a new territory, perforation and dissection).
   - Clinical status with the NIHSS score at 24 (±6) hours, 5-7 days (or discharge if earlier), 90 (±15) days.
   - Blinded 12 (±1)-month mRS score.
3. Secondary safety endpoints:
   - Rate of patients eligible to IV rt-PA alone.
   - Rate of ICH.
   - Rate of stroke mimics
   - Rate of patients requiring secondary stroke imaging.
   - Rate of intracerebral hemorrhagic transformation of ischemic stroke according to the European Cooperative Acute Stroke Study III classification.[14]
   - Rate of mortality at 90 (±15) days and 12 (±1) months
   - Rate of decompressive hemicraniectomy.
4. Cost-utility assessment include health-related quality of life assessment at 90 (±15) days and 12 (±1) months and assessment of costs from the time of randomization to the 12-month follow-up:
   - Costs of hospitalization.
   - Institutionalized living.
   - Outpatient care.
   - Informal care provided by relatives.
   - Cost of lost productivity.

**Recruitment**

Patients are expected to be included during a 30 months period starting in April 2020.

2016–2017: Protocol, approvals from ethics committee (CPP IDF I) and the French Medicine Agency (Agence Nationale de Sécurité du Médicament et des produits de santé, ANSM); trial tool development (online case report form (CRF) and randomisation system).

2020-2023: Inclusion of patients.

2023-2024: cleaning and closure of the database, data analyses, writing of the manuscript and submission for publication.

**Trial status**

The current protocol is 2.0. Study started enrolment in 27th April 2020. To date (14h May 2020), 0 patients have been randomised in the study.

**Patient and public involvement**

Patients will not be invited to comment on study design or conduction of the trial.

## METHODS: ASSIGNMENT OF INTERVENTIONS

**Allocation and sequence generation**

After inclusion and before arrival, patients are randomized in two arms using a web-based centralized system with a 1:1 ratio to either DAT or standard management **(Figure 1)**. The randomization sequence is provided by an independent statistician (who did not take part in assessing the patients at any point in the study) using computer-generated random numbers. The randomization sequence is implemented in the electronic case report form system to ensure a centralized real-time randomization procedure. Subjects are enrolled and randomized by emergency physicians, neurologists or neuroradiologists.

**Blinding**

For the primary outcome, a centralized certified clinical research nurse from the trial center, who will be unaware of the treatment group assignments, records the mRS at 90 days and 1 year by telephone with the patient, proxy, or health care provider.[8,9] All neuroimaging readings including determination of the ASPECTS score, arterial occlusion site, clot burden score, and hemorrhagic transformation are performed by the imaging core laboratory, which is also blinded to procedure allocation.

## METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

**Data collection and management**

The entire study is conducted using eCRFs, where all clinical data on enrolled subjects are entered (single-keyed) by the site personnel. The eCRF was developed using CleanWeb (Tentelemed) software. The essential data necessary for monitoring the primary and secondary endpoints are identified and managed at regular intervals throughout the trial. Data are monitored by members of the CIC 1433 Technological

Innovation of Nancy University Hospital using the predefined rules and queries are automatically edited. Lastly, overall automated monitoring is performed by the data manager after completion of data entry. In cases of discrepancies, queries can be edited to resolve the problems encountered.

**Patient withdrawal**

Evaluated procedure is tested during the management of endovascular thrombectomy. Nevertheless, participant can withdraw consent at any time without need for further explanation. Data will be destroyed and a new patient will be randomized for the complete sample size.

**Statistical methods**

Sample size estimation

Based on the literature,[2,5-7] we expect a 90-day mRS 0-2 rate of 30% in the control arm. We assume that DAT approach (intervention arm) will be associated with an absolute increase of 20% (corresponding to a 90-day mRS 0-2 rate of 50%) due to 1 hour delay to reperfusion reduction. To detect this effect size, with a two-sided test at the 0.05 level of significance, and a power of 80%, 93 subjects per arm will be required. To account for an anticipated rate of 10% drop-out (i.e. patients lost to follow-up and without LVO), we planned to include a total of 208 subjects (104 per arm).

Interim analysis

One interim analysis is planned once 50% of patients have been included, for the study to be stopped early owing either to compelling evidence of efficacy (using a pre-specified Haybittle–Peto efficacy boundary with an alpha level of 0.001) or of futility. The independent data and safety monitoring board (DSMB) could recommend stopping the study if prolongation of the trial clearly compromises patient safety (in case of serious adverse reactions (SARs) or suspected unexpected serious adverse reactions (SUSARs)). The steering committee will be responsible to continue, hold or stop the study based on the DSMB recommendations.

Statistical analyses

Statistical analyses will be carried out independently by the CIC 1433 Technological Innovation of Nancy University hospital under the responsibility of Professor Jacques Felblinger, where statisticians and investigators will be aware of the treatment group allocation. Baseline characteristics will be described for each treatment group; categorical variables will be expressed as frequencies and percentages and quantitative variables will be expressed as means ± standard deviation or medians (interquartile range) for non-Gaussian distribution. Normality of distributions will be assessed graphically and by using the Shapiro-Wilk test. No formal statistical comparisons of baseline characteristics will be done; clinical importance of any imbalance will be noted. All analyses will be performed using all randomized participants based on their original group of randomization, according to the intention-to-treat principle. The intention to treat analysis will analyze all included patients and patients will be analyzed according to the randomization scheme. This analysis will include all patients with LVO but also with ICH, stroke mimics, ischemic stroke without LVO

at admission, independently of receiving MT or not. A per protocol analysis will be considered only for primary endpoint as a secondary analysis. Per protocol population will include all randomized patients excluding those without LVO strokes. Furthermore, the costs avoided analysis will take into account a cost-difference between the two randomization arms at 12 (±1) months and will extrapolate this difference over an expected lifetime using a Markov model. The cost-utility analysis will be also performed with health-related quality of life estimated with EQ-5D-5L questionnaire. The CONSORT statement recommendations will be applied for drafting the final report.

## METHODS: MONITORING

### Data monitoring

Before the start of the study, neurological and neuroradiological medical and paramedical teams are trained at each site for the study protocol by study coordinators. Physicians are in charge of patient screening and inclusion. Data will be collected in a web-based eCRF by trial personnel. Each centre will only have access to site-specific data. Each patient will receive a unique trial identification number. Only the investigators and research team will have access to any protected health information of study participants and any study data.

Data monitoring and quality control will be conducted in each center after the first 10 inclusions then after the next 20 inclusions and at the end of the study by official representatives of the study promoter (Department of Clinical Research and Innovation, Nancy University Hospital). Data will be handled according to the French law. All originals records (including consent forms, reports of SUSARs and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years. Only the principal investigators and the statistician will have access to the final dataset.

### Harms

Every adverse event that could be related to the trial will be reported to the trial coordinating center. According to the French law, all suspected serious adverse events will be reported to the ANSM. The DSMB will also be informed. DSMB is independent from the trial investigators and will perform an ongoing review of safety parameters and study conduct. The members of the DSMB are not participants of the DIRECT ANGIO consortium and not involved in the clinical trial. The DSMB is composed by one neuroradiologist, one pharmacovigilance specialist and one methodologist, who are not participating in the study and are not affiliated with the sponsor and who have skills and expertise in clinical neuroscience and clinical research. The DSMB will be responsible for safeguarding the interests of trial participants, assessing the safety of the interventions during the trial and for monitoring the overall conduct of the trial. DSMB could also formulate recommendations related to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control. No formal criteria are set to stop the study. However, recommendations for pausing or

stopping the study could be made by DSMB in case of SARs and SUSAR. The scientific committee will be responsible for promptly reviewing the DSMB recommendations and to decide whether to continue, hold or stop the study, and to determine whether amendments to the protocol are needed.

## ETHICS AND DISSEMINATION

Any change to eligibility criteria, outcomes and analyses will be communicated to investigators, the ethics committee and the ANSM to obtain their approval.

