Project protocol:

„Mobile Stroke Unit"-concept for triage of subjects with suspected stroke regarding the target hospital: a randomised trial"

Clinical Trial Protocol Synopsis

Trial No.:	
Title: **Study Type:**	**„Mobile Stroke Unit"-concept for triage of subjects with suspected stroke regarding the target hospital"** **a randomized, trial**
Principal Investigators: **Institute/ Department:**	Prof. Dr. K. Faßbender, Dr. A. Ragoschke-Schumm, PD Dr. med. S. Walter Department of Neurology, University of the Saarland D-66424 Homburg/Saar, Kirrbergerstr. Phone: ++49/6841/1624103 FAX: ++49/6841/164137 E-mail: Klaus.fassbender@uks.eu
Date of Protocol:	May 11, 2015
Planned Dates of Trial	Start: June 1, 2015 End: after inclusion of 550 patients
Planned Study Period	Recruitment period: 36 month, or after recruitment and follow-up of the last patient
Objectives: to investigate whether the concept of stroke diagnosis already at the emergency site, enabled by an ambulance equipped with all relevant tools to diagnose stroke patients ("mobile stroke unit") improves accuracy of the stroke triage decision to the most appropriate hospital	
No. of subjects: To be assessed for eligibility (n = 550) To be allocated to trial (n = 250) To be analyzed (n = 232)	
Main criteria for inclusion: • Symptoms of acute stroke reported to the EMS dispatcher office (extended FAST Score) and verified by the EMS (after glucose testing) • Reported onset of symptoms until call ≤ 8 hours, "wake-up" strokes • Age ≥ 18 years • Patient is willing to participate voluntarily and to sign a written informed consent.	
Test Procedure:	Prehospital triage decision based on pre-hospital diagnosis of patients with stroke symptoms with a Mobile Stroke Unit
Reference Procedure:	Optimized conventional stroke management
Primary efficacy endpoint:	Proportion of stroke patients with accurate triage decision between primary stroke unit and neurovascular centre according to an algorithm
Secondary efficacy endpoints:	• Proportion of secondary transfers of stroke patients between primary stroke unit and neurovascular centre in all stroke patients and in subgroups with

	ischemic and hemorrhagic stroke • Proportion of patients with large vessel occlusion a) being directly transferred to a neurovascular centre, and b) being evaluated/treated by the interventionalist team • Time between symptom onset/alarm and evaluation/treatment by the neurointerventionalist team in case of large vessel occlusion • Proportion of patients with haemorrhage being a) directly transferred to a neurovascular centre, and being b) evaluated/treated by the neurosurgical team • Time between symptom onset/alarm and evaluation/treatment by the neurosurgical team in case of haemorrhage • Proportion of patients treated with rt-PA • Time between symptom onset/ alarm and start of thrombolysis • Number of patients being treated within 1 hour • Functional (mRS) and neurological (NIHSS) status (D7, D90) • Proportion of patients in which the triage decision was not realized
Safety endpoints	• Patient survival at day 0 and 7 • Stroke-related and neurological deaths • Symptomatic cerebral hemorrhage defined as any blood accumulation in the brain or intracranially associated with a clinical deterioration of ≥ 4 points of the NIHSS for which the hemorrhage has been identified as the dominating cause of the neurologic deterioration • Symptomatic peripheral hemorrhage • Symptomatic edema defined as any edema associated with a clinical deterioration of ≥ 4 points of the NIHSS for which the edema has been identified as the dominating cause of the neurologic deterioration
Further variables to be assessed	• Epidemiological and clinical variables • Diagnostic accuracy of acute stroke work up compared with diagnosis at discharge • Times of symptom onset to alarm, EMS and MSU arrival, admission to the hospitals and key diagnostic procedures (CT, laboratory) • Distances of MSU/hospital to the emergency site • Setting of the emergency site and the MSU/ hospital (rural/ urban) • Time between symptom onset/ alarm and onset of etiology-specific RR management • Time between symptom onset/ alarm until antagonization of anticoagulants in patients with intracerebral hemorrhage • Reasons for not transferring a patient between primary hospital and neurovascular centre according to the triage algorithm • Triage results of stroke mimics • Indicators of cost-effectiveness, costs of secondary transfers
Statistical methods	Primary analysis: The proportions of stroke patients accurately triaged between primary stroke unit and neurovascular centre will be compared between the two treatment arms using the Cochran-Mantel-Haenszel test stratifying for centre. Secondary analysis: For all proportion related secondary endpoints the same approach as for the primary endpoint will be used. Times between symptom onset or emergency call and therapy decision will be analysed for differences using the Wilcoxon rank sum test. The mRS at day 7 and 90 will be analysed using logistic regression adjusting for baseline mRS and centre. Safety analysis: Incidence and severity of AEs will be described for all included patients by treatment arm and by MedDRA classification.

