

The SITS Monitoring Study II SITS-MOST II

Safety and Efficacy Outcomes of
Treatment Interventions
in Stroke



Study Protocol

2015-03-27

An international, prospective, multicentre,
observational study of safety and efficacy of
treatment interventions in stroke in the clinical
routine setting

An international, prospective, multicentre, observational study
of safety and efficacy of treatment interventions in stroke in
the clinical routine setting

PROTOCOL SUMMARY

Study Title	The SITS Monitoring Study II (SITS-MOST II): An international, prospective, multicentre, observational study of safety and efficacy of treatments in acute stroke and secondary prevention in the clinical routine setting
Study Design	International, prospective, multicentre, observational study based on the SITS registry platform, of treatments such as intravenous thrombolysis (IVT), neurothrombectomy, and secondary prevention, in consecutively enrolled acute stroke patients.
Primary Hypothesis	Patients with acute stroke receiving treatments will have similar outcomes and similar safety in clinical routine as in the active arms of controlled trials
Study Objective	To monitor the safety and benefit of clinical routine treatments for acute stroke, such as IVT, neurothrombectomy, decompressive neurosurgery and secondary prevention, such as, anticoagulants, platelet inhibitors, antihypertensives, and lipid lowering.
Clinical Site Locations	All clinical centres worldwide, performing treatments in acute ischaemic stroke, are encouraged to join if they accept <ul style="list-style-type: none"> - to consecutively register all patients meeting criteria - to accept source data monitoring - to collaborate on evaluating any adverse reactions <p>Centres may define whether they prefer to restrict their registrations to certain treatments, such as i.v. thrombolysis or neurothrombectomy, although the requirement of consecutive registration applies to the preferred indication.</p>
Enrolment	Patients with acute stroke and agreeing with centre's preferred treatment registry. <p>Since this study aims to document treatment in clinical routine, all consecutive patients with the specified treatment for acute stroke will be included in the registry.</p> <p>Only patients meeting evidence based treatment criteria, the per protocol population, will be considered for the analysis of the primary hypothesis.</p>
Primary outcome variables	For <i>efficacy of acute intervention</i> : Functional independence on modified Rankin Scale score at 3 months (mRS 0-2); for efficacy of secondary prevention: Proportion of patients with recurrent stroke or other vascular events within 3 months <p>For <i>safety of acute intervention</i>: Symptomatic intracranial haemorrhage according to the modified SITS-MOST definitions below; and mortality within 3 months; for safety of secondary prevention: Major intra and extracranial haemorrhage and mortality within 3 months</p> <p>All analyses of main and secondary outcome variables will be done separately for the per protocol population and the all patients population</p>

Secondary outcome variables	<p>Proportion of patients with excellent recovery (mRS score 0-1) at 3 months</p> <p>Neurological improvement (difference in NIHSS from baseline to 2h/12h, to 24h and to 7D after initiation of acute treatment or to discharge if earlier than 7D)</p> <p>Study outcomes for mild stroke (NIHSS < 7), moderately severe stroke at baseline (NIHSS 7-12) and for severe stroke (NIHSS 13-)</p> <p>Length of in-hospital stay (days to discharge from in-hospital ward to home/secondary care for survivors)</p> <p>Number of days the patient stayed at home within the first 3 months after stroke onset</p> <p>Time between onset of stroke to arrival at hospital, to imaging and to treatment</p> <p>Systemic embolism (SE), Myocardial infarction (MI), Pulmonary Embolism (PE)</p>
Safety outcome variables	<p>Symptomatic intracerebral haemorrhage (SICH according to SITS-MOST definition).</p> <p>Symptomatic intracranial haemorrhage (SICH according to modified SITS-MOST definition); in addition to usual SITS-MOST criteria blood may be anywhere in the intracranial space (including in the intraventricular, intraparenchymal and/or subarachnoid space).</p> <p>All-cause mortality at 3 months.</p> <p>Death within 7 days post treatment</p> <p>Symptomatic intracranial haemorrhage according to NINDS and ECASS II definitions</p> <p>Distal embolism/reocclusion demonstrated by follow-up CTA/MRA</p> <p>Any adverse reactions related to treatment</p>

TABLE OF CONTENTS

TABLE OF CONTENTS	5
1 ABBREVIATIONS	8
2 ADMINISTRATIVE INFORMATION	10
2.1 SCIENTIFIC COMMITTEE	10
2.2 INTERNATIONAL COORDINATOR	11
2.3 REGIONAL COORDINATORS (applies to certain regions only)	11
2.4 NATIONAL COORDINATORS	11
2.5 INTERNATIONAL COORDINATION CENTRE	11
3 BACKGROUND	12
3.1 THROMBOLYSIS	12
3.2 THROMBECTOMY	12
3.2.1 SUMMARY OF THE LATEST THROMBECTOMY CLINICAL TRIALS	12
3.2.2 BRIDGING CONCEPT	14
3.3 OTHER TREATMENTS DOCUMENTED IN SITS	14
4 OBJECTIVES	14
5 OUTCOMES	14
5.1 PRIMARY OUTCOME VARIABLES	14
5.2 SECONDARY OUTCOME VARIABLES	15
5.3 SAFETY OUTCOME VARIABLES	15
6 DESIGN	15
6.1 OUTLINE	15
6.2 INVITATION OF STUDY CENTRES	16
6.3 ASSESSMENTS AND PROCEDURES	16
6.3.1 Clinical And Laboratory Procedures	16
6.3.2 In-Hospital Post Treatment Assessment	16
6.3.3 Outcome assessment at 3 Months (90 ± 14 days)	17
6.4 CRITERIA FOR TREATMENTS	17
7 DEVICES AND CRITERIA FOR PARTICIPATION	17
7.1 CRITERIA FOR PARTICIPATION IN SITS-MOST-II	17
8 ASSESSMENT OF EFFICACY AND SAFETY	17
8.1 CT/MR IMAGING	17
8.2 TREATMENTS DETAILS	18
8.3 REQUIREMENTS OF CLINICAL MEASUREMENTS	18
8.4 MODIFIED RANKING SCALE AT 3 MONTHS	18
8.5 CLINICAL SAFETY ASSESSMENT	18
8.5.1 Clinical examination	18
8.5.2 Monitoring of vital signs	18
8.5.3 Laboratory tests	18
8.5.4 Imaging safety assessment	18
8.5.5 Classification of Intracerebral haemorrhage	19
8.5.6 Classification of Cerebral oedema	19
8.5.7 Definition of Symptomatic Intracerebral/Intracranial Haemorrhage (SICH)	19

8.5.8	Adverse Events and Reactions	19
8.6	<i>CLINICAL EFFICACY ASSESSMENTS</i>	19
9	IMAGING EVALUATION	20
9.1	<i>BASELINE AND 24 H CT/MR AND CTA/MRA EXAMINATIONS</i>	20
9.2	<i>OPTIONAL PRE-PROCEDURE CT PERFUSION OR MR DWI/PWI IMAGING</i>	20
10	PROCEEDINGS FOR ADVERSE REACTIONS	20
10.1	<i>DEFINITION OF ADVERSE REACTIONS (AR)</i>	21
10.2	<i>ASSESSMENT OF ADVERSE REACTIONS</i>	21
10.3	<i>FOLLOW-UP OF ADVERSE REACTIONS</i>	22
10.4	<i>SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSAR)</i>	22
11	STATISTICS AND DATA MANAGEMENT	22
11.1	<i>DATA MANAGEMENT</i>	22
11.2	<i>STATISTICAL ANALYSIS</i>	23
11.2.1	Determination of sample size	23
11.2.2	Analysis of primary and secondary outcomes	23
11.2.3	Other planned analyses	23
12	DIRECT ACCESS TO SOURCE DOCUMENTS	23
13	QUALITY CONTROL AND QUALITY ASSURANCE	24
13.1	<i>SOURCE DATA</i>	24
13.2	<i>MONITORING</i>	24
14	ETHICS	24
14.1	<i>INDEPENDENT ETHICS COMMITTEE</i>	24
14.2	<i>ETHICAL CONDUCT OF THE TRIAL</i>	24
14.3	<i>SUBJECT INFORMATION AND INFORMED CONSENT</i>	24
14.4	<i>RISK/BENEFIT ASSESSMENT</i>	25
14.4.1	Potential risks of thrombolysis	25
14.4.2	Potential benefits of thrombolysis	25
14.4.3	Minimisation of Risk of thrombolysis	25
14.4.4	Potential risks of thrombectomy	25
14.4.5	Potential benefits of thrombectomy	26
14.4.6	Minimisation of Risk of Thrombectomy	26
14.4.7	Potential Risks and Benefits of Neuro Imaging	26
14.4.8	Other Potential Risks	27
15	DATA HANDLING AND RECORD KEEPING	27
15.1	<i>CASE REPORT FORMS AND RECORD KEEPING</i>	27
16	FINANCING AND INSURANCE	27
17	PUBLICATION POLICY	27
18	SUPPLEMENTS	28
18.1	<i>AMENDMENTS</i>	28
18.2	<i>PERSONNEL INFORMATION</i>	28
19	REFERENCES	28

20 SIGNED AGREEMENT OF THE PROTOCOL	31
21 APPENDICES	32
21.1 SCHEDULE OF INVESTIGATIONAL EVENTS	32
21.2	32
STUDY CENTRES	32
21.3 NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)	34
21.4 MODIFIED RANKIN SCALE (MRS)	36
21.5 STRUCTURED INTERVIEW MODEL FOR MRS ASSESSMENT	37
21.6 SITS GLOBAL OUTCOME SCALE (SITS-GOS)	38
21.7 THROMBOLYSIS IN CEREBRAL INFARCTION (TICI) SCORE	39
TICI score for angiographical assessment	39
Modified TICI score for CTA assessment	39
22 ATTACHMENTS	40
22.1 1. Guideline for intravenous thrombolysis	40
Indications	40
Contraindications	40
Comments	41
22.2 2. Preliminary guideline for thrombectomy	42
Reference Treatment criteria	42
Reference Exclusion criteria	42
22.3 3. Instructions for mRS Assessment	43
22.4 4. Rehabilitation guidelines	46
22.5 5. Informed consent	47
Information for a registry participant	47
22.6 6. NATIONAL COORDINATORS	48

1 ABBREVIATIONS

AE	Adverse event
BP	Blood Pressure
BA	Basilar artery
Car-T	Terminal Carotid Artery
CI	Coordinating Investigator
CCI	Co-Coordinating Investigator
CRF	Case Record Form
CT	Computer Tomography
CTA	Computer Tomography Angiography
DCNS	Decompressive Neurosurgery
DSMB	Data and Safety Monitoring Board
DWI	Diffusion weighted imaging
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HI	Haemorrhagic Infarction
IA	Intraarterial
ICH	Intracerebral Haemorrhage
IEC	Independent Ethics Committee
INR	International Normalised Ratio
ITT	Intention to Treat
IV	Intravenously
IVT	Intravenous Thrombolysis
LC	Local Coordinator
M1	Proximal Middle Cerebral Artery
MCA	Middle Cerebral Artery
MFS	Mission Fighting Stroke (Uppdrag Besegra Stroke)
MR	Magnetic Resonance
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NC	National Coordinator
NIHSS	National Institutes of Health Stroke Scale

