Frühzeitige Tracheotomie versus prolongierte orotracheale Intubation bei Patienten mit akutem Schlaganfall 2

SETPOINT2

Stroke-Related Early Tracheostomy versus Prolonged Orotracheal Intubation in Neurocritical care Trial 2

Principal Investigator:
Prof. Dr. med. Julian Bösel
Director, Section of Acute and Critical Care Neurology
Department of Neurology, Heidelberg University Hospital
Im Neuenheimer Feld 400

69120 Heidelberg

Phone: 0049/6221/56-39145
Mail: Julian.boesel@med.uni-heidelberg.de

Co-Principal Investigator:
Dr. med. David Seder, MD
Director of Neurocritical Care
Maine Medical Center
22 Bramhall Street, Portland, USA
Mail: sederd@mmc.org

Serious adverse event coordinator:
Dr. med. Wolf-Dirk Niesen
Attending Neurocritical Care Unit
Freiburg University Hospital
Breisacher Strasse 64
79106 Freiburg

Phone: 0761-270-5157
Mail: Wolf-dirk.niesen@uniklinik-freiburg.de

Medical Coordinator:
Dr. med. Silvia Schönenberger
Attending Neurointensive Care Unit
Department of Neurology, Heidelberg University Hospital
Im Neuenheimer Feld 400
69120 Heidelberg
Phone: 0049/6221/56-37549
Mail: Silvia.schoenenberger@med.uni-heidelberg.de

Further parties involved (selection):
Institute of Medical Biometry and Informatics (IMBI), Heidelberg University Hospital
Biostatistican
Prof. Dr. Meinhard Kieser
Head of Institute
Im Neuenheimer Feld 130.3
69120 Heidelberg
Phone: 06221-56-4140
Mail: Meinhard.kieser@imbi.uni-heidelberg.de

Data Management
Christina Klose
Institute of Medical Biometry and Informatics (IMBI), Heidelberg University Hospital
Im Neuenheimer Feld 130.3
69120 Heidelberg
Phone: 06221-56-5500
Mail: Klose@imbi.uni-heidelberg.de

Heidelberg, 2017-03-23

version 2.0

Dr. Silvia Schönenberger
(Medical coordinator)

Prof. Dr. Julian Bösel
(Principal Investigator)

Summary

Patients being treated on intensive care units due to prolonged respiratory insufficiency or dysphagia with risk of aspiration are believed to benefit from an early tracheostomy after an appropriate period of orotracheal ventilation. This is necessary in order to prevent complications commonly seen in long-term orotracheal intubation (e.g. nose sinus widening). Additional benefits of early tracheostomy in neurological patients may include a reduction in the amount of sedatives needed as well as a faster and safer weaning process. Studies have already shown the advantages of early tracheostomy in non-neurological patient cohorts. However there are several aspects which make questions concerning optimal ventilation of neurological patients more difficult to answer than in their non-neurological counterparts: Neurological intensive care patients tend to require longer periods of ventilation because of their underlying conditions and weaning is often more difficult to perform. Even in cases where patients are stable from a respiratory standpoint there remains a significant risk of aspiration and pneumonia following extubation due to the prevalence of decreased consciousness or dysphagia in this patient cohort. Patients with intracerebral hemorrhage or intracerebral edema may be harmed by precipitating early extubation trials or rapid weaning and may instead benefit from prolonged ventilation via tracheostomy. The best tool at the disposal of the neurointensivist for clinical monitoring of an ICU patient remains the clinical examination which is only possible in patients with minimal sedation. This is often not possible in patients with orotracheal intubation who require higher doses of sedatives than patients who have received early tracheostomy. Neurological intensive care patients are also expected to benefit from early rehabilitative measures which also require reduced sedation.

Several studies have proven the benefit of early tracheostomy in surgical and internal medicine ICU patients. Limited data has shown similar results in neurosurgical patients most of whom had been admitted due to concussion. These studies have demonstrated that patients, who received an early tracheostomy required less sedatives, had reduced ICU treatment duration and completed weaning more quickly than patients who received a delayed tracheostomy. There has only been one prospective pilot study that has investigated the benefits of early tracheostomy in neurological patients that has been published to date. The pilot study „Stroke-Related Early Tracheostomy versus Prolonged Orotracheal Intubation in Neurocritical Care Trial“(SETPOINT) was conducted from 2009 to 2011 as a single center study in our neurological department. The study proved both the safety and feasibility of early tracheostomy in neurological patients and showed that the cohort required fewer sedatives than the control group. The results of the pilot study also suggested that the early tracheostomy may improve the neurological outcome and reduce mortality in neurological patients. However further studies are necessary to confirm these findings.

Percutaneous tracheostomy has emerged in recent years as a safe and reliable alternative to the classical surgical approach performed by ENT physicians. Percutaneous tracheostomy can be performed by virtually any intensive care physician with the appropriate training. The trachea is punctured while under sight by bronchoscopy and then dilated via a guidewire catheter before the tracheostomy cannula is inserted. The percutaneous approach can be used in the great majority of cases. It is easier to perform, faster, less invasive and less costly than the surgical approach. However in cases of increased risk of hemorrhage or anatomical anomalies of the neck the surgical approach remains the preferred method.

This is a proposal for an international multicenter, randomized interventional study which will compare the outcome of stroke patients who will receive either an early tracheostomy within the first 5 days or a late tracheostomy >= day 10 following intubation. The primary endpoint is defined as the mRS as long-term functional outcome. Secondary outcomes include mortality, length of required ventilation, length of tracheostomy, number of days treated in an ICU, length of hospital stay, amounts of sedatives required and the incidence of complications.
The pilot study SETPOINT mentioned above was also conducted under the stewardship of PD Dr. J. Bösel at our department. The study protocol for SETPOINT 2 has been published in English because it is an international multicenter follow up study.
The study started as an investigator initiated study which was conducted with limited external funding. Some funding (about 50 000 Euros) was provided from third party funds by the principal investigator and other foundations to provide for data management by the IMBI and other organizational aspects of the study. The principal investigator and the US co-principle investigator-David B. Seder, M.D.) together applied for research funding to several foundations and medical associations and in December 2016 received confirmation of funding from the Patient-Centered Outcomes Research Institute (PCORI). Based on this award, some additional endpoints (e.g. neuromonitoring, patient and family experience) were added as secondary endpoints in this study. The core version of this study remained unchanged. There will be no industry funding of the SETPOINT 2 study. This is not an investigation of any specific medical products or medications.

STUDY SYNOPSIS	
COORDINATING INVESTIGATOR	Prof Dr Julian Bösel Department of Neurology, University of Heidelberg Im Neuenheimer Feld 400, D-69120 Heidelberg, Germany Tel 06221/5639145, Fax 06221/565654, EM julian.boesel@med.uni-heidelberg.de
TITLE OF STUDY	Stroke-related Early Tracheostomy vs. Prolonged Orotracheal Intubation in Neurocritical care Trial 2 (SETPOINT2)
CONDITION	Severe ischemic and hemorrhagic stroke requiring intensive care and mechanical ventilation
OBJECTIVE(S)	Does early tracheostomy as opposed to prolonged intubation in ventilated patients with severe stroke improve outcome 6 months after admission?
INTERVENTION (S)	Experimental intervention: Percutaneous dilational tracheostomy (PDT) within 5 days after intubation Control intervention: Ongoing orotracheal intubation with the aim to wean and extubate, if not successful or not deemed feasible, PDT from day10 after intubation Follow-up per patient: During ICU stay, at discharge from ICU, at 6 months after admission
KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: Admission to ICU for severe ischemic stroke, intracerebral/intraventricular hemorrhage or subarachnoid hemorrhage; Intubation and ventilation estimated necessary for 2 weeks or more by clinical score (SET Score >10) and clinical judgement. Age 18 or older, Key exclusion criteria: Intubated for more than 4 days; Definitive need for permanent tracheostomy; Concomittant brain disease other than those above; Life expectancy less than 1 year by underlying disease other than those above; No legal representative / next of kin available for informed consent; CIs for PDT
OUTCOME(S)	Primary efficacy endpoint: Functional outcome 6 months after admission to ICU, as measured by mRS, dichotomized 0-4 (=success) versus 5 + death (=failure), evaluated by a blinded observer Key secondary endpoints: Outcome (mRS) at 6 months after admission, dichotomized 0-3 vs 4-6; mRS shift at 6 months; Mortality and cause of mortality during ICU-stay and within 6 months from admission; Timing and reasons for withdrawal of life support measures; Quality of life by EuroQol at 6 months; ICU-Length of stay; Ventilation duration; Sedation duration; Relevant Intracranial pressure rises before and after tracheostomy Assessment of safety: Rates of pre-defined adverse events and serious adverse events during ICU stay and after 6 months
STUDY TYPE	Multicenter, prospective, randomized, observer-blinded, controlled trial with parallel groups
STATISTICAL ANALYSIS	Efficacy: Comparison of 6-month functional outcomes (mRs) between patients that undergo tracheostomy within 5 days after intubation (experimental) and those with ongoing orotracheal intubation (control) whose tracheostomy is performed >= day 10 after intubation Description of the primary efficacy analysis and population: The confirmatory test for treatment group difference with regard to the primary endpoint will be done using a binary logistic regression model that includes the covariates age, Glasgow Coma Scale, tracheostomy procedure and centre (two-sided type I error rate 0.05). The rate difference and the corresponding two-sided 95% confidence interval will be calculated. The primary analysis will be conducted according to the intention-to-treat principle and includes all randomized patients. Safety: Calculation and descriptive comparison of the rates of adverse and serious adverse events based on all included patient Secondary endpoints: Descriptive analyses of differences between treatment groups (ITT- and PP-population) and in subgroups
SAMPLE SIZE	To be assessed for eligibility (n = 1000), To be allocated to trial (n = 380) To be analysed (ITT, n = 380)
TRIAL DURATION	First patient in to last patient out: 24 months Duration of the entire trial: 36 months
PARTICIPATING CENTERS	n = 20 8 IGNITE-associated centers in Germany, 8 NCS-associated centers in the US

Abbreviations:

AE – adverse event
AHA – American Heart Association
AIS – acute ischemic stroke
APACHEII – acute physiology and chronic health evaluation II
APS – acute physiology score
CI – contraindication
COI – confidence interval
CT – computed tomography
eCRF – electronic case report form
DCS – decompressive surgery
DGNI – German Neurocritical Care Society
DSMB – data safety and monitoring board
FAS – full analysis set
FiO2 – fraction of inspired oxygen
GCS – Glasgow Coma Scale
HIPAA – Health Insurance Portability and Accountability Act
IAT – intraarterial thrombolysis
ICH – intracerebral hemorrhage
ICP – intracranial pressure
IGNITE – Initiative for German Neuro Intensive Trial Engagement
Infra – infratentorial
ITT – intention-to-treat
IVT – intravenous thrombolysis
IMBI – Institute of Medical Biometry and Informatics
LIS – lung injury score
MCA – middle cerebral artery
MEOI – medical events of interest
mRS – modified Rankin Scale
NCS – Neurocritical Care Society
NCCU – neurocritical care unit
NCSRN – Neurocritical Care Society Research Network

NIHSS – National Institute of Health Stroke Scale
OR – odds ratio
PaO2 – partial arterial pressure of oxygen
PCO2 – partial pressure of carbon dioxide
PDT – percutaneous dilational tracheostomy ICU – intensive care unit
PEEP – positive end-expiratory pressure
PP – per protocol
RCT – randomized clinical trial
ROC – receiver operating characteristic
SAE – serious adverse event
SAH – subarachnoid hemorrhage
SAS – sedation and agitation score
SOP – standard operating procedure
SpO2 – peripheral capillary oxygen saturation
Supra – supratentorial
TT – Tracheostomy
UK – United Kingdom
WFNS – World Federation of Neurological Surgeons (WFNS) subarachnoid hemorrhage grading

I: Specific Aims

Ischemic and hemorrhagic stroke is frequent disease (e.g. affects about 700,000 Americans annually), and when stroke is accompanied by respiratory failure, outcomes historically have been poor [1, 2]. Because these patients may have prolonged coma or failed airway protective reflexes, they are at high risk of pulmonary aspiration, and often remain intubated for prolonged periods of time despite adequate cardiopulmonary function. Early tracheostomy in such patients may potentially result in shorter duration of mechanical ventilation, decreased sedation and analgesic administration, shorter time to "wake-up" and participation in rehab activities, lower incidence of pneumonia, improved survival and functional outcomes, and decreased cost of care.