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1. INTRODUCTION
1.1. MEDICAL BACKGROUND

Stroke is the most common cause of permanent disability, the second most common cause of dementia and the third most common cause of death in elderly in Western countries (Johnston et al, Lancet Neurol 2009). Approximately 85% of all strokes are due to cerebral ischemia, whereas 15% to cerebral hemorrhage. In European countries, an estimated 8.3 million persons were affected in 2010 with estimated annual costs of 64.1 billion €. In Germany, over 260,000 strokes occur annually, and within the next decade the yearly direct costs for stroke can be estimated to about 27 billion € (Kolominsky-Rabas et al, Stroke 2006).

Today, for stroke patients 3 different treatment options exist. 1. Thrombolysis with rt-PA is an effective treatment for many acute stroke patients as evidenced by several large randomized trials (NINDS rt-PA Stroke Study group, N Engl J Med 1995; Lees et al, Lancet 2010). 2. More recently, mechanical clot removal via catheters has been developed. There is currently increasing evidence that in obstruction of large brain vessels such endovascular treatment is superior to systemic thrombolysis in regard to recanalization rates and outcome (Rha & Saver, Stroke 2007; Bhatia et al, Stroke 2010). 3. For treatment of intracranial hemorrhage, patients should – according to international stroke management guidelines – be transferred to hospitals with neurosurgical treatment options such as ventricular drainage or hematoma removal.

Stroke is a medical emergency for which "time-is-brain". Indeed, a huge body of animal experimental and clinical evidence exists that demonstrates that reducing the time to thrombolytic therapy is the most important variable in prevention of the disability. However, most stroke patients arrive to hospital too late: Only an estimated 19–60% of stroke patients present within 3 hours after symptom onset (Evenson et al, Int J Stroke 2009; Albers & Olivot, Lancet 2007).

However, due the availability of endovascular and neurosurgical treatment options only in very few highly specialized neurovascular centres with 24/7 service of neurointerventionalists and of neurosurgeons, rational triage of stroke patients according to the individually required treatment is of high medical and financial relevance. It is likely that this question will become even more relevant in the future, i.e., when guidelines more strongly recommend use of differential stroke treatment. Thus, at the one side it should be prevented that patients with large vessel obstruction (e.g., basilar artery thrombosis) are transferred to centres without 24/7 endovascular treatment service. The same is true for the treatment of intracranial hemorrhage, which should be performed in centres with neurosurgical treatment options. At the other side, it should be avoided that every patient will be transferred to such specialized centres, thereby preventing efficient use of their limited resources. Importantly, secondary transfers from a primary hospital to a neurovascular centre are not only expensive, but also cause delay so that time-sensitive specific treatments usually comes too late. Consequently, patients should be triaged directly to the most appropriate hospital.

Preliminary work

For more than 20 years our group has experience in research in the field of stroke research. We extensively studied the pathophysiological aspects of neurodegeneration in acute ischemic stroke, e.g., analyzed vascular risk factors such as hyperhomocysteinemia (Fassbender et al, Lancet 2000), or first described adverse effects of thrombolysis on coagulation and fibrinolysis (Fassbender et al, Stroke 1999). Recently, we demonstrated feasibility of prehospital stroke treatment for the first time (Fig. 1).