### Consent or assent

Whenever possible to include the patient, written inform consent will be searched. Nevertheless, related to neurological injury and emergency, the patient may be unable to provide written informed consent. In this case, written informed consent could be obtained from the patient next of kin if immediately available. Otherwise, an emergency consent procedure is used with investigator signature countersigned by an independent physician. As soon as possible after recovery, written informed consent from

### Study organization and funding

DIRECT ANGIO is a French-funded, investigator-initiated and conducted clinical trial. Coordination and project management will be provided by Prof. Benjamin Gory (Department of Diagnostic and Therapeutic Neuroradiology, University Hospital Nancy, France). The study is sponsored by Centre Hospitalier Regional Universitaire (CHRU) Nancy. DIRECT ANGIO is registred at ClinicalTrials.gov (ClinicalTrials.gov Identifier NCT03969511).

## DISCUSSION

Few studies evaluated the impact of DAT in the management of suspected LVO stroke patients, especially in the setting of primary admission. DIRECT ANGIO is a French PROBE, two-arm randomized trial comparing DAT versus standard management for patients with acute severe neurological deficit before hospital admission and thus suspected to anterior circulation LVO eligible to MT. Randomization is performed before hospital admission and within 5 hours of onset. Primary endpoint is the 90-day functional independence. The study will provide efficacy and safety data as well as socioeconomic evidence for the DAT management for patients with acute severe stroke.

### Collaborators

**CHRU Nancy:** Benjamin Gory, Isabelle Costa, Serge Bracard, René Anxionnat, Marc Braun, Anne-Laure Derelle, Romain Tonnelet, Liang Liao, François Zhu, Emmanuelle Schmitt, Sophie Planel, Sébastien Richard, Lisa Humbertjean, Gioia Mione, Jean-Christophe Lacour, Nolwenn Riou-Comte, Gabriela Hossu, Marine Beaumont, Mitchelle Bailang, Gérard Audibert, Marie Reitter, Agnès Masson, Lionel Alb, Adriana Tabarna, Marcela Voicu, Iona Podar, Madalina Brezeanu.

**CHU Besançon:** Alessandra Biondi, Giovanni Vitale, Fortunato Di Caterino, Guillaume Charbonnier, Panagiotis Primikiris, Thierry Moulin, Elisabeth de Bustos Medeiros, Benjamin Bouamra, Louise Bonnet, Fabrice Vuillier, Thibaut Desmettre

**CH Colmar:** Pablo A. Lebedinsky, Mariano Musacchio, Frederico Bolognini, Francis Vuillemet, Nicolas Kempf,

**CH Mulhouse:** Eric Schlück, Mathilde Goudot, Alessandro Laporta.

**CHU Reims:** Sébastien Soize, Solène Moulin, Laurent Pierot, Pierre-François Manceau, Maher Sahnoun, Christophe Gelmini, Nathalie Caucheteux, Vi Tuan Hua, Isabelle Serre, Mickaël Hoang.

**CHU Bordeaux:** Catherine Pradeau, Gaultier Marnat, Florent Gariel, Xavier Barreau, Jérôme Berge, Louis Veunac, Patrice Menegon, Igor Sibon, Ludovic Lucas, Stéphane Olindo, Pauline Renou, Sharmila Sagnier, Mathilde Poli, Sabrina Debruxelles, Jean-Marc Mene, Musa Sesay.

**CHU Montpellier:** Vincent Costalat, Caroline Arquizan, Cyril Dargazanli, Grégory Gascou, Pierre-Henri Lefèvre, Imad Derraz, Carlos Riquelme, Nicolas Gaillard, Isabelle Mourand, Lucas Corti.

**Fondation Adolphe de Rothschild:** Michel Piotin, Raphael Blanc, Hocine Redjem, Simon Escalard, Jean-Philippe Desilles, Gabriele Ciccio, Stanislas Smajda, Mikael Mazighi, Mikael Obadia, Candice Sabben, Ovide Corabianu, Thomas de Broucker, Didier Smadja, Sonia Alamowitch, Olivier Ille, Eric Manchon, Pierre-Yves Garcia, Guillaume Taylor, Malek Ben Maacha.

**Hôpital Foch:** Adrien Wang, Serge Evrard, Maya.tchikviladze, Nadia Ajili, Bertrand Lapergue, David Weisenburger, Lucas Gorza, Oguzhan Coskun, Arturo Consoli, Federico Di Maria, Georges Rodesh, Morgan Leguen, Julie Gratieux, Fernando Pico, Haja Rakotoharinandrasana, Philippe Tassan, Roxanna Poll, Sylvie Marinier.

**CHU Limoges:** Aymerci Rouchaud, Suzana Saleme, Charbel Mounayer, Francisco Macian-Montoro, Dominique Cailloce.

**Contributors** NRC, AC, SR, LN, FG, GH and BG are members of DIRECT ANGIO scientific committee and contributed to the conception and design of the research protocol. NRC, AC, SR and BG provided critical skills concerning trial interventions and procedures. NRC and BG wrote the first version of the protocol. BG wrote this manuscript. GH designed the statistical analysis plan. NRC, FZ, AC, SR, FG, GH and BG are involved in acquisition, analysis and interpretation of the data. NRC, FZ, SR, LN, GA, HA, VC, CA, OB, AC, BL, TL, AR, FM, DC, AB, TM, TD, GM, IS, XC, APL, FV, NK, LP, SM, PL, MM, RB, CS, ES, SB, RA, BG are involved in acquisition of the data. All authors revised the final protocol and approved his submission.

**Funding** DIRECT ANGIO trial was supported by funding from French Ministry of Health (Programme Hospitalier de Recherche Clinique Inter Régional (PHRC IR 2018) and from the university hospital of Nancy (PI: Benjamin Gory. Funding amount: 295 990 euros).

**Disclaimer** The funder had no role in study design, study conduction, writing or submitting the manuscript.

***Competing interests*** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Acknowledgments** DIRECT ANGIO boards and institutions: DSMB, CHRU Nancy, CIC-IT, CIC-EC, DRI.

**Patient consent for publication** Not required.

**Ethics approval** The DIRECT ANGIO study is conducted in accordance with the Declaration of Helsinki. The trial was approved by the ethics committee CPP IDF I on 27 September 2019 (approval number 2019-A01454-53) and ANSM on 26 September 2019 (approval number 2019-092600159).

## REFERENCES

1. Waqas M, Rai AT, Vakharia K, *et al*. Effect of definition and methods on estimates of prevalence of large vessel occlusion in acute ischemic stroke: a systematic review and meta-analysis. *J Neurointerv Surg* 2020;12:260-5.

2. Bracard S, Ducrocq X, Mas JL, *et al*. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol* 2016;15:1138-47.

3. Saver JL, Goyal M, van der Lugt A, *et al*. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA* 2016;316:1279-88.

4. Campbell BCV, Majoie CBLM, Albers GW, *et al*. Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. *Lancet Neurol* 2019;18:46-55.

5. Psychogios MN, Behme D, Schregel K, *et al*. One-stop management of acute stroke patients: minimizing door-to-reperfusion times. *Stroke* 2017;48:3152-5.

6. Ribo M, Boned S, Rubiera M, *et al*. Direct transfer to angiosuite to reduce door-to-puncture time in thrombectomy for acute stroke. *J Neurointerventional Surg* 2018;10:221-4.

7. Jadhav AP, Kenmuir CL, Aghaebrahim A, *et al*. Interfacility transfer directly to the neuroangiography suite in acute ischemic stroke patients undergoing thrombectomy. *Stroke* 2017;48:1884-9.

8. Schulz KF, Altman DG, Moher D, et al. Statement: updated guidelines for reporting parallel group randomised trials. Bmj 2010;2010.

9. Chan A-W, Tetzlaff JM, Gotzsche PC, et al. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;346:e7586.

10. van Swieten JC, Koudstaal PJ, Visser MC, *et al*. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604-7.

11. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.

12. Barber PA, Demchuk AM, Zhang J, *et al*. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. *Lancet* 2000;355:1670-4. [Erratum, Lancet 2000;355:2170.]