SETPOINT 2 is a randomized, assessor-blinded Phase III clinical trial of early tracheostomy vs. prolonged intubation and ventilator weaning for respiratory support of patients with severe ischemic and hemorrhagic strokes. The primary aim of the trial is to test for advantageous functional long-term outcome by early tracheostomy, secondary aims are to test for advantages in the ICU course of these patients, including cost of treatment. The trial is a joint venture of the United States Neurocritical Care Society Research Network (NCSRN) and the research network Initiative for German Neuro Intensive Trial Engagement (IGNITE) of the German Neurocritical Care Society (DGNI).

II: Background and Significance

According to United States data from the National Inpatient Sample, about 1.3% of 1.5 million patients (20,300) hospitalized with ischemic stroke from 2007-2009 underwent tracheostomy – while the number of tracheostomies performed for hemorrhagic stroke is unknown [3]. Historically, mechanically ventilated patients with ischemic or hemorrhagic strokes have had poor functional outcomes [1, 2, 4, 5], and care of such patients is extremely expensive[6-8]. Effective interventions to improve survival, improve functional recovery, decrease costs, and increase cost-effectiveness are urgently needed. Early tracheostomy of selected medical and surgical patients allows for decreased sedation and analgesia[9], and is associated with improved outcomes [10]. Preliminary data from a pilot study of early tracheostomy in patients with hemorrhagic or ischemic stroke suggest that such patients may also have improved survival and long-term functional outcomes [11], but a large, multicenter clinical trial is needed to confirm these findings.

Physiologic rationale for early tracheostomy in severe stroke:

Unlike the medical and surgical critically ill, many patients with stroke who require prolonged intubation do not require mechanical ventilation. Most often, these patients cannot reliably clear secretions from the airway due to decreased bulbar function, decreased airway protective reflexes, and a weak cough [12, 13]. Accordingly, tracheostomy offers the opportunity to disconnect such patients from mechanical ventilation while maintaining airway protection from large-volume aspiration, and provides the ability to directly suction secretions from the lower airways. Spontaneous ventilation preserves respiratory muscle function and allows patients to autoregulate their pCO_2, acid base status, and accordingly, cerebral vascular tone. Most

importantly, tracheostomy is more comfortable, allowing for the rapid discontinuation of analgesia and sedation, which may be crucial in allowing brain injured patients to awaken, wean off ventilation, and begin early aggressive rehabilitation regimens. Early initiation of rehabilitation activities is associated with improved functional outcomes after stroke and traumatic brain injury [14-16].

Current standards of care regarding tracheostomy for patients with severe stroke:

Current tracheostomy practices vary widely between hospitals, and widely among patients. Percutaneous tracheostomy, a bedside procedure, is increasingly popular compared to surgical tracheostomy, which is more resource-intensive, with a worse safety profile but similar long-term outcomes [17-23].Traditional indications for tracheostomy include an anticipated duration of mechanical ventilation greater than 14–21 days, to prevent complications of prolonged intubation such as vocal cord injury, tracheomalacia, and ventilator-associated pneumonia, and to facilitate discharge from the intensive care unit. Extubation delay is associated with higher morbidity, mortality, length of intensive care unit and hospital stay, and cost [22, 24-26]. Because of inconclusive trials in a general medical surgical population, a recent review of early tracheostomy trials concluded that “In patients who otherwise lack indication for surgical airway, clinicians should defer tracheostomy placement for at least 2 weeks following the onset of acute respiratory failure to insure need for ongoing ventilatory support” [27].

Early tracheostomy in a general ICU population:

Tracheostomy is eventually necessary in all ICU patients who cannot be weaned from mechanical ventilation. Five randomized controlled trials (RCTs) have investigated early tracheostomy (within 7 days after admission) in populations of medical, surgical, trauma and burn patients (406 in total) and report advantages to earlier tracheostomy such as less ventilator-associated pneumonia, less need for analgesia and sedation [9], shorter duration of mechanical ventilation and ICU stay and – in one trial – lower mortality [28]. A meta-analysis of these trials reported significantly reduced duration of mechanical ventilation (weighted mean difference -8.5 days, 95% COI -15.3 to -1.7) and shorter stay in intensive care (-15.3 days, -24.6 to -6.1) [29]. Large multicenter randomized trials of early vs delayed tracheostomy have been conducted in a mixed ICU populations with disappointing results [30, 31] while even larger retrospective analyses likewise showed only a marginal benefit of early tracheostomy for survival, time of ventilation and ICU length of stay [32]. On these grounds, it is appropriate to investigate subpopulations, such as those with brain injury, who may benefit most from early therapy, rather than large heterogeneous ICU populations.

Early tracheostomy in a neurocritical care and stroke population – medical considerations:

The airway-pathophysiology of traumatic brain injury is similar to stroke, and several studies favor early over delayed tracheostomy [33-35]. Until recently, the question of early tracheostomy in non-traumatic brain diseases including stroke had not been addressed. A retrospective study of 97 patients with long-term ventilation and tracheostomy after ischemic or hemorrhagic stroke reported a favorable outcome in 25%. The same study showed shorter ICU-length of stay with earlier tracheostomy [36], as did a retrospective study of 69 ventilated

stroke patients with infratentorial lesions [37]. A third retrospective analysis in 28 ICU-patients with non-traumatic brain injuries suggested lower mortality (47% vs 9%, P=0.04) among patients receiving early tracheostomy [38]. A retrospective cohort study comparing percutaneous tracheostomy of brain injured patients performed by neurointensivists to surgical tracheostomy showed a shorter time to tracheostomy (median 8 days compared to 12 days) which corresponded to shorter ICU and hospital length of stay, with no increase in adverse events [22]. Finally, a recent analysis of the timing of tracheostomy in 13,165 patients in the National Inpatient Sample suggested that tracheostomy performed before day 10 was associated with decreased incidence of ventilator-associated pneumonia (8.5 vs 6.2 days, OR: .688, P = .026), and decreased length of stay, (29.1 vs. 36.8 days, P < .001) compared to later tracheostomy [39].

Early tracheostomy in a neurocritical care and stroke population – cost considerations:

Several studies suggest dramatic decreases in hospital costs when tracheostomy is performed earlier in the ICU stay of neurological patients. In one study, percutaneous tracheostomy performed on day 8 resulted in lower median ICU charges ($123,404 vs. $156,311, P = 0.01) and hospital charges ($339,332 vs. $264,820, P=0.07) than surgical tracheostomy performed on day 12 [22]. A second study showed an 18% reduction in total hospital costs (P < .001) when tracheostomy was performed before day 10 compared to day 11-25 [39]. In a retrospective subgroup analysis of 129 patients in a mixed-specialty ICU, the 31 neurological / neurosurgical patients were fastest to be weaned from the ventilator after tracheostomy compared to other subgroups [40]. Finally, the large study cited above performed using National Inpatient Sample data showed lower total cost of hospitalization ($300,226 vs. $395,939, P<.001) when tracheostomy was performed before day 10 compared to later[38]. Potential cost benefits of early tracheostomy in ventilated stroke patients remain to be proven prospectively [41].

Difficulty of predicting which stroke patients will require tracheostomy:

One potential disadvantage of early tracheostomy is that unnecessary procedures might be performed in patients who are incorrectly predicted to require tracheostomy. In the UK – TracMan study, which randomized patients predicted to need prolonged mechanical ventilation to early or delayed tracheostomy, only 45% of patients in the delayed tracheostomy group actually required the procedure, because the others were successfully extubated during the delay period [31]. That trial demonstrated that accurate prediction of the need for prolonged intubation in a general medical respiratory-failure population is difficult – in that case, the high rate of successful extubation in the delayed tracheostomy group suggested early tracheostomy probably resulted in many unnecessary procedures, subjecting patients to unnecessary risk and diluting any benefit in those that did require the procedure. Brain injuries are different, however, because of the slow pace of neurological recovery, and high frequency and predictability, based on the location of the injury, of failed airway protective reflexes [37, 42, 43]. Several studies have addressed the prediction of prolonged intubation in a neurologically ill population. One study of patients with infratentorial lesions showed that GCS≤7 and cranial nerve deficits were strongly associated with failed extubation or tracheostomy, and that the probability of successful extubation, or death before extubation or tracheostomy decreased to 5.8% after translaryngeal intubation for >8 days [37]. Another identified patients requiring tracheostomy after intracerebral hemorrhage, finding that the initial Glasgow Coma Scale (GCS) score (P < 0.003), hydrocephalus (OR:12.5; P < 0.002), septum pellucidum shift (OR: 9; P < 0.025), and location of ICH in the thalamus (OR: 9; P < 0.025) were potent predictors of the need for tracheostomy, and proposed a TRACH score that combined these factors and

predicted the need for tracheostomy with a ROC AUC = 0.92, sensitivity of 94%, positive predictive value of 83%, and negative predictive value of 95%[43]. A third study also limited to intracerebral haemorrhage showed that hydrocephalus, 3rd and 4th ventricular hemorrhage, and ICH volume correlated with the subsequent need for tracheostomy[42]. In SETPOINT, described below, 30 patients were assigned to prolonged intubation, and all 18 that survived until at least day 10 required tracheostomy [11]. Such studies suggest that accurate prediction of the need for tracheostomy among stroke patients may be easier than those with other causes of respiratory failure.

