

The

SITS Open Artery by Thrombectomy in Acute Occlusive Stroke Study



Project Plan

2017-02-24

An international, multicentre controlled study of
safety and efficacy of thrombectomy in acute
occlusive stroke

An open, prospective, blinded evaluation, international, multicentre, controlled study of safety and efficacy of thrombectomy and standard stroke care in clinical routine treatment of acute occlusive stroke compared to standard stroke care only

Sponsored by



**Karolinska
Institutet**

In collaboration with



Hjärt  Lungfonden



1. INTRODUCTION

Purpose of Plan

The Project Plan will provide a definition of the project:

- Introduction
- Partners and Collaborators
- Objectives
- Project management
- Appendices

Background Information

Ischemic stroke, caused by blood clot, which stops the blood flow in a cerebral artery, needs prompt recognition and treatment. In recent years, development of diagnostic imaging methods has enabled rapid localization of cerebral artery occlusions and their impact on cerebral blood flow and tissue integrity. Standard urgent treatment of ischaemic stroke is to restore the blood flow in the artery by administering the clot-dissolving medication intravenously, but the new data suggest that large occlusions caused by big and dense clots may not be dissolved by intravenous treatment alone. Additional use of mechanical thrombectomy, i.e. use of medical device which disrupts the clot and extracts it out of blood vessel, is demonstrating promising results but currently is not established in guidelines as evidence based therapy.

Project Approach

The protocol is designed to provide a higher level of evidence for mechanical thrombectomy through a direct comparison between mechanical thrombectomy and a concurrent control of medical management alone.

The approach is based on prospectively enrolled control patients from centres that lack the possibility to perform thrombectomy procedures with patients from centres with proven thrombectomy skills. The study is designed as an open, prospective, international, multicentre, controlled study of safety and efficacy of thrombectomy in acute occlusive stroke following initiation with intravenous thrombolysis with alteplase in accordance with accepted guidelines, compared to intravenous thrombolysis only.

Karolinska Institutet, Department of Clinical Neuroscience sponsors the trial. The clinical trial is a part of "Mission: Fighting Stroke" (Uppdrag: Besegra Stroke) and financially supported by manufactures of thrombectomy devices; Stryker, Phenox and Covidien. The participating centres are members of the SITS international network and the SITS database carries the eCRF of the clinical trial. Independent experts blinded to the patient information and treatment, ensures a robust study design evaluate key endpoints.