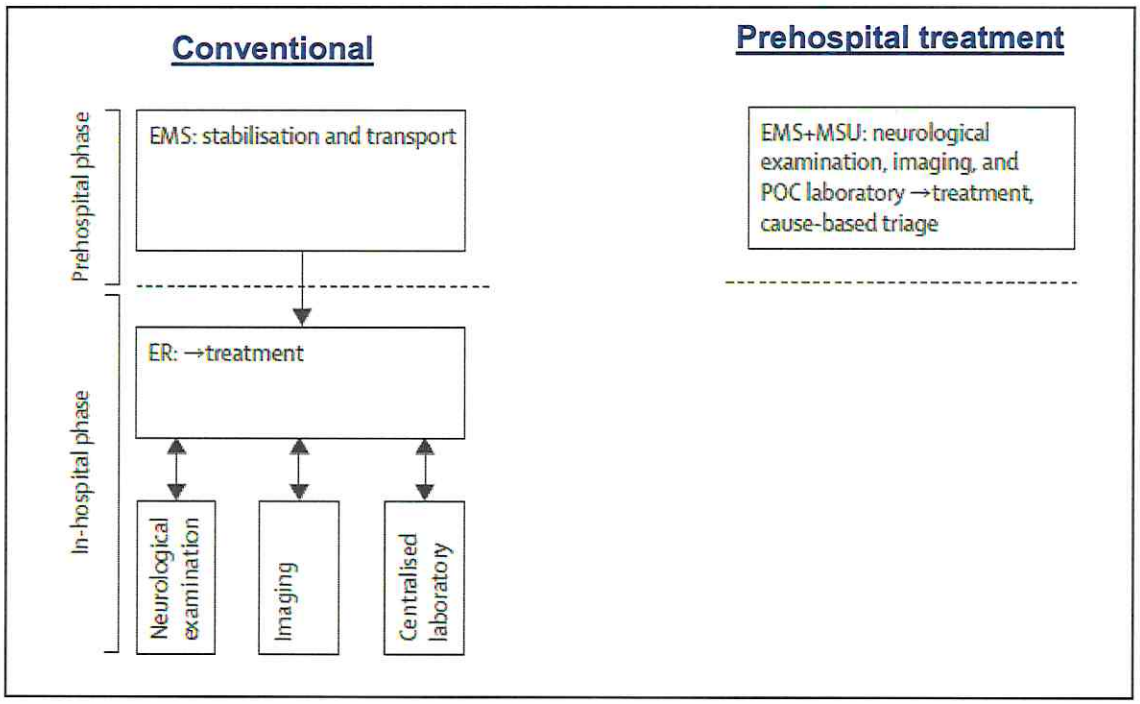

Fig. 1. Left: Conventional stroke management, characterized by awaiting patient's arrival at the hospital for treatment and multiple interfaces between consecutively activated health care personnel; right: prehospital stroke diagnosis and treatment by an ambulance equipped with all diagnostic tools to diagnose and treat stroke patients.

This was accomplished by use of an ambulance (Mobile Stroke Unit, MSU), equipped with computed tomography for multimodal imaging, a point-of-care laboratory system for examination of PTT/INR, blood glucose, blood count, liver or pancreas enzymes, and telemedicine connection to the hospital (Walter et al, Ann Neurol 2011; Walter et al, Lancet Neurol 2012; Kostopoulos et al, Neurology 2012; Fassbender et al, Lancet Neurol 2013).

In a recently published monocentric randomized trial we demonstrated a 50% reduction of delay until therapy decision and therapy when diagnosis and treatment is directly delivered at the emergency site rather than awaiting hospital arrival (Fig. 2). Importantly, median alarm-to-therapy-decision times were 35 min, thus, dramatically breaking all currently known time limits for stroke management, i.e., the door-to-needle times of 60 min defined as a benchmark by current guidelines (AHA and ESO guidelines for stroke treatment, Adams et al, Stroke 1996; European Stroke Initiative, Cerebrovasc Dis 2000) or the >60-minute times encountered in daily clinical practice. Importantly, 57% versus 4% of the patients could obtain final therapy decision even within 60 min after symptom onset (the "golden hour of stroke").

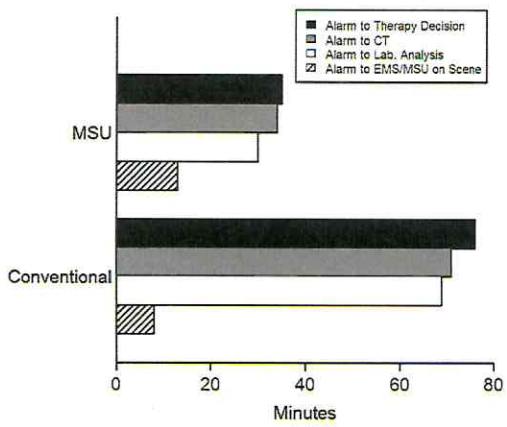

Fig. 2. A 50% reduction of the alarm-to therapy decision time and associated stroke management subintervals was reached by the MSU–based stroke management in a recent trial (Walter et al, Lancet Neurol 2012).

1.2. RATIONALE FOR PERFORMING THE TRIAL

Triage of stroke suspects regarding the most appropriate target hospital according to the underlying etiology and the specific therapeutic needs must be as accurate and as fast as possible. The aim of this randomized trial is to show feasibility, safety and clinical benefit of a strategy of diagnosis directly at the emergency site for rational triage regarding the most appropriate target hospital.

1.3 BENEFIT/RISK ASSESSMENT

There is no evidence that diagnostic procedures including CT scan or laboratory examinations, performed in the same way as in the hospital but already at the emergency site, is less effective or has more complications than in a hospital. There is even evidence that, e.g., earlier treatment is associated with better outcome and less side-effects (Lees KR et al., Lancet 2010). However, without a conclusive evidence of the medical benefit and safety of the MSU approach in triaging patients with suspicion of acute stroke this strategy can, in future, not be implemented in clinical routine. Therefore, the benefit/risk assessment argues for a clinical trial to prove the effectiveness of the concept of a triage strategy based on a "Mobile Stroke Unit" in the clinical practice.

2. STUDY OBJECTIVES

2.1. GENERAL AIM/PRIMARY OBJECTIVE

Triage of stroke suspects regarding the most appropriate target hospital according to the underlying etiology and the specific therapeutic needs must be as accurate and fast as possible. The aim of this randomized trial is to show feasibility, safety and clinical benefit of a strategy of diagnosis directly at the emergency site for rational triage regarding the most appropriate target hospital (Fig. 3). The effects on clinically and financially relevant reduction of delays until evaluation / treatment by neurointerventionalists and neurosurgeons and of secondary transfers will be assessed. First estimations of cost-effectiveness will also be performed.