III: Preliminary Studies:

Pilot data in support of early tracheostomy following stroke

SETPOINT, a pilot study of early tracheostomy vs. prolonged intubation in stroke patients, was carried out from 2009 to 2011 [39], [11]. This study included 60 patients with severe ischemic or hemorrhagic stroke admitted to the ICU of the University Hospital, Heidelberg, Germany, who was predicted to need prolonged mechanical ventilation for at least two weeks, based on clinical score and the clinical judgement of two intensivists. Patients were randomized to early tracheostomy within 3 days from intubation, or prolonged intubation and tracheostomy performed between day 7 and 14 if they remained intubated.
In SETPOINT, there was a significant reduction in sedation use (sedated during 42% vs 62% of ICU days, P=0.02), and a dramatic reduction of ICU-mortality in the early tracheostomy group (16% vs 45%, P<0.01)[8]. Mortality and functional outcome (measured by the modified Rankin Score (mRS) at 6 months also trended toward better in the early tracheostomy group (mortality: 33% vs 56%, mRS1-4: 48% vs 30%). The trial also showed safety of the procedure and provided data for a sample size calculation for a larger confirmatory trial.

The need for a trial

Patients with ischemic or hemorrhagic stroke that demand critical care and mechanical ventilation face mortality rates between 30 and 70%, and those who survive may be left with profound neurological impairment. Improved ICU management to improve survival and enhance rehabilitation potential are urgently needed. Early tracheostomy, which allows for rapid discontinuation of life support and early initiation of rehabilitation measures, targets both of these needs. Based on preliminary data, it may additionally offer significant cost saving. The potential benefits of early tracheostomy have not been prospectively addressed in stroke patients, other than in the SETPOINT pilot trial. That trial demonstrated safety and suggested substantial benefits in this burdened population. Positive trial results could lead to important changes in the course of individual patients: less compromise by potentially harmful ICU treatments especially sedation and mechanical ventilation, greater chance of survival and transfer to rehabilitation, greater rehabilitation potential, better long-term outcome, and a better understanding of the costs of care.

IV: Research Design and Methods

Design

SETPOINT 2 is a prospective, randomized, controlled, outcome observer-blinded, multicenter, two-armed, comparative trial. Patients are randomized 1:1 to either the experimental group – who undergo percutaneous tracheostomy (PDT) as soon as feasible and within 5 days after intubation ("early tracheostomy") or to the control group ("standard of care" group), in which PDT is performed >= day 10 from intubation if the application of an in-house weaning protocol did not lead to successful extubation. Otherwise, no differences in intensive care treatment are intended, and each participating institution's standard operating procedures will be applied to ensure uniform management decisions in fields such as weaning, ventilation, analgesia and sedation, transfusion, and neurological monitoring and management.
Blinding to the treatment assignment is impossible for treating physicians, patients and legal representatives as well as for most of the investigators. However, the primary endpoint of long-term outcome, causes of mortality, and cost will be assessed by trial-independent adjudicators blinded to the timing of tracheostomy. Because of the potential confounding effects of clinician bias (patients receiving the experimental intervention might be more likely to have prolonged care, and those with the standard intervention might be more likely to have early withdrawal of life support measures) on outcomes, the cause of death and in particular the circumstances of withdrawal of life support measures will be carefully tracked.

United States/German Collaboration and Coordination

This collaborative trial between the United States and Germany requires a primary trial Coordinating Center (Dr. Bösel- University of Heidelberg) and a United States Coordinating Center (Dr. Seder - Maine Medical Center).

Inclusion/exclusion criteria

Inclusion criteria are crafted to ensure that a broad and clinically pertinent population is investigated in this trial. The predefined admission diagnosis, and the criteria for ICU admission, intubation, and mechanical ventilation select for a high severity of stroke. The estimation of at least two weeks of endotracheal intubation is achieved by employing a prediction score (SETscore), which accurately predicted the need for prolonged intubation in stroke patients in the SETPOINT pilot study [11], and by the formal opinion of the attending intensivist at the patient's institution. The SETscore is based on clinical and radiological features shown to be associated with prolonged intubation and the need for tracheostomy in retrospective studies described above.

Subjects meeting all of the following criteria will be considered for inclusion in the trial:

1. Age 18 years or older
2. One of the following confirmed admission diagnoses
    a. non-traumatic acute ischemic infarction (AIS)
    b. non-traumatic intracerebral hemorrhage (ICH)
    c. non-traumatic subarachnoid hemorrhage (SAH)
3. Anticipated need of prolonged at least assisted mechanical ventilation for 2 weeks or more

    based on the SETscore> 10:

    a. Dysphagia (4)
    b. Observed aspiration (3)

c. Glasgow Coma Scale (GCS) on admission<10 (3)
d. Brainstem lesion (4)
e. Space-occupying cerebellar lesion (3)
f. Ischemic stroke > 2/3 MCA territory (4)
g. Intracerbral hemorrhage > 25 ml volume (4)
h. Diffuse lesion (3)
i. Hydrocephalus (4)
j. Invasive intracranial intervention (2)
k. Additional chronic respiratory disease (3)
l. PaO2/Fraction of inspired oxygen (FiO2) < 150 (2)
m. Acute Physiology Score (APS of APACHEII) > 20 (4)
n. Lung Injury Score (LIS) > 1 (2)
o. Sepsis (3)

based on the clinical judgement of the treating neurointensivist

4. Informed consent by the patient and/or legal proxy

5. Principle indication for tracheostomy (at least one of the following):
   a. ongoing demand of suctioning bronchotracheal secretions
   b. CNS-related respiratory insufficiency
   c. aspiration or danger of aspiration due to dysphagia

Exclusion criteria preclude patients in whom the investigated question is pre-determined (for example, they will need a permanent tracheostomy for clinical reasons unrelated to the stroke or due to extensive destruction of the brainstem), or in whom assessment of relevant outcome parameters is jeopardized by unrelated factors (for example, underlying comorbidities reduce life expectancy or disproportionately compromise airway management). Having tested these inclusion/exclusion criteria in the pilot study, the investigators are confident that these both allow for sufficient recruitment and are valid for generalization and representation of the patient population in question.

The following criteria will exclude patients from participation:

1. Premorbid modified Rankin Scale (mRS) >1
2. Artificial ventilation for more than 4 days
3. Any emergency situation either currently or anticipated for early time point of TT compromising the patient's well-being, such as
   a. Intracranial pressure (ICP) persistently > 25 mmHg
   b. Difficult airway management, anticipated problems with extubation / re-intubation
   c. Contraindications for a percutaneous tracheostomy
   d. Oxygenation impairment: Positive end-expiratory pressure (PEEP) >12, or FiO2 > 0.6
4. Expected need for a permanent surgical tracheostomy
5. Pregnancy
6. Participation in any other interventional trial

7. Life expectancy < 3 weeks
8. Patient/family unwilling or unlikely to opt for at least 3 weeks of aggressive therapy prior to consideration of transition to comfort measures/discontinuation of life support measures

Screening and randomization

Every patient that has been admitted to the ICU for requirement of invasive mechanical ventilation due to the severity of his acute cerebrovascular disease should be screened for the study.

Screening logs will be maintained by the study centers. After admission, clinical and radiological examination, verification of inclusion and exclusion criteria, and informed consent from the patient or their legal, patients will be randomly assigned to one of the two treatment groups: 1. Percutaneous tracheostomy as soon as possible, but not later than 5 days from intubation. 2. Ongoing orotracheal intubation (with attempts to wean and extubate), and tracheostomy >= day 10 if extubation was not accomplished. Randomization will be performed using a central web-based randomization tool to achieve comparable treatment groups (www.randomizer.at). Block randomization will be applied stratified for the participating centers to achieve equal group sizes per center.

Controls/Comparators

Control group

Patients in the control group (**standard treatment group**) will undergo all usual and aggressive efforts to be weaned from the ventilator and extubated, **not** left inactively on the ventilator to receive a late tracheostomy. Only if extubation trials fail or is deemed infeasible (for example, due to impaired airway protective reflexes and presence of copious secretions) will these patients will be tracheostomized after >= 10 days - a standard time point in many ICUs, and supported by survey data from the US and German Neurocritical Care Societies (unpublished survey data). As such, controls receive standard treatment. The clinical goal for the controls - as for the intervention patients - is to be woken, weaned from mechanical ventilation, and engaged in rehabilitation activities as soon as safe and feasible [44, 45].

Experimental group

The intervention (PDT) is performed in the **“early tracheostomy” group** as soon as feasible and always within 5 days after intubation.

The percutaneous, dilational tracheostomy procedure

In an open, surgical tracheostomy procedure, the anterior trachea is incised under direct visualization, an opening created, and the tracheal wall sutured to the external skin, creating a “permanent” stoma [46, 47] that requires surgical reversal when no longer needed. In 1985, a guide-wire based dilational technique that could be performed at bedside was pioneered, [48, 49] and rapidly gained popularity due to ease, safety, and decreased resource utilization. A recent meta-analysis comparing 13 studies of percutaneous vs. open tracheostomy found advantages of percutaneous tracheostomy in terms of complication rates and cost, but overall

outcomes appeared comparable [50]. Dilational tracheostomy is reversible by simply removing the cannula, with the skin closing in a matter of days [51].
In percutaneous dilational tracheostomy (PDT), the trachea is punctured through an anterior neck incision, often under direct bronchoscopic visualization, and a blunt-tipped guide-wire inserted. Serial dilations are performed over the guide-wire, and a tracheostomy tube is inserted over a dilator on the final pass [49]. PDT technique has been modified and refined – at least 6 methods of PDT are now performed -, and an increasing body of literature supports percutaneous dilational tracheostomy techniques over open surgical tracheostomy in patients whose need for tracheostomy is perceived to be temporary. In order to minimize variability in process, this trial will be limited to centers employing PDT techniques. The PDT procedure has been routinely employed at the leading trial centers for more than 15 years, and is standard of care [18].

The intubated and ventilated patient is positioned for ideal exposure of the trachea, and sufficient analgesia, sedation and relaxation are administered. With standard monitoring and emergency precautions in place, sterile skin preparation, barrier precautions, and infiltration of the skin with local anesthesia and epinephrine are applied. Additional measures that may be applied for procedural planning include bronchoscopic guidance and ultrasound evaluation of the neck [52, 53]. The orotracheal tube is retracted to position the cuff just underneath the vocal chords. After incising the neck, the trachea is punctured between two tracheal rings, and a guide-wire introduced. Different techniques can then be used to dilate the puncture site, with the single-tapered dilator technique being the most popular. The dilator and eventually the tracheostomy tube are passed over the wire, which is then removed. The endotracheal tube is removed from the airway only after multiple confirmations of intratracheal tracheostomy placement, as well as the orotracheal tube after confirmation of proper intratracheal cannula placement, and the cannula is affixed to the neck. Following weaning from mechanical ventilation, and when the tracheostomy tube is no longer needed for secretions management or maintenance of the upper airway, it is removed and the stoma dressed. Closure typically occurs spontaneously over 2-4 days.

Standard treatment for patients with severe stroke:
The following care is in accordance with established AHA/ASA Guidelines [54-57], and pertains to all patients in both treatment arms.

1. Intubation and mechanical ventilation: Patients are intubated at a Glasgow Coma Scale (GCS) score<8, when there are any signs of respiratory insufficiency (arterial pO_2<60 mmHg and/orpCO_2>48 mmHg), reduced swallowing or coughing reflexes, or when the airway is compromised. Earlier intubation (i.e. for diagnostic / therapeutic procedures) is left at the discretion of the physician in charge. Ventilation is based on each institution's standard operating procedures (SOP), and is weaned as soon as possible according to standard hospital practices.