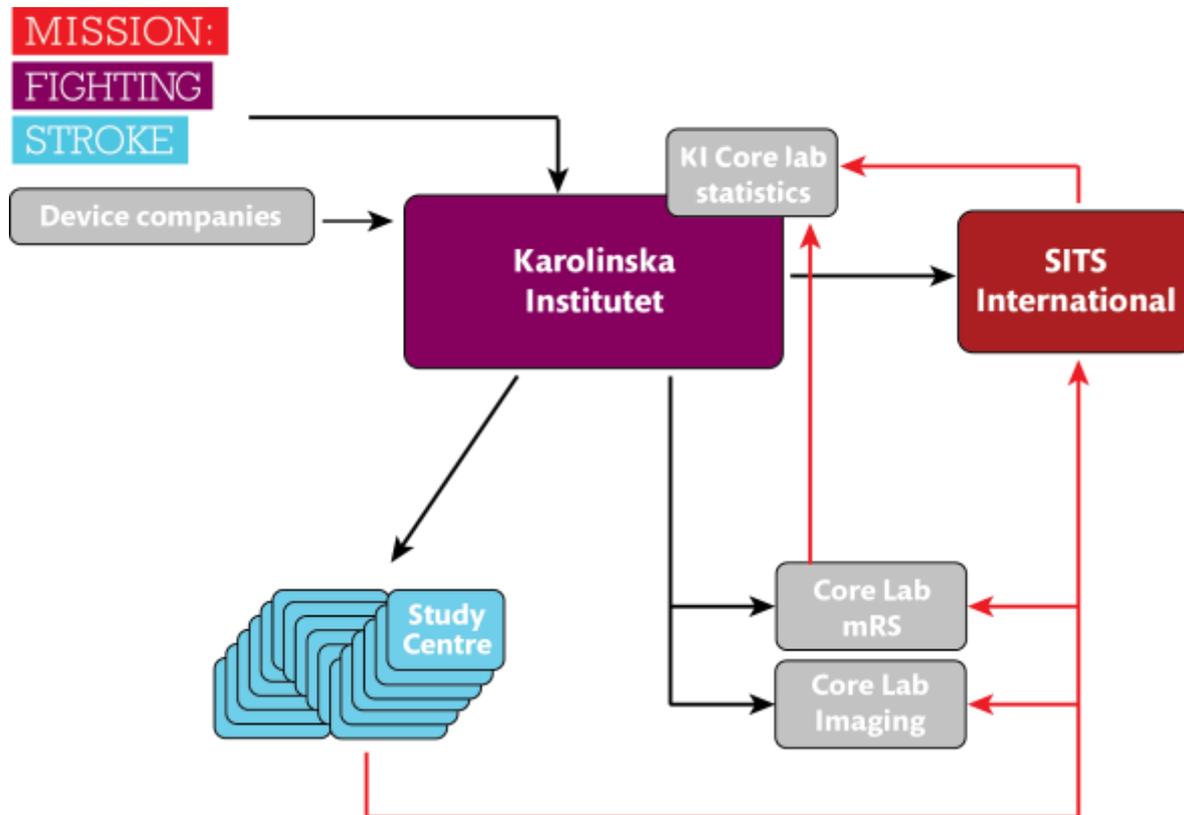


Figure 1. The study will be conducted at hospitals within the SITS network and evaluated by core laboratories. Economical resources are provided by “Mission: Fighting Stroke” and device companies. Black arrows indicate flow of money and red arrows flow of data.

2. PARTNERS AND COLLABORATORS

Karolinska Institutet

The Department of Neuroscience at Karolinska Institutet is the sponsor of the SITS Open clinical trial. Professor Nils Wahlgren is the Coordinating Investigator, employed by Karolinska Institutet. Basic funding for the trial is provided by the Karolinska Institutet project, “Mission: Fighting Stroke. The coordinating team at Karolinska Institutet will support the investigators and supervise partner activities.

SITS International

SITS (Safe Implementation of Treatments in Stroke) is an academic-driven, independent, international collaboration, organised in order to increase the quality of acute stroke care worldwide. It is an initiative by the medical professional community aimed at driving excellence in acute stroke treatment and secondary prevention, and to develop knowledge of the present state of affairs in the stroke field and establish leading research. The SITS Stroke Registry is an internet-based interactive stroke registry developed by SITS. The SITS Stroke Registry has been adapted to serve as an electronic Case Report Form (eCRF) for clinical studies.

The coordinating team will have access to the electronic database and reports, and also to eCRF in order to follow progression and perform audits.

Evaluations and adjudications of primary and secondary endpoints are performed by the independent experts at the core laboratories, in the way that the assessors will be blinded to any information about the patient and the treatment. Data required by the independent core laboratories will be collected separately and will be inaccessible to SITS and any other personnel or organisation, involved in the trial, until the trial is terminated and the data is locked. SITS is coordinating the network of study centres.

Core laboratories

Two core facilities are performing independent analyses of study data.

The Department of Neuroradiology at the University Hospital at Dresden, Germany, will analyse all computer tomography (CT-scans), both native and angiographic images, magnetic resonance imaging (MR-scans), native and angiographic, if supplied by centres, and angiographic images from the endovascular procedures. Images will be downloaded after removal of personal identity details and addition of study numbers and administered at the coordination centre. Images will be transferred to the core lab in a way that keeps blindness for treatment alternatives when analysing CT- and MR-scans. The core lab will enter all data through a database available only at the independent statistical centre.

The Stroke Research team in the institute of Cardiovascular and Medical Sciences at the University of Glasgow will arrange for video recordings of patient interviews to be securely stored within the Robertson Centre for Biostatistics at the University of Glasgow and will analyse all video recordings of patient interviews on their functional status at three months after onset of symptoms. The recordings will be evaluated independently by four adjudicators who will agree on a score on the modified Rankin scale, which will form the study's primary outcome variable. All adjudicators are blinded to the treatment alternatives.