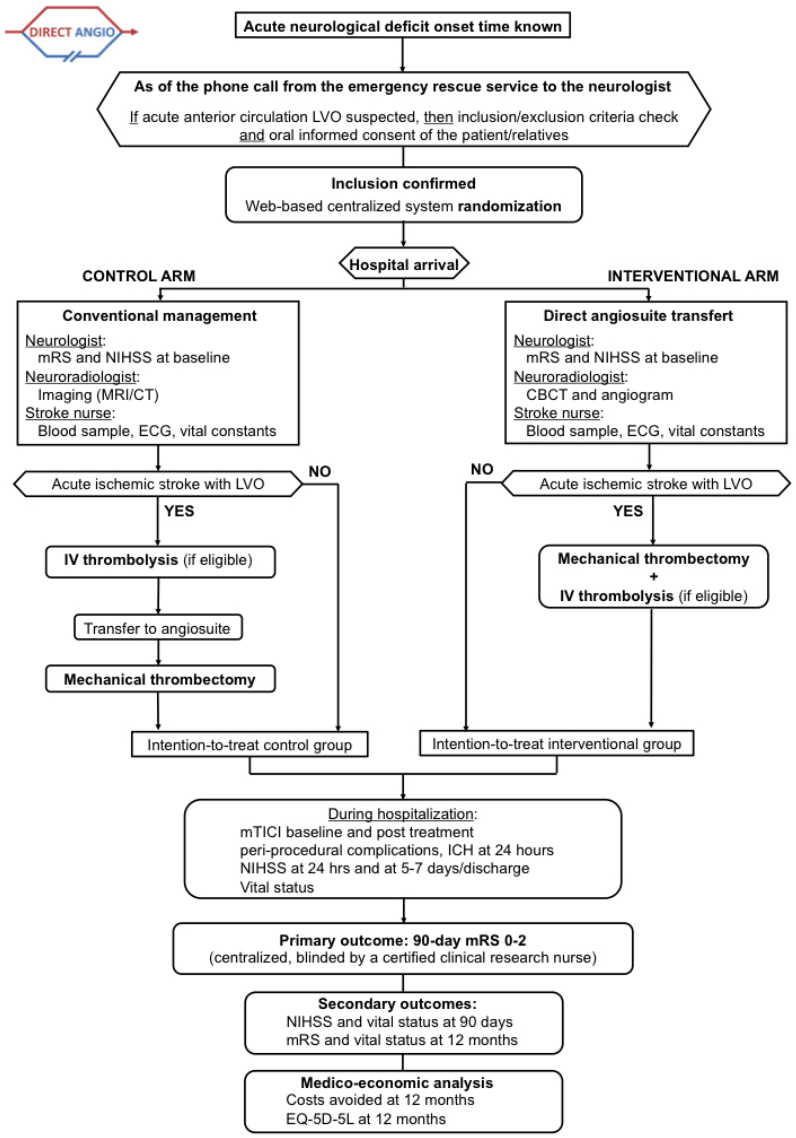
13. Zaidat OO, Yoo AJ, Khatri P, *et al*. Cerebral Angiographic Revascularization Grading (CARG) Collaborators; STIR Revascularization working group; STIR Thrombolysis in Cerebral Infarction (TICI) Task Force. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke* 2013;44:2650-63.

14. Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317-29.

**Table 1.** DIRECT ANGIO inclusion and exclusion criteria

| Inclusion | Exclusion |
|---|---|
| ✓ Adult ≤75 years<br>✓ Prestroke mRS 0-2<br>✓ Acute severe neurological deficit defined as:<br>• Hemiplegia/paresis<br>and<br>• ≥1 cortical symptom (apahsia, hemianospia, unilateral neglect, and/or gaze deviation)<br>✓ Projected last seen well time to hospital admission ≤5 hours<br>✓ Patients directly admitted to an endovascular-capable center<br>✓ Immediate availability of the angioroom and endovascular treatment team at the admission<br>✓ Affiliation to / beneficiary of a social regime | ✓ Severe allergy to contrast agents<br>✓ Pregnant or breastfeeding women<br>✓ Consent refusal or opposition of the relatives<br>✓ Under legal protection<br>✓ Any terminal illness such that patient would not be expected to survive more than 90 days |

**Figure 1.** CONSORT diagram of the DIRECT ANGIO trial illustrating the randomization and flow of patients in the study. LVO, large vessel occlusion; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; MRI, magnetic resonance imaging; CT, computed tomography; CBCT, conebeam CT; ECG, electrocardiogram; IV, intravenous; mTICI, modified Thrombolysis In Cerebral Infarction; ICH, intracerebral hemorrhage; EQ-5D-5L, 5 dimensions and 5 levels EuroQol questionnaire.




254x375mm (72 x 72 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **PAGE 1** |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry **PAGE 3** |
| | 2b | All items from the World Health Organization Trial Registration Data Set |
| Protocol version | 3 | Date and version identifier **PAGE 9** |
| Funding | 4 | Sources and types of financial, material, and other support **PAGE 12** |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors **PAGE 1-2** |
| | 5b | Name and contact information for the trial sponsor **PAGE 2** |
| | 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 12** |
| | 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 5** |
| | 6b | Explanation for choice of comparators **PAGE 5** |
| Objectives | 7 | Specific objectives or hypotheses **PAGE 5** |

| | | |
|---|---|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **PAGE 5** |

**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 6-7** |
| | 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 6-7** |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **PAGE 6-7** |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial **PAGE 6-7** |
| 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 7-8** |
| 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 8-9** |
| 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 11** |

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

Allocation:

| | | |
|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **PAGE 9** |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **PAGE 9** |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **PAGE 9** |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **PAGE 9** |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **PAGE 9** |
| **Methods: Data collection, management, and analysis** | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **PAGE 9-10** |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **PAGE 9-10** |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **PAGE 9-10** |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **PAGE 10-11** |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) **PAGE 10-11** |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **PAGE 10-11** |

**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** |
| | 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 11** |
| 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 11** |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **PAGE 11** |

**Ethics and dissemination**

| | | |
|---|---|---|
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **PAGE 12** |
| 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 12** |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **PAGE 12** |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **PAGE 12** |
| 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 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site **PAGE 13** |
| 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 10** |
| 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 |

| | | |
|---|---|---|
| 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 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |
| **Appendices** | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

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

BMJ Open

# Direct transfer to angiosuite for patients with severe acute stroke treated with thrombectomy: the multicenter randomized controlled DIRECT ANGIO trial protocol



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-040522.R2 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 19-Oct-2020 |
| Complete List of Authors: | Riou-Comte, Nolwenn; CHRU de Nancy, Neurology, Stroke Unit<br>Zhu, François; CHRU de Nancy, Neuroradiology<br>CHERIFI, Aboubaker; CHU Nancy, INSERM CIC-IT 1433<br>Richard, Sébastien; CHRU de Nancy, Neurology, Stroke Unit<br>Nace, Lionel; CHRU de Nancy, Urgences<br>Audibert, Gérard; CHRU Nancy, Hôpital Central, Service d'Anesthésie-Réanimation<br>ACHIT, Hamza; Centre Hospitalier Universitaire de Nancy, CIC-1433 Epidémiologie clinique,<br>Costalat , Vincent ; Centre Hospitalier Universitaire de Montpellier,<br>Arquizan, Caroline; CHU Montpellier, Neurology, Stroke Unit<br>Beaufils, Olivier; CHU Montpellier, Urgences<br>Consoli, Arturo; Azienda Ospedaliero Universitaria Careggi, Neuroradiology; Hopital Foch, Neuroradiology<br>Lapergue, Bertrand; Hôpital Foch, Neurology, Stroke Unit<br>Loeb, Thomas; APHP, SAMU 92<br>Rouchaud, Aymeric; CHU Limoges, Interventional Neuroradiology<br>Macian, Francisco; CHU Limoges, Neurology, Stroke Unit<br>Cailloce, Dominique; CHU Limoges, SAMU<br>Biondi, Alessandra; CHU Besancon, Neuroradiology<br>Moulin, Thierry; CHU Besancon, Neurology, Stroke Unit<br>Desmettre, Thibaut; University of Franche Comté, Emergency<br>Marnat, Gaultier; CHU de Bordeaux, Neuroradiology<br>Sibon, Igor; CHU Bordeaux, Neurology, Stroke Unit<br>Combes, Xavier; CHU de Bordeaux, Anesthesiology<br>Lebedinsky, Ariel; CH Colmar, Neuroradiology<br>Vuillemet, Francis; CH Colmar, Neurology, Stroke Unit<br>Kempf, Nicolas; CH Colmar, SAMU<br>Pierot, Laurent; CHU Reims, Neuroradiology<br>Moulin, Solene; CHU Reims, Neurology, Stroke Unit<br>Lemmel, Philippe; CHU Reims, Urgences<br>Mazighi, Mikael; Fondation Rothschild, Interventional Neuroradiology<br>Blanc, Raphael; Fondation Rothschild, Interventional Neuroradiology<br>Sabben, Candice ; Fondation Rothschild, Neurology, Stroke Unit<br>Schluck, Eric<br>Bracard, Serge; CHRU de Nancy, Neuroradiology<br>Anxionnat, René; CHRU de Nancy, Neuroradiology<br>Guillemin, Francis; CHRU de Nancy, CIC EC<br>HOSSU, Gabriela; CHU Nancy, INSERM U1254; CHU Nancy, CIC-IT 1433 |