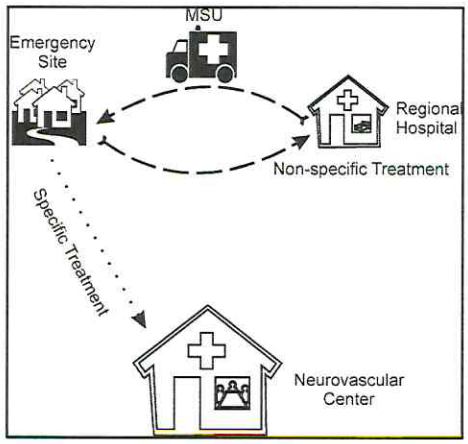

Fig. 3. Mobile Stroke Unit (MSU)–strategy for triage of subjects with suspicion of acute stroke in regard to the appropriate target hospital (regional hospital versus neurovascular centre)

2.2 PRIMARY EFFICACY ENDPOINT

- Proportion of stroke patients with accurate triage decision between primary stroke unit and neurovascular centre according to an algorithm

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2.3 SECONDARY EFFICACY ENDPOINTS

- Proportion of secondary transfers of stroke patients between primary stroke unit and neurovascular centre in all stroke patients and in subgroups with ischemic and hemorrhagic stroke
- Proportion of patients with large vessel occlusion a) being directly transferred to a neurovascular centre, and b) being evaluated/treated by the interventionalist team
- Time between symptom onset/alarm and evaluation/treatment by the neurointerventionalist team in case of large vessel occlusion
- Proportion of patients with haemorrhage being a) directly transferred to a neurovascular centre, and being b) evaluated/treated by a neurosurgeon
- Time between symptom onset/alarm and evaluation/treatment by the neurosurgeon team in case of haemorrhage
- Proportion of patients treated with rt-PA
- Time between symptom onset/ alarm and start of thrombolysis
- Number of patients being treated within 1 hour
- Functional (mRS) and neurological (NIHSS) status (D7, D90)
- Proportion of patients in which the triage decision was not realized, and causes

2.4 SAFETY ENDPOINTS

- Patient survival at day 0, 7
- Stroke-related and neurological deaths
- Symptomatic cerebral hemorrhage defined as any blood accumulation in the brain or intracranially associated with a clinical deterioration of ≥ 4 points of the NIHSS for which the hemorrhage has been identified as the dominating cause of the neurologic deterioration
- Symptomatic peripheral hemorrhage
- Symptomatic edema defined as any edema associated with a clinical deterioration of ≥ 4 points of the NIHSS for which the edema has been identified as the dominating cause of the neurologic deterioration

2.4 FURTHER VARIABLES TO BE ASSESSED

- Epidemiological and clinical variables
- Diagnostic accuracy of acute stroke work up compared with diagnosis at discharge
- Times of symptom onset to alarm, EMS and MSU arrival, admission to the hospitals and key diagnostic procedures (CT, laboratory)
- Distances of MSU/primary stroke unit/ neurovascular centre to the emergency site
- Setting of the emergency site and the MSU/ hospital (rural/ urban)
- Time between symptom onset/ alarm and onset of etiology-specific RR management
- Time between symptom onset/ alarm until antagonization of anticoagulants in patients with intracerebral hemorrhage
- Reasons for not transferring a patient between primary hospital and neurovascular centre according to the triage algorithm
- Triage results of stroke mimics
- Indicators of cost-effectiveness, costs of secondary transfers

3. STUDY POPULATION

3.1 NUMBER OF SUBJECTS PLANNED:

To be assessed for eligibility (n = 550)
To be allocated to trial (n = 250)
To be analyzed (n = 232)

3.2 INCLUSION CRITERIA

- Symptoms of acute stroke reported to the EMS dispatcher office (modified FAST Score, Table I) and verified by the EMS (after glucose testing)
- Reported onset of symptoms until call: ≤ 8 hours; "wake-up" strokes
- Age ≥ 18 years
- Patient (or representative) is willing to participate voluntarily and to sign a written informed consent

3.3. EXCLUSION CRITERIA

- Cardiopulmonary unstable medical conditions requiring immediate treatment in an intensive care unit)
- Pregnancy
- Preexisting most severe/terminal disease
- Inavailability of vascular imaging
- Known allergy or contraindications to contrast agents

4. PROCEDURES

4.1. INVESTIGATIONAL PROCEDURES

Integration of the trial in routine emergency medical service (EMS)

The study will be conducted in cooperation between hospitals of different level of care (Neurovascular centres or primary stroke units). Response times are from 8 a.m. to 6 p.m., 7 days/ week. All emergency calls to one central EMS coordinating office will be screened for stroke symptoms by the EMS dispatcher using a scale asking for one or more of the following neurological deficits: paralysis of arm or leg, facial paralysis, aphasia or dysarthria, and additionally, and acute reduction of consciousness (Table I). Compared to more frequently used scales such as the Face-Arm-Speech-Time (FAST) scale, this scale (extended FAST scale) has been extended in order to also include patients with large vessel obstructions in the posterior circulation (basilar artery) that could profit from endovascular intervention.