Device Companies

Manufacturers of the leading thrombectomy devices have been invited to financially support the clinical trial. The companies will not be involved in the trial execution, but are encouraged to provide educational support to participants with regard to their products. The financial support will provide a possibility to achieve the key evidence support of mechanical thrombectomy as an effective and safe complement to currently recommended pharmacological treatment. After trial termination, the companies will receive detailed data of subjects treated with their specific device.

Detailed information is stated in the Funding Agreement.

Study Centres

Highly qualified clinical centres with the best expertise in stroke care within the SITS network have been invited to the SITS Open trial. The centres have been evaluated by the steering committee according to criteria specified in the Clinical Trial Protocol.

Study planning includes approximately 45 centres, and it is expected that each centre will recruit 10-40 study patients. In total, 600 active subjects and 300 control subjects will be enrolled.

The centres are expected to keep their medical strategy of treating patients with acute stroke unchanged for the whole study period, thus, switching from control to active centre and vice versa is not allowed.

3. OBJECTIVES

Objective Definition

Primary Objective

To determine the benefit and safety of TBY in clinical routine practice by selected stent retrievers or other selected novel devices in addition to standard care in patients with major cerebral artery occlusion as compared to standard care only. Standard care may include IVT in accordance with current guidelines.

Secondary Objective

- To determine the benefit and safety of TBY by selected stent retrievers or other selected novel devices as additional therapy in proximal cerebral artery occlusion (Carotid T, M1, Basilar Artery) in patients receiving IVT according to current guidelines within 4.5 hours of ischaemic stroke onset as compared to stand-alone IVT.
- To determine whether TBY without prior IVT impacts the functional outcome of patients compared to standard stroke care including IVT, when indicated according to current guidelines.
- To determine the benefit and safety of TBY in clinical routine practice by selected stent retrievers or other selected novel devices in patients with major cerebral artery occlusion as compared to active arm of the pooled analyses of 5 randomized controlled trials, HERMES (1).
- To determine the study outcomes for patients in following subgroups: 1) In patients with M1/Car-T/BA occlusion, 2) M2/A1/P1 occlusion, 3) basilar artery occlusion, 4) in patients without prior treatment with IVT, 5) length of the occluding thrombus 8 mm, 6) moderately severe stroke at baseline (NIHSS 7-12) and for severe stroke (NIHSS 13-).

Items Beyond Objectives

The clinical trial does not have the intention and statistical power to compare devices.

Risk Assessment

All study procedures and investigations are considered within the range of routine clinical practice. Since study treatments, procedures and devices are approved for clinical use, their implementation is unlikely to result in unexpected events.

A comparison between devices is beyond the scope of the trial. However, if any device poses a safety threat or found deficient in the trial, this will be reported.

An even distribution of device is desired. The objective of the study is to provide evidence for the treatment and not for certain devices. The scope of the trial is to reflect the standard thrombectomy treatment and the doctor is free to choose any of the devices included in the trial. The study centres have answered a survey with questions about device specific preferences and experience. Their answers are used for centre selection and a tool to promote balanced distribution of devices with out constraining the study centre.

The invited study centres have been chosen by strict criteria and are approved by the steering committee. Nevertheless, if obvious safety issues are identified, the steering committee will act to stop further recruitment at the specific study centre.

The Data and Safety Monitoring Board will monitor the safety events during the study and advise or recommend the steering committee to make actions/adjustments if necessary. The patient receive standard treatment at the study centre, study specific activities are restricted to analysis of treatment success and patient recovery. Therefore, early termination of the trial is not envisaged.

Stroke is one of the most frequent causes of morbidity in the developed as well as developing countries, and centres involved in the study are large stroke units, each of those accepts several stroke patients per day; for this reason, the risk of slow recruitment can be considered low. Nevertheless, study period can be extended until recruitment of the planned number of cases, or upon the recommendation of DSMB.

4. PROJECT MANAGEMENT APPROACH

Start-up

The EC application has been approved by the Swedish Ethics Committee. The trial will be initiated at the respective centre as soon as local EC approval is obtained.