| | |
|---|---|
| | Gory, Benjamin; Hôpital Central, Neuroradiology |
| Primary Subject Heading: | Neurology |
| Secondary Subject Heading: | Radiology and imaging, Emergency medicine |
| Keywords: | Interventional radiology < RADIOLOGY & IMAGING, STROKE MEDICINE, Clinical trials < THERAPEUTICS |
| | |

*I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.*

*The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.*

*Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.*

# Direct transfer to angiosuite for patients with severe acute stroke treated with thrombectomy: the multicenter randomized controlled DIRECT ANGIO trial protocol

Nolwenn Riou-Comte,[1] François Zhu,[2] Aboubaker Cherifi,[3] Sébastien Richard,[1,4] Lionel Nace,[5] Gérard Audibert,[6] Hamza Achit,[7] Vincent Costalat,[8] Caroline Arquizan,[9] Olivier Beaufils,[10] Arturo Consoli,[11] Bertrand Lapergue,[12] Thomas Loeb,[13] Aymeric Rouchaud,[14] Francisco Macian,[15] Dominique Cailloce,[16] Alessandra Biondi,[17] Thierry Moulin,[18] Thibaut Desmettre,[19] Gaultier Marnat,[20] Igor Sibon,[21] Xavier Combes,[22] Ariel P. Lebedinsky,[23] Francis Vuillemet,[24] Nicolas Kempf,[25] Laurent Pierot,[26] Solène Moulin,[27] Philippe Lemmel,[28] Mikael Mazighi,[29] Raphaël Blanc,[29] Candice Sabben,[30] Eric Schluck,[31] Serge Bracard,[2,3] René Anxionnat,[2,3] Francis Guillemin,[5] Gabriela Hossu,[3] Benjamin Gory,[2,3] on behalf of the DIRECT ANGIO Investigators*

[1] Université de Lorraine, CHRU-Nancy, Department of Neurology, Stroke Unit, F-54000, Nancy, France.

[2] Université de Lorraine, CHRU-Nancy, Department of Diagnostic and Therapeutic Neuroradiology, F-54000 Nancy, France.

[3] CIC INSERM 1433 Technological Innovation, Nancy University Hospital, Université de Lorraine, Nancy, France.

[4] CIC INSERM 1433 Plurithematic, Nancy University Hospital, Université de Lorraine, Nancy, France.

[5] Université de Lorraine, CHRU-Nancy, Emergency and Reanimation Department, F-54000, Nancy, France.

[6] Université de Lorraine, CHRU-Nancy, Department of Anesthesiology and Critical Care Medicine, F-54000 Nancy, France.

[7] CIC INSERM 1433 Clinical Epidemiology, Nancy University Hospital, Université de Lorraine, Nancy, France.

[8] Department of Neuroradiology, CHRU Gui de Chauliac, Montpellier, France.

[9] Department of Neurology, CHRU Gui de Chauliac, Montpellier, France.

[10] Department of Emergency, CHRU Gui de Chauliac, Montpellier, France.

[11] Department of Diagnostic and Interventional Neuroradiology, Foch Hospital, Versailles Saint-Quentin en Yvelines University, Suresnes, France.

[12] Department of Neurology, Stroke Unit, Foch Hospital, Versailles Saint-Quentin en Yvelines University, Suresnes, France.

[13] Emergency Medical Services (SAMU) 92, Raymond Poincaré Hospital, Garches, France.

[14] Department of Interventional Neuroradiology, CHU Dupuytren, Limoges, France.

[15] Department of Neurology, Stroke Unit, CHU Dupuytren, Limoges, France.

[16] SAMU/SMUR, CHU Dupuytren, Limoges, France.

[17] Department of Neuroradiology and Endovascular Therapy, Besançon University Hospital, Besancon, France.

[18] Department of Neurology, Stroke Unit, Besançon University Hospital, Besancon, France.

[19] Department of Emergency, Besançon University Hospital, Besançon, France.

[20] Department of Neuroradiology, University Hospital of Bordeaux, Bordeaux, France.

[21] Department of Neurology, Stroke Center, University Hospital of Bordeaux, Bordeaux, France.

[22] Department of Emergency, University Hospital of Bordeaux, Bordeaux, France.

[23] Department of Interventional Neuroradiology, Hospital of Colmar, Colmar, France.

[24] Department of Neurology, Stroke Unit, Hospital of Colmar, Colmar, France.

[25] Department of Emergency, Hospital of Colmar, Colmar, France.

[26] Department of Neuroradiology, Université Reims Champagne-Ardenne, Hospital Maison-Blanche, CHU de Reims, Reims, France.

[27] Department of Neurology, Stroke Unit, Université Reims Champagne-Ardenne, Hospital Maison-Blanche, CHU de Reims, Reims, France.

[28] SAMU/SMUR, CHU Reims, Reims, France.

[29] Department of Interventional Neuroradiology, Rothschild Foundation Hospital, Paris, France.

[30] Department of Neurology, Stroke Unit, Rothschild Foundation Hospital, Paris, France.

[31] Department of Neurology, Stroke Unit, Mulhouse, France.

**Correspondence to**

Pr. Benjamin Gory, CHRU Nancy, Service de Neuroradiologie Diagnostique et Thérapeutique, Nancy 54035, France ; benjagory@gmail.com

**Cover title:** DIRECT ANGIO Trial Protocol

**Word count:** 4988

**Itemized list of tables and figures:**

**Figure 1.** CONSORT diagram of the DIRECT ANGIO trial illustrating the randomization and flow of patients in the study.

**Table 1.** DIRECT ANGIO inclusion and exclusion criteria.

## ABSTRACT

**Introduction** Mechanical thrombectomy (MT) increases functional independence in patients with acute ischemic stroke with anterior circulation large vessel occlusion (LVO), and the probability to achieve functional independence decreases 20% for each 1 hour delay to reperfusion. Therefore, we aim to investigate whether direct angiosuite transfer (DAT) is superior to standard imaging/emergency department-based management in achieving 90-day functional independence in patients presenting with an acute severe neurological deficit likely due to LVO and requiring emergent treatment with MT.