NNT	Number of needed to treat
PCA	Posterior Cerebral Artery
pcASPECTS	Posterior circulation Acute Stroke Prognosis Early CT score
PH	Parenchymal Haemorrhage
PI/c	Principle Clinical Investigator
PI/i	Principle Interventional Investigator
PP	Per Protocol
PWI	Perfusion weighted imaging
rt-PA	Recombinant Tissue Plasminogen Activator
SAE	Serious Adverse Event
SICH	Symptomatic Intracerebral Haemorrhage
SITS	Safe Implementation of Treatments in Stroke
SITS-MOST	SITS Monitoring Study
TBY	Thrombectomy
TCD	Transcranial Doppler study
TICI	Thrombolysis In Cerebral Infarction (score)
UBS	Uppdrag Besegra Stroke (Mission Fighting Stroke)
WHO	World Health Organisation

2 ADMINISTRATIV INFORMATION

2.1 SCIENTIFIC COMMITTEE

Chair

Nils Wahlgren, MD, PhD

Karolinska University Hospital/Karolinska Institutet
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Members:

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<p>2.2 INTERNATIONAL COORDINATOR</p>	<p>Nils Wahlgren, MD, PhD Karolinska University Hospital Karolinska Institutet Stockholm, Sweden</p>
<p>2.3 REGIONAL COORDINATORS (applies to certain regions only)</p>	<p><u>SIECV-SITS (Latin America)</u> Exuperio Diez-Tejedor, MD, PhD Department of Neurology Hospital Universitario La Paz Madrid, Spain</p> <p><u>SITS-EAST (Central and Eastern Europe):</u> Robert Mikulik, MD, PhD Neurology Department St Anne 's Univeristy Hospital Brno, Czech Republik</p> <p><u>SITS MENA (Middle East and North Africa):</u> Suhail Al-Rukn, MD, PhD Department of Neurology Rashid University Hospital Dubai, United Arab Emirates</p>
<p>2.4 NATIONAL COORDINATORS</p>	<p>Listed in Attachment 6</p>
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3 BACKGROUND

3.1 THROMBOLYSIS

Intravenous thrombolysis (IVT) by recombinant tissue plasminogen activator (Alteplase) is an effective treatment within 4.5 hours after onset of neurological symptoms in patients with acute ischemic stroke.¹⁻⁷ There is an increased risk of symptomatic, even fatal, intracranial haemorrhage, but this is offset by a reduction in the proportion of patients being dead or dependent.^{3,6,7} The proportion of patients who benefit from thrombolysis by at least one point on the modified Rankin Scale (mRS) has been estimated to 32%.⁸ In August 2014, a metaanalysis of all individual data from 9 randomised controlled trials concluded that standard treatment with alteplase (0.9 mg/kg given as an infusion over 1 hour) resulted in an absolute 10% increase of patients being functionally recovered (modified Rankin score 0-1) if treated within 3 hours after onset, and an absolute 5% increase if treated within 3-4.5 hours⁹.

IVT has been shown improve outcomes across a wide range of baseline neurological severities as these were expressed on the National Institutes of Health Stroke Scale (NIHSS)¹⁰. Accumulating experience suggests that although intravenous thrombolysis improves outcomes also for severe ischaemic stroke, the improvements are frequently incomplete and may leave patients with a significant neurological and functional deficit. In the Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) based study of patients with dense Middle Cerebral Artery (MCA) sign on admission, representing the proximal MCA occlusion, has demonstrated that up to 45% of patients do not respond to IVT, and their outcomes are poor: mortality 30%, independence (mRS 0-2 on day 90) 19%.¹¹ Moreover, evidence of recanalisation of previously occluded vessel accompanied by early neurological improvement after IVT result in 75% of mRS 0-2 at 3 months in this subgroup.¹² Additional strategies for recanalisation of occluded arteries would be needed to improve final outcome. Mechanical removal of the thromboembolic occlusion, thrombectomy, has a potential to fill this role and is currently in fast development.¹³⁻¹⁵

3.2 THROMBECTOMY

The randomized controlled trials presented results indicating a significant effect of NT with stent retrievers in addition to other standard therapy in the acute phase of ischemic stroke caused by a blood clot in the anterior cerebral circulation¹⁶⁻²⁰ In general, patients were also treated with intravenous thrombolysis, if indicated, and patients were randomised to this standard treatment only or to NT if computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) had shown a blood clot in one of the larger vessels in the brain. Functional status after three months, according to modified Rankin Scale (mRS) has been the primary outcome variable in these studies. The studies have shown significant differences in functional independence (mRS 0-2) between active and control at follow-up (33% -19% Mr. CLEAN; 53% -29% ESCAPE; 71% -40% EXTEND IA; 60% -36% SWIFT Prime). The studies have shown a trend to lower mortality; ESCAPE a significantly lower mortality. No increase in bleeding after treatment, compared with only intravenous thrombolysis, could be established.

3.2.1 SUMMARY OF THE LATEST THROMBECTOMY CLINICAL TRIALS

The **MR CLEAN** trial (Multicenter Randomized Clinical trial of Endovascular Treatment in the Netherlands)¹⁶ using stent retrievers in 97% of the cases, showed benefit of endovascular therapy up to 6 h after stroke onset in the proximal anterior circulation in addition to best medical therapy (IVT up to 4.5 h in most patients). Onset to IVT was 85-87 min in both intervention and control groups and onset time to arterial puncture was 260 min. The endovascular procedure was associated with a shift to improved function at 90 days, as reflected in more patients in the lower mRS categories, with an adjusted common odds ratio (acOR) of 1.67 (95% confidence interval [CI], 1.21 - 2.30).

Secondary outcome parameters (NIHSS at 24h and 1wk, recanalization at 24h and final infarct at 1wk) were all statistically significantly favoring the intervention group. Treatment effect was consistent in all pre-defined subgroups.

The **ESCAPE** trial (Endovascular treatment for Small Core and Anterior circulation proximal occlusion with Emphasis on minimizing CT to recanalization times) was prematurely halted after randomization of 316 patients due to a positive interim analysis¹⁷.

To be randomized, patients needed to have a NIHSS > 5, a CTA confirmed occlusion of the carotid T or the middle cerebral artery (MCA, M1 or large M2 segment), good collaterals on multiphase CTA, a CT-ASPECTS > 5, and had to be enrolled < 12 hours. rtPA before randomization was given if patients were eligible. *Results*: The adjusted risk ratio for a mRS shift with NT at 90 days was 3.1 (CI : 2.0 – 4.7). A favourable modified Rankin score (mRS) of 0-2 at 90 days was seen in 53.0% in NT vs. 29.3% in controls (NNT=4), and reduction of mortality was significant. All subgroups of patients had similar benefit, including the elderly and patients treatable after 6 hours from onset time.

About 75% of patients received IVT and stent retrievers were used in 86.1%.

The **SWIFT PRIME** trial (Solitaire™ With the Intention For NT as PRIMARY treatment for acute ischemic stroke) was prematurely stopped after a positive interim analysis of the first 196 patients¹⁸. To be randomized, all patients needed to have received IVT < 4.5 hours, a NIHSS between 8 and 29, a CTA or MRA showing an occlusion of the intracranial carotid or M1 segment of the MCA without extracranial carotid occlusion, an ASPECTS > 6 and CT hypodensity (or MRI hyperintensity) < 1/3 of the MCA territory, and treatable < 6 hours. *Results* (two co-primary endpoints): The OR for a mRS shift at 90 days with NT using the Solitaire™ FR stent retriever was highly significant ($p < 0.001$), and mRS 0-2 at 90 days was 60.2% in NT patients vs. 35.5% in controls ($p < 0.001$, NNT=4). There was a trend for reduced mortality. The onset-to-arterial-puncture delay was 252 min. All subgroups of patients had similar benefit.

The **EXTEND-IA** trial (EXTending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy), a phase II trial looking at early reperfusion and neurological improvement on day 3, was prematurely stopped because of a positive interim analysis of the first 70 randomized patients¹⁹. To be randomized, all patients needed to have received IVT < 4.5 hours, a CT or MR angiography showing an occlusion of the intracranial carotid, M1 or M2 segment of the MCA, significant mismatch and limited core on MR- or CT perfusion (using the RAPID® software), and had to be treatable < 6 hours. *Results* (two co-primary endpoints): Early reperfusion of the ischemic tissue at 24h hours with NT with the Solitaire™ FR stent retriever was 100% vs. 37% in the control group ($p < 0.001$), a NIHSS reduction ≥ 8 points or NIHSS 0-1 at 3 days with NT was 80% vs 37% in the control group ($p < 0.001$). mRS 0-2 at 90 days was 71% in NT patients and 40% in controls ($p < 0.01$, NNT = 3). There was a trend towards reduction of mortality. The onset-to arterial-puncture delay was 210 min.

A recently published SITS registry study found National Institute of Health Stroke Scale (NIHSS) scores of 11 and 12 points as predictors of baseline vessel occlusion and functional independence at 3 months in a cohort of 11,632 patients with available baseline imaging data and 3 month functional outcome²¹. Moreover, if imaging was performed 3 h after stroke onset, NIHSS scores thresholds decreased to 9 and 10 points in predicting baseline vessel occlusion and functional outcome at 3 months, respectively. These results are in line with an initial single-centre retrospective study of 162 patients showing that a NIHSS score of 10 or more points up to 6 h after stroke onset increased by 16.9-fold the odds of unfavourable outcome or death ($p = 0.013$), and by 7.13-fold the odds of proximal vessel occlusion ($p = 0.013$ and $p < 0.038$, respectively; sensitivity, 83%; specificity, 78%)²². Aspects to be covered for a broader implementation of thrombectomy

We are now within reach of offering a broad group of patients a treatment that will save brains and lives. However, not all hospitals can offer, or will not even in the near future, be able to offer NT, which is a highly specialized treatment. We have identified three areas to be covered to enable a fast and powerful breakthrough of NT in Sweden and to ensure as many patients as possible get access to the treatment.

3.2.2 BRIDGING CONCEPT

The accepted explanation of comparatively modest clinical efficacy reported in TBY studies is that the advantage of higher rates of recanalisation with TBY is weakened by longer time needed to achieve it compared to IVT.^{23,24} To avoid the pitfall of time delay and keep the good chance for final successful recanalisation, a combination of IVT and endovascular treatment, the so-called bridging concept, was proposed and first tested in a randomised trial of combined IVT and local intra-arterial (IA) rt-PA therapy for stroke within 3 hours of onset of symptoms versus standard IVT alone²⁵. In a recent meta-analysis, pooled estimates associated with bridging therapy of any kind were 69.6% for recanalisation rates, 48.9% for favourable outcome, 17.9% for mortality, and 8.6% for SICH,²⁶ thus confirming the safety and efficacy of bridging approach in stroke patients.

