SITS Open Arteries by Thrombectomy in Acute Occlusive Stroke Study
SITS Open

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SITS Open

- Introduction
In recent years, development of diagnostic imaging methods has enabled rapid localisation of cerebral artery occlusions and their impact on cerebral perfusion and tissue integrity. New data suggest that thromboembolic occlusions 8 mm or longer may not be dissolved by intravenous treatment alone.\textsuperscript{15}

Mechanical thrombectomy (TBY) is currently not established in guidelines as evidence based therapy, although new evidence has been presented during 2015 and resulting in new recommendations (International Journal of stroke, consensus statement Karolinska stroke update).

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.
"Studies comparing active centres (IVT + possibility for thrombectomy) with control centres who do not yet have access to thrombectomy (IVT treatment alone), e.g. SITS-OPEN, should continue its recruitment to strengthen the level of evidence.

There are many reasons to recommend this approach such as the need for confirmatory studies, the desirability of narrowing the confidence interval to get a tighter estimate of the effect size for health economic reasons and the necessity for a wide range of data allowing subgroup analysis with adequate power. This type of design will also test thrombectomy in standard clinical practice in experienced centres.”
INTRODUCTION - The rationale for the study design – Why not a randomised design?

- Many highly experienced thrombectomy centres find it difficult to randomise patients with a perceived high likelihood of beneficial outcome compared to no treatment.

- The non-randomised design avoids the risk that patients with a high likelihood to benefit are excluded from the trial because consent is not provided and the patient is treated outside the trial. Thus the data from SITS Open may be an important complement to the RCTs.
INTRODUCTION - Cont. The rationale for the study design –
Strong points of the design

- Reflects routine clinical practice
- The participation in the trial does not affect the choice of treatment for the patient.
- Blinded evaluation of imaging
- Blinded evaluation of the primary outcome (mRS)
- Statistical analysis includes a matching procedure to achieve maximum comparability between treatment groups.
- Valuable complement to prior thrombectomy trials
INTRODUCTION - Purpose of continuing with SITS Open

➢ To strengthen the evidence for thrombectomy. Although many positive studies, the total number of reported patients is low.

➢ Important to examine and follow up randomised trials in the routine setting to ensure both safety and efficacy.

➢ To answer additional questions on e.g.:

  ▪ Clot size
  ▪ Blood pressure
  ▪ Basilar Artery occlusion
  ▪ General anesthesia or conscious sedation
  ▪ Expanding time window
INTRODUCTION – The registry structure

The SITS Registry offers 6 types of data forms, as well as study specific data forms:

- **IVTP-standard**
  - Thrombolysis

- **IVTP-minimal**

- **IVTP+TBYP bridge**

- **TBYP-standard**
  - Thrombectomy

- **APP-standard**
  - Non-interventional

- **SITS AF study, SITS Fertile Women study, Seizures in stroke study**

- **Cerebrolysin study**

- **SITS Open study**

- **SITS OPEN STUDY**
SITS Open is sponsored by:

- Karolinska Institute within the research programme Mission Fighting Stroke, supported by the Swedish Heart and Lung Foundation.

- The study is also supported by device companies through unrestricted grants to Karolinska Institute.

- University Hospital of Schleswig-Holstein is co-coordinating the study.
INTRODUCTION – Organization of the study
SITS Open

• The SITS Open Team
SITS Open Coordination Team

Karin Flood
Project Manager

Elin Hammar
Executive Research Assistant

Nils Wahlgren
Chairman

Arturo Consoli
Coordinator Italy

Sabine Krieter
Coordinator Germany

Susanne Becke
Coordinator Germany

Matthew Walters
Coordinator UK

GGHB ?
Steering Committee

Neurointerventionists, Neurologists and Stroke physicians

Nils Wahlgren
Sweden

Olav Jansen
Germany

Staffan Holmin
Sweden

Salvatore Mangiafico
Italy

Lawrence Wong
Hong Kong

Kennedy Lees
UK

14
Committees and Research team

- **Imaging – University of Edinburgh**
  - Eleni Sakka

- **Chair Imaging Core lab**
  - Rüdiger von Kummer

- **Chair mRS Adjudication Team**
  - Kennedy Lees

- **Data and Safety Monitoring Board**
  - Gary Ford - England
  - Markku Kaste - Finland
  - David Liebeskind - USA
Research team members