2. Sedation and analgesia: Analgesia and sedation are routinely applied for pain, agitation and anxiety, and allow tolerance of intubation, mechanical ventilation, and invasive procedures. The mode of analgesia and sedation depends on the estimated time for need of sedation and is performed by using either longer-lasting or short-lasting agents according to institutional SOPs. Locally customary agents are routinely utilized to assure patient comfort, and titrated to sedation scales such as the Sedation and Agitation Scale (SAS) of 3-4 [58-60].

3. Monitoring consists of standard ICU monitoring comprising continuous blood pressure, heart rate, arterial O_2 saturation, respiratory rate, and temperature measurement. Disease dependent extended multi-modal neurological monitoring may include varying patterns of intracranial pressure, cerebral perfusion, cerebral oxygenation, cerebral temperature and neurochemical measurements. This bedside monitoring is complemented by intermittent neuroradiological imaging. Monitoring is disease-dependent and institution-specific and will not be controlled between study groups.

4. Feeding and gastrointestinal management: This is applied according to institutional SOPs to all patients. Early enteral feeding and augmentation of gastrointestinal motility are advised.

5. Blood pressure control: Blood pressure is managed according to current AHA/ASA guidelines, and the latest literature on the treatment of acute ischemic stroke, intracerebral haemorrhage and subarachnoid hemorrhage, following institutional SOPs.

6. Body core temperature: Normothermia is recommended. Elevated body temperature is treated as soon as it exceeds 37.5 °C. The maintenance of normothermia or the application of hypothermia is based on institutional SOPs.

7. Blood glucose level: The recommended target blood glucose level is 80-144 mg/dl (8 mmol/l), using insulin if necessary. Hypoglycemia is treated with infusions of 10% or 20% glucosesolution.

8. Hemoglobin concentration: Based on institutional SOPs.

9. Infection control: Standardized hygienic measures are in place to avoid infections. Infections are screened for daily by clinical examination, continuous temperature measurements andlaboratory assessments. Antibiotic treatment is based on institutional SOPs.

10. ICP management: ICP is measured and managed according to institutional SOPs, in summary, at a sustained ICP over 20 mmHg, osmotic agents such as mannitol and hypertonic saline are applied as boluses or infusions, before more definitive measures (e.g. surgical decompression) are undertaken. Hyperventilation is only applied as a “bridge” before surgery. Escalation of nonsurgical measures may include the use of barbiturates or hypothermia.

11. Vasospasm management: Vasospasm, a common complication of SAH, is diagnosed and managed by institutional SOPs. Patients with aneurysmal subarachnoid hemorrhage will bemanaged according to guidelines[55], with identical strategies in both study groups.

12. Neurosurgery: Neurosurgical interventions, such as decompressive hemicraniectomy, occipital trepanation, hematoma evacuation, aneurysm clipping or coiling, and placement of ventricular drains or shunts, are applied according to clinical necessity after consultation of local neurosurgeons without any differences in approach between the two study groups.

13. Neuroendovascular interventions: In case of acute large vessel cerebrovascular occlusions, basilar artery occlusions, cerebral or precerebral arterial stenoses, cerebral

venous thrombosis, cerebral aneurysms or vasospasm, neuroendovascular catheter interventions such as balloon dilatation, stent placement, thrombectomy, coiling, gluing, or flow-diversion may be warranted. These measures are decided upon individually after consultation with our neuroendovascular specialists without differences between the study groups, and independent of the study protocol.

By this Guideline-based and systematically standardized management, we hope to ensure a fairly uniform treatment approach in both study groups. The duration of acute inpatient therapy is highly variable, and may range from 2 – 8 weeks or longer. According to the trial protocol, screening, inclusion, randomization and documentation of the ICU-stay are followed by a telephone interview with the patient, caregiver, and/or treating physician at 6 months after the stroke. Documentation of the hospital stay and telephone interview are performed by investigators not involved in the patient's treatment. The 6-month outcome interview is the last follow-up in both arms.

Outcome measures

Primary outcome

Dichotomized functional outcome (a modified Rankin Scale (mRS) score of 0-4 (favorable outcome) vs 5,6 (poor outcome)) at 6 months after admission to ICU is the primary study endpoint. Modified Rankin Scale is a clinically relevant, easily determined 7-point functional scale ranging from 0 (normal) to 6 (dead) [61, 62]. mRS is a patient-centered outcome, as increased survival with severe deficits might not be regarded as a good outcome by many patients and physicians. The time point of 6 months was chosen to allow sufficient time for clinically relevant recovery (after 3 months many patients are still recovering) [63, 64]. mRS is the best-validated and most widely established assessment tool in clinical stroke research and has been used in major stroke trials such as NINDS [65], ECASS [66], CLEAR III [67], DESTINY [68], and DESTINY II [69]. The mRS outcome will be assessed by trained, certified research personnel applying a pre-structured telephone interview.

Secondary outcomes

Secondary outcomes will include dichotomized (0-3, 4-6) and continuous analysis of the mRS as a continuous variable, daily neurocritical care unit assessments (extubation trials, need of sedation or vasopressor infusions, evaluation of consciousness and sedation scores (Richmond Agitation Sedation Scale Score [70] or Riker Sedation-Agitation-Score [59]), duration of mechanical ventilation, ICU, and hospital length of stay, in-hospital and 6-month mortality, time-to-first-coma-free-day, assessment of the caregiver burden at the time of discharge from the NCCU and after 6 months, 6-month quality of life assessment,adverse events, and assessment of the patient and caregivers satisfaction with the processes and results of care. EuroQol will be used to assess quality of life [71, 72] at 6-months as well as time-to-first autonomous breathing, time-to-cessation of sedation, vasopressors and antibiotics (individually). As part of mortality assessment, particular attention will be paid to document withdrawal/discontinuation of life support measures and the cause of death. The other secondary endpoints are either clinically important, allow for relevant safety assessments in a larger population, or help establish scientifically important pathophysiology.

Methods to reduce bias

Minimizing *selection bias*: Consecutively screened and eligible patients will be included in the trial at each center. The decision to randomize will be based on the SETscore, and estimation of treating physicians as described above.

Minimizing *performance bias*: The trial centers are high-volume, academic neurocritical care units. Strong recommendations will be made in the protocol to adhere to guideline-based standards of care [54-57] as were applied in the pilot trial. Although this will ensure a reasonable homogeneity of care between centers, treating physicians will be allowed adequate freedom to reflect the clinical reality of variable practices, and meet ethical requirements. Block randomization will assure equal allocation within each center.

Minimizing *detection bias*: Based on the performed interventions (i.e. early tracheostomy vs. ongoing intubation) blinding of patients and clinicians is not feasible as well as a central and assessment of all patients. Outcome assessment by pre-structured telephone interview and observer blinding (see above), however, will be used to minimize bias.

Bias by potential influential factors (age, GCS, center) will be addressed by inclusion as covariates in the primary statistical analysis. The trial will be registered and the trial protocol will be published. Publication of trial results will be prepared according to the recently revised CONSORT-reporting guidelines.

Patient Safety and DSMB

(Serious) adverse event (SAE) monitoring will be managed through the SAE coordinating center in Freiburg, Germany, with an actualized report of events issued to the Data Safety Monitoring Board (DSMB) at predefined enrolment milestones (for details see below). The DSMB will recommend continuation or discontinuation of the trial to the Steering Committee. Planning and implementation of the trial procedures as well as the analysis is done in consultation with the Institute of Medical Biometry and Informatics (IMBI), Heidelberg.
Data safety and monitoring will be in place before enrollment begins, and monitoring will be performed throughout subject enrollment and treatment. The DSMB consists of Dr. Eric Juettler (Chair, Clinician, Germany), Dr. Niklas Nielsen (Clinician, Sweden), and Dr. Tim Friede (Statistician, Germany) all very experienced clinical trialists and completely independent of this trial. The DSMB will be responsible for ongoing monitoring of reports of significant adverse events (SAEs) and early stopping for efficacy/futility (after full data analysis of 33% enrollment) If necessary, it will suggest measures to be taken to prevent the occurrence of particular adverse events. In the event of unexpected SAEs or an unduly high rate of SAEs in one group ot both groups of enrolled subjects, the DSMB will be responsible for notifying the Steering Committee, which may even result in stopping the trial. The DSMB will employ a charter on their responsibilities and procedures and a form for their regular reports.

3. (Serious) adverse events

SAE will be acknowledged in the eCRF (only that an SAE occurred) and further specified in the local paper CRF as well as on a special form that has to be submitted to the SAE coordinator (Dr Niesen, University Hospital Freiburg, Department of Neurology, Breisacher Strasse 64, 79106 Freiburg) within 24 hours after the SAE becomes known or at the latest the next working day. Dr Niesen will revise all SAEs as soon as possible and in very severe occurrences inform the rest of Steering Committee and the DSMB to discuss a solution. SAEs will be collected by Dr Niesen and a current list sent to the IMBI for statistical analysis which

will then pass that list and analysis on to the DSMB after 33% and 50% enrollment.

3.1. Adverse Events (AE)

Only AE in relation to the procedure (TT), i.e. those of special interest, will be recorded per eCRF. This is because a large range of AEs are expected in this burdened population and would be subject to very extensive definitions, and the burden of data collection has to be kept low at the sites. The AE are differentiated according to the timely relation to the TT in which they appear and according to intensity (two grades). This again constitutes a compromise between being comprehensive and being pragmatic.

Definitions

Periprocedural AE: during up to 2h after TT

Early AE: from 2h after TT to discharge

Late AE: from discharge to follow-up

AE grade I: The AE can be managed by the treating intensivists themselves without additional invasive procedure or material, is transient and without further clinical consequences.

AE grade II: The AE requires consultation from other disciplines and/or further invasive procedures and/or is not transient and/or has lasting consequences i.e. precipitates clinical deterioration or is fatal. Some of these AE may fulfill the definition of a severe AE (SAE, see below).

Periprocedural TT-related AE

6. Ventilation

    a. Relevant hypoxia during tracheostomy (SpO_2< 90%) requiring augmentation of ventilation
    b. Significant atelectasis requiring recruitment
    c. Pneumothorax
    d. Hemothorax

7. Bleeding

    a. Venous bleeding
    b. Arterial bleeding

8. Local trauma

a. Puncture of the tracheal pars membranacea
b. Dilatation of the tracheal pars membranacea
c. Cannula misplacement
d. Subcutaneous emphysema or pneumomediastinum
e. Fracture of tracheal cartilage
f. Damage to larynx or neighboring structures

9. Accidental decannulation requiring reintubation

10. Cerebral compromise

a. ICP > 25 mmHg for > 5 min requiring treatment
b. Neurological deterioration (>4 points in NIHSS)

3.2. Early TT-related AE

Infection

a. Local infection at tracheostomy site
b. (Aspiration) pneumonia within first 48h post TT
c. Mediastinitis

Tracheostomy tube

a. Cuff leak or rupture requiring change of cannula
b. Patient discomfort (e.g. coughing, gagging) or malpositioning (e.g. cuff leak) requiring revision

3.3 Late TT-related AE

a. Recurrent / chronic infection at tracheostomy site
b. Scarring / disturbed wound healing at tracheostomy site
c. Tracheocutanous fistula
d. Tracheal instability/tracheomalacia with respiratory insufficiency or disturbance of vocalization
e. Clinically relevant tracheal stenosis
f. Complicated change of cannula
g. Need for surgical revision of stoma

3.4 Severe adverse events (SAE)

Severe adverse events are any adverse events, related to the procedure or not, that occurs after enrollment into the study with one of the following consequences:

1. Death
2. Life-threatening situation
3. Prolonged hospital stay or re-admission to hospital
4. Related prolonged deterioration of health

Definitions:

Mild: Symptoms are tolerable without or with transient, non-invasive treatment. SAE does not change the previous level of activity or state of health.