If the patient is eligible, either the MSU pathway or the conventional pathway will be initiated according to a week-wise randomization schedule. In the first case, the MSU team, in addition to the regular EMS will be notified, and in the latter, the EMS team will be notified. Finally, the physician either of the MSU or in the clinic reevaluates the inclusion and exclusion criteria (incl. reevalution of the extended FAST score, Table I) and obtains the informed consent.

Table I. Modified FAST scale

Sudden facial drop – One side of face does not move as well as the other

Sudden arm and/or leg drift or sensory deficit – One arm and/or leg does not move or drifts downward when held extended, or feels numb

Sudden speech disorder – Patient slurs words, uses the wrong word, or cannot speak or understand

Sudden consciousness disorder – Patient acutely not awake

A denegation of the patient will not have any influence on either diagnostic or therapeutic procedures. In the case of denegation, the patient will be treated in the conventional way without entering the study. Details of both study interventions are outlined below:

Mobile Stroke Unit-based stroke management

The MSU and the conventional EMS will meet at the emergency site (due to its still experimental stage the MSU is not allowed not replace the normal EMS ambulance at present in the Saarland). The patient's medical history, the physical examination will directly be performed by a physician (reassessment of the extended FAST score). Laboratory analyses will be analyzed by a point of care (POC) laboratory (PTT/INR; blood glucose, blood count, creatinine, liver and pancreas enzymes). CT/CT-angiography analysis (optionally including CT-perfusion) will be performed.

MSU Personnel: As in most regions of Germany, an emergency physician has to be disposed in case of suspicion of acute stroke in the Saarland. Moreover, due to current rules that imply that a CT scan can only be activated by a radiology technician or by a radiologist, the staff will include either a stroke trained physician with education in radiology, a radiology technician or a radiologist, as recently described (Walter et al, Lancet Neurol 2012). (With currently developed novel telemedicine interaction capabilities between EMS ambulance and hospital, this situation will highly likely change in the near future).

After performance of the acute stroke diagnostic work-up the patients will be triaged according to the diagnostic results as indicated in Table II.

Table II. Triage algorithm for patients with suspicion of acute stroke*

Stroke due to large vessel occlusion** or to intracranial hemorrhage → neurovascular centre

Stroke without large vessel occlusion or without hemorrhage→ primary hospital with regional stroke unit

*presence or absence of large vessel disease or hemorrhage in imaging confirmed by a certified neuroradiology core center
**occlusion of the intracranial carotid artery (carotid T) and/ or M1 branches or basilar artery.

A possibly indicated thrombolysis might be performed already at the emergency site in the MSU arm. Cardiorespiratory critically diseased patients will directly be transferred to the closest hospital with intensive care unit, and, thus, being excluded from the study.

Optimized control stroke management
After performing patient's medical history, physical examination) and glucose testing by the (stroke trained) emergency personnel, the patient will be transported– according to current best clinical practice and current expert recommendations which suggest triage based on clinical examination (Los Angeles Motor Scale) and time consideration (Grotta JC et al., Stroke. 2013), and the individual situation (severe premobidities etc.) - either transferred to a primary stroke unit or to a neurovascular centre. The hospital stroke team will be prenotified by the EMS. In each hospital, the patient will directly be further examined, including determination of the underlying cerebrovascular pathology (i.e., assessment in regard to large vessel occlusion and to hemorrhage). In case of inaccurate triage the patient might be secondarily transferred to the more appropriate institution.

4.2 CONCOMITANT THERAPY

Every treatment may be given according to patient needs.

4.3 AFTERTREATMENT

All patients will be admitted to every necessary diagnostic or therapeutic procedure including rehabilitative treatment according to current stroke management guidelines.

5. OBSERVATIONS

Four visits will be conducted during the study (Table III).

At visit 1 (baseline/ D0): documentation of in-/exclusion criteria, demographics, medical history, physical examination (reassessment of the extended FAST score, NIH Stroke Scale, the modified Rankin Scale), vital signs, CT and CT-A (further imaging as indicated), POC-laboratory examinations. Analysis of stroke management timing will include documentation of times until imaging, until laboratory result transmission, and until evaluation and eventual treatment by ED/ stroke physicians, neuroradiologists and neurosurgeons).
At visit 2 (D7) documentation of physical examination and adverse events will be done. Documentation of modified Rankin Scale and NIH Stroke Scale (NIHSS).
At visit 3 (D90) in stroke patients: documentation of medical history, adverse events and modified Rankin Scale. The patient termination record will be filled for all study patients.