Tiago Moreira
Sweden

Tatiana Kharitonova
Russia

Niaz Ahmed
Sweden
SITS Open

- Current Status
Current status

- Patient recruitment
- Completeness of CRF
- mRS uploads
- CT images sent to University in Edinburgh
- Completed Physician’s Verification Forms
Current status – Patient recruitment

- 1st patient in the study – 21 March 2014
- Today - 191 Patients
Current status – Completeness of CRF

Status of confirmed timepoints in CRF

SITS OPEN - Confirmed Timepoints in CRF

Percentage

Summa av confirmed_baseline, Summa av confirmed_treatment, Summa av confirmed_12h, Summa av confirmed_24h, Summa av confirmed_7d, Summa av confirmed_3m
17 centres are now recruiting. Centres from the following countries has started their recruitment:

- Italy
- Germany
- Finland
- Sweden
- Portugal
- Belgium
- Norway
- Turkey
- Austria
SITS Open

- Project Plan
<table>
<thead>
<tr>
<th>Year Q</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>2013 Q1</td>
<td>The Clinical Trial Protocol and the eCRF is finalized</td>
</tr>
<tr>
<td>2013 Q2</td>
<td>National Ethics Committee Approval in coordinating country</td>
</tr>
<tr>
<td>2013 Q4</td>
<td>Initiation of Swedish study centres</td>
</tr>
<tr>
<td>2014 Q1</td>
<td>First Patient in</td>
</tr>
<tr>
<td>2016 Q4</td>
<td>Data and Safety Monitoring Board recommendation of extension of the study after 200 + 200 patients</td>
</tr>
<tr>
<td>2017 Q3</td>
<td>Last patient out</td>
</tr>
<tr>
<td>2018 Q2</td>
<td>Report</td>
</tr>
</tbody>
</table>
Sits Open

- Study Protocol
Study Protocol – Study Design and Aim

### Study design
- Prospective
- International
- Multicentre
- Controlled

### Aim
To determine the benefit and safety of thrombectomy by selected stent retrievers as additional therapy in major artery occlusions in patients fulfilling the criteria for and receiving intravenous Thrombolysis (IVT) within 4.5 hours of ischaemic stroke onset as compared to stand-alone IVT.
Study Protocol - Study design

Clinical site location

- 30 active centres from highly specialised/experienced hospitals
- 30 control centres from hospitals that do NOT have access to thrombectomy

Enrolment

- 300 patients in active arm
- 300 patients in control arm
- Patients are enrolled after informed consent is obtained
- Screening documentation is performed before thrombectomy (active arm) or within 2 hour after IVT initiation (control arm)

Arms

- ACTIVE - Patients fulfilling criteria for thrombectomy after initiation of IVT according to accepted guidelines
- CONTROL – Patients treated with IVT according to accepted guidelines at centres that do not have access to thrombectomy (nor can refer patients to nearby centres for tby)
Study Protocol – Number of patients/centre

• Control Centres: 30 Patients/centre

• Active Centres: 20 Patients/centre
Study Protocol – Inclusion Criteria

- Eligible for IVT according to clinical guidelines, and IVT initiated within 4.5 hours after stroke onset.
- Clinical signs and symptoms consistent with a diagnosis of acute ischemic stroke prior to initiation of intravenous thrombolysis.
- Angiography confirming proximal occlusion of the middle cerebral artery (M1), terminal carotid artery (Car-T) or the basilar artery (BA) consistent with the clinical symptoms.
- Upon initiation of intravenous thrombolysis: 7 ≥ NIHSS score ≥ 25 for occlusions in anterior circulation and ≥ 7 with no upper limit for occlusions in posterior circulation.
- Age ≥ 18 years.
- Anticipated life expectancy of at least 6 months.
- Informed consent for participation in the study has been obtained, thereby permitting input and storage of data and follow-up procedures. When patients cannot personally give consent due to their condition, or because of death, and no family members are present, the local attending study physician (principle investigator) is justified to sign the consent form provided that no clear information is available indicating that the patient had any objections.
- Initiation of endovascular procedure (DSA/TBY, defined as start with groin puncture) within 2 hours from the start of IVT.
- CTA not done later than 15 minutes after IVT start.
Study Protocol – Exclusion Criteria