**Methods and analysis** DIRECT ANGIO (Effect of DIRECT transfert to ANGIOsuite on functional outcome in patient with severe acute stroke treated with thrombectomy: the randomized DIRECT ANGIO Trial) trial is an investigator-initiated, multicenter, prospective, randomized, open-label, blinded endpoint (PROBE) study. Eligibility requires a patient ≤75 years, pre-stroke modified Rankin Scale (mRS) 0-2, presenting an acute severe neurological deficit and admitted within 5 hours of symptoms onset in an endovascular-capable center. A total of 208 patients are randomly allocated in a 1:1 ratio to DAT or standard management. The primary outcome is the rate of patients achieving a functional independence, assessed as mRS 0-2 at 90 days. Secondary endpoints include patients presenting confirmed LVO, patients eligible to intravenous thrombolysis alone, patients with intracerebral hemorrhage and stroke-mimics, intra-hospital time metrics, early neurological improvement (reduction in National Institutes of Health Stroke Scale by ≥8 points or reaching 0-1 at 24 hours), and mRS overall distribution at 90 days and 12 months. Safety outcomes are death and intracerebral hemorrhage transformation. Medico-economics analyses include health-related quality of life, and costs utility assessment.

**Ethics and dissemination** The DIRECT ANGIO trial was approved by the ethics committee of Ile de France 1. Study began in April 2020. Results will be published in an international peer-reviewed medical journal.

**Trial registration number** NCT03969511.

**Strengths and limitations of this study**

- DIRECT ANGIO trial is the first multicenter randomized clinical trial to directly comparing direct angiosuite transfert (DAT) versus standard management for highly suspected patients with anterior circulation large vessel occlusion ischemic stroke.
- DIRECT ANGIO aims to provide further evidence of the clinical benefit of DAT, as well as socioeconomic positive impact for the global health system.
- The multicenter setting and large pragmatic inclusions criteria compatible with current clinical practice and recommendations will allow external validity.
- Primary outcome measure will allow evaluation of functional independence at 90 days. Secondary outcomes will measure the safety and medico-economic impact of DAT.

# INTRODUCTION

## Background and rationale

Strokes remain a large cause of death and disability, and prevalence of large vessel occlusion (LVO) among patients with suspected acute ischemic stroke ranged from 13% to 52%, with overall prevalence of 30.0%.[1] Mechanical thrombectomy (MT) has become the standard of care for reperfusion therapies in acute anterior LVO strokes,[2] and is strongly dependent on time with 20% decreased probability of functional independence for each 1 hour delay to reperfusion.[3] HERMES meta-analysis demonstrated that prognosis is directly related to combined ischemic core volume with age and expected imaging-to-reperfusion time after successful reperfusion.[4] While the stroke network reorganization reduced symptoms-to-needle time and increased accessibility to endovascular-capable centers, it is currently crucial to achieve fast triage and initiation of endovascular therapy. To date, patients with a suspected stroke are firstly admitted in the radiology/emergency department and secondary transfer to the angiosuite for MT if LVO is confirmed. This approach results in prolonged delays in delivering definitive therapy in the setting of LVO, whereas the angiosuite has imaging facilities to rule out intracranial hemorrhage (ICH) and confirm proximal arterial occlusion (Conebeam CT [CBCT]), and therefore the ability to triage patients. Retrospective studies reported a clinical benefit of a direct angiosuite transfer (DAT).[5-7] The aim of DIRECT ANGIO (Effect of DIRECT transfert to ANGIOsuite on functional outcome in patient with severe acute stroke treated with thrombectomy: the randomized DIRECT ANGIO Trial) trial is to compare the effectiveness and safety of DAT versus conventional management in patients presenting an acute severe neurological deficit and thus mainly due to LVO eligible to MT.

## Objectives

Primary objective

The primary objective of the study is to determine whether DAT compared to conventional management is associated with improved 90-day functional independence in patients presenting with pre hospital acute severe neurological deficit likely to require treatment with MT. Functional independence is defined as a modified Rankin Scale (mRS) score 0-2 at 90 days.

Secondary objectives

The study will also explore the feasibility, efficacy and safety of DAT, as well as cost-utility assessment.

## Trial design

DIRECT ANGIO trial is a prospective, multicenter, randomized, open-label, blinded-endpoint (PROBE), two-arms, clinical trial to compare the effectiveness and safety of DAT compared to standard management in patients with acute pre hospital severe neurological deficit suspected to LVO of the anterior circulation.

## CONSORT diagram

Figure 1 shows the shows the Consolidated Standards of Reporting Trials (CONSORT) diagram of the DIRECT ANGIO trial.[8]

## METHODS AND ANALYSIS

### Participants, interventions and outcomes

This manuscript was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines.[9]

### Study setting

The DIRECT ANGIO trial takes place in 9 comprehensive stroke centers in France (CHRU-Nancy, CHU Besançon, CH Colmar, CHU Strasbourg, CHU Reims, Foch, CHRU Montpellier, CHU Limoges, and CHU Bordeaux).

### Eligibility criteria

Inclusion criteria

Adult patients ≤75 year-old, pre-stroke mRS 0-2, with acute severe neurological deficit at pre hospital stage and directly admitted at an endovascular-capable center within 5 hours of symptoms onset and who meet all eligibility criteria is considered for study enrolment. Secondary transfer patients are not eligible in the trial. As the study objective is to target a completely autonomous population that can be assumed to have neither cognitive problems, nor a history of stroke age was limited to 75 years old. **Table 1** lists the inclusion and exclusion criteria.

As of the phone call from the emergency rescue service, inclusion and exclusion criteria are checked and then the patient randomize during the hospital travel (before admission). We are modifying the timing of randomization. Randomization will be performed after severe stroke confirmation by a neurologist immediately after admission (version 3.0). Oral informed consent will be sought via telephone conversations from patient or from their relatives. Emergency consent procedure may be considered if consent is not possible by the subject or a proxy. Written informed consent for continuation will be then collect as soon as possible, within 3 months.

### Interventions

Experimental arm (DAT approach)

Upon arrival in angiosuite and after rapid neurological examination (using National Institutes of Health Stroke Scale [NIHSS] and mRS scores) and blood sample, the patient undergoes CBCT in order to exclude non-ischemic stroke and angiogram to confirm LVO (tandem, intracranial internal carotid artery, M1 or

proximal M2 segment of the middle cerebral artery, basilar artery or P1 segment of the posterior cerebral artery). Several managements can be performed:

1. Whatever the NIHSS score at admission, patients with no ICH and with LVO were treated with MT and, if eligible, with intravenous recombinant tissue plasminogen activator (IV rt-PA) as soon as possible. A low Alberta Stroke Program Early CT Scale (ASPECTS) or low collateral score was not an exclusion criterion for MT.
2. Patients with no ICH and with a distal vessel occlusion were treated with IV rt-PA alone, if eligible.
3. Patients with no ICH and with no arterial occlusion were started on IV rt-PA, if eligible, and received an additional stroke imaging (MRI or CT) to decide on further treatment.
4. Patients with an ICH and no occlusion were treated as per institutional standards.
5. Patients with an ICH and LVO were treated with MT after an individualized case discussion between neurologist, neuroradiologist and patient or his/her proxy.

However, the subject will remain in the intention-to-treat population.

Control Arm (conventional approach)

Arrival is in the imaging/emergency department and after neurological examination and blood sample, patient undergoes stroke imaging (MRI or CT). After LVO confirmation, patient is treated with IV rt-PA, if eligible, and transfer to angiosuite for MT as soon as possible. In the setting of no LVO, patients are treated according to as per institutional standards.

**Clinical assessment**

Baseline characteristics include prestroke mRS score, symptoms, and intra-hospital time metrics. Neurological deficit is assessed using the NIHSS score at baseline, after 24 (±6) hours, at 5-7 days (or discharge if earlier), and at 90 (±15) days. At 90 (±15) days and 12 (±1) months, outcome assessment is also evaluated with the mRS score and health-related quality of life (EQ-5D-5L).[10,11]

**Imaging protocol**

In the standard management group, baseline imaging (MRI or CT) and in the DAT group (CBCT and angiogram) is performed. Baseline imaging, angiographic imaging before, and at the end of endovascular procedure as well as follow-up imaging at 24 (±6) hours for ICH are assessed by an independent core laboratory. The core laboratory evaluates the findings on the baseline imaging for the ASPECTS (range 0 to 10, with 1 point subtracted for any evidence of early ischemic change in each defined region on the CT scan or diffusion-weighted imaging sequence),[12] baseline vessel imaging (CT angiogram or MR angiogram) for the location of the occlusion. The core laboratory assessed also angiographic outcomes on digital subtraction angiography, using the modified Thrombolysis in Cerebral Infarction (mTICI) score, which ranges from 0 (no reperfusion) to 3 (complete reperfusion).[13] Radiological outcome measures will be centrally analyzed, blinded to treatment allocation.