5.1 EFFICACY

The major goal of this study is to assess efficacy of the MSU strategy in rational triage of patients with suspicion of acute stroke regarding to the most appropriate target hospital. For the list of endpoints see chapter 2.2-2.5.

5.2 SAFETY

5.2.1 Definitions

5.2.1.1 Adverse Event

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurence in a subject participating in a clinical trial. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not related to the trial intervention.

An AE may be:

- New symptoms/medical conditions
- New diagnosis
- Changes of laboratory parameters
- Intercurrent diseases and accidents
- Worsening of medical conditions/diseases existing before clinical trial start
- Recurrence of disease
- Increase of frequency or intensity of episodical diseases.

AEs fall into the categories "non-serious" and "serious".

5.2.1.2 Serious Adverse Event

A serious adverse event (SAE) is one that:

- Results in death
- Is life-threatening
- Requires subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

5.2.2 Period of Observation and Documentation

All AEs reported by the subject or detected by the investigator, will be collected during the trial and must be documented on the appropriate pages of the CRF. AEs must also be documented in the subject's medical records.

In this trial, all AEs that occur after the subject has signed the informed consent document will be documented on the pages provided in the CRF. All subjects who have AEs, whether considered associated with the use of the trial medication or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up by the time of resolve or normalization of changed laboratory parameters or until it has changed to a stable condition.

The intensity of an AE should be assessed by the investigator as follows:

mild: temporary event which is tolerated well by the subject.

moderate:	event which results in discomfort for the subject and impairs his/her normal activity.
severe:	event which results in substantial impairment of normal activities of subject.

The investigator will evaluate each AE regarding the coherency with the trial treatment possibly exist:

certain:	if there is a reasonable possibility that the event may have been caused by trial participation. A certain event has a strong temporal relationship and an alternative cause is unlikely.
probable:	An AE that has a reasonable possibility that the event is likely to have been caused by trial participation. The AE has a **timely relationship** to the trial treatment(s) and **follows a known pattern of response**, but a potential alternative cause may be present.
possible:	An AE that has a reasonable possibility that the event may have been caused by trial participation. The AE has a timely relationship to the trial treatment(s); however, follows no known pattern of response, and an alternative cause seems more likely, or there is significant uncertainty about the cause of the event.
unlikely:	Only a remote connection exists between the trial treatment and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event.
unrelated:	An AE that does not follow a reasonable temporal sequence from trial participation and that is likely to have been produced by the subject's clinical state, other modes of therapy or other known etiology.
not assessed:	Inadequate data for assessment, no other data may be expected

5.2.3 Reporting of Adverse Events by Investigator

SAEs must be reported to the Principle Investigators within 24 hours after the SAE becomes known. The initial report must be as complete as possible including details of the current illness and (serious) adverse event and an assessment of the causal relationship between the event and the trial treatment and the event's onset. The principal investigator is responsible for notification of SAEs to the trial monitor as requested.

5.2.4 Safety endpoints

For the list of safety endpoints see chapter 2.4. Safety, incidences and severity of adverse events will be assessed at all visits. Stroke-related and neurological complications (including symptomatic hemorrhage with change of NIHSS ≥ 4, death, symptomatic edema with change of NIHSS ≥ 4, and peripheral bleedings) will be evaluated.

6. INVESTIGATIONAL PLAN

6.1 STUDY DESIGN AND PLAN

This is a prospective, randomized parallel-grouped trial in subjects suspected with acute stroke.

6.2./ 6.3 STUDY PRODEDURES AT EACH VISIT AND VISIT SHEDULE

For visit 1 (D0), in the MSU and control group: first contact to a stroke-trained physician, no time window. For visit 2 (D7), a window between + 24 and –24 hours is acceptable. For visit 3 (D90), a window between +14 and –14 days is acceptable.

Table III. Flow Chart / Visit Schedule.

Visit	1 (D0)	2 (D7)	3 (D 90)
Hour/Day Window	Baseline (=1st physician contact)	7 Days +/- 24 Hrs	90 Days +/- 14 Days
In-/Exclusion Criteria	X		
Demographics	X		
Medical History	X		
Physical Exam.	X	X	
Informed Consent And subject Information	X		
Vital Signs	X		
Laboratory	X		
CT, CT-A#	X		
Specific stroke treatment (thrombolysis, mechanical recanalization, neurosurgical intervention) as indicated	X		
Control Image (CT or MRI)#	as indicated		
NIH stroke scale	X	X	
Modified Rankin Scale*	X	X	X**
Adverse Events	X	X	
Pat. Termination Record			X

further CT or MRI will be performed upon clinical indication
* pre-ictus mRankin scale will also be determined
** blinded assessement

7. STATISTICS

7.1 STATISTICAL DESIGN/MODEL

This is a prospective, multicentre, randomized, parallel-group study. The use of MSU will be compared to optimized conventional treatment. For practical reasons, use of MSU or optimized conventional treatment is randomized on a weekly basis, stratified by centre, i.e. when MSU is randomized to the first centre optimized conventional treatment will be used as control in the second, and vice versa.