- Fulfilment of any exclusion criteria for IVT.
- Serious known physical disabilities before onset of stroke (mRS ≥ 2)
- Major ischemic changes seen on CT scan (defined as more than one third of MCA territory or more than half of other areas)
- Time between initiation of intravenous thrombolysis and initiation of thrombectomy exceeds 2 hours.
- Extended early ischemic changes for basilar artery occlusion, according to the judgement of treating physician based on routine clinical practice of the hospital; if technical possibility exists, early irreversible ischemic changes may be confirmed by pc-ASPECTS score <8 on CTASI 40 or extensive DWI lesion on pre-treatment MRI.
- NIHSS score <7 for all strokes or > 25 for stroke in anterior circulation
- Terminal disease in which patient is not expected to live longer than 6 months
- Patient has condition that could be worsened by intravenous thrombolysis
- Known pregnancy
- Current use of oral anticoagulants and prolonged prothrombin time (INR> 1.7), intake of dabigatran over the past 4 hours or aPTT above normal limit
- Use of heparin, with exception of low-dose subcutaneous heparin over past 48 hours
- Use of glycoprotein IIb-IIIa inhibitors over past 72 hours
- Participation in any other investigational drug or device study, currently or in the previous 30 days.
Study Protocol - Inclusion criteria occlusions

CTA-evidence of the following major cerebral artery occlusions:

- Proximal MCA (M1) Occlusion
- Terminal Carotid Artery (Car-T) Occlusion
- Basilar Artery (BA) Occlusion

- It is always the first CTA done as soon as possible after (or immediately before) IVT initiation that qualifies for inclusion!

- It is important that the CTA is done not later then 15 minutes after IVT initiation. If CTA is done later than 15 min after IVT initiation the patients can not be included in the study.
Study Protocol - Inclusion criteria

- Acute stroke onset, CT verified ischaemic origin.
- CTA-evidence of major cerebral artery occlusion
- Fulfilment of accepted criteria for IVT
- IVT initiated within 4.5 h.
- NIHSS before IVT should be 7 or higher. (max 25 for anterior circulation stroke and no upper limit for posterior circulation strokes)

QUALIFIES FOR INCLUSION?
- MAKE REGISTRATION CALL!
Study Protocol - Study flow chart

- Admission of acute stroke
- IVT initiated in agreement with clinical guidelines
- Baseline CTA
- Telephone notification, preliminary enrolment
- Informed consent
- ACTIVE ARM
  - Persistent occlusion
    - YES: Thrombectomy procedure
    - NO
- CONTROL ARM
  - Follow-up CT and CTA at 22-36 h
  - Patient monitored during hospital stay
  - DISCHARGE
  - Primary and secondary endpoints
To be paid by KI for completed (locked) patients

<table>
<thead>
<tr>
<th>Activity</th>
<th>€ (excl. VAT)</th>
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<tbody>
<tr>
<td>CT Angiography at Baseline</td>
<td>0</td>
</tr>
<tr>
<td>CT Angiography at 24 hours*</td>
<td>500</td>
</tr>
<tr>
<td>Image transfers (CT, MR)</td>
<td>150</td>
</tr>
<tr>
<td>Video recording and upload of mRS interview</td>
<td>70</td>
</tr>
<tr>
<td>Source data transfer</td>
<td>50</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td><strong>770</strong></td>
</tr>
</tbody>
</table>
Please see the GUIDANCE Document
After an eligible patient for the study is identified:

Registration call:
CALL 24 h always available free telephone number for registration
+468 5177 6114

Informed consent is not necessary at this level: do not delay procedures
INFORMED CONSENT

Informed Consent will be collected after procedures are completed and always within 20 hours after IVT initiation:

✧ It is of utmost importance that informed consent is granted independently of their outcome – in particular for patients who cannot communicate or passed away early.

✧ Ethics Committee applications will include a possibility for the study physician to consent on patient’s behalf if patient cannot communicate or family members are not available.
TRAINING

Protocol

NIHSS Certification link:

Centre should archive the certificate in the Investigator Folder

mRS Certification
http://europeanacademictrials-sits-open.trainingcampus.net

Centre should archive the certificate in the Investigator Folder
Additional training is available in the investigator Folder
Training will be provided by Adjudication team in Glasgow

Images
See separate Imaging Procedures Manual

CRF
See separate User’s guide

GCP
It is highly recommended that site team member are educated in Good Clinical Practice.
Centre should archive the certificate of GCP education in Investigator Folder (if applicable)
The primary outcome of the study is the categorical shift in mRS score at three months.