Moderate: Symptoms definitely require non-invasive and/or invasive treatment. SAE reduces the previous level of activity or state of health at least transiently.

Severe: Symptoms require non-invasive treatment for more than 1 week, invasive treatment, or are not treatable any more. SAE reduces the previous level of activity or state of health permanently or may lead to death.

Feasibility of recruitment

Feasibility of a comparable protocol was demonstrated by completion of the pilot study within 2 years. The proposed multicenter trial SETPOINT 2 will be performed among centers belonging to active German and US Neurocritical Care Research Networks (IGNITE group of the DGNI in Germany, and the NCS Research Network in the United States). These high-volume neurological/neurosurgical centers, mostly of university or academic type, provide patient populations that include up to 80% patients meeting screening criteria for SETPOINT II. Centers have been working successfully together in other neurocritical care trials. About 20 centers have already agreed to participate. The estimated recruitment number of 10-15 patients per year per center is deemed realistic by the involved centers, accounting for factors such as the recruitment in the pilot trial (30/yr), differences in patients' legal representation, and the existence of competing trials.

Data management

An efficient electronic data capture and data management infrastructure will be employed. An electronic case report form (eCRF) will be used for data collection. To assure a safe and secure environment for data acquired, the system used for remote data entry is validated and is compliant with FDA 21 CRF part 11. Data transmission is encrypted with secure socket layer (SSL) technology. The web server and database server will be two separate servers and both will be located securely behind a firewall. The system provides an infrastructure to support user roles and rights. Only authorized users are able to enter or edit data, the access is restricted to data of the patients in the respective centre. All changes to data are logged with a computerized timestamp in an audit trail. All data will be pseudonymized. A daily backup will be performed.

The investigator or a designated representative must enter all protocol-required information in the eCRF. The eCRF should be completed as soon as possible after the information is collected, preferably on the same day when a trial subject is seen for an examination, treatment, or any other trial procedure. In order to guarantee high quality of data completeness, validity and plausibility of data as defined in a data validation plan will be checked using validating programs that will generate queries. The investigator or the designated representatives are obliged to clarify or explain the queries. A tracking system for eCRF data and queries will be established to guarantee that data is managed in a timely manner. If no further corrections are to be made in the database, eCRF data will be locked. Data will be finally downloaded and used for statistical analysis.

All data management procedures will be conducted according to written defined standard operating procedures (SOPs) of the IMBI that guarantee an efficient conduct complying with GCP (Good Clinical Practice). All data collected will be integrated in a statistical analysis system. The data access is restricted to the data manager, and the biometrician responsible for the trial.

At the end of the study, the data will be transformed into different data formats (eg, csv-files) for archiving and to ensure that it can be reused.

Statistical analysis

Analyses of primary and clinical secondary outcome measures will be performed at University of Heidelberg using SAS or SPSS software. The aim of the trial is a comparison between early tracheostomy and ongoing orotracheal intubation (control) with respect to the proportion of patients with mRS 0-4 (=success) 6 months after admission of ICU.

1. Sample size

Sample size considerations are based on the primary endpoint “treatment success (mRS 0-4) after 6 months”. Analysis of the pilot trial SETPOINT showed a treatment success rate after 6 months of 30% in the control group (prolonged orotracheal intubation) and a clinically relevant higher success rate of 48% in the intervention group (tracheostomy before day 3). However, since several considerations of the authors of the publication of the SETPOINT study (see discussion in [A]) led to the conclusion that the true treatment effect might indeed be slightly smaller than observed in that pilot trial and since the authors considered an effect size of 15% as highly clinically relevant, sample size calculation for SETPOINT 2 was performed assuming a treatment success rate after 6 months of 30% in the control group and of 45% in the experimental group. The sample size was determined for the implemented two-stage group sequential design according to O’Brien and Fleming [B] at overall two-side level $\alpha=0.05$ and with power $1-\beta=0.80$ at the above specified alternative when applying a chi-square test. The calculations were carried out using ADDPLAN, version 6.1.1. At total of 326 patients (163 patients per group) is required under these assumptions. For the primary analysis, a binary logistic regression model will be applied including the factor treatment group and the covariates age, Glasgow Coma Scale at admission, and centre. Applying this adjusted analysis, it can be expected that the actual power will be increased as compared to the power provided by the chi-square test. In analogy to the pilot trial SETPOINT, we assume a rate of about 15% for drop-outs and patients lost to follow-up. Although missing values for outcome will be imputed for the primary analysis, there will be some loss of information due to incomplete data. For this reason, the total number of patients to be randomized will be increased by about 15% to compensate the potential dilution of the treatment effect caused by information loss. The total number of patients to be randomized in the SETPOINT2 trial is therefore chosen as 380 (190 per group).

2. Statistical design and analysis

2.1 Group sequential design

To allow for early stopping in case of an overwhelming large treatment effect, a two-stage group sequential design with one interim analysis is employed. The critical levels for the two-sided p-values for rejecting the null hypotheses assessed in confirmatory analysis are calculated according to O’Brien and Fleming [B] to assure an overall two-side level of $\alpha=0.05$. For this design, early stopping occurs only in case of a large treatment effect (i.e., a small p-

value observed in the interim analysis), and (as a consequence) the significance level to be applied in the final analysis has to be adjusted only slightly. The interim analysis is performed when the result for the primary endpoint is available for one third of the maximum total sample size, i.e. for 127 patients). The related two-sided local type I error rates for the interim and final analysis, respectively, are α_1=0.0006 and α_1= 0.0498 (calculations performed using ADDPLAN, version 6.1.1.).

2.2 Statistical hypotheses

The primary aim of the trial is a comparison between early tracheostomy (experimental treatment) and ongoing orotracheal intubation (control) with respect to the proportion of patients with mRS 0-4 (=treatment success) 6 months after admission in ICU. Secondarily, the overall death rates 6 months after admission in ICU will be compared. The related null hypothesis state that there is no difference in the success rate or overall death rate, respectively, between the treatment groups.

To formalize the statistical approach, the following notation will be used:

$p_{S,E}$ / $p_{S,C}$: treatment success rate in the early tracheostomy (experimental) group / in the ongoing orotracheal intubation (control) group.

$p_{D,E}$ / $p_{D,C}$: overall death rate in the early tracheostomy (experimental) group / in the ongoing orotracheal intubation (control) group.

The following two-sided test problems are defined:

$H_{0,S}$: $p_{S,E} = p_{S,C}$ vs. $H_{1,S}$: $p_{S,E} \neq p_{S,C}$

$H_{0,D}$: $p_{D,E} = p_{D,C}$ vs. $H_{1,S}$: $p_{D,E} \neq p_{D,C}$

2.3 Analysis sets

Each patient's allocation to the different analysis populations (full analysis set (FAS), per protocol (PP) analysis set, safety analysis set) will be defined prior to the analysis. The allocation will be documented in the statistical analysis plan. During the data review, deviations from the protocol will be assessed as „minor" or „major". FAS is defined according to the intention-to-treat (ITT) principle and will thus include all randomized patients. Major deviations from the protocol will lead to the exclusion of FAS patients from the PP analysis set. The safety analysis set includes all patients treated with one of the interventions studied in this trial.

2.4 Confirmatory analysis of primary endpoints

The multiplicity of test problems to be assessed and the hierarchy with respect to the importance of the research questions are taken into account by applying the multiple test procedure for *a priori* hierarchically ordered hypotheses: $H_{0,S}$ is tested first at local level α_i, i=1, 2 denoting the interim of final analysis, respectively. The test procedure stops with acceptance of $H_{0,S}$ and $H_{0,D}$ if $H_{0,S}$ cannot be rejected; if $H_{0,S}$ can be rejected, $H_{0,D}$ is tested at local level α_i. The procedure controls the experiment wise type I error rate at α=0.05 if the local levels of the two-stage O'Brien and Fleming group sequential design given in the preceding subsection are applied [C].

The confirmatory analysis of $H_{0,S}$ and $H_{0,D}$ will be done using a binary logistic regression model including the factor treatment group and adjusting for the covariates age, Glasgow Coma Scale at admission, and centre (where US-American and European centres are combined) at two-sided local type I error rates α_1=0.0006 and α_1= 0.0498at the interim or final analysis, respectively (see description of the multiple testing procedure above). The crude and adjusted rate difference together with the corresponding two-sided 95% as well as repeated confidence intervals will be calculated. The primary analysis will be conducted based on the full analysis set which includes all randomized patients. In case of patients lost to follow up before

evaluation of the primary endpoint, missing data for the outcome will be imputed using multiple imputation as described by Allison [D] and van Buuren [E].

2.5 Analysis of secondary endpoints

Analyses of secondary endpoints will be descriptive and will include the calculation of appropriate summary measures of the empirical distributions (continuous variables: mean, standard deviation, median, interquartile range, minimum, maximum; categorical variables: frequencies and percentages) as well as of descriptive two-sided p-values. Graphical methods (e.g. boxplots, Kaplan-Meier estimator curves for overall survival and length of ICU-stay) will be used to visualize the findings. Sensitivity analyses will be conducted for the per-protocol set (patients without major protocol violations) and for predefined subgroups.

The safety analysis includes a comparison of frequencies of adverse events and frequencies stratified by intensity and causality. Furthermore, statistical methods are used to assess the quality of data and the homogeneity of intervention groups with respect to baseline data. All analyses will be done using SAS version 9.4 or higher.

A detailed description of the analysis will be given in a statistical analysis plan that will be finalized before start of the evaluation.

References for statistical analysis

A. Bösel J, Schiller P, Hook Y, Andes M, Neumann JO, Poli S, Amiri H, Schönenberger S, Peng Z, Unterberg A, Hacke W, Steiner T. Stroke-related Early Tracheostomy versus Prolonged Orotracheal Intubation in Neurocritical Care Trial (SETPOINT): a randomized pilot trial. *Stroke* 2013; **44**:21-811.
B. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979; **35**:549-556
C. Kieser M, Bauer P, Lehmacher W. Inference on multiple endpoints in clinical trials with adaptive interim analyses. *Biometrical Journal* 1999; **41**:261-277.
D. Allison PD. Missing Data*. Sage Publications*, Thousand Oaks, CA, 2001.
E. Van Buuren S. Flexible Imputation of Missing Data. *Chapman & Hall/CRC,* Boca Raton, FL, 2012.