The advantage of combined IVT+TBY approach was demonstrated by a prospective registry-based study of patients with confirmed arterial occlusion: successful recanalisation was achieved in 87% of patients treated with combination of IVT and endovascular treatment.²⁶ However, most of the studies of TBY after failed IVT come from small observational studies (or from subgroups of subjects in larger studies),^{23,27,28} and have been criticized because they lacked concurrent control arms, and the primary endpoints were procedural (e.g. recanalisation), as opposed to clinical (e.g. mRS outcomes at 3 months).

There are published data suggesting that IVT, even if failed, enhances the efficacy of subsequent mechanical revascularisation,^{23,29} though this observation was not tested in a controlled study.

3.3 OTHER TREATMENTS DOCUMENTED IN SITS

The following treatments are also documented in SITS:

- Decompressive neurosurgery
- Anticoagulants
- Platelet inhibitors
- Antihypertensives
- Lipid lowering
- Carotid artery surgery and stenting

4 OBJECTIVES

To monitor the safety and benefit of clinical routine treatments for acute stroke, such as intravenous thrombolysis, neurothrombectomy, decompressive neurosurgery and secondary prevention, such as, anticoagulants, platelet inhibitors, antihypertensives, and lipid lowering.

5 OUTCOMES

5.1 PRIMARY OUTCOME VARIABLES

- For *efficacy of acute intervention*: Functional independence on modified Rankin Scale score at 3 months (mRS 0-2);
- For efficacy of secondary prevention: Proportion of patients with recurrent stroke or other vascular events within 3 months
- For *safety of acute intervention*: Symptomatic intracranial haemorrhage according to the modified SITS-MOST definitions below; and mortality within 3 months; for safety of secondary prevention: Major intra and extracranial haemorrhage and mortality within 3 months
- All analyses of main and secondary outcome variables will be done separately for the per protocol population and the all patients population

5.2 SECONDARY OUTCOME VARIABLES

- Proportion of patients with excellent recovery (mRS score 0-1) at 3 months
- Neurological improvement (difference in NIHSS from baseline to 2h/12h, to 24h and to 7D after initiation of acute treatment or to discharge if earlier than 7D)
- Study outcomes for mild stroke (NIHSS < 7), moderately severe stroke at baseline (NIHSS 7-12) and for severe stroke (NIHSS 13-)
- Length of in-hospital stay (days to discharge from in-hospital ward to home/secondary care for survivors)
- Number of days the patient stayed at home within the first 3 months after stroke onset
- Time between onset of stroke to arrival at hospital, to imaging and to treatment

5.3 SAFETY OUTCOME VARIABLES

- Symptomatic intracerebral haemorrhage (SICH according to SITS-MOST definition).
- Symptomatic intracranial haemorrhage (SICH according to modified SITS-MOST definition); in addition to usual SITS-MOST criteria blood may be anywhere in the intracranial space (including in the intraventricular, intraparenchymal and/or subarachnoid space).
- All-cause mortality at 3 months.
- Death within 7 days post treatment
- Symptomatic intracranial haemorrhage according to NINDS and ECASS II definitions
- Distal embolism/reocclusion demonstrated by follow-up CTA/MRA
- Any adverse reactions related to treatment
- Major bleeding defined as a reduction in the haemoglobin level of at least 20 g per litre, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ.

6 DESIGN

6.1 OUTLINE

- International, prospective, multicentre, observational study based on the SITS registry platform,
- Participating centres can decide to join the following data entry protocols: Intravenous Thrombolysis Protocol following a standard or minimal design (IVTPs; IVTPm), Thrombectomy Protocol (TBYP), All Patients Protocol, standard or minimal design (APPs; APPm); Atrial Fibrillation Protocol (AFP). The data entry protocols can overlap in individual patients when appropriate.
- Treatment decisions are the responsibility of the local stroke clinician
- All patients under selected data entry protocols will be entered in the registry, whether they fulfill accepted treatment recommendations or not
- Treatment recommendations are attached to this protocol; separate analyses will be performed for patient treatments in agreement with recommendations (per protocol analyses) and for all patients (all patients analyses)
- All centres have access to an on-line report which is updated immediately after data entry. The report includes statistical summaries for important variables, with comparisons to outcomes within the same nation and within the global registry (anonymised). Users may also form self-designed report for a wide range of variables, filtered for different baseline data conditions. The report system includes a download function for all local data.
- All analyses are based on anonymised data. Patient identity is only kept at centre level to enable source data monitoring.
- Every centre can design and save, as favourites, regular (e.g. monthly) reports formatted according to their preference. These reports may serve as a basis for internal benchmarking purposes, or used for research and development
- SITS will release annual reports on overall data from the registry

6.2 INVITATION OF STUDY CENTRES

- All clinical centres world wide, performing treatments for acute ischaemic stroke, and secondary prevention, are encouraged to join if they accept
 - to consecutively register all patients meeting criteria
 - to accept source data monitoring
 - to collaborate on evaluating any adverse reactions
- If a centre is not previously a SITS registry centre, a local coordinator must register the centre through a link at the SITS International web site. Registration is only possible if the above criteria are accepted. When registration is submitted, the National Coordinator for the respective country is consulted before final approval. Other Local users may be registered after approval of the Local coordinator.
- If a centre is already a SITS registry centre, the Local coordinator activates the SITS-TBY registry at the centre home page. A local interventionist coordinator may register as a local user, and then be upgraded to local interventional coordinator by the local clinical coordinator

6.3 ASSESSMENTS AND PROCEDURES

6.3.1 Clinical And Laboratory Procedures

All tests included in this protocol are considered within the range of standard clinical care pre- and post- intervention. Appendix 1 (20.1) provides a detailed schedule of events.

6.3.2 In-Hospital Post Treatment Assessment

In the acute phase, neurological status, described by NIHSS total score and subscores, will be assessed and recorded 5 times in addition to baseline (see figure and 22.3).

NIHSS assessment will be performed at baseline (prior to start of IVT), at 2 h for IVT or before the start of thrombectomy (for which the 2-hour assessment in the eCRF applies), 12h after IVT start for TBY patients, at 24h and on day 7 (± 2) or day of discharge, whichever first. If general anaesthesia was used for a thrombectomy procedure and its effect interferes with the neurologic assessment at 12h, NIHSS may be assessed later than 12h as soon as the patient completely recovers (at a flexible time point, date and time will be recorded in the registry).

Event number	1	2	3	4	5
Name of time point	Baseline	2h	12h	24h	7days/ discharge
IVT	Before IVT start	90-150 min after IVT start		22-36h post IVT	
Bridging IVT-TBY	Before IVT	Immediately before TBY	10-14h post IVT*	22-36h post IVT	7 \pm 2 days post IVT/TBY/arrival or at discharge**
TBY only	Before baseline imaging scan	Immediately before TBY	10-14h post TBY*	22-36h post TBY	
APP	At arrival			22-36h post arrival	

IVT = intravenous thrombolysis; TBY = thrombectomy

*If general anaesthesia is used, this time point should be postponed until complete recovery from the anaesthesia

**The day of discharge if the patient is discharged before day 5.

Blood pressure (systolic and diastolic) should be measured and recorded at the same time as the NIHSS assessments.

Within 22-36 hours after IVT initiation, or, in case of TBY without IVT, after TBY initiation, a CT or MR will be obtained to assess haemorrhage, infarct and oedema.

At 7 days (± 2) after the procedure/arrival, or prior to hospital discharge, whichever is earlier, the patient's neurological status will be assessed and recorded using the NIHSS, and mRS. Local investigators will enter their evaluation using the mRS (see 22.4-22.5 and Attachment 4).

6.3.3 Outcome assessment at 3 Months (90 \pm 14 days)

Patient neurological and medical status will be assessed and recorded using the mRS (22.4-22.5). Follow-up mRS assessment is the last study procedure and is done at the last visit on day 90 \pm 14 after treatment. Preferably this evaluation is done at a physical visit, but if not possible information can also be collected by telephone.

6.4 CRITERIA FOR TREATMENTS

Criteria for IVT are provided in Attachment 1

Criteria for TBY are provided in Attachment 2

7 DEVICES AND CRITERIA FOR PARTICIPATION

7.1 CRITERIA FOR PARTICIPATION IN SITS-MOST-II

All clinical centres world wide, performing treatments in acute ischaemic stroke, are encouraged to join if they accept

- to consecutively register all patients meeting criteria
- to accept source data monitoring
- to collaborate on evaluating any adverse reactions

For TBY, participating centres should apply a team model for treatment decision including stroke clinician and neurointerventionist.

8 ASSESSMENT OF EFFICACY AND SAFETY

A schedule of investigational events is presented in attachment 21.2

8.1 CT/MR IMAGING

- All CT and or MR results can be documented at baseline, at 22-36 hours and at a free time point. Data include presence of infarct or haemorrhage, localisation of any occlusion, TICI grade, presence of perfusion deficit and oedema.

8.2 TREATMENTS DETAILS

Time point for start and end of the thrombolysis and thrombectomy procedure, choice of general or local anaesthesia if used, angiography results, devices used, results of the intervention, TICI score before and after procedure and other details are documented.

8.3 REQUIREMENTS OF CLINICAL MEASUREMENTS

- NIHSS – Doctors or other staff should be certified in the collection of NIHSS may perform the assessments.
- Mortality – Cause of death will be recorded for all patients that expire during the study.

8.4 MODIFIED RANKING SCALE AT 3 MONTHS

- The local investigator or sub-investigators will perform a structured interview for determining the mRS score (see,23.3, Attachment 3) and document this in the eCRF.

8.5 CLINICAL SAFETY ASSESSMENT

8.5.1 Clinical examination

Physical and neurological examination of the patient will be performed by a medical professional at baseline, initiation of treatment/procedure, 12h, 24h, 7 (\pm 2) days or day of discharge home/secondary care, if earlier. The NIH-Stroke Scale (NIHSS) will be used for standardised evaluation of the neurological deficit. Certification in NIHSS use is recommended for the rater. Post-procedure assessment should include evaluation of arterial puncture site for the signs of bleeding.

8.5.2 Monitoring of vital signs

Vital signs taken at baseline are arterial blood pressure (systolic and diastolic), heart rate, respiratory rate, and body temperature. Endovascular treatment is performed under the supervision of anaesthesiologist when required; method of anaesthesia, if applied, and intraoperational monitoring is chosen according to the local standard clinical practice. Type of anaesthesia and medications given should be recorded in the eCRF.