7.2 NULL AND ALTERNATIVE HYPOTHESIS

The primary objective of the study is to demonstrate that use of MSU based stroke management is superior to optimized conventional treatment with regard to the primary endpoint, i.e., accurate triage decision between primary stroke unit and neurovascular centre. The null hypothesis is that there is no difference between MSU and conventional treatment. The alternative 2-sided hypothesis is that there is a difference.

7.3 PLANNED ANALYSIS

7.3.1 Primary analysis

The proportion of stroke patients with accurate triage decision between primary stroke unit and neurovascular centre according to the algorithm will be compared between the two treatment arms using the Cochran-Mantel-Haenszel test stratifying for centre.

7.3.2 Secondary analysis

For all proportion related secondary endpoints the same approach as for the primary endpoint will be used. Times between symptom onset/ emergency call and milestones of diagnostic and therapeutic procedures will be analysed for differences using the Wilcoxon rank sum test. The mRS at day 7 and 90 will be analysed using logistic regression adjusting for baseline mRS and centre.

7.3.3 Safety analysis

Incidence and severity of AEs will be described for all included patients by treatment arm and by MedDRA classification.

7.3.4 Interim analysis

An interim analysis is planned to be performed after 116 included stroke patients. For details, see section 7.6.

7.4. HANDLING OF MISSING DATA

All efforts will be made to collect complete information according to the protocol. This refers to all included patients. No missing values regarding survival status are expected. However, the last-observation-carried-forward (LOCF) method will be applied in the sense that data from the previous day or measurement will substitute the missing data. In case of missing values due to death, the worst score principle will be applied.

7.5. RANDOMISATION

Eligible patients will be included into the trial. As in our previous trial (Walter et al, Lancet Neurol 2012), study procedures will be randomized on a weekly basis (in blocks of four), stratified by centre. The allocation ratio to either MSU or optimized conventional treatment is 1:1. In case that there are 2 participating regions, the MSU can be deployed either in the one or the other region, according to the predefined randomization plan. The respective hospital without MSU in this week would then serve as control.

7.6 SAMPLES SIZE ISSUES

Among all proven strokes we assume a frequency of ischemic strokes without large vessel occlusions (LVO) of 75-85% and a frequency of hemorrhagic strokes or LVOs of 15-25%. For the purpose of sample size planning we assume that the proportion of accurately triaged stroke patients will be 80% in the treatment arm using standard care. By using MSU this proportion is likely to be increased to more than 95%. Under these assumptions 116 patients with proven stroke per treatment arm are necessary to achieve an anticipated power of 90% in a group-sequential (one interim analysis) 2-sided test at level alpha=0.05.

An interim analysis will be conducted after 116 patients with proven stroke have been included; the trial will be stopped if both null hypotheses are rejected at alpha=0.00305 (O'Brien-Fleming boundary). In case the trial is not stopped after the interim analysis, after inclusion of 232 acute stroke patients the study will be terminated and the final analysis will be conducted at alpha=0.049.

Assuming that the proportion of proven strokes is at least 42%, a total number of 550 patients with suspect of stroke to be evaluated for possible enrolment will likely be sufficient to achieve the anticipated power for the primary endpoint.

8. ADMINISTRATIVE MATTERS

8.1.1 Data collection

All findings including clinical and laboratory data will be documented in the subject's medical record and in the CRF. The investigator is responsible for ensuring that all sections of the CRF are completed correctly and that entries can be verified against source data.

Each completed CRF must be dated and signed by the responsible investigator upon completion. A copy of the original CRF will be transferred to the trial leading investigator. The original CRF will be remained with the regional investigators.

8.1.2 STORAGE AND ARCHIVING OF DATA

The investigator will archive all trial data (subject identification code list, source data and investigator's file) and relevant correspondence in the Investigator Site File (ISF). The ISF, all source data and all documents itemized in section 8 of the ICH Consolidated Guideline on GCP will be archived after finalization of the trial according to the legal regulations.

8.2 ETHICAL AND LEGAL ASPECTS

8.2.1 Good Clinical Practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial are designed to ensure that all persons involved in the trial abide by Good Clinical Practice (GCP) and the ethical principles described in the current revision of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements. A positive votum has already been given by the Ethical Committee of the Ärztekammer of the Saarland.

8.2.2 Subject Information and Informed Consent

Before being admitted to the clinical trial, the subject must consent to participate after the nature, scope, and possible consequences of the clinical trial have been explained in a form understandable to him or her. The subject must give written consent. Informed consent will be obtained from each patient personally or the subject's legally authorized representative. Patients who are unable to sign but who are able to understand the meaning of participation in the study may give an oral witnessed informed consent. These patients have to make undoubtfully clear that they are willing to participate voluntarily and must be able to understand an explanation of the contents of the information sheet.
A copy of the signed informed consent document must be given to the subject. The documents must be in a language understandable to the subject and must specify who informed the subject.