The safety analysis includes a comparison of frequencies of adverse events and frequencies stratified by intension and causality. Furthermore, statistical methods are used to assess the quality of data and the homogeneity of intervention groups with respect to baseline data.

V. Ethical Aspects of the Proposed Research

Participating sites will obtain and maintain formal approval for their participation from the local Institutional Review Board. Confidential patient screening will be performed by the local co-investigators and screening logs maintained by local research staff. Risks and potential benefits of study participation will be fully disclosed to all prospective research subjects, and the voluntary nature of patient involvement emphasized. Informed consent will be obtained from the patient's medicolegal power of attorney, with the patient's agreement when appropriate and feasible. Consent will be recorded as per local IRB standards, maintained by the local co-investigators, and audited at intervals by the Coordinating Centers. Patients will not receive financial incentives for their participation. Privacy and confidentiality of medical and financial records will be protected in accordance with HIPAA policies and procedures.

Patients and their families will not incur any costs related to study participation, and their own responsibility for the costs of standard care will be clearly stated at the time of informed consent. Patients will be allowed to withdraw from the trial at any time, upon their written request. (Serious) adverse events will be strictly recorded and monitored by the DSMB, and the trial immediately suspended or discontinued in the event of proven harm to either study group.

The safety, i.e. low number of complications, of the tracheostomy procedure (percutaneous dilational) has been demonstrated by numerous trials [8, 19, 48]. The risk of taking part in this trial is that a patient receives a safe procedure that was not necessary. In that case, the tracheal cannula can be removed easily and quickly. However, the likelihood of this is low because of our screening selection strategies (see above). Potential advantages (increased ICU survival, reduced sedation need, trendwise better long-term functional outcome, decreased costs) from early tracheostomy outweigh the risk of an unnecessary tracheostomy.

The SETPOINT pilot trial was approved by the ethical committee of the medical faculty of the University of Heidelberg. SETPOINT 2 is larger, but does not contain important ethical differences. Protocols and standard operating procedures allow for the delivery of best medical treatment to all patients.

This trial will be planned, conducted and analysed in accordance with the relevant national and international guidelines and regulations (Declaration of Helsinki, ICH-GCP).

VI. Trial Registration

SETPOINT2 is registered at www.clinicaltrials.gov (NCT02377167).

VII. References

1. Grotta, J., et al., *Elective intubation for neurologic deterioration after stroke.* Neurology, 1995. **45**(4): p. 640-4.
2. Bushnell, C.D., et al., *Survival and outcome after endotracheal intubation for acute stroke.* Neurology, 1999. **52**(7): p. 1374-81.
3. Walcott, B.P., et al., *Tracheostomy after severe ischemic stroke: a population-based study.* J Stroke Cerebrovasc Dis, 2014. **23**(5): p. 1024-9.
4. Steiner, T., et al., *Prognosis of stroke patients requiring mechanical ventilation in a neurological critical care unit.* Stroke, 1997. **28**(4): p. 711-5.
5. Gujjar, A.R., et al., *Mechanical ventilation for ischemic stroke and intracerebral hemorrhage: indications, timing, and outcome.* Neurology, 1998. **51**(2): p. 447-51.
6. Skolarus, L.E., et al., *Acute care and long-term mortality among elderly patients with intracerebral hemorrhage who undergo chronic life-sustaining procedures.* J Stroke Cerebrovasc Dis, 2013. **22**(1): p. 15-21.
7. Harvey, R.L., et al., *Stroke rehabilitation: clinical predictors of resource utilization.* Arch Phys Med Rehabil, 1998. **79**(11): p. 1349-55.
8. Luengo-Fernandez, R., A.M. Gray, and P.M. Rothwell, *Population-based study of determinants of initial secondary care costs of acute stroke in the United Kingdom.* Stroke, 2006. **37**(10): p. 2579-87.
9. Nieszkowska, A., et al., *Impact of tracheotomy on sedative administration, sedation level, and comfort of mechanically ventilated intensive care unit patients.* Crit Care Med, 2005. **33**(11): p. 2527-33.
10. Siempos, II, et al., *Effect of early versus late or no tracheostomy on mortality of critically ill patients receiving mechanical ventilation: a systematic review and meta-analysis.* Lancet Respir Med, 2014.
11. Bosel, J., et al., *Stroke-related Early Tracheostomy versus Prolonged Orotracheal Intubation in Neurocritical Care Trial (SETPOINT): a randomized pilot trial.* Stroke, 2013. **44**(1): p. 21-8.
12. Seder, D.B., et al., *Emergency neurological life support: airway, ventilation, and sedation.* Neurocrit Care, 2012. **17 Suppl 1**: p. S4-20.
13. McPhee L, S.D., *The Neurocritical Care Airway.*, in *The Neuro-ICU Book*, L. K, Editor. 2012, McGraw Hill: New York. p. 655-671.
14. Horn, S.D., et al., *Stroke rehabilitation patients, practice, and outcomes: is earlier and more aggressive therapy better?* Arch Phys Med Rehabil, 2005. **86**(12 Suppl 2): p. S101-s114.
15. Maulden, S.A., et al., *Timing of initiation of rehabilitation after stroke.* Arch Phys Med Rehabil, 2005. **86**(12 Suppl 2): p. S34-s40.
16. Veerbeek, J.M., et al., *What is the evidence for physical therapy poststroke? A systematic review and meta-analysis.* PLoS One, 2014. **9**(2): p. e87987.
17. Antonelli, M., et al., *Percutaneous translaryngeal versus surgical tracheostomy: A randomized trial with 1-yr double-blind follow-up.* Crit Care Med, 2005. **33**(5): p. 1015-20.
18. Cobean, R., et al., *Percutaneous dilatational tracheostomy. A safe, cost-effective bedside procedure.* Arch Surg, 1996. **131**(3): p. 265-71.
19. Delaney, A., S.M. Bagshaw, and M. Nalos, *Percutaneous dilatational tracheostomy versus surgical tracheostomy in critically ill patients: a systematic review and meta-analysis.* Crit Care, 2006. **10**(2): p. R55.
20. Freeman, B.D., et al., *A prospective, randomized study comparing percutaneous with surgical tracheostomy in critically ill patients.* Crit Care Med, 2001. **29**(5): p. 926-30.
21. Freeman, B.D., et al., *A meta-analysis of prospective trials comparing percutaneous and surgical tracheostomy in critically ill patients.* Chest, 2000. **118**(5): p. 1412-8.
22. Seder, D.B., et al., *Safety and feasibility of percutaneous tracheostomy performed by neurointensivists.* Neurocrit Care, 2009. **10**(3): p. 264-8.

23. Silvester, W., et al., *Percutaneous versus surgical tracheostomy: A randomized controlled study with long-term follow-up.* Crit Care Med, 2006. **34**(8): p. 2145-52.
24. Chevron, V., et al., *Unplanned extubation: risk factors of development and predictive criteria for reintubation.* Crit Care Med, 1998. **26**(6): p. 1049-53.
25. Coplin, W.M., et al., *Implications of extubation delay in brain-injured patients meeting standard weaning criteria.* Am J Respir Crit Care Med, 2000. **161**(5): p. 1530-6.
26. Nava, S., et al., *Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial.* Ann Intern Med, 1998. **128**(9): p. 721-8.
27. Freeman, B.D. and P.E. Morris, *Tracheostomy practice in adults with acute respiratory failure.* Crit Care Med, 2012. **40**(10): p. 2890-6.
28. Rumbak, M.J., et al., *A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients.* Crit Care Med, 2004. **32**(8): p. 1689-94.
29. Griffiths, J., et al., *Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation.* BMJ, 2005. **330**(7502): p. 1243.
30. Terragni, P.P., et al., *Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial.* JAMA, 2010. **303**(15): p. 1483-9.
31. Young, D., et al., *Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: the TracMan randomized trial.* JAMA, 2013. **309**(20): p. 2121-9.
32. Scales, D.C., et al., *The effect of tracheostomy timing during critical illness on long-term survival.* Crit Care Med, 2008. **36**(9): p. 2547-57.
33. Rodriguez, J.L., et al., *Early tracheostomy for primary airway management in the surgical critical care setting.* Surgery, 1990. **108**(4): p. 655-9.
34. Bouderka, M.A., et al., *Early tracheostomy versus prolonged endotracheal intubation in severe head injury.* J Trauma, 2004. **57**(2): p. 251-4.
35. Dunham, C.M. and C. LaMonica, *Prolonged tracheal intubation in the trauma patient.* J Trauma, 1984. **24**(2): p. 120-4.
36. Rabinstein, A.A. and E.F. Wijdicks, *Outcome of survivors of acute stroke who require prolonged ventilatory assistance and tracheostomy.* Cerebrovasc Dis, 2004. **18**(4): p. 325-31.
37. Qureshi, A.I., et al., *Prediction and timing of tracheostomy in patients with infratentorial lesions requiring mechanical ventilatory support.* Crit Care Med, 2000. **28**(5): p. 1383-7.
38. Pinheiro Bdo, V., et al., *Early versus late tracheostomy in patients with acute severe brain injury.* J Bras Pneumol, 2010. **36**(1): p. 84-91.
39. Villwock, J.A., M.R. Villwock, and E.M. Deshaies, *Tracheostomy timing affects stroke recovery.* J Stroke Cerebrovasc Dis, 2014. **23**(5): p. 1069-72.
40. van der Lely, A.J., et al., *Time to wean after tracheotomy differs among subgroups of critically ill patients: retrospective analysis in a mixed medical/surgical intensive care unit.* Respir Care, 2006. **51**(12): p. 1408-15.
41. Bosel, J., *Tracheostomy in stroke patients.* Curr Treat Options Neurol, 2014. **16**(1): p. 274.
42. Bosel, J., et al., *Benefits of early tracheostomy in ventilated stroke patients? Current evidence and study protocol of the randomized pilot trial SETPOINT (Stroke-related Early Tracheostomy vs. Prolonged Orotracheal Intubation in Neurocritical care Trial).* Int J Stroke, 2012. **7**(2): p. 173-82.
43. Szeder, V., et al., *The TRACH score: clinical and radiological predictors of tracheostomy in supratentorial spontaneous intracerebral hemorrhage.* Neurocrit Care, 2010. **13**(1): p. 40-6.
44. MacIntyre, N., *Discontinuing mechanical ventilatory support.* Chest, 2007. **132**(3): p. 1049-56.
45. MacIntyre, N.R., et al., *Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine.* Chest, 2001. **120**(6 Suppl): p. 375S-95S.