8.5.3 Laboratory tests

Laboratory testing at baseline should comply with the standard guidelines for IVT patients; these include CBC, serum glucose, serum cholesterol, urea, creatinine, bilirubin and liver enzymes, electrolytes, coagulation tests (PT, APTT, INR). Blood glucose, cholesterol, platelet count, APTT and INR are recorded in the CRF.

8.5.4 Imaging safety assessment

A local radiologist will evaluate of 22-36 h CT scan. CT and/or MR scans will be evaluated for any type haemorrhage (including SAH) and the degree of cerebral oedema, if present.

If detection of haemorrhage on the follow-up CT scan is ambiguous because of suspected extravasation of contrast media after mechanical thrombectomy, dual-energy imaging or another follow-up CT scan (preferably the next day after 24-hour assessment) is required.

8.5.5 Classification of Intracerebral haemorrhage

HI1:	Small petechiae along the margins of the infarct
HI2:	More confluent petechiae within the infarct area but without space-occupying effect
PH1:	Blood clot(s) not exceeding 30% of the infarct area with some mild space-occupying effect
PH2:	Blood clots exceeding 30% of the infarct area with significant space occupying effect
PHr1:	Small or medium sized blood clots located remote from the actual infarct; a mild space occupying effect could be present
PHr2:	Large confluent dense blood clots in an area remote from the actual infarct; significant space occupying effect may be present
SAH:	Presence of haemorrhage in any compartment of the subarachnoid space

8.5.6 Classification of Cerebral oedema

COED 1:	Focal brain swelling up to one third of the hemisphere
COED 2:	Focal brain swelling greater than one third of the hemisphere
COED 3:	Brain swelling with midline shift

8.5.7 Definition of Symptomatic Intracerebral/Intracranial Haemorrhage (SICH)

SICH will be defined as follows:

SITS-MOST definition: local or remote parenchymal haemorrhage type 2 on the 22- to 36-hour post-treatment imaging scan, combined with a neurological deterioration of ≥ 4 points compared with baseline NIHSS or the lowest NIHSS value or death between baseline and 24 hours

Modified SITS-MOST definition: in addition to the SITS-MOST criteria listed above, extravasated blood may be anywhere in the intracranial space (including in the intraventricular, intraparenchymal and/or subarachnoid space).

ECASS III definition: any apparently extravascular blood in the brain or within the cranium that was associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified by core lab evaluation as the predominant cause of the neurologic deterioration

Modified ECASS III definition: NIHSS decline of 4 points within 7 days associated with any haemorrhage judged by core lab evaluation to be responsible for the decline; blood may be anywhere in the intracranial space including in the intraventricular, intraparenchymal and/or subarachnoid space

8.5.8 Adverse Events and Reactions

Investigators and other study personnel will monitor each subject for possible adverse events caused by the study procedure, i.e. adverse reactions. Documenting and reporting of adverse reactions is described at Chapter 10.

8.6 CLINICAL EFFICACY ASSESSMENTS

- Functional outcome is evaluated on the modified Rankin Scale (mRS) on day 90 according to the Saver structured interview (see reference 20.6) and the instructions in Attachment 3.

- National Institutes of Health Stroke Scale (NIHSS) is used for evaluation of neurological symptoms (see reference 20.4)
- Post-procedure TIC1 score is used for actively treated population; revascularisation of the occluded territory is defined as at least TIC1 2b flow in the treated territory after procedure (see reference 20.8)
- Time from stroke onset to revascularisation to TIC1 grades 2 and/or 3 for actively treated population
- CTA (recanalisation at 24h)
- CT (infarct size at 24 h)

9 IMAGING EVALUATION

9.1 BASELINE AND 24 H CT/MR AND CTA/MRA EXAMINATIONS

- Baseline CT (or MR) examinations will be evaluated for early infarct signs (hypodensity, dense artery sign) and findings, which may contraindicate IVT. Appropriate indication for IVT will be confirmed or rejected.
- Baseline CTA/MRA examinations, when indicated, will be evaluated for location of the artery occlusion (e.g., M1/M2, A1/A2, Car-T, BA), and for any proximal artery stenosis
- 24 (22-36 h) hour CT/MR examinations will define any haemorrhage and score per the haemorrhage classification (8.5.5); in addition an evaluation of infarct volume will be performed. If required and available, differentiation of blood and contrast using double-energy technique should be applied.
- An additional CT examination (next day after 24 h follow up assessment) will be performed if necessary to differentiate between haemorrhage and contrast extravasation on 24 hour CT – as an alternative to double-energy technique at 24 h images.
- In the case of renal insufficiency developing after CTA/thrombectomy procedure or in the case of impending renal failure or other clinical contraindications to repeated contrast administration, TCD could be used instead of follow-up CTA if the patient is already included in the study. TCD should be performed by an accredited neurosonologist.

9.2 OPTIONAL PRE-PROCEDURE CT PERFUSION OR MR DWI/PWI IMAGING

- Centres that routinely perform pre-procedure CT Perfusion or MR DWI/PWI are encouraged to enter these data in the data form.

10 PROCEEDINGS FOR ADVERSE REACTIONS

Adverse reactions (AR) are recorded in the case report form.

All Serious Adverse Reactions should be reported on the appropriate data form in the study. A Serious Adverse Reactions (SAR) is defined as:

- Death
- Life-threatening events resulting in extended hospitalisation or death
- Events which result in permanent impairment of a body function or permanent damage to body structure
- Events which necessitate medical or surgical intervention by a health care professional (this includes medications)
 - to preclude permanent impairment of a body function or permanent damage to body structure; (or)
 - to relieve unanticipated temporary impairment of a body function or unanticipated temporary damage to body structure.

In addition to events covered by the above definition, as a primary measure for assessing safety, all cases of symptomatic intracranial haemorrhage, any suspected vessel perforation, any suspected vessel dissection, embolization to a previously uninvolved territory, and arterial puncture site complication requiring surgical repair or blood transfusion should be considered SARs, regardless of whether or not the patient experienced any clinical sequelae associated with that event.

The local investigator at each site will review all clinical adverse reactions and will be responsible for relaying information regarding serious adverse reactions to the Coordinating centre, as required.

SARs Unanticipated Adverse Reactions (UAR) or Unanticipated Adverse Device Effects (UADR) are defined as those not listed in the section "Risk/Benefit Assessment". Investigational sites must report any UAR/UADR within 24 hours by filling the printed form (which can be downloaded from SITS website) and sending it by fax to the Coordinating centre + 46 8 736 6158.

In the event of unforeseen death, efforts will be made to secure a copy of any autopsy results and to obtain post-mortem specimens, for gross and histological evaluation.

In the event of unforeseen death, efforts will be made to secure a copy of any autopsy results and to obtain post-mortem specimens, for gross and histological evaluation.

10.1 DEFINITION OF ADVERSE REACTIONS (AR)

- ARs in this study should be collected and reported in the data entry form. An adverse reaction is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition in a clinical investigation subject who was treated by the study procedure/device and which is judged to have a causal relationship with the treatment under study (i.e., thrombectomy combined with IVT).
- The study population consists of the subjects who are acutely and severely ill, and frequently have a number of comorbidities. Expected fluctuations or expected deterioration of the underlying disease and other pre-existing conditions should not be recorded as an AR, if not causally related to the study procedure.

10.2 ASSESSMENT OF ADVERSE REACTIONS

Adverse reactions will be documented if they occur during the acute phase, lasting up to and including 7 days or the day of discharge from the hospital if this occurs earlier, and continued to be monitored until the last visit when 3 months outcome is assessed. ARs will be documented in the appropriate part of the electronic case record form (eCRF).

- Key features to be reported:
 - Reaction type:
 - Serious: Definition above
 - Non-serious: Not meeting above definition
 - Timing of reaction
 - Kind of reaction
 - Relation of reaction to thrombectomy or IVT
 - Degree of intensity of non-serious reaction:
 - **Mild:** Sign(s) or symptom(s) is/are easily tolerated
 - **Moderate:** Discomfort which interferes with usual activity
 - **Severe:** Incapacitating or causing inability to work or to perform usual activities or leading to death.
- If serious adverse reaction, categorisation:

- Death
- Life-threatening events resulting in extended hospitalisation or death
- Events which result in permanent impairment of a body function or permanent damage to body structure
- Events which necessitate medical or surgical intervention by a health care professional (this includes medications) –
 - to preclude permanent impairment of a body function or permanent damage to body structure; (or)
 - to relieve unanticipated temporary impairment of a body function or unanticipated temporary damage to body structure.

The investigator assesses the relationship between the study intervention and the occurrence of AR, based on his/her medical judgement. Presence or absence of causality should be recorded in CRF.

10.3 FOLLOW-UP OF ADVERSE REACTIONS

The investigator who has reported an AR is supposed to actively follow the subject's condition and provide further information to the coordination centre. The duration of follow-up is determined by the time needed for AR resolution or stabilisation of patient's condition, or until the event is otherwise explained, or until the subject is lost to follow-up. Follow-up of AR may require additional laboratory tests or investigations, or consultation with other health care professionals, which will be managed by the investigator.

10.4 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSAR)

SUSAR is an uncommon or unexpected serious adverse reaction (i.e. reaction the nature and severity of which is not consistent with the applicable information about the study device) observed during the study and related to the study procedure. A reasonable possibility of a causal relationship between the adverse event and the study procedure is implied. The immediate report of SUSAR to the Coordinating Centre should be made as soon as possible, not exceeding 24h following knowledge of the event. The immediate report should be followed by a detailed written report, which contains all the relevant information. The Coordinating Centre will report the SUSAR to the national competent authority, to the Ethics committee, and will inform the investigators. Life-threatening and fatal events are to be reported to the national competent authority and to the Ethics committee no later than in 7 days after knowledge of the event; other events must be reported no later than 15 days after knowledge.

11 STATISTICS AND DATA MANAGEMENT

11.1 DATA MANAGEMENT

All study data must be recorded in the eCRF (see User's Guide). The eCRF should be completed promptly after each observation (results of in-hospital observations within 2 weeks after discharge, 3-months outcome data within 2 weeks after the last visit). The investigator is responsible for the verification of accuracy of data entries. In parallel, all the relevant information should be recorded in hospital medical files in accordance with local regulations. A copy of any information that is collected only for the purposes of the study and for which the eCRF is the source, may be filed in the medical records. The eCRF will be compared with source documents to check for accuracy. The source documents provide evidence for the case and verify the data in eCRF.

For any data transfer, measures will be undertaken to protect patient data handed over against disclosure to unauthorized third parties and patient confidentiality will be maintained at all times. Data validation and data queries will be handled by the source data monitoring team.

11.2 STATISTICAL ANALYSIS

Statistical analysis of the primary and main secondary outcomes will be performed by the Coordination team of the study. Additional secondary analyses will be performed after decision by the Scientific Committee.