**Outcomes**

Primary outcome

The proportion of patients with functional independence defined as mRS score 0-2 at 90 (±15) days between DAT and conventional admission in patients ≤75 year-old presenting an acute severe neurological deficit at pre hospital stage and directly admitted at an endovascular-capable center within 5 hours of onset.

Secondary outcomes

1. Secondary feasibility endpoints:
   - Rate and site of LVO.
   - Intra-hospital time metrics (admission to imaging/needle/puncture/reperfusion, imaging to puncture/reperfusion, and puncture to reperfusion).
2. Secondary efficacy endpoints:
   - Quality of reperfusion according to the mTICI score.
   - Procedural complications (embolus in a new territory, perforation and dissection).
   - Clinical status with the NIHSS score at 24 (±6) hours, 5-7 days (or discharge if earlier), 90 (±15) days.
   - Blinded 12 (±1)-month mRS score.
3. Secondary safety endpoints:
   - Rate of patients eligible to IV rt-PA alone.
   - Rate of ICH.
   - Rate of stroke mimics
   - Rate of patients requiring secondary stroke imaging.
   - Rate of intracerebral hemorrhagic transformation of ischemic stroke according to the European Cooperative Acute Stroke Study III classification.[14]
   - Rate of mortality at 90 (±15) days and 12 (±1) months
   - Rate of decompressive hemicraniectomy.
4. Cost-utility assessment include health-related quality of life assessment at 90 (±15) days and 12 (±1) months and assessment of costs from the time of randomization to the 12-month follow-up:
   - Costs of hospitalization.
   - Institutionalized living.
   - Outpatient care.
   - Informal care provided by relatives.
   - Cost of lost productivity.

**Recruitment**

Patients are expected to be included during a 30 months period starting in April 2020.

2016–2017: Protocol, approvals from ethics committee (CPP IDF I) and the French Medicine Agency (Agence Nationale de Sécurité du Médicament et des produits de santé, ANSM); trial tool development (online case report form (CRF) and randomisation system).

2020-2023: Inclusion of patients.

2023-2024: cleaning and closure of the database, data analyses, writing of the manuscript and submission for publication.

**Trial status**

The current protocol is 2.0. Study started enrolment in 27th April 2020. To date (31 January 2021), 7 patients have been randomised in the study (1 center open).

**Patient and public involvement**

Patients will not be invited to comment on study design or conduction of the trial.

## METHODS: ASSIGNMENT OF INTERVENTIONS

**Allocation and sequence generation**

After inclusion, patients are randomized in two arms using a web-based centralized system with a one to one ratio to either DAT or standard management **(Figure 1)**. The randomization sequence is provided by an independent statistician (who did not take part in assessing the patients at any point in the study) using computer-generated random numbers and stratified by center and delay from onset to hospital admission (before or after 2.5 hours). The randomization sequence is implemented in the electronic case report form system to ensure a centralized real-time randomization procedure. Subjects are enrolled and randomized by emergency physicians, neurologists or neuroradiologists.

**Blinding**

For the primary outcome, a centralized certified clinical research nurse from the trial center, who will be unaware of the treatment group assignments, records the mRS at 90 days and 1 year by telephone with the patient, proxy, or health care provider.[8,9] All neuroimaging readings including determination of the ASPECTS score, arterial occlusion site, clot burden score, and hemorrhagic transformation are performed by the imaging core laboratory, which is also blinded to procedure allocation.

## METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

**Data collection and management**

Similarly to others studies,[15] the entire study is conducted using eCRFs, where all clinical data on enrolled subjects are entered (single-keyed) by the site personnel. The eCRF was developed using CleanWeb (Tentelemed) software. The essential data necessary for monitoring the primary and secondary endpoints are

identified and managed at regular intervals throughout the trial. Data are monitored by members of the CIC 1433 Technological Innovation of Nancy University Hospital using the predefined rules and queries are automatically edited. Lastly, overall automated monitoring is performed by the data manager after completion of data entry. In cases of discrepancies, queries can be edited to resolve the problems encountered.

**Patient withdrawal**

Evaluated procedure is tested during the management of endovascular thrombectomy. Nevertheless, participant can withdraw consent at any time without need for further explanation. Data will be destroyed and a new patient will be randomized for the complete sample size.

**Statistical methods**

Sample size estimation

Based on the literature,[2,5-7] we expect a 90-day mRS 0-2 rate of 30% in the control arm. We assume that DAT approach (intervention arm) will be associated with an absolute increase of 20% (corresponding to a 90-day mRS 0-2 rate of 50%) due to 1 hour delay to reperfusion reduction. To detect this effect size, with a two-sided test at the 0.05 level of significance, and a power of 80%, 93 subjects per arm will be required. To account for an anticipated rate of 10% drop-out (i.e. patients lost to follow-up and without LVO), we planned to include a total of 208 subjects (104 per arm).

Interim analysis

One interim analysis is planned once 50% of patients have been included, for the study to be stopped early owing either to compelling evidence of efficacy (using a pre-specified Haybittle–Peto efficacy boundary with an alpha level of 0.001) or of futility. The independent data and safety monitoring board (DSMB) could recommend stopping the study if prolongation of the trial clearly compromises patient safety (in case of serious adverse reactions (SARs) or suspected unexpected serious adverse reactions (SUSARs)). The steering committee will be responsible to continue, hold or stop the study based on the DSMB recommendations.

Statistical analyses

Statistical analyses will be carried out independently by the CIC 1433 Technological Innovation of Nancy University hospital under the responsibility of Professor Jacques Felblinger, where statisticians and investigators will be aware of the treatment group allocation. Baseline characteristics will be described for each treatment group; categorical variables will be expressed as frequencies and percentages and quantitative variables will be expressed as means ± standard deviation or medians (interquartile range) for non-Gaussian distribution. Normality of distributions will be assessed graphically and by using the Shapiro-Wilk test. No formal statistical comparisons of baseline characteristics will be done; clinical importance of any imbalance will be noted. All analyses will be performed using all randomized participants based on their original group of randomization, according to the intention-to-treat principle. The intention to treat analysis

will analyze all included patients and patients will be analyzed according to the randomization scheme. This analysis will include all patients with LVO but also with ICH, stroke mimics, ischemic stroke without LVO at admission, independently of receiving MT or not. A per protocol analysis will be considered only for primary endpoint as a secondary analysis. Per protocol population will include all randomized patients excluding those without LVO strokes. Furthermore, the costs avoided analysis will take into account a cost-difference between the two randomization arms at 12 (±1) months and will extrapolate this difference over an expected lifetime using a Markov model. The cost-utility analysis will be also performed with health-related quality of life estimated with EQ-5D-5L questionnaire. The CONSORT statement recommendations will be applied for drafting the final report.

## METHODS: MONITORING

### Data monitoring

Before the start of the study, neurological and neuroradiological medical and paramedical teams are trained at each site for the study protocol by study coordinators. Physicians are in charge of patient screening and inclusion. Data will be collected in a web-based eCRF by trial personnel. Each centre will only have access to site-specific data. Each patient will receive a unique trial identification number. Only the investigators and research team will have access to any protected health information of study participants and any study data.

Data monitoring and quality control will be conducted in each center after the first 10 inclusions then after the next 20 inclusions and at the end of the study by official representatives of the study promoter (Department of Clinical Research and Innovation, Nancy University Hospital). Data will be handled according to the French law. All originals records (including consent forms, reports of SUSARs and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years. Only the principal investigators and the statistician will have access to the final dataset.