Milestones

2013 Q1	The Clinical Trial Protocol and the eCRF is finalized
2013 Q2	National Ethics Committee Approval in coordinating country
2013 Q4	Initiation of Swedish study centres
2014 Q1	First Patient in
2017 Q4	Last patient out
2018 Q2	Report

Project Roles and Responsibilities

<p>Sponsor</p>	<ul style="list-style-type: none"> • Major funding and resource allocation strategies, and significant changes to funding/resource allocation • Approves extension of the trial on request of Steering Committee, depending on whether additional funding is required and secured • Decides about data ownership issues, with consideration of the full access to data and right to decide on publications by the Steering Committee • Financial management • Study Centre Reimbursement 	<p>Department of Clinical Neuroscience, Karolinska Institutet, representatives:</p> <p>Prefekt: Jan Hillert, M.D., Ph.D.</p> <p>Department of Clinical Neuroscience, Karolinska Institutet</p> <p>Nils Wahlgren, M.D., Ph.D.</p> <p>Department of Clinical Neuroscience, Karolinska Institutet</p>
<p>Consortium committee</p>	<ul style="list-style-type: none"> • Oversees the study progress • Handles matters relating to the collaboration between consortium members • Reports on the study progress to the Scientific Committee of Mission Fighting Stroke (Uppdrag Besegra Stroke) • Provides advice to the Project, and in particular to the Steering Committee 	<p>Chair:</p> <p>Nils Wahlgren, M.D., Ph.D Department of Clinical Neuroscience, Karolinska Institutet</p> <p>Kia Bengtsson, COO SITS International</p> <p>Kennedy Lees, M.D., FRCP, Professor University of Glasgow Glasgow, United Kingdom</p> <p>Rüdiger von Kummer, Prof.Dr.med University Hospital of Dresden Dresden, Germany</p>

<p>Coordinating investigator</p>	<ul style="list-style-type: none"> • Overall responsibility for study budget, coordination and performance • Decides whether any extension of the trial requested by the Steering Committee will be covered by existing budget or if additional funding is required • Responsible for Study Protocol preparation and amendments • Publication of the Study Protocol before start • Applicant for Ethical Committee Application • Chairs the Consortium Committee and the Steering Committee • Communicating author of main publications in peer reviewed scientific journal 	<p>Nils Wahlgren, M.D., Ph.D. Department of Clinical Neuroscience Karolinska Institutet Stockholm, Sweden</p>
<p>Steering committee</p>	<ul style="list-style-type: none"> • Approves the Study Protocol • Approves centre recruitment • Recommends sponsor to extend the study, following proposal from Data and Safety Monitoring Board • Provides scientific advice to the Coordinating investigator • Reviews project deliverables • Resolves conflicts and issues • Has full access to all study data and decides about major publication issues in agreement with the study protocol 	<p>Chair Nils Wahlgren, M.D., Ph.D. Karolinska Institutet Stockholm, Sweden</p> <p>Co-chair Olav Jansen, M.D., Ph.D. University Hospital of Schleswig-Holstein Kiel, Germany</p> <p>Staffan Holmin, M.D., Ph.D. Karolinska Institutet Stockholm, Sweden</p> <p>Kennedy Lees, M.D., FRCP, Professor University of Glasgow Glasgow, United Kingdom</p> <p>Salvatore Mangiafico, M.D., Ph.D. Careggi University Hospital Florence, Italy</p> <p>Lawrence Wong, M.D., Ph.D. Chinese University of Hong Kong Hong Kong, China</p>

<p>Data and Safety Monitoring Board</p>	<ul style="list-style-type: none"> • Make recommendations to the Steering Committee regarding safety of the study. • Make recommendations to the Steering Committee on extending the trial. 	<p>Chair: Gary Ford, M.D., FRCP, Freeman Hospital Stroke Service Magdalen Centre North, UK</p> <p>Markku Kaste, M.D., Ph.D Department of Neurology Helsinki Central University Hospital Helsinki, Finland</p> <p>David Liebeskind, MD UCLA Stroke Center Los Angeles, USA</p>
<p>Project manager and Project coordinator</p> <p>SITS International</p>	<ul style="list-style-type: none"> • Manages project in agreement with the Coordinating investigator • Supervises partners, collaborators, subcontractors and consultants • Provides overall project direction • Directs/leads team members toward project objectives • Handles problem resolution • Manages the project budget • eCRF • Networking activities • Meeting arrangements • Compiling data • Data quality overview • A web-based scoreboard will be designed and opened for all coordinating staff to ensure the control of timeline and completeness of data. 	<p>Project Manager/Coordinator: Sara Lundin</p> <p>Kia Bengtsson, COO</p> <p>Johan Lundberg, Project leader SITS Database development</p> <p>Michael Mazya, Project leader International Network</p>