8.2.3 Confidentiality

During the clinical trial, subjects will be identified solely by means of their of birth, and an individual identification code (subject number, randomization number). Trial findings stored on a computer will be stored in accordance with local data protection law and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation will be fulfilled in its entirety. Authorized persons (clinical monitors) may inspect the subject-related data collected during the trial ensuring the data protection law. The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

8.2.4 Responsibilities of each Investigator

Each investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the trial treatments, and their trial-related duties and functions. The investigator should maintain a list of subinvestigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

8.2.5 Approval of Trial Protocol and Amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent EC. Formal approval by the EC should preferably mention the title of the trial, the trial code, the trial site, and any other documents reviewed. It must mention the date on which the decision was made and must be

officially signed by a committee member. Before the first subject is enrolled in the trial, all ethical and legal requirements must be met. The EC must be informed of all protocol amendments. The investigator must keep a record of all communications with the EC and the regulatory authorities.

8.2.6 Ongoing Information for Independent Ethics Committee

The EC must be informed of all subsequent protocol amendments which require formally approval in accordance with local legal requirements.

The EC must be informed of trial process regularly if not otherwise stated in the vote. The EC must be informed of the end of the trial.

8.3. MONITORING

In order to ensure quality, patients' welfare, and compliance with ethical and legal stipulations, a study centre, the Interdisciplinary centre for clinical studies (IZKS), Mainz, Germany (IZKS) will provide randomly clinical monitoring according to SOPs of the IZKS which are based on ICH-GCP guidelines. Monitoring will be done by personal visits from a clinical monitor. The monitor will review the entries into CRFs on the basis of source documents. The investigator must allow the monitor to look at all essential documents and must provide support at all times to the monitor.

9. SIGNATURE PAGE

Principal Investigators: date May 30, 2015

Name: Prof. Dr. Klaus Fassbender

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Investigator: date 30.5.15

Name: PD Dr. Silke Walter

Organization/Department: Department of Neurology University of the Saarland

Investigator: date 30/05/2015

Name: Dr. Andreas Ragoschke-Schumm

Organization/Department: Department of Neurology University of the Saarland

Certified Core Neuroradiology Centre: date

Name: Prof. I. Q. Grunwald

Organization/Department: Department of Neuroscience and Medical Affairs, PMI, Anglia Ruskin University Chelmsford, United Kingdom

Trial Statistician: date

Name: Dr. Schumacher

Organization/Department: Boehringer Ingelheim, Ingelheim, Germany

Quality Assurance: date

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10. REFERENCES

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APPENDIX 11.1: National Institute of Health Stroke Score, NIHSS

1a. Level of consciousness	0	Alert
	1	Non alert, but arousable with minimal stimulation
	2	Not alert, requires repeated stimulation to attend
	3	Coma
1b. Ask patient the month and their age	0	Answers both correctly
	1	Answers one correctly
	2	Both incorrect
1c. Ask patient to open/close eyes and form/release first	0	Obeys both correctly
	1	Obeys one correctly
	2	Both incorrect
2. Best gaze (only horizontal eye movements)	0	Normal
	1	Partial gaze palsy
	2	Forced gaze deviation
3. Visual field testing	0	No visual field loss
	1	Partial hemianopsia
	2	Complete hemianopsia
	3	Bilateral hemianopsia (blind, incl. Cortical blindness)
4. Facial paresis (Ask patient to show teeth or raise eyebrows and close eyes tightly)	0	Normal symmetrical movement
	1	Minor paralysis /flattened nasolabial fold, asymmetry on
	2	Partial paralysis (total or near total paralysis of lower face)
	3	Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)
5a. Motor Function Right arm	0	Normal (extends arm 90° or 45° for 10 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)
5b. Motor function Left arm	0	Normal (extends arm 90° or 45° for 10 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)

6a. Motor Function Right leg	0	Normal (holds leg in 30° positon for 5sec without drift)
	1	Drift
	2	Some effort against gravity
	3	No effort against gravity
	4	No movement
	9	Untestable (joint fused or limb amputated)
6b. Motor function Left leg	0	Normal (holds leg in 30° positon for 5sec without drift)
	1	Drift
	2	Some effort against gravity
	3	No effort against gravity
	4	No movement
	9	Untestable (joint fused or limb amputated)
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 (describe picture, name items)	0	No aphasia
	1	Mild to moderate aphasia
	2	Severe aphasia
	3	Mute
10. Dysarthria (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
11. Extinction an inattention (use visual double simulation 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

APPENDIX 11.2: Modified Rankin Scale, mRS

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead
Total (0-6): _____	