46. Price, D.G., *Techniques of tracheostomy for intensive care unit patients.* Anaesthesia, 1983. **38**(9): p. 902-4.
47. McGregor, I.A. and R.S. Neill, *Tracheostomy and the Bjork flap.* Lancet, 1983. **2**(8361): p. 1259.
48. Ciaglia, P., R. Firsching, and C. Syniec, *Elective percutaneous dilatational tracheostomy. A new simple bedside procedure; preliminary report.* Chest, 1985. **87**(6): p. 715-9.
49. JA, S.D.a.Y., *Percutaneous tracheostomy*, in *The Neuro-ICU Book*, K. Lee, Editor. 2012, McGraw Hill: New York. p. 723-33.
50. Cabrini, L., et al., *Percutaneous tracheostomy, a systematic review.* Acta Anaesthesiol Scand, 2012. **56**(3): p. 270-81.
51. Kornblith, L.Z., et al., *One thousand bedside percutaneous tracheostomies in the surgical intensive care unit: time to change the gold standard.* J Am Coll Surg, 2011. **212**(2): p. 163-70.
52. Corso, R.M. and G. Gambale, *Percutaneous tracheostomy: let's play it safe.* J Trauma Acute Care Surg, 2012. **73**(3): p. 779-80; author reply 780.
53. Kollig, E., et al., *Ultrasound and bronchoscopic controlled percutaneous tracheostomy on trauma ICU.* Injury, 2000. **31**(9): p. 663-8.
54. Connolly, E.S., Jr., et al., *Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association.* Stroke, 2012. **43**(6): p. 1711-37.
55. Morgenstern, L.B., et al., *Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.* Stroke, 2010. **41**(9): p. 2108-29.
56. Wijdicks, E.F., et al., *Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the American Heart Association/American Stroke Association.* Stroke, 2014. **45**(4): p. 1222-38.
57. Adams, H.P., Jr., et al., *Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.* Circulation, 2007. **115**(20): p. e478-534.
58. Jarrah, S., et al., *Surface cooling after cardiac arrest: effectiveness, skin safety, and adverse events in routine clinical practice.* Neurocrit Care, 2011. **14**(3): p. 382-8.
59. Riker, R.R., J.T. Picard, and G.L. Fraser, *Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients.* Crit Care Med, 1999. **27**(7): p. 1325-9.
60. Simmons, L.E., et al., *Assessing sedation during intensive care unit mechanical ventilation with the Bispectral Index and the Sedation-Agitation Scale.* Crit Care Med, 1999. **27**(8): p. 1499-504.
61. Rankin, J., *Cerebral vascular accidents in patients over the age of 60. II. Prognosis.* Scott Med J, 1957. **2**(5): p. 200-15.
62. Farrell, B., et al., *The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results.* J Neurol Neurosurg Psychiatry, 1991. **54**(12): p. 1044-54.
63. Navi, B.B., et al., *Trajectory of functional recovery after hospital discharge for subarachnoid hemorrhage.* Neurocrit Care, 2012. **17**(3): p. 343-7.
64. Wilson, D.A., et al., *Time course of recovery following poor-grade SAH: the incidence of delayed improvement and implications for SAH outcome study design.* J Neurosurg, 2013. **119**(3): p. 606-12.
65. *Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group.* N Engl J Med, 1995. **333**(24): p. 1581-7.
66. Hacke, W., et al., *Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS).* JAMA, 1995. **274**(13): p. 1017-25.

67. Ziai, W.C., et al., *A multicenter, randomized, double-blinded, placebo-controlled phase III study of Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III).* Int J Stroke, 2014. **9**(4): p. 536-42.
68. Juttler, E., et al., *Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial.* Stroke, 2007. **38**(9): p. 2518-25.
69. Juttler, E., et al., *Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke.* N Engl J Med, 2014. **370**(12): p. 1091-100.
70. Ely, E.W., et al., *Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS).* JAMA, 2003. **289**(22): p. 2983-91.
71. Dorman, P., et al., *Qualitative comparison of the reliability of health status assessments with the EuroQol and SF-36 questionnaires after stroke. United Kingdom Collaborators in the International Stroke Trial.* Stroke, 1998. **29**(1): p. 63-8.
72. Dorman, P.J., et al., *Are proxy assessments of health status after stroke with the EuroQol questionnaire feasible, accurate, and unbiased?* Stroke, 1997. **28**(10): p. 1883-7.

VIII. Appendix:

1. CRF

Patient Details

Record ID _____

Center ID _____

Screening No. _____

Age at study entry (years) _____

Sex ◯ Male ◯ Female

Race
◯ American Indian/Alaska Native
◯ Asian
◯ Black/African American
◯ Hawaiian/Pacific Islander
◯ White
◯ Multi-race
◯ Other

Ethnicity
◯ Hispanic (Latino/Latina)
◯ Non-Hispanic

Pre-hospital mRS
◯ 0 ◯ 1 ◯ 2 ◯ 3
◯ 4 ◯ 5

Date of infomed consent (YYYY/MM/DD) _____

Date of onset (YYYY/MM/DD) OR Date last seen well (YYY/MM/DD) _____

Date of admission to hospital (YYYY/MM/DD) _____

Scores on admission to hospital

GCS Score

Eye opening
◯ Spontaneous
◯ Respons to verbal command
◯ Response to pain
◯ No eye opening

Best verbal response
◯ Oriented
◯ Confused
◯ Inappropriate words
◯ Incomprehensible sounds
◯ No verbal response

Best motor response
◯ Obeys commands
◯ Localizing response to pain
◯ Withdrawal response to pain
◯ Flexion to pain
◯ Extension to pain
◯ No motor response

GCS Total (calculated) _____

NIH Stroke Scale

1a. Level of Consciousness	◯ Alert; keenly responsive ◯ Not alert; but arousable by minor stimulation to obey, answer or respond ◯ Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements ◯ Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic
1b. LOC Questions	◯ Answers both questions correctly ◯ Answers one question correctly ◯ Answers neither question correctly
1c. LOC Commands	◯ Performs both tasks correctly ◯ Performs one task correctly ◯ Performs neither task correctly
2. Best Gaze	◯ Normal ◯ Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present ◯ Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver
3. Visual	◯ No visual loss ◯ Partial hemianopia ◯ Complete hemianopia ◯ Bilateral hemianopia (blind including cortical blindness)
4. Facial Palsy	◯ Normal symmetrical movements ◯ Minor paralysis (flattened nasolabial fold, asymmetry on smiling) ◯ Partial paralysis (total or near-total paralysis of lower face) ◯ Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)
5a. Motor Arm: Left Arm	◯ No drift; limb holds 90 (or 45) degree for full 10 seconds ◯ Drift; limb holds 90 (or 45) degree, but drifts down before full 10 seconds; does not hit bed or other support ◯ Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts downn to bed, but has some effort against gravity ◯ No effort against gravity; limb falls ◯ No movement
5b. Motor Arm: Right Arm	◯ No drift; limb holds 90 (or 45) degree for full 10 seconds ◯ Drift; limb holds 90 (or 45) degree, but drifts down before full 10 seconds; does not hit bed or other support ◯ Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts downn to bed, but has some effort against gravity ◯ No effort against gravity; limb falls ◯ No movement

6a. Motor Leg: Left Leg	◯ No drift; leg holds 30-degree position for full 5 seconds ◯ Drift; leg falls by the end of the 5-seconds period but does not hit bed ◯ Some effort against gravity; leg falls to bed by 5 seconds; but has some effort against gravity ◯ No effort against gravity; leg falls to bed immediately ◯ No movement
6b. Motor Leg: Right Leg	◯ No drift; leg holds 30-degree position for full 5 seconds ◯ Drift; leg falls by the end of the 5-seconds period but does not hit bed ◯ Some effort against gravity; leg falls to bed by 5 seconds; but has some effort against gravity ◯ No effort against gravity; leg falls to bed immediately ◯ No movement
7. Limb Ataxia	◯ Absent ◯ Present in one limb ◯ Present in two limbs
8. Sensory	◯ Normal; no sensory loss ◯ Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick; but patient is aware of being touched ◯ Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg
9. Best Language	◯ No aphasia, normal ◯ Mild-to-moderate aphasia ◯ Severe aphasia ◯ Mute, global aphasia; no usable speech or auditory comprehension
10. Dysarthria	◯ Normal ◯ Mild-to-moderate dysarthria ◯ Severe dysarthria
11. Extinction and Inattentrion (formerly Neclect)	◯ No abnormality ◯ Visual, tactile, auditroy, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities ◯ Profound hemi-inattention or extinction to more than on modality; does not recognize own hand or orients to only one side of space
NIHS total Score (calculated)	_____

APS Score of APACHE II Score

Temperature rectal (°C)

- ◯ >=41
- ◯ 39-40.9
- ◯ 38.5-38.9
- ◯ 36-38.4
- ◯ 34-35.9
- ◯ 32-33.9
- ◯ 30-31.9
- ◯ < =20.9

Mean arterial pressure (mmHg)

- ◯ >=160
- ◯ 130-159
- ◯ 110-129
- ◯ 70-109
- ◯ 50-69
- ◯ < =49

Heart rate (/min)

- ◯ >=180
- ◯ 140-179
- ◯ 110-139
- ◯ 70-109
- ◯ 55-69
- ◯ 40-54
- ◯ < =39

Respiratory Rate (/min)

- ◯ >=50
- ◯ 35-49
- ◯ 25-34
- ◯ 12-24
- ◯ 10-11
- ◯ 6-9
- ◯ < =5

Oxygenation (mmHg)

- ◯ AaDO2: >=500
- ◯ AaDO2: 200-349
- ◯ AaDO2: < 200 / paCO2: >70
- ◯ paCO2: 61-70
- ◯ paCO2: 55-60
- ◯ paCO2: < 60

Arterial pH

- ◯ >=7.7
- ◯ 7.6-7.69
- ◯ 7.5-7.59
- ◯ 7.33-7.49
- ◯ 7.25-7.32
- ◯ 7.15-7.24
- ◯ < =7.15

Serum Sodium (mmol/l)

- ◯ >=180
- ◯ 160-179
- ◯ 155-159
- ◯ 150-154
- ◯ 130-149
- ◯ 120-129
- ◯ 111-119
- ◯ < =110

Serum Potassium (mmol/l)	◯ >=7 ◯ 6-6.9 ◯ 5.5-5.9 ◯ 3.5-5.4 ◯ 3-3.4 ◯ 2.5-2.9 ◯ < =2.5
Serum Creatinine (mg/dl)	◯ >=3.5 ◯ 2-3.4 ◯ 1.5-1.9 ◯ 0.6-1.4 ◯ < 0.6
Acute renal failure	◯ Yes ◯ No
Hematocrit (%)	◯ >=60 ◯ 50-59.9 ◯ 46-49.9 ◯ 30-45.9 ◯ 20-29.9 ◯ < 20
White Blood Count (1000/mm³)	◯ >=40 ◯ 20-39.9 ◯ 15-19.9 ◯ 3-14.9 ◯ 1-2.9 ◯ < 1
APS Score (calculated)	_____

SETScore

Dysphagia	◯ yes ◯ no
Observed aspiration	◯ yes ◯ no
GCS on admission < 10	◯ yes ◯ no
Brainstem	◯ yes ◯ no
Space-occupying cerebellar	◯ yes ◯ no
Ischemic infarct > 2/3 MCA territory	◯ yes ◯ no
ICH volume > 25 ml	◯ yes ◯ no
Diffuse lesion	◯ yes ◯ no
Hydrocephalus	◯ yes ◯ no
(Neuro)surgical intervention	◯ yes ◯ no
Additional respiratory disease	◯ yes ◯ no
PaO2/FiO2 < 150	◯ yes ◯ no
APS (of APACHEII) > 20 - derived field	_____
LIS > 1	◯ yes ◯ no

Sepsis	○ yes ○ no
SETScore (calculated)	_____

Abbrev.: APACHEII = acute physiology and chronic health evaluation II; APS = acute physiology score; FiO2 = fraction of inspired oxygen; GCS Glasgow Coma Scale, ICH intracerebral hemorrhage, LIS = lung injury score; MCA = middle cerebral artery; PaO2 = partial arterial pressure of oxygen.