### Harms

Every adverse event that could be related to the trial will be reported to the trial coordinating center. According to the French law, all suspected serious adverse events will be reported to the ANSM. The DSMB will also be informed. DSMB is independent from the trial investigators and will perform an ongoing review of safety parameters and study conduct. The members of the DSMB are not participants of the DIRECT ANGIO consortium and not involved in the clinical trial. The DSMB is composed by one neuroradiologist, one pharmacovigilance specialist and one methodologist, who are not participating in the study and are not affiliated with the sponsor and who have skills and expertise in clinical neuroscience and clinical research. The DSMB will be responsible for safeguarding the interests of trial participants, assessing the safety of the interventions during the trial and for monitoring the overall conduct of the trial. DSMB could also formulate recommendations related to the recruitment/retention of participants, their

management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control. No formal criteria are set to stop the study. However, recommendations for pausing or stopping the study could be made by DSMB in case of SARs and SUSAR. The scientific committee will be responsible for promptly reviewing the DSMB recommendations and to decide whether to continue, hold or stop the study, and to determine whether amendments to the protocol are needed.

## ETHICS AND DISSEMINATION

Any change to eligibility criteria, outcomes and analyses will be communicated to investigators, the ethics committee and the ANSM to obtain their approval. The DIRECT ANGIO trial was approved by the ethics committee (CPP) of Ile de France 1.

### Consent or assent

Whenever possible to include the patient, written inform consent will be searched. Nevertheless, related to neurological injury and emergency, the patient may be unable to provide written informed consent. In this case, written informed consent could be obtained from the patient next of kin if immediately available. Otherwise, an emergency consent procedure is used with investigator signature countersigned by an independent physician. As soon as possible after recovery, written informed consent from

### Dissemination

Results will be published in an international peer-reviewed medical journal.

## DISCUSSION

Few studies evaluated the impact of DAT in the management of suspected LVO stroke patients, especially in the setting of primary admission. DIRECT ANGIO is a French PROBE, two-arm randomized trial comparing DAT versus standard management for patients with acute severe neurological deficit before hospital admission and thus suspected to anterior circulation LVO eligible to MT. Randomization is performed before hospital admission and within 5 hours of onset. Primary endpoint is the 90-day functional independence. The study will provide efficacy and safety data as well as socioeconomic evidence for the DAT management for patients with acute severe stroke.

### Collaborators

**CHRU-Nancy:** Benjamin Gory, Isabelle Costa, Serge Bracard, René Anxionnat, Marc Braun, Anne-Laure Derelle, Romain Tonnelet, Liang Liao, François Zhu, Emmanuelle Schmitt, Sophie Planel, Sébastien Richard, Lisa Humbertjean, Gioia Mione, Jean-Christophe Lacour, Nolwenn Riou-Comte, Gabriela Hossu, Marine Beaumont, Mitchelle Bailang, Gérard Audibert, Marie Reitter, Agnès Masson, Lionel Alb, Adriana Tabarna, Marcela Voicu, Iona Podar, Madalina Brezeanu.

**CHU Besançon:** Alessandra Biondi, Giovanni Vitale, Fortunato Di Caterino, Guillaume Charbonnier, Panagiotis Primikiris, Thierry Moulin, Elisabeth de Bustos Medeiros, Benjamin Bouamra, Louise Bonnet, Fabrice Vuillier, Thibaut Desmettre

**CH Colmar:** Pablo A. Lebedinsky, Mariano Musacchio, Frederico Bolognini, Francis Vuillemet, Nicolas Kempf,

**CH Mulhouse:** Elie Cohen-Khallas, Andreas Fickl, Eric Schluck, Mathilde Goudot, Sylvie Courtois, Sohrab Mostoufizadehghalamfarsa, Alessandro La Porta.

**CHU Reims:** Sébastien Soize, Solène Moulin, Laurent Pierot, Pierre-François Manceau, Maher Sahnoun, Christophe Gelmini, Nathalie Caucheteux, Vi Tuan Hua, Isabelle Serre, Mickaël Hoang.

**CHU Bordeaux:** Catherine Pradeau, Gaultier Marnat, Florent Gariel, Xavier Barreau, Jérôme Berge, Louis Veunac, Patrice Menegon, Igor Sibon, Ludovic Lucas, Stéphane Olindo, Pauline Renou, Sharmila Sagnier, Mathilde Poli, Sabrina Debruxelles, Jean-Marc Mene, Musa Sesay.

**CHU Montpellier:** Vincent Costalat, Caroline Arquizan, Cyril Dargazanli, Grégory Gascou, Pierre-Henri Lefèvre, Imad Derraz, Carlos Riquelme, Nicolas Gaillard, Isabelle Mourand, Lucas Corti.

**Fondation Adolphe de Rothschild:** Michel Piotin, Raphael Blanc, Hocine Redjem, Simon Escalard, Jean-Philippe Desilles, Gabriele Ciccio, Stanislas Smajda, Mikael Mazighi, Mikael Obadia, Candice Sabben, Ovide Corabianu, Thomas de Broucker, Didier Smadja, Sonia Alamowitch, Olivier Ille, Eric Manchon, Pierre-Yves Garcia, Guillaume Taylor, Malek Ben Maacha.

**Hôpital Foch:** Adrien Wang, Serge Evrard, Maya Tchikviladze, Nadia Ajili, Bertrand Lapergue, David Weisenburger, Lucas Gorza, Oguzhan Coskun, Arturo Consoli, Federico Di Maria, Georges Rodesh, Morgan Leguen, Julie Gratieux, Fernando Pico, Haja Rakotoharinandrasana, Philippe Tassan, Roxanna Poll, Sylvie Marinier.

**CHU Limoges:** Aymerci Rouchaud, Suzana Saleme, Charbel Mounayer, Francisco Macian-Montoro, Dominique Cailloce.

**Contributors** NRC, AC, SR, LN, FG, GH and BG are members of DIRECT ANGIO scientific committee and contributed to the conception and design of the research protocol. NRC, AC, SR and BG provided critical skills concerning trial interventions and procedures. NRC and BG wrote the first version of the protocol. BG wrote this manuscript. GH designed the statistical analysis plan. NRC, FZ, AC, SR, FG, GH and BG are involved in acquisition, analysis and interpretation of the data. NRC, FZ, SR, LN, GA, HA, VC, CA, OB, AC, BL, TL, AR, FM, DC, AB, TM, TD, GM, IS, XC, APL, FV, NK, LP, SM, PL, MM, RB, CS, ES, SB, RA, BG are involved in acquisition of the data. All authors revised the final protocol and approved his submission.

**Funding** DIRECT ANGIO trial was supported by funding from French Ministry of Health (Programme Hospitalier de Recherche Clinique Inter Régional (PHRC IR 2018) and from the university hospital of Nancy (PI: Benjamin Gory. Funding amount: 295 990 euros).

**Disclaimer** The funder had no role in study design, study conduction, writing or submitting the manuscript.

***Competing interests*** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Acknowledgments** DIRECT ANGIO boards and institutions: DSMB, CHRU Nancy, CIC-IT, CIC-EC, DRI.

**Patient consent for publication** Not required.

**Ethics approval** The DIRECT ANGIO study is conducted in accordance with the Declaration of Helsinki. The trial was approved by the ethics committee CPP IDF I on 27 September 2019 (approval number 2019-A01454-53) and ANSM on 26 September 2019 (approval number 2019-092600159).

**Provenance and peer review** Not commissioned; externally peer reviewed.



## REFERENCES

1. Waqas M, Rai AT, Vakharia K, *et al*. Effect of definition and methods on estimates of prevalence of large vessel occlusion in acute ischemic stroke: a systematic review and meta-analysis. *J Neurointerv Surg* 2020;12:260-5.

2. Bracard S, Ducrocq X, Mas JL, *et al*. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol* 2016;15:1138-47.

3. Saver JL, Goyal M, van der Lugt A, *et al*. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA* 2016;316:1279-88.

4. Campbell BCV, Majoie CBLM, Albers GW, *et al*. Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. *Lancet Neurol* 2019;18:46-55.