<p>Outcomes Adjudication Committee</p>	<ul style="list-style-type: none"> • Controls the collection of outcome data (video records) from the investigators • Organizes adjudication of outcome data by independent experts 	<p>Chair: Kennedy Lees, M.D., FRCP, Professor University of Glasgow Glasgow, United Kingdom</p> <p>Medical outcomes manager: Jesse Dawson, M.D., University of Glasgow Glasgow, United Kingdom</p>
<p>NEUROIMAGING CORE LABORATORY</p>	<ul style="list-style-type: none"> • Handle all administration, management and archiving of the images • Evaluate all images sent from centres 	<p>Chair Rüdiger von Kummer, Prof.Dr.med University Hospital of Dresden Systematic Management Archiving and reviewing Trial Images service (SMARTIS) University of Edinburgh (Neurosciences Imaging) Att: Eleni Sakka</p>
<p>Study centres</p>	<ul style="list-style-type: none"> • Medically responsible for the patient • Responsible for accuracy and timeliness of entering the data into eCRF according to instructions in the protocol • Sending imaging DVDs to project management • Upload mRS videos to Core lab. 	
<p>Device Companies</p>	<ul style="list-style-type: none"> • Financially contribute to the study as a donation to the sponsor • Educational support to centres 	

Study coordination responsibilities

<p>Nils Wahlgren, Coordinating Investigator</p>	<ul style="list-style-type: none"> • Controls the overall progress of the project in accordance to the project plan and study protocol • Communicates with Steering Committee and DSMB • Approves major funding and resource allocation strategies, and significant changes to funding/resource allocation
<p>Olav Jansen, Co-Coordinating Investigator</p>	<ul style="list-style-type: none"> • Controls the overall progress of the project in accordance to the project plan and study protocol, with a focus on thrombectomy intervention. • Communicates with Steering Committee and DSMB
<p>Kia Bengtsson COO at SITS International</p>	<ul style="list-style-type: none"> • Manages the project budget
<p>Niaz Ahmed, Senior Researcher</p>	<ul style="list-style-type: none"> • Advice on study protocol, design of data collection • Statistical analysis of data
<p>Sara Lundin Project Manager/Coordinator</p>	<ul style="list-style-type: none"> • Direct/lead team members toward project objectives • Provides overall project direction • Main contact for study centres • Supervises the completeness and timeliness of data collection and work of collaborators, subcontractors and consultants • Controls the collection and upload of imaging data for core lab • Checks telephone screening log of the study patients on daily basis
<p>Tatiana Kharitonova, Scientist Tiago Moreira, Scientist</p>	<ul style="list-style-type: none"> • Advice on study protocol, design of data collection • Statistical analysis of data
<p>Kennedy Lees, Chairman of the mRS adjudication committee</p>	<ul style="list-style-type: none"> • Controls the collection of outcome data (video records) from the investigators • Organizes adjudication of outcome data by independent experts
<p>Rüdiger von Kummer, Chairman of the Imaging analysis committee</p>	<ul style="list-style-type: none"> • Receives study imaging source data and organizes/performs its evaluation by independent experts

Data Handling

The local principal investigator is responsible for entering data without delay in the eCRF. Analysis of neuroradiological images and mRS assessments are performed at the study centre and results are entered into the eCRF, however they will not be used in the primary statistical analysis of the trial, but may be analysed in secondary publications. Source data, i.e. CT and/or MR images, angiography and thrombectomy records, and mRS interview videos are sent or uploaded to the respective core laboratory.

Adjudications of imaging data and mRS will be performed by independent experts blinded to the patients' allocation to treatment at core laboratories. Data generated by the core laboratories will be stored separately at the laboratories until trial termination and data lock. The data is exported to the coordinating team, to be compiled with data from the eCRF. This step will unblind the data.