11.2.1 Determination of sample size

Since this is a prospective, observational, study of treatments in acute stroke patients, including IVT and TBY in clinical routine during a period following presentation of the first positive randomised TBY trials within the indication, we find it essential to build a sample size of several thousand patients to enable evaluation of efficacy and safety in new as well as experienced centres. This is in the line with SITS-MOST study after provisional approval of IVT with Alteplase in 2002, when registration by SITS registry was a condition for this decision. SITS-MOST then collected 6483 patient files during three years as a basis for the conclusion that IVT was as efficacious as safe in clinical routine as in randomised controlled trials. We plan to continue recruitment for a period of five years, and after appropriate analysis of primary and secondary outcomes decide whether it is motivated to prepare for a prolongation with a new study protocol.

11.2.2 Analysis of primary and secondary outcomes

Primary and secondary endpoints will be presented using descriptive statistics. For categorical data, the number with the condition, the number evaluated, the percentage, and the exact 95% confidence intervals on the percentage will be provided. For continuous variables, the summary statistics (N, mean, median, standard deviation, interquartile range, minimum and maximum) will be reported. For each endpoint or measure, results will be summarized for all enrolled patients. Proportion of patients who achieve functional independence ($mRS \leq 2$) at 90 days in the active and control groups, as well as the other binary endpoints (proportion of excellent recovery, mRS 0-1; proportion of dead; etc.) and safety outcomes, will be explored using appropriate statistical methods, including multiple logistic regression with adjustment for the prognostically important covariates with active arms of randomised controlled trials, both predefined from the previous knowledge (like age, baseline NIHSS score) and those which appear significant after exploratory analysis. Continuous endpoints (onset-to-treatment time, length of in-hospital stay, home time) may be analysed with linear regression and quantile regression when the model assumptions are met. Wherever possible, centre effect will be incorporated to the multivariable models.

11.2.3 Other planned analyses

- The clinical temporal profile, as reflected by the curve of NIHSS assessments at baseline and after the treatment and/or procedure, will be analysed in relation to vessel recanalisation status described by CTA.
- The correlation of blood pressure with the vessel recanalisation status will be analysed.
- Outcomes in per-protocol vs. non-per-protocol patients
- Outcomes in IVT+TBY patients vs. TBY only patients
- Outcomes in new vs. experienced centres
- Outcomes for 3-4.5 h and > 4,5 h will be analysed
- Outcomes for different doses of IVT

12 DIRECT ACCESS TO SOURCE DOCUMENTS

Source data monitoring may occur during the course of the study. The Coordination centre source data group must be given direct access to source documents (scanned copies of original documents,

or if required, original documents). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the study.

An investigator Source Document Verification Agreement will be completed and signed for each site in order to describe where source data for each data item can be found and how source data verification by scanning should be implemented.

The Local investigator will ensure that site staff completes the eCRFs.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 SOURCE DATA

- Source data verification may occur during the course of the study
- Inclusion in the study and the study inclusion number must be documented in the hospital patient file (HPF).
- The Coordination centre or NC asks PIs to send source data for monitoring. Medical record extracts are scanned and email to the NC who compares the eCRF with medical records, for basic information according to instructions, appendix 9. (Medical records in local language, thus the NC is best suited to monitor, and communicate with Coordination Centre).

13.2 MONITORING

If required, additional source data monitoring may be performed by on-site visits.

14 ETHICS

14.1 INDEPENDENT ETHICS COMMITTEE

The study plan will be submitted to the appropriate Ethics Committee by the coordinating centre. The investigator will ensure that all SAEs will be collected and recorded throughout the trial period and report all SAE's immediately (within 24 hours) to the coordinating centre. The coordinating centre will ensure the notification of the Ethics Committee, of all SAEs occurring in the trial in accordance with local legal requirements.

14.2 ETHICAL CONDUCT OF THE TRIAL

The study will be conducted in agreement with the study protocol, GCP principles and the Helsinki Declaration (2008)

The study procedures implemented in the present study are within the range of routine clinical practice, with sufficient amount of previous experience in stroke patients. Hence, no ethical approval is needed for accepted treatments and procedures. Ethical approval for the participation in the registry and documentation of the data should be obtained in each participating country in accordance with national legislation.

14.3 SUBJECT INFORMATION AND INFORMED CONSENT

Since centres use thrombectomy in clinical practice, consent for the treatment is granted by clinical routine procedures, as will all routine treatments. Patients will receive written information about the registry and its purpose, and how to contact a member of the staff if they do not agree that their patient data are added to the registry.

Written information and oral explanations will be provided, and the patient may decline to be included in the registry. To avoid time delay in the acute stroke setting, the patient information will

be provided after the urgent treatments/procedures are done, given the fact that clinical strategy is not changed by the study protocol, and the patient will be given the opportunity to decline the registration of data.

For the patient information (Swedish and English version), please see Attachment 5.

14.4 RISK/BENEFIT ASSESSMENT

All study procedures and investigations are considered within the range of routine clinical practice. Nevertheless, any of the treatments, including intravenous thrombolysis, thrombectomy of large intracranial vessels does, oral anticoagulants and imaging studies, may carry risk to the patient. Since study treatments, procedures and devices are approved for clinical use, their implementation is unlikely to result in unexpected events.

14.4.1 Potential risks of thrombolysis

The potential risks associated with the current thrombolysis treatments:

- Symptomatic intracerebral haemorrhage
- Bleeding in the access site or elsewhere
- Low blood pressure
- Allergy to thrombolytic drugs

14.4.2 Potential benefits of thrombolysis

IVT improves functional outcome irrespective of age and stroke severity, and significantly improves the overall odds of a good outcome in acute ischaemic stroke patients treated within 4.5 hours after stroke onset, with earlier treatment associated with bigger proportional effects. The average absolute increase in disability-free survival is about 10% for patients treated within 3 hours and 5% for patients treated within the interval of 3-4.5 hours after stroke onset.

14.4.3 Minimisation of Risk of thrombolysis

- The physician will make an accurate medical history, physical examination and go through a current list of medications
- Stop or pause the medication that can influence with the thrombolysis treatment
- Coagulations tests will be performed before treatment

14.4.4 Potential risks of thrombectomy

The potential risks associated with the current mechanical procedures used to remove blood clots from the brain include:

- An air bubble (air embolus) introduced into the blood vessels
- Bleeding or bruising in the access site, or where the puncture is made
- Infection at the access site, or sepsis
- Embolization of a fragment, or of the entire thrombus, to a previously uninvolved territory
- Vessel spasm
- New clot formation (thrombosis)
- A blood vessel tear or puncture

- Distal thrombus – embolization of pieces of the original thrombus “downstream” in the same vascular territory as the original thrombus
- Blood vessel becomes acutely occluded (re-thrombosis)
- Ischemia (reduced blood flow) in the brain
- Intra-cerebral haemorrhage (bleeding into the brain)
- False aneurysm formation
- Neurological deficits, including a new stroke
- Headache/pain during the retrieval procedure
- Death

14.4.5 Potential benefits of thrombectomy

Stent-retrievers were designed to restore blood flow to the occluded vessel(s) and it has been shown that revascularisation increases the chance of a good clinical outcome in revascularised patients. Based on pre-clinical testing and recently reported randomised controlled trials, it is believed that the new generation of thrombectomy devices, stent retrievers, will add benefit to best evidence based medical treatment for patients with acute ischaemic stroke and confirmed major cerebral artery occlusion.

14.4.6 Minimisation of Risk of Thrombectomy

Study management procedures designed to minimize risks to patients:

- Only trained and experienced physicians will be allowed to use or supervise the use of the study devices within the study.
- Only CE-marked devices will be used in this study.
- Patients will be closely monitored during and after the procedure through discharge, and will be followed for up to 90 days post procedure to assess clinical outcomes.
- Study personnel at each site will receive training on proper informed consent procedures, required study data points, NIHSS and mRS assessment tools, data collection forms and/or use of eCRF, and proper reporting of adverse events and adverse device effects.
- Reported adverse events/unanticipated serious adverse device effects/device malfunctions will be reviewed and analysed on an on-going basis throughout the study, and appropriate medical measures will be taken by the treating physician(s) to resolve the adverse events.
- The study will be monitored remotely by reviewing the submitted data collection and/or EDC forms for inconsistencies and/or missing information.

14.4.7 Potential Risks and Benefits of Neuro Imaging

- Angiography, CT and MR are standard neuro-imaging procedures that aid physicians in diagnosing and treating large vessel occlusions in patients experiencing an acute ischemic stroke. The risks and benefits are well studied and understood within the medical community, and these procedures are used routinely in this same patient population at the same time points to determine eligibility for endovascular procedures, and / or to assess neurological decline and / or the presence of haemorrhage post treatment/procedure.
- CT/MR scans of the brain obtained at baseline and at 22-36 hours post treatment/procedure are considered standard medical care. The radiation dose that is received is the same dose that would be received from the clinical care to assess and treat the underlying medical condition.
- CT angiography (CTA) is widely used in the work-up of stroke patients with large vessel occlusion to access the occlusion site, guide the treatment decisions and estimate the individual prognosis. It is increasingly included into the standards of acute stroke imaging in tertiary as well as in primary care stroke centres. The risks associated with performing a follow-up CTA in control patients are the ionizing radiation exposure and potential adverse effects of administration of contrast dye. However, it is accepted by medical community that benefit of an

accurate visualisation of cerebral vessels in stroke patients will generally outweigh the small radiation risks of a single study. National and international radiology technical standards are developed to use the lowest radiation dose possible while producing the best images for evaluation, provided adjustment of the scan parameters to one's body type and weight and thorough limitation of the scanning area to the area of interest to avoid unnecessary radiation to other body parts.

Procedure-related complications of CTA may include:

- Allergic reaction to contrast material
- Kidney failure in patients who already have borderline kidney function or severe diabetes (advanced kidney disease is a contraindication to CTA).
- Leakage of contrast dye from the peripheral vein and other problems related to the peripheral venous access
- Nevertheless, in a clinical study of stroke patients who received IVT and were performed CT angiography even without knowledge of baseline creatinine level serious renal injury was never observed.⁴⁴
- If CTA and MRA with contrast enhancement are not available or contraindicated, these follow-up studies may be replaced by a transcranial Doppler study, though this is the least preferable option.

14.4.8 Other Potential Risks

- Possible discomfort from vital sign monitoring and related equipment during, and immediately following, the procedure.
- Possible discomfort from frequent neurological examinations performed before, during, and after the procedure.
- Pain or bruising at the site of blood draw.
- There also may be risks and discomforts which are yet unknown.

15 DATA HANDLING AND RECORD KEEPING

15.1 CASE REPORT FORMS AND RECORD KEEPING

SITS MOST-II will use an electronic case report form (eCRF) for each included patient. Investigators will ensure completion and review of the eCRF. Investigators have personal responsibility for the accuracy and authenticity of all clinical and laboratory data that are entered into the eCRF. User's Guide provides list of variables included into the eCRF with the explanations.