3 months after stroke, the patient is interviewed through a video recording. The video-based interview is evaluated by mRS core lab in Glasgow. A camera will be sent to your center, which will also include instructions on how to upload the video into eCRF and how to become certified. mRS Core lab at the Western Infirmary in Glasgow will provide you with all material.

- 3 months after stroke
- Performed by Principal Investigator
- Certification
- Upload via the database
- Camera
Handling of CT imaging data:

◊ Read the Imaging Procedure Manual

◊ All pictures shall be in DICOM format.

◊ Each time point shall be saved on a separate CD: one for Baseline, one for 24 h Follow-up and one for procedure/angio.

◊ CDs sent to University of Edinburgh

◊ If an additional CT is made, it shall be sent to University of Edinburgh on a separate CD marked “Additional”.

◊ The CD’s shall only contain raw data.

◊ The patients name shall be replaced with the study number (ex. SITS OPEN-0000).

◊ The pictures shall be anonymized, but keep the date and time for the CT.

◊ All CD’s shall be accompanied by a transmittal sheet
All downloaded images:
Baseline CT
Baseline CTA
Procedural angio
Follow up CT
Follow up CTA
Any additional
Thrombectomy (for active sites only)

ID shall be replaced by study number!
NIHSS

Time points to perform NIHSS

◆ Before IVT
  (It is always the NIHSS score done just before the IVT initiation that qualifies for inclusion.)

◆ 2h (control centres)

◆ Before Thrombectomy (Active centres)

◆ 12h

◆ 24h

◆ 7 days or at discharge (whichever is later)
Delegation log:
This log has two purposes:

- Documentation of signatures and initials of all staff that collect and record data, study documentation attributed to specific staff members may be verified.
- List of study related activities that staff members may do per delegation by the Local Clinical PI.

Enrolment log:
This log is a record of all enrolled patients in the study at your centre. This log should stay at the clinic and archived in Investigator Folder according to local regulations.
Source data verification will be performed by a “PHYSICIAN’S MEDICAL VERIFICATION FORM”.

The form will be completed by principle or sub investigator and signed off for each patient included in the study. The completed “PHYSICIAN’S MEDICAL VERIFICATION FORM” will be send to SITS Open Coordination Team by email or regular mail.

This verification will confirm that medical data of the patient and inclusion into SITS Open is accurate.
Medical record

Remember to document information about the participation in the study in the Medical Record for the patient. This information should include: Study description, Enrolment number for the patient, date when Informed Consent was obtained, version of Informed Consent used, confirmation that patient is eligible for the study (Inclusion and Exclusion Criteria considered).

All changes made in the record should be trackable. The Medical record needs to be signed by the person who enter the data.
AE, SAE and SUSARS

Report SAE/AE’s on the "Adverse Events" page in the eCRF. In case of death, please report this both on the "Death" page in the eCRF and also in the "Adverse Events" page since death is a serious adverse event.

SAE should be reported within 24 hours!

There is no obligation to report AE/SAE beyond the eCRF.

SUSARS should be reported according to clinical practise and reported (marked as a SUSAR) in the CRF on “Adverse Event” page.
DATA COLLECTION

Study Center Principal Investigator enter data into the eCRF, X-ray images and mRS videos are uploaded through external links

Core lab Image

eCRF
SITS database

Core lab mRS

Statistical Analysis Data is compiled and unblinded.

Trial termination

Data locked

SITS Open
Images to University of Edinburgh

All images should be sent to University of Edinburgh within 3 working days.
All mRS should be uploaded to Adjudication team (via CRF) within immediately after mRS interview has been performed.
Clinical data are collected through the SITS electronic CRF, based on the thrombectomy registry (SITS-TBY) platform.

✧ Investigators registering data in the SITS Open study all need to be registered users in the register. For those who are not yet registered, please register here: https://sitsinternational.org/sits-user-application-form/userStep2Page

✧ The investigator need to register a test patient in the registry (separate instruction will be sent to you)

✧ A Enrolment number will be created when the patient is registered in the SITS database. Add the patient data and gain an Enrolment number in eCRF within 2 days after registration call.