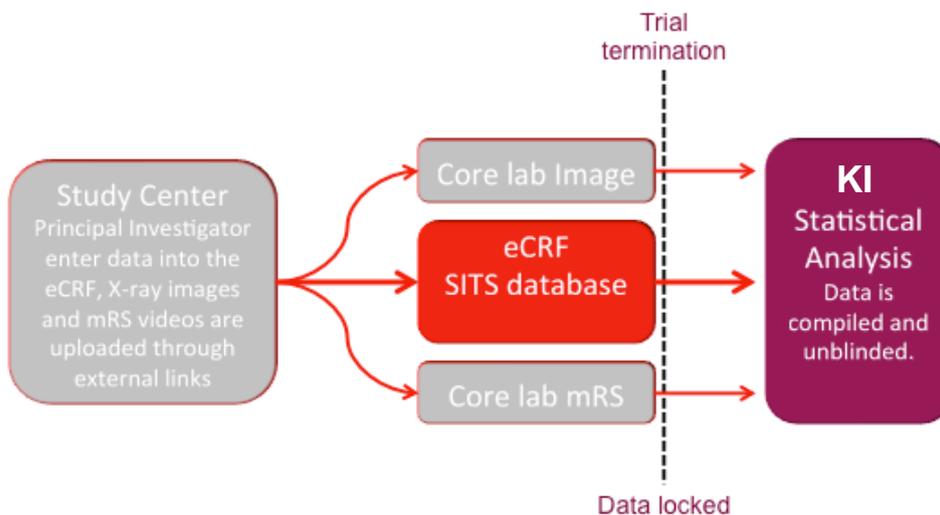


Figure 3: Flow of data. Statistical analysis is described in the SITS Open protocol.

Quality Control Plan

The Coordinating Investigator and Project Manager will supervise the project on a daily basis. Compliance to the Clinical Trial Protocol will be verified by evaluation of data and possibly by audits.

By establishing agreement with all stakeholders, the expenses are regulated. The partners have separate responsibilities with separate budgets.

The time plan for the project is dependent on subject enrolment, i.e. patients meeting the criteria and their consent to be included. A large number of hospitals are participating in the study to avoid discrepancy in patient flow.

Meetings

Steering Committee Meetings

The Steering Committee has regular teleconferences and at least two face-to-face meetings during the course of the trial.

Meetings and Monitor

Meetings with local investigators will be held at three occasions; before start, during the trial and after trial termination.

During: At some point during the study, a representative for the study should either visit or ask the local investigating team to verify source data. Informed consent and device should be noted in the medical record.

After: The centre may be visited after the study has been terminated for assuring that all necessary documents are completed and stored in a proper manner.

The meetings will be arranged and coordinated by KI with support of the SITS network organisation.

Communications Plan

Before trial start

The Clinical Trial Protocol will be published by KI in the international database for clinical trials, www.clinicaltrials.gov, and made publically available through the SITS International and Mission: Fighting Stroke webpages (www.sitsinternational.org and www.uppdragstroke.org).

During the trial

The communication platform with Investigators is the eCRF and SITS webpage. Announcements will be made via email or by telephone. Procedures for adverse reaction and other medical issues are described in the Clinical Trial Protocol.

After trial termination

The results of the trial will be published in an international peer-reviewed scientific journal not later than 12 months after the study has ended. The Steering Committee will discuss the findings of the statistical analyses and approve the manuscripts. The Coordinating Investigator will serve as communicating author of main publications, with the address Department of Clinical Neuroscience, KI.

Authorship

Authorship will be determined in accordance with academic standard.

Karolinska Institutet owns all compiled data from the trial.

5. AGREEMENTS

- **Consortium Agreement**
- **Clinical Trial Agreement**
- **Funding Agreement**

6. APPROVALS

The Sponsor and Coordinating Investigator approve the Project Plan.

Date: _____

Date: _____

Jan Hillert

Prefect, professor

Department of Clinical Neuroscience

Karolinska Institutet

Nils Wahlgren

Professor

Department of Clinical Neuroscience

Karolinska Institutet