5. Psychogios MN, Behme D, Schregel K, *et al*. One-stop management of acute stroke patients: minimizing door-to-reperfusion times. *Stroke* 2017;48:3152-5.

6. Ribo M, Boned S, Rubiera M, *et al*. Direct transfer to angiosuite to reduce door-to-puncture time in thrombectomy for acute stroke. *J Neurointerventional Surg* 2018;10:221-4.

7. Jadhav AP, Kenmuir CL, Aghaebrahim A, *et al*. Interfacility transfer directly to the neuroangiography suite in acute ischemic stroke patients undergoing thrombectomy. *Stroke* 2017;48:1884-9.

8. Schulz KF, Altman DG, Moher D, et al. Statement: updated guidelines for reporting parallel group randomised trials. Bmj 2010;2010.

9. Chan A-W, Tetzlaff JM, Gotzsche PC, et al. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;346:e7586.

10. van Swieten JC, Koudstaal PJ, Visser MC, *et al*. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604-7.

11. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.

12. Barber PA, Demchuk AM, Zhang J, *et al*. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. *Lancet* 2000;355:1670-4. [Erratum, Lancet 2000;355:2170.]

13. Zaidat OO, Yoo AJ, Khatri P, *et al*. Cerebral Angiographic Revascularization Grading (CARG) Collaborators; STIR Revascularization working group; STIR Thrombolysis in Cerebral Infarction (TICI) Task Force. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke* 2013;44:2650-63.

14. Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317-29.

15. Chabanne R, Fernandez-Canal C, Degos V, *et al*. Sedation versus general anaesthesia in endovascular therapy for anterior circulation acute ischaemic stroke: the multicentre randomised controlled AMETIS trial study protocol. *BMJ Open* 2019;9:e027561.

**Table 1.** DIRECT ANGIO inclusion and exclusion criteria

| Inclusion | Exclusion |
|---|---|
| ✓ Adult ≤75 years<br>✓ Prestroke mRS 0-2<br>✓ Acute severe neurological deficit at hospital admission confirmed by neurologist defined as:*<br>• Unilateral motor deficit with a score ≥5<br>○ Facial palsy (item 4 NIHSS 0 to 2)<br>○ Arm (item 5 NIHSS 0 to 4)<br>○ Leg (item 6 NIHSS 0 to 4)<br>AND<br>• Cortical symptom with a score ≥1<br>○ Language (item 9 NIHSS 0 to 3)<br>○ Extinction (item 11 NIHSS 0 to )<br>✓ Hospital admission ≤5 hours<br>✓ Patients directly admitted to an endovascular-capable center<br>✓ Immediate availability of the angioroom and endovascular treatment team at the randomization<br>✓ Affiliation to / beneficiary of a social regime | ✓ Severe allergy to contrast agents<br>✓ Pregnant or breastfeeding women<br>✓ Consent refusal or opposition of the relatives<br>✓ Under legal protection<br>✓ Any terminal illness such that patient would not be expected to survive more than 90 days |

*new criteria of the version 3.0

**Figure 1.** CONSORT diagram of the DIRECT ANGIO trial illustrating the randomization and flow of patients in the study. LVO, large vessel occlusion; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; MRI, magnetic resonance imaging; CT, computed tomography; CBCT, conebeam CT; ECG, electrocardiogram; IV, intravenous; mTICI, modified Thrombolysis In Cerebral Infarction; ICH, intracerebral hemorrhage; EQ-5D-5L, 5 dimensions and 5 levels EuroQol questionnaire.

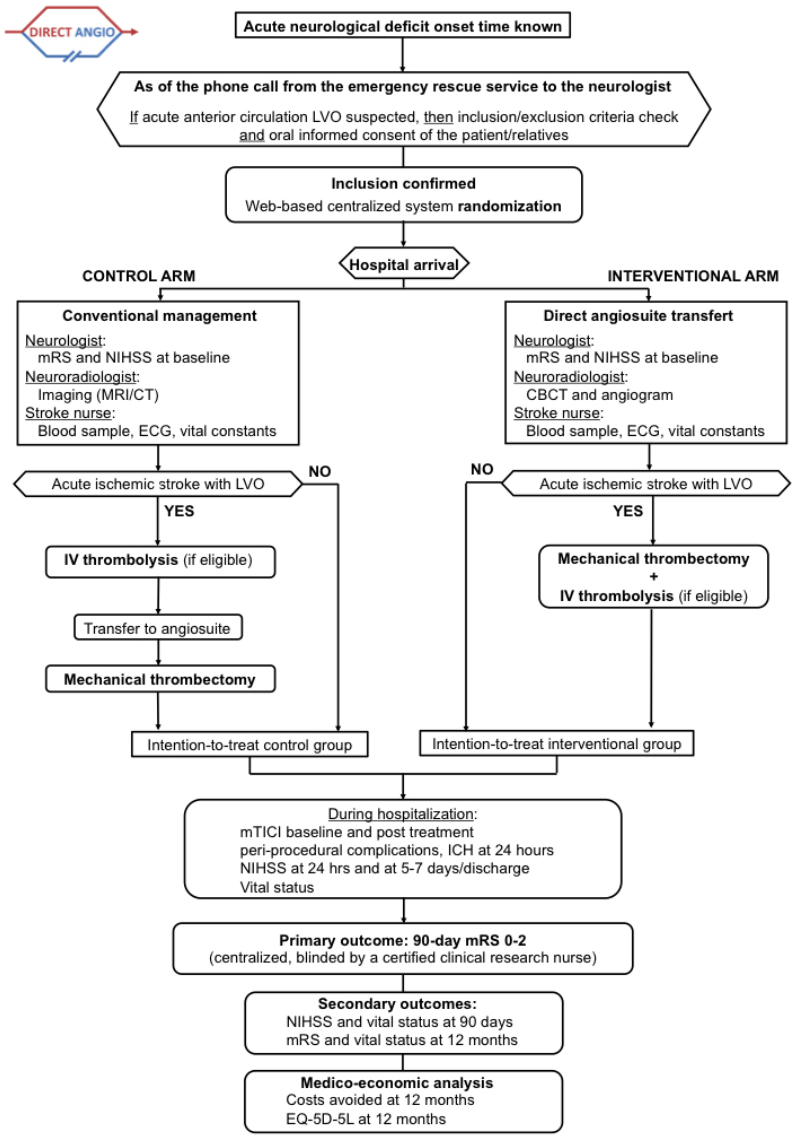



Figure 1

254x375mm (72 x 72 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **PAGE 1** |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry **PAGE 3** |
| | 2b | All items from the World Health Organization Trial Registration Data Set |
| Protocol version | 3 | Date and version identifier **PAGE 9** |
| Funding | 4 | Sources and types of financial, material, and other support **PAGE 12** |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors **PAGE 1-2** |
| | 5b | Name and contact information for the trial sponsor **PAGE 2** |
| | 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 12** |
| | 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 5** |
| | 6b | Explanation for choice of comparators **PAGE 5** |
| Objectives | 7 | Specific objectives or hypotheses **PAGE 5** |

| | | |
|---|---|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **PAGE 5** |

**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 6-7** |
| | 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 6-7** |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **PAGE 6-7** |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial **PAGE 6-7** |
| 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 7-8** |
| 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 8-9** |
| 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 11** |

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

Allocation:

| | | |
|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **PAGE 9** |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **PAGE 9** |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **PAGE 9** |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **PAGE 9** |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **PAGE 9** |
| **Methods: Data collection, management, and analysis** | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **PAGE 9-10** |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **PAGE 9-10** |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **PAGE 9-10** |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **PAGE 10-11** |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) **PAGE 10-11** |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **PAGE 10-11** |

**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** |
| | 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 11** |
| 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 11** |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **PAGE 11** |

**Ethics and dissemination**

| | | |
|---|---|---|
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **PAGE 12** |
| 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 12** |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **PAGE 12** |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **PAGE 12** |
| 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 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site **PAGE 13** |
| 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 10** |
| 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 |

| | | |
|---|---|---|
| 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 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |
| **Appendices** | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

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