The eCRF is accessed through secure Internet connection and with high security level password protection. The eCRFs will be electronically archived.

16 FINANCING AND INSURANCE

Separate financial protocol will be set up.

Financing and insurance will be in accordance with the regulations of individual countries and are addressed in separate documents. Since all the study procedures are the part of approved care, no insurance responsibility from the study organisation is required.

17 PUBLICATION POLICY

The results of the study will be published in the name of all investigators in an international peer-reviewed scientific journal not later than 12 months after the study has ended.

Research data collected during the study are owned by the investigators in the SITS-MOST-II study at SITS International. SITS International Coordinating Centre has the responsibility for storage and maintenance of the data and preparations of study reports.

SITS Scientific Committee has the primary role in planning and approval of publications. All manuscripts based on SITS-TBY data will be presented to the Steering Committee members for discussion and approval before submission to any scientific journal.

18 SUPPLEMENTS

18.1 AMENDMENTS

- The CI decides about amendment of the study protocol and is responsible to request approval from the Ethics Committee.

18.2 PERSONNEL INFORMATION

- The Principle Investigator is accountable for the conduct of the trial at the site. If any tasks are delegated, the Principle Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant trial-related duties

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20 SIGNED AGREEMENT OF THE PROTOCOL

Coordinating
investigator

Date

Signature

Nils Wahlgren

Name

Local Coordinator

Date

Signature

Name

Centre, code

Centre name

21 APPENDICES

21.1 SCHEDULE OF INVESTIGATIONAL EVENTS

Trial Period	Baseline	¹ Check point 1	² Check point 2	24h post admission/IVT/TBY	7 ± 2 days or discharge	Final follow-up 90 ± 14 days
Visit No.	1	2	3	4	5	6
Day of visit	0	0	0	1	7 (5-9)	89 (75-104)
Information/consent	X					
Time of stroke onset	X					
Time of rtPA/TBY start	X					
Demographic data	X					
Medical history	X ³					
Intake of medications at stroke onset	X ³					
CBC, including platelet count	X				X	
Biochemistry panel, including blood glucose and cholesterol	X				X	
Coagulation tests	X				X	
NIHSS	X	X	X	X	X	
Blood pressure	X	X	X	X	X	
CT	X		X ^{4,5}	X ⁶		
MRI ⁵	X		X ^{4,5}	X ^{5,6}		
CTA or MRA	X ⁷			X ^{5,7}		
TCD ⁵	X	X	X	X		
IVT	X					
Prescription of medications at discharge					X	
ADR/SAE reporting	X	X	X	X	X	X
Final stroke diagnosis					X	
Global Outcome					X	
Modified Rankin Scale, mRS	X ¹⁰				X	X

¹ Check point 1
For IVT: 90-150 min post-IVT start
For TBY: just before TBY

² Check point 2
For TBY: 10-14h post-IVT start or after the full recovery from anaesthesia

³ by interview

⁴ in case of suspected ICH, at the discretion of the investigator

⁵ optional

⁶ after IVT, TBY; accepted interval 22-36h

⁷ For TBY

¹⁰ mRS before stroke

21.2

STUDY CENTRES

21.3 NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)

National Institute of Health Stroke Scale (NIHSS)		
Date and time	DD-MM-YYYY	HH:MM (24h)
<p>1.a. Level of Consciousness</p> <p>0: Alert</p> <p>1: Not alert, but arousable with minimal stimulation</p> <p>2: Not alert, requires repeated stimulation to attend</p> <p>3: Coma</p>		
<p>1.b. LOC questions (Ask patient the month and her/his age)</p> <p>0: Answers both correctly</p> <p>1: Answers one correctly</p> <p>2: Both incorrect</p>		
<p>1.c. LOC commands (Ask patient to open/close eyes & form/release fist)</p> <p>0: Obeys both correctly</p> <p>1: Obeys one correctly</p> <p>2: Both incorrect</p>		
<p>2. Best gaze (only horizontal eye movement)</p> <p>0: Normal</p> <p>1: Partial gaze palsy</p> <p>2: Total gaze paresis or Forced deviation</p>		
<p>3. Visual Field testing</p> <p>0: No visual field loss</p> <p>1: Partial hemianopia</p> <p>2: Complete hemianopia</p> <p>3: Bilateral hemianopia (blind including cortical blindness)</p>		
<p>4. Facial Paresis (Ask patient to show teeth/ raise eyebrows & close eyes tightly)</p> <p>0: Normal symmetrical movement</p> <p>1: Minor paralysis (flattened nasolabial fold, asymmetry on smiling)</p> <p>2: Partial paralysis (total or near total paralysis of lower face)</p> <p>3: Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)</p>		
<p>5. Motor Function – Arm</p> <p>0: Normal (extends arms 900 (or 450) for 10 seconds without drift)</p> <p>1: Drift</p> <p>2: Some effort against gravity</p> <p>3: No effort against gravity</p> <p>4: No movement</p>		Right
		Left

9: Untestable (Joint fused or limb amputated) (do not add score)	
6. Motor Function - Leg 0: Normal (hold leg in 300 position for 5 sec without drift) 1: Drift 2: Some effort against gravity 3: No effort against gravity 4: No movement 9: Untestable (Joint fused or limb amputated) (do not add score)	Right
	Left
7. Limb Ataxia 0: No ataxia 1: Present in one limb 2: Present in two limbs	
8. Sensory (Use pinprick to test arms, legs, trunk and face- compare side to side) 0: Normal 1: Mild to moderate decrease in sensation 2: Severe to total sensory loss	
9. Best Language (Ask patient to describe picture, name items, read sentences) 0: No aphasia 1: Mild to moderate aphasia 2: Severe aphasia 3: Mute	
10. Dysarthria (Ask patient to read several words) 0: Normal articulation 1: Mild to moderate slurring of words 2: Near unintelligible or unable to speak 9: Intubated or other physical barrier (do not add score)	
11. Extinction and inattention (Formerly Neglect) (Use visual or sensory double stimulation) 0: Normal 1: Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities 2: Severe hemi-inattention or hemi-inattention to more than one modality	
Total Score	

21.4 MODIFIED RANKIN SCALE (MRS)

Date/time	DD-MM-YYYY	HH:MM (24h)
0	No symptoms at all	
1	No significant disabling symptoms	
2	Slight disability but does not require substantial help from other person, can walk	
3	Moderate disability, requires substantial help from other person, can walk	
4	Moderately severe disability, requires substantial help from other person, unable to walk	
5	Severe disability, bedbound	
6	Dead	
9	Not known	

21.5 STRUCTURED INTERVIEW MODEL FOR MRS ASSESSMENT

(also see instructions – attachment 3)

6	DEATH	
5	BEDRIDDEN	
5.1	Is the person bedridden?	Yes (5) / No
4	ASSISTANCE TO WALK	
4.1	Is another person's assistance essential for walking?	Yes (4) / No
3	ASSISTANCE TO LOOK AFTER OWN AFFAIRS	
3.1	Is assistance ABSOLUTELY essential for preparing a simple meal?	Yes (3) / No
3.2	Is assistance ABSOLUTELY essential for basic household chores?	Yes (3) / No
3.3	Is assistance ABSOLUTELY essential for looking after household expenses?	Yes (3) / No
3.4	Is assistance ABSOLUTELY essential for local travel?	Yes (3) / No
3.5	Is assistance ABSOLUTELY essential for local shopping?	Yes (3) / No
2	USUAL DUTIES AND ACTIVITIES	
2.1	Work Has the new stroke substantially reduced (compared to prestroke status) the person's ability to work (or, for a student, study)?	Yes (2) / No
2.2	Family responsibilities Has the new stroke substantially reduced (compared to prestroke status) the person's ability to look after family at home?	Yes (2) / No
2.3	Social & leisure activities Has the new stroke reduced (compared to prestroke status) the person's regular free-time activities by more than one half as often?	Yes (2) / No
2.4	Other physical/medical condition Are the patient's work, family, and/or social/leisure activities substantially reduced by a physical/medical condition other than the stroke that led to trial enrollment?	Yes (2) / No
1	SPONTANEOUSLY REPORTED SYMPTOMS	
1.1	Does the patient have any symptoms resulting from the new stroke?	Yes (1) / No
1.2	SYMPTOM CHECKLIST	
1.2.1	Does the person have difficulty reading or writing as a result of the new stroke?	Yes (1) / No
1.2.2	Does the person have difficulty speaking or finding the right word as a result of the new stroke?	Yes (1) / No
1.2.3	Does the person have problems with balance or coordination as a result of the new stroke?	Yes (1) / No
1.2.4	Does the person have visual problems as a result of stroke?	Yes (1) / No

1.2.5	Does the person have numbness (face, arms, legs, hands, feet) as a result of the new stroke?	Yes (1) / No
1.2.6	Does the person have weakness or loss of movement (face, arms, legs, hands, feet) as a result of the new stroke?	Yes (1) / No
1.2.7	Does the person have difficulty with swallowing as a result of the new stroke?	Yes (1) / No
1.2.8	Does the person have any other symptoms related to the new stroke?	Yes (1) / No
RANKIN GRADE =		

21.6 SITS GLOBAL OUTCOME SCALE (SITS-GOS)

Global outcome	
Condition	
Much better	
Better	
Unchanged	
Worse	
Much worse	
Dead	

The scale reflects the global impression of the patient's performance, according to the judgement of the treating clinician. A global impression would include not only estimation of change in neurological functions but also of the patient's general medical and psychological condition. An approximate reference for change in neurological functions depends on baseline severity; for a baseline severity of 12 points on NIHSS 'unchanged' may correspond to absence of change or change of NIHSS score between -1 and +4 from baseline; "much better", equivalent of dramatic/major neurological improvement by 8-10 points reduction from baseline or total recovery; "much worse" an increase in NIHSS score by 8-10 points from baseline, or death.

21.7 THROMBOLYSIS IN CEREBRAL INFARCTION (TICI) SCORE

TICI score for angiographical assessment

Grade 0	No perfusion. No antegrade flow beyond the point of occlusion.
Grade 1	Penetration With Minimal Perfusion. The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.
Grade 2	Partial Perfusion. The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction; but at slow rate.
Grade 2a	Partial filling (<50%) of the entire vascular territory is visualized.
Grade 2b	Filling of $\geq 50\%$ or greater of the expected vascular territory is visualized, but the filling is slower than normal.
Grade 3	Complete Perfusion. Rapid filling and clearance.

Modified TICI score for CTA assessment

Grade 0	No perfusion.
Grade 1	Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion.
Grade 2a	Perfusion of less than half of the vascular distribution of the occluded artery.
Grade 2b	Perfusion of half or greater of the vascular distribution of the occluded artery
Grade 3	Full perfusion with filling of all distal branches

22 ATTACHMENTS

22.1 1. Guideline for intravenous thrombolysis

Patient undergoing thrombolytic therapy should be transferred to an intensive care or semi-intensive care/monitoring unit with the possibility to monitor vital signs and neurological status as soon as the radiological and (for active study centres only) any subsequent endovascular procedure is completed. Invasive procedures (e.g. gastric tube, urinary catheter, arterial line) should be avoided.