✧ All available patient data shall be entered in to the database as soon as possible, at a maximum 7 days after registration call.
DEMO OF CRF
CRF
**Inclusion in clinical study**
- Include in clinical study: No
- SITS-OPEN
- Patient informed consent received: Yes
- Fulfilled enrollment criteria: Yes

**Date and time for telephone notification**
- Year: [ ]
- Month: [ ]
- Day: [ ]
- Hour: [ ]
- Min: [ ]
- Time unknown: [ ]

**Patient data**
- Date of birth: Year [ ] Month [ ] Day [ ]
- Not available: [ ]
- Gender: Select
- Patient initials: e.g. AB
- Social security number:
  - Format: yyyymmdd-xxxx (e.g. 19121212-1212)

**Acute phase intervention** (Required)
- Select all acute interventions that were done for this patient regardless of in which hospital they were performed in.

- No specific intervention
- LV thrombolysis
- Stroke unit care
- IA thrombolysis
- Thrombectomy
- Hemicraniectomy
- Carotid endarterectomy
- Angioplasty/stenting, intracranial
- Angioplasty/stenting, extracranial
- Any other specific intervention

**SITS-OPEN (Active)**

Based on the acute phase intervention(s) you have selected, the patient's data form will be:

Show comparison of SITS data forms
The Logistics section of the form includes fields for the date and time of stroke, patient admission before time of stroke onset, date and time of arrival to first hospital, and additional hospital information.

- **Date and time of stroke**: (Required) [Year / Month / Day / Hour / Min] [Time unknown]
- **Patient admission before time of stroke onset**: [Yes]
- **Date and time of arrival to first hospital**: (Required) [Year / Month / Day / Hour / Min] [Time unknown]
- **Specify hospital of first arrival**: (Required) [Select]
- **Additional hospital**: Allows entering information about additional hospitals involved in the care of the patient, including date and time of arrival and hospital selection.

Additional instructions are provided: "Additional hospital that share the same care episode for this patient. For example, if the primary stroke centre sends the patient to comprehensive centre for rescue thrombectomy, the primary centre where I.v. thrombolysis was done should be entered as the hospital of first arrival, and the comprehensive centre where thrombectomy was done as the additional hospital."
CRF

### SITSOPEN-0000 - Patient summary

**Patient data**
- **Notes**: Age at stroke onset: 14
- **Gender**: Female
- **Patient Id**: xxxxxxx x

**Data completeness**

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<thead>
<tr>
<th>Data Set</th>
<th>Baseline</th>
<th>Treatment</th>
<th>2h</th>
<th>12h</th>
<th>24h</th>
<th>7d</th>
<th>Discharge</th>
<th>3m</th>
<th>Death</th>
<th>Adverse event</th>
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</table>

**Acute interventions**

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>No specific intervention</th>
<th>Intravenous thrombolysis</th>
<th>Stroke unit care</th>
<th>Intravenous thrombolysis</th>
<th>Thrombectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

**Treatments**

<table>
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<th>Date</th>
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<th>Subject</th>
<th>Value</th>
<th>Add Treatments (via scoreboard)</th>
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**Observations**

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<th>Subject</th>
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**Imaging**

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<th>Method</th>
<th>Value</th>
<th>Time</th>
<th>Add Imaging (via scoreboard)</th>
</tr>
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**List all data for this patient**
## Baseline

### Logistics

**Date and time of stroke onset**

- Year: [2000]
- Month: January
- Day: 1
- Hour: 00
- Minute: 00
- Time unknown

**Patient was admitted before time of stroke onset**

- [ ]

**Date and time of arrival to first hospital**

- Year: [2000]
- Month: January
- Day: 1
- Hour: 01
- Minute: 00
- Time unknown

**Specify hospital of first arrival**

- [Test OPEN Control (TTOPC)]

**Hospital is not in list**

- [ ]

**Modified Rankin Scale before stroke**

- [ ]

**mRS score before stroke**

- [Please Select]

### Other clinical trials

- [ ]

### Other treatments

- [Aspirin]

---

**Smart Fill**
ADVERSE EVENTS

Add new adverse event

Adverse event type
- Serious

Date and time
- - - - - - Smart Fill

☐ Time unknown

Serious adverse event
- Please Select-

Add other serious adverse event or specify
- Insert text

☐ Suspected unexpected serious adverse reaction (SUSAR)

Adverse event reasonably related to:
- I.V. Thrombolysis

Criteria of serious adverse event:
- Please Select-

Add
CRF
INVESTIGATOR FOLDER and PATIENT FILE
QUESTIONS?
Final Slide!

THANK YOU