Thrombolytic therapy consists of intravenously administered Alteplase (0.9 mg/kg body weight, maximum dose 90mg) given within 4.5 hours after stroke onset by a 10% of total dose in bolus and 90% by a 1-hour infusion. For active centres bridging to thrombectomy, there is no need to wait for the infusion to be completed or to discontinue the infusion before artery puncture, but this decision is on the investigator's discretion. The final dose of Alteplase must always be documented in eCRF.

Reasons for discontinuation of rtPA infusion are severe headache, acute hypertension, nausea/vomiting, hypersensitivity /anaphylactic reaction (e.g. angio-edema, bronchospasm, rash, urticaria, hypotension, shock or any other symptom associated with allergic reactions). If a systolic blood pressure is above 180 mm Hg or if a diastolic blood pressure is above 105 mm Hg, intravenous antihypertensive medications should be started.

Indications

- Clinical diagnosis of ischaemic stroke
- Age \geq 18 years
- Time from stroke onset \leq 4.5 hours
- Absence of haemorrhage on admission CT scan

Contraindications

- Hypersensitivity to rtPA or to any of the medication compounds.
- Severe stroke as assessed clinically (e.g. NIHSS $>$ 25 for anterior circulation stroke) and/or extensive early ischaemic changes on admission CT scan (defined as more than one third of the MCA territory or one half of other territories)
- Other thrombolytic treatment within the previous 72h
- Known platelet count below 100,000/mm³
- Clinically significant hypoglycaemia
- Uncontrollable hypertension (blood pressure exceeding: systolic 185 mm Hg and diastolic - 110 mm Hg on at least 2 measurements made with 10-minute interval) or aggressive management (by the discretion of the investigator, usually implying intravenous pharmacotherapy) necessary to reduce BP to these limits
- Current use of oral anticoagulants and a prolonged prothrombin time (INR $>$ 1.7) or intake of direct oral anticoagulants with APTT above normal limits or within the latest 4 hours
- Use of glycoprotein IIb-IIIa inhibitors within the past 72 hours
- Clinical suspicion of subarachnoid haemorrhage (even if CT-scan is normal)
- Use of heparin in previous 48 hours, if aPTT is exceeding the upper limit of normal for laboratory
- Recent history of central nervous system damage (intracranial haemorrhage neoplasm, ruptured aneurysm, intracranial or spinal surgery)
- Active bleeding or acute trauma on examination, or recent severe or dangerous bleeding
- Known haemorrhagic diathesis/ bleeding disorder
- Recent (less than 10 days) traumatic external heart massage, obstetrical delivery, recent puncture of a non-compressible blood-vessel (e.g. subclavian or jugular vein puncture)
- Prior stroke in previous 3 months
- Major surgery within the preceding 14 days, which poses a risk in the opinion of the investigator

- Documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial aneurysm, arterial/venous malformations
- Seizure at onset of stroke only if there is a clinical suspicion of postictal residual neurological impairments which mimics stroke
- Any condition that may be associated with increased bleeding risk or could impose hazards to the patient if intravenous thrombolysis is initiated (e.g., severe microangiopathy such as haemolytic uraemic syndrome or thrombotic thrombocytopenic purpura), at the discretion of the treating physician

Comments

Upper age limit was not set in the present study guidelines, since the recent research ⁴⁵⁻⁴⁷ has demonstrated the beneficial effect of IVT even in very elderly patients. Consideration of patient's advanced age should be made on individual basis with regard to the general state of health and concomitant diseases.

The population of the present study is not a general stroke population, but a subgroup with severe stroke, as indicated by large cerebral vessel occlusion at baseline. For this reason, rapidly improving symptoms should not preclude vascular imaging.

22.2 2. Preliminary guideline for thrombectomy

Reference Treatment criteria

A clinical diagnosis of acute stroke, with a deficit on the National Institutes of Health (NIH) stroke scale of 2 points or more

Computerised tomography (CT) or magnetic resonance imaging (MRI) scan ruling out intracranial hemorrhage

- Intracranial arterial occlusion of the distal intracranial carotid artery or middle (M1/M2) or anterior (A1/A2) cerebral artery, or the basilar artery, demonstrated with Computed Tomography Angiography (CTA), magnetic resonance angiography (MRA), Digital subtraction angiography (DSA) or transcranial Doppler / duplex (TCD)
- The possibility to start treatment within 6 hours from onset, or within x hours for basilar artery occlusion
- Age ≥ 18 years

Reference Exclusion criteria

General:

- Arterial blood pressure $> 185/110$ mmHg
- Blood glucose < 2.7 or > 22.2 mmol/L
- Intravenous treatment with thrombolytic therapy in a dose exceeding 0.9 mg/kg Alteplase or 90 mg
- Intravenous treatment with thrombolytic therapy despite contra-indications, i.e. major surgery, gastrointestinal bleeding or urinary tract bleeding within the previous 2 weeks, or arterial puncture at a non-compressible site within the previous 7 days
- Laboratory evidence of coagulation abnormalities, i.e. platelet count $< 40 \times 10^9/L$, activated partial thromboplastin time (APTT) > 50 sec or International Normalised Ratio (INR) > 3.0

For intended intra-arterial thrombolysis:

- Cerebral infarction in the distribution of the relevant occluded artery in the previous 6 weeks
- History of intracerebral hemorrhage
- Severe head injury (contusion) in the previous 4 weeks
- Clinical or laboratory evidence of coagulation abnormalities, i.e. platelet count $< 90 \times 10^9/L$, APTT > 50 sec or INR > 1.7

22.3 3. Instructions for mRS Assessment

Note that only symptoms arising since the stroke should be considered. In determining the Rankin score walking aids or other necessary mechanical devices are disregarded provided that the patient can use these without external assistance.

The **score of 0** is awarded to patients who have no residual symptoms after their stroke, not even minor symptoms.

If patients have any symptoms resulting from the stroke, whether physical or mental, then they should be **scored at least 1** on the Rankin scale. For example, if they have any new difficulty in speech, reading or writing, in physical movement, sensation, vision or swallowing, or any change in their mood that does not limit their activities, they still should score 1. Patients in this category can continue to take part in all of their previous work, social and leisure activities. For this purpose, “usual” is regarded as any activity that they used to undertake for a monthly basis or more frequently.

If there is any activity that they used to undertake that they can no longer do since the stroke, whether because of a physical limitation or because they have chosen to give up the activity as a result of the stroke, then they should be **scored 2** on the Rankin. In this category the patient has slight disability and is unable to carry out all his previous activities, but he is still able to look after all of his own affairs without any external assistance. For example, a patient would be scored in this category if he used to play golf and is no longer able to do so, or if he used to have a job whereas he now no longer works. The patient should still be able to look after himself without any daily help. In other words he will be able to dress, move around, eat, go to the toilet, prepare simple meals, undertake shopping and make short journeys by himself. He will not require any supervision from other people and could safely be left at home for periods of a week or more without any concern. An inability to drive purely because of legal impediment, i.e. where the participant is otherwise physically able, would not warrant a score of 2.

Rankin **category 3** is for patients who have moderate disability. These patients require some external help for daily activities but are able to walk without assistance. They may use a stick or a frame for walking but the assistance of another person is not required for this. They will be able to manage daily activities such as dressing, toileting, feeding etc, but will need help for more complex tasks such as shopping, cooking or cleaning or will need to be visited more often than weekly for some other purpose. The external help may simply be advisory, for example supervision for their financial affairs.

Patients with moderately severe disability who are unable to walk without assistance and are unable to attend to their own bodily needs by themselves are given a **score of 4**. These patients are not independently mobile and will need help with daily tasks such as dressing, toileting or eating. They will need to be visited at least daily or will need to live in close proximity to a carer. To discriminate patients in category 4 from those in the most severe category, consider whether the patient can regularly be left along for moderate periods of a few hours during the day.

Patients who cannot be left alone even for a few hours should be given the **score of 5**. Patients in category 5 have severe disability and are usually bedridden, incontinent and require constant nursing care and attention. Someone else will always need to be available during the day and at time during the night, although this will not necessarily be a trained nurse.

Thus, in summary, to distinguish between patients in category 0 or 1 consider whether the patient has any remaining symptoms. To distinguish between categories 1 and 2 consider whether the patient can undertake all of his previous activities. If the patient is independent of others in activities of daily living, then he should be scored 2 rather than 3. To distinguish between category 3 and category 4 the crucial question is whether the patient can walk without the assistance of other people. Finally, a patient who can be left by himself for a few hours during the day would be given a score of 4 rather than 5.

It is important to note that patients do not always fall neatly into one category and some judgement is usually required when scoring them. When in doubt between 2 categories, always stick to the key discriminators of the scale. Thus if the patient has remaining symptoms he scores at least 1. If the patient is unable to undertake previous activities he scores at least 2. If he is dependent upon others **in activities of daily living** he must score at least 3. If the patient is unable to walk without assistance he must score at least 4 and if the patient is bedridden and requires constant nursing care he will score 5. Finally, if there is still some doubt between two alternatives on the scale, and both options appear equally valid, then the worse option should be chosen.

As an example we have included some key discriminating questions that should be considered when using the modified Rankin scale. These are shown in more detail below (the official definitions of each category are shown below in bold and the italicized text provides guidance that may reduce inter-observer variability, without requiring a structured interview).

0. **No symptoms at all**
The patient should be unaware of any new limitation of symptom caused by the stroke, however minor.
1. **No significant disability despite symptoms; able to carry out all usual duties and activities**
The patient has some symptoms as a result of the stroke, whether physical or cognitive – for example affecting speech, reading or writing; or physical movement; or sensation; or vision; or swallowing; or mood – but can continue to take part in all previous work, social and leisure activities. The crucial question to distinguish grade 1 from grade 2 (below) may be, ‘is there anything that you can no longer do that you used to do until you had the stroke? As a guide, an activity that was undertaken more frequently than monthly could be regarded as a ‘usual activity’.
2. **Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance**
The patient will be unable to undertake some activity that was possible before the stroke (e.g. driving a car, dancing, reading or working) but is still able to look after him/herself without help from others on a day-to-day basis. Thus, the patient can manage dressing, moving around, feeding, toileting, preparing simple meals, shopping, and travelling locally without needing assistance from anyone else. Supervision is not necessary. This grade assumes that the patient could be left alone at home for periods of a week or more without concern.
3. **Moderate disability; requiring some help, but able to walk without assistance**
At this grade the patient is independently mobile (using a walking aid or frame if necessary) and can manage dressing, toileting, feeding, etc. but needs help from someone else for more complex tasks. For example, someone else may need to undertake shopping, cooking or cleaning and will need to visit the patient more often than weekly to ensure that these activities are completed. The assistance can be advisory rather than physical: for example, a patient who needs supervision or encouragement to cope with financial affairs would be in this grade.
4. **Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance**
The patient requires someone else to help with some daily tasks, whether walking, dressing, toileting or eating. This patient will be visited at least once and usually twice or more times daily, or must live in proximity to a carer. To distinguish grade 4 from grade 5 (below), consider whether the patient can regularly be left alone for moderate

periods during the day.

5. Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
Someone else will always need to be available during the day and at times during the night, though not necessarily a trained nurse.

22.4 4. Rehabilitation guidelines

Rehabilitation aims to enable people with disabilities to reach and maintain optimal physical, intellectual, psychological and/or social function.

None of the non-modifiable factors, such as stroke severity, gender, stroke aetiology, age, and topography of lesion should influence decisions on rehabilitation.

Rehabilitation for the stroke patients is recommended to be started in a stroke unit by a coordinated multidisciplinary team with stroke expertise. The rehabilitation program should start as early as possible, preferably in the first 24h of stroke onset if clinical condition of the patient allows it. Start of the rehabilitation program within 20–30 days is a due. Patients that are undergoing active rehabilitation are recommended to get physiotherapy and occupational therapy as much as possible, the recommended minimum is 1 h of active practice per day at least 5 days per week.

For medically stable patients with mild or moderate impairment early discharge from stroke unit to a rehabilitation unit is a preference.

Rehabilitation program may include the following items in accordance with the individual clinical symptoms and deficits:

- Physiotherapy
- Occupational therapy
- Speech and language disorders assessment and appropriate treatment
- Cognitive deficits assessment and appropriate treatment
- Monitoring for post-stroke depression for all patients; antidepressants and psychological interventions if indicated
- Medications for post-stroke emotionalism and mood disorders
- Tricyclic or anticonvulsant medications for post-stroke neuropathic pain, if indicated
- Botulinum toxin for post-stroke spasticity, if indicated
- Involvement of other therapists depending on patient-specific goals (dietitians, orthoptists, social workers, etc.)

For the severely disabled patients who are unable to participate actively, passive movements to prevent contractures or pressure sores have been recommended.

22.5 5. Informed consent

Name of the registry: Safe Implementation of Treatments in Stroke (SITS-Registry)

International Coordinator Nils Wahlgren, MD, PhD at Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden

Information for a registry participant

Patient information for SITS-Registry (Safe Implementation of Treatments in Stroke)

You have received treatment after being diagnosed with stroke. This treatment aims to reduce the impact of your stroke and to protect against new incidents. In order to that future stroke treatments ought to be given in the most safe and best way, it is important with an accurately follow up. Selected treatment (data) is recorded in an international data registry: SITS-Registry (Safe Implementation of Treatments in Stroke). The purpose of the registry is to continue to improve future care and treatment. The registry will enable research and quality improvement by allowing detailed comparisons between the treatment and the results.

If you do not wish to participate with your treatment records in the research registry, you can notify a responsible nurse or doctor (see below). All data collected is treated confidentially.

The following treatments and data will be recorded:

- Date and time of stroke onset and time to hospital arrival and received treatment
- Information about your stroke such as severity, disability, etc.
- Risk factors such as diabetes, hypertension, heart disease, etc.
- Results of CT scan of the brain and other medical examinations
- Medication and other treatments
- Your condition at follow-up after about three months, and sometimes even 1 year after onset of the stroke.

Important to know:

- Listing of your information in the registry is entirely voluntary and will not affect in any way the care you receive
- You can at anytime request an extract from the registry records or cancel your participation in the registry. In such a case, you may contact your responsible doctor or nurse, (see below)
- If you have questions about the SITS-registry, contact your local responsible physician or nurse
- Your data in the registry is protected from unauthorized access. Access to the registry is done through a secure login
- Your data in the research registry will be used only for research, statistics and quality improvement in health care. Research studies based on registry data requires an approval from an ethics board (EPN)
- Responsible for Personal data is Karolinska Institutet, Dept of Clinical Neuroscience, 171 76 Stockholm

Responsible Doctor:	Responsible Nurse:
E-mail:	E-mail:
Mobile phone:	Mobile phone:

22.6 6. NATIONAL COORDINATORS

Region	Country	Name	Hospital
Africa, Middle East	Algeria	Selma Kesraoui	Hopital Frantz Fanon
Africa, Middle East	Iran	Behnam Mansouri	Imam Husain Hospital
Africa, Middle East	Israel	Roni Eichel	Hadassah Ein-Kerem University Hospital
Africa, Middle East	Lebanon	Souheil Gebeily	The Libanese Hospital
Africa, Middle East	Lybia	Husen Abdulrahman	Benghazi Medical Centre
Africa, Middle East	Marocco	Belahsen Faouzi	HASSAN II University hospital
Africa, Middle East	Pakistan	Mohammad Wasay	Aga Khan University Hospital
Africa, Middle East	Qatar	Atlantic Souza	-
Africa, Middle East	United Arab Emirates	Suhail Alrukn	Rashid Hospital
Africa, Middle East	Algeria	Selma Kesraoui	Hopital Frantz Fanon
Africa, Middle East	Iran	Behnam Mansouri	Imam Husain Hospital
Asia Pacific, India	Australia	Markus Romesh	St Vincent Hospital
Asia Pacific, India	China	Yongjun Wang	Tiantan Hospital, Beijing, China,
Asia Pacific, India	Hong Kong	Thomas wai hong Leung	Prince of Wales Hospital
Asia Pacific, India	India	Dheeraj Khurana, M.V. Padma Srivastava	Indian Postgraduate Institute, All India Institute of Medical Sciences
Asia Pacific, India	Japan	-	-
Asia Pacific, India	Korea	Joung-Ho Rha	Inha University Hospital,
Asia Pacific, India	New Zealand	John N Fink	Christchurch Hospital
Asia Pacific, India	Singapore	Kim En-Lee	National Neuroscience Institute
Asia Pacific, India	Thailand	Yongchai Nilanont	An internal medicine department
Asia Pacific, India	Vietnam	-	-
European	Austria	Raoul Eckhardt	Landeskrlinikum Tulln
European	Belarus	Sergey Kulesh	Grodno Regional Hospital

European	Belgium	Patrice Laloux, Geert Vanhooren	Mont-Godinne University Hospital, AZ Sint Brugge
European	Bulgaria	Silva Andonova	University Hospital Sveta Marina
European	Croatia	Vanja Basic Kes	Sestre milosrdnice University Hospital
European	Czech Republic	Robert Mikulik	St. Anne's University Hospital
European	Denmark	Grethe Andersen, Helle Iversen	Århus University Hospital
European	Estonia	Janika Kõrv	University of Tartu
European	Finland	Risto Roine, Turgut Tatlisumak	Turku University Hospital, Helsinki University Central Hospital
European	France	Didier Leys	Lille University Hospital
European	Germany	Peter Ringleb	University hospital of Heidelberg
European	Greece	Jobst Rudolf, Giorgios Tsigoulis	Papageorgiou General Hospital, University Hospital of Alexandroupolis
European	Hungary	László Csiba, Klara Fekete	University Medical School in Debrecen
European	Iceland	Albert Páll	Landspítali University Hospital
European	Ireland	Killian O'Rourke	Mater Misericordiae University Hospital
European	Italy	Danilo Toni	Hospital Policlinico Umberto I
European	Lithuania	Dalius Jatuzis, Aleksandras Vilionskis	Vilnius University Hospital Santariskiu clinics
European	Moldova	Stanislav Groppa	Institute of Neurology and Neurosurgery, 2 Korolenko str.
European	Netherlands	Maarten Uyttenboogaart	Groningen University Medical Centre
European	Norway	Titto Iddicul, Arnstein Tveiten	Haukeland University Hospital, Sørlandet Sykehus Kristiansand

European	Poland	Anna Czlonkowska, Adam Kobayashi	2nd Department of Neurology, Warsaw
European	Portugal	Teresa Pinho e Melo	Santa Maria Hospital
European	Russia	Veronika Skvortsova, Nikolay Shamalov	Russian State Medical University
European	Serbia	Ljiljana Beslac- Bumbasirevic	Institute of Neurology Clinical Center
European	Slovakia	Zuzana Gdovinová	University hospital of L. Pasteur
European	Slovenia	Viktor Svigelj	University Hospital Ljubljana
European	Spain	José Castillo	Santiago de Compostela, Spain
European	Sweden	Jesper Petersson	Malmö University Hospital
European	Switzerland	Hansjoerg Hungerbuehler	Kantonsspital Aarau
European	Turkey	Yakup Krespi	Memorial Hizmet Hospital
European	Ukraine	Liliya Zviyagina	Odessa Regional Medical Centre
European	United Kingdom	Gary Ford, Kennedy Lees	Newcastle upon Tyne Hospitals NHS Foundation Trust, Western Infirmary
USA, Latin America, Caribbean	Argentina	Sebastian Ameriso	Fleni Hospital
USA, Latin America, Caribbean	Brazil	Octávio Pontes Neto	Hospital das Clínicas de Ribeirão Preto
USA, Latin America, Caribbean	Chile	Arnold Hoppe	Clinica Alemana de Santiago
USA, Latin America, Caribbean	Colombia	German Enrique Perez	Clinica Universitaria Universidad Nacional de Colombia
USA, Latin America, Caribbean	Costa Rica	Franz Chavez-Sell	Clinica Biblica
USA, Latin America, Caribbean	Cuba	-	-
USA, Latin America, Caribbean	Dominican Republic	Margarita Cerda	Juan Pablo Pina Hospital

USA, Latin America, Caribbean	Ecuador	Patricio Abad	Hospital Metropolitano
USA, Latin America, Caribbean	El Salvador	William Arias Sifontes	Hospital Diagnostico Escalon
USA, Latin America, Caribbean	Guatemala	Luis Salguero	Hospital Herrera Llerandi
USA, Latin America, Caribbean	Honduras	Marco T. Medina	Hospital Escuela/UNAH
USA, Latin America, Caribbean	Mexico	Fernando Gongora-Rivera, Antonio Arauz Gongora	Hospital Universitario UANL, Instituto Nacional de Neurologia y Neurocirugia
USA, Latin America, Caribbean	Nicaragua	Jorge Martinez Cerrato	Hospital Metropolitano
USA, Latin America, Caribbean	Panama	-	-
USA, Latin America, Caribbean	Paraguay	Gloria Meza Rojas	Hospital Central del Instituto de Prevision Social
USA, Latin America, Caribbean	Peru	Carlos Abanto	Instituto Nacional de Ciencias Neurológicas, Lima Peru
USA, Latin America, Caribbean	USA	-	-
USA, Latin America, Caribbean	Venezuela	-	-