Some items of the SETscore deserve further definition:

All items should be assessed on admission to hospital, except for the physiology scores PaO2/FiO2, APS, and LIS. Use the worst value for each physiological variable in the first 24 hours after admission to the admission.
Dysphagia has either been reported from a transferring neurological department or been observed by clinical signs on admission, e.g. by a non-successful swallowing test, impaired saliva handling or loss/reduction of gag reflex. If the patient is intubated on admission, score 0 points on SETscore scale.
(Neuro)surgical intervention constitutes a relevant operation, such as decompressive surgery, hematoma removal, or non-cranial major surgery, but not EVD or probe placement, no thrombectomy, no angioplasty for vasospasm or coiling.
Diffuse lesion is multilocular or widespread affection of the brain such as SAH, brain edema, multiple infarcts or hematomas.
Hydrocephalus is distension of ventricles requiring EVD placement.
Sepsis is assessed according to the current guidelines of the surviving sepsis campaign [74].

Lung Injury Score

1. Chest roentgenogram score	◯ No alveolar consolidation ◯ Aveolar consolidation confined to 1 quadrant ◯ Aveolar consolidation confined to 2 quadrant ◯ Aveolar consolidation confined to 3 quadrant ◯ Aveolar consolidation in all 4 quadrant
2. Hypoxemia score	◯ PaO2/FiO2: > 300 ◯ PaO2/FiO2: 225-299 ◯ PaO2/FiO2: 175-224 ◯ PaO2/FiO2: 100-174 ◯ PaO2/FiO2: < 100
3. PEEP score (when ventilated)	◯ PEEP: < 5 cm H2O ◯ PEEP: 6-8 cm H2O ◯ PEEP: 9-11 cm H2O ◯ PEEP: 12-14 cm H2O ◯ PEEP: > 15 cm H2O
4. Respiratory system compliance score (when available)	◯ Compliance: > 80 ml/cmH2O ◯ Compliance: 60-79 ml/cmH2O ◯ Compliance: 40-59 ml/cmH2O ◯ Compliance: 20-39 ml/cmH2O ◯ Compliance: < 19 ml/cmH2O
Final LIS value (calculated)	_____

Diagnosis

Diagnosis	◯ AIS ◯ ICH ◯ SAH

Diagnosis details if AIS

supratentorial	◯ Yes ◯ No
infratentorial	◯ Yes ◯ No
IVT therapy	◯ Yes ◯ No
IAT therapy	◯ Yes ◯ No
DCS therapy	◯ Yes ◯ No

Diagnosis details if ICH

supratentorial	◯ Yes ◯ No
infratentorial	◯ Yes ◯ No
Volume	◯ < = 30 cc ◯ > 30 cc - 60 cc ◯ > 60 cc
GCS (for ICH Score) - calculated	_____
Age (for ICH Score) - calculated	_____
Location (ICH Score) - calculated	_____
ICH volume (for ICH Score) - calculated	_____
Intraventricular blood (ICH score)	◯ Yes ◯ No
ICH Score (calculated)	_____

Diagnosis details if SAH

WFNS	◯ GCS:15 / Motor deficit: - ◯ GCS: 14-13 / Motor deficit: - ◯ GCS: 14-13 / Motor deficit: + ◯ GCS: 12-7 / Motor deficit: +/- ◯ GCS: 6-3 / Motor deficit: +/-
Fisher	◯ No blood detected ◯ Diffuse deposition or thin layer with all vertical layers less than 1 mm thick ◯ Localized clot and/or vertical layers 1 mm or more in thickness ◯ Intracerebral or intraventricular clot wiht dffuse or no subarachnoid bloos

Admission to NCCU / Intubation

Date of admission to NCCU (YYYY/MM/DD)	_____
Date of intubation (YYYY/MM/DD)	_____

Eligibility Inclusion criteria

One of the following confirmed admission diagnoses: 1) non-traumatic acute ischemic infarction (AIS) 2) non-traumatic intracerebral hemorrhage (ICH) 3) non-traumatic subarachnoid hemorrhage (SAH)	◯ Yes ◯ No
Anticipated need of prolonged at least assisted (> 2weeks) mechanical ventilation, based on: The SETscore > 10 ?	◯ Yes ◯ No
Anticipated need of prolonged at least assisted (> 2weeks) mechanical ventilation, based on: The clinical judgement of the treating neurointensivist	◯ Yes ◯ No
Informed consent by the patient and/or legal proxy	◯ Yes ◯ No
Age 18 years or older	◯ Yes ◯ No
Principle indication for tracheostoma (at least one of the following): 1) ongoing demand of suctioning bronchotracheal secretions 2) CNS-related respiratory insufficiency 3) aspiration or danger of aspiration due to dysphagia	◯ Yes ◯ No

Exclusion criteria

Mechanical ventilation for more than 4 days	◯ Yes ◯ No
Any emergency situation either currently or anticipated for early time point of TT compromising the patient's well-being, such as: Contraindications for a percutaneous tracheostomy?	◯ Yes ◯ No
Any emergency situation either currently or anticipated for early time point of TT compromising the patient's well-being, such as: Intracranial pressure (ICP) persistently > 25 mmHg?	◯ Yes ◯ No
Any emergency situation either currently or anticipated for early time point of TT compromising the patient's well-being, such as: Difficult airway management, anticipated problems with extubation / re-intubation?	◯ Yes ◯ No
Any emergency situation either currently or anticipated for early time point of TT compromising the patient's well-being, such as: Oxygenation impairment: Positive end-expiratory pressure (PEEP)>12, or fraction of inspired oxygen > 0.6?	◯ Yes ◯ No
Expected need for a permanent surgical tracheostomy	◯ Yes ◯ No
Pregnancy	◯ Yes ◯ No

Participation in any other interventional trial	◯ Yes ◯ No
Life expectancy < 3 weeks	◯ Yes ◯ No
Patient/family unwilling or unlikely to opt for at least 3 weeks of aggressive therapy prior to consideration of transition to comfort measures/discontinuation of life support measures	◯ Yes ◯ No
Premorbid modified Rankin Score (mRS)>1	◯ Yes ◯ No

Randomization

Randomization Number	_____
Randomization Result	◯ Early tracheostomy ◯ Prolonged intubation

NCCU Course

Tracheostomy performed ◯ Yes ◯ No

If no, what is the reason?
◯ Death
◯ Extubation
◯ Other

Please specify other reason _____

Date of tracheostomy (YYYY/MM/DD)? _____

Type of tracheostomy
◯ Percutaneous Dilatational Tracheostomy
◯ Surgical Tracheostomy

Extubation trial

Extubation Trials ◯ Yes ◯ No

1. Trial: Date (YYYY/MM/DD) _____

Successful (> 48 h) ◯ Yes ◯ No

if not successful, reason _____

2. Trial: Date (YYYY/MM/DD) _____

Successful (>48 h) ◯ Yes ◯ No

if not successful, reason _____

3. Trial: Date (YYYY/MM/DD) _____

Successful (>48 h) ◯ Yes ◯ No

if not successful, reason _____

Start of Respiratior Weaning / End of Mechanical Ventilation / Decannulation

Start of Respirator Weaning (YYYY/MM/DD) _____

End of Mechanical Ventilation (YYYY/MM/DD) _____

Decannulation ◯ Yes ◯ No

if yes: Date of decannulation (YYYY/MM/DD) _____

Medications

Sedatives: Popofol and/or Midazolam	◯ Yes ◯ No
if yes: Date of last intake(YYYY/MM/DD)	_____
Sedatives: Other	◯ Yes ◯ No
if yes: Date of last intake (YYYY/MM/DD)	_____
Analgesics: Opioids	◯ Yes ◯ No
if yes: Date of last intake (YYYY/MM/DD)	_____
Vasopressors	◯ Yes ◯ No
if yes: Date of last intake (YYYY/MM/DD)	_____
Rounds of antibiotics	_____

Periprocedural TT-related Adverse Events (during up to 2 hours after TT)

Ventilation - Relevant hypoxia during tracheostomy (SpO_2 < 90%) requiring augmentation of ventilation	◯ No	◯ Grade I	◯ Grade II
Ventilation - Significant atelectasis requiring recruitment	◯ No	◯ Grade I	◯ Grade II
Ventilation - Pneumothorax	◯ No	◯ Grade I	◯ Grade II
Ventilation - Hematothorax	◯ No	◯ Grade I	◯ Grade II
Bleeding - Venous bleeding	◯ No	◯ Grade I	◯ Grade II
Bleeding - Arterial bleeding	◯ No	◯ Grade I	◯ Grade II
Local trauma - Puncture of the tracheal pars membranacea	◯ No	◯ Grade I	◯ Grade II
Local trauma - Dilatation of the tracheal pars membranacea	◯ No	◯ Grade I	◯ Grade II
Local trauma - Cannula misplacement	◯ No	◯ Grade I	◯ Grade II
Local trauma - Subcutaneous emphysema or pneumomediastinum	◯ No	◯ Grade I	◯ Grade II
Local trauma - Fracture of tracheal cartilage	◯ No	◯ Grade I	◯ Grade II
Local trauma - Damage to larynx or neighboring structures	◯ No	◯ Grade I	◯ Grade II
Local trauma - Accidental decannulation requiring reintubation	◯ No	◯ Grade I	◯ Grade II
Cerebral compromise - ICP > 25 mmHg for > 5 minutes requiring treatment	◯ No	◯ Grade I	◯ Grade II

Cerebral compromise - Neurological deterioration (> 4 points in NIHSS)	◯ No ◯ Grade I ◯ Grade II

Serious Adverse Events / ICP-increases

Any Serious Adverse Event	◯ Yes ◯ No
ICP-increases > 25 mmHg	◯ Yes ◯ No ◯ Not measured
If yes: number of episodes requiring treatment before tracheostomy	_____
If yes: number of episodes requiring treatment after tracheostomy	_____

NCCU Mortality

Withdrawal of Therapy	◯ Yes ◯ No
if yes: Decided on (YYYY/MM/DD)	_____
Reason	_____
Death	◯ Yes ◯ No
if yes: Date of death (YYYY/MM/DD)	_____
if yes: Death brain-related?	◯ Yes ◯ No
if yes: Cause of death	_____

Early TT-related Adverse Events (from 2 hours after TT to discharge)

Infection - Local infection at tracheostomy site	◯ No ◯ Grade I ◯ Grade II
Infection - (Aspiration) pneumonia within first 48h post TT	◯ No ◯ Grade I ◯ Grade II
Infection - Mediastinitis	◯ No ◯ Grade I ◯ Grade II
Tracheostomy tube - Cuff leak or rupture requiring change of cannula	◯ No ◯ Grade I ◯ Grade II
Tracheostomy tube - Patient discomfort (e.g. coughing, gagging) or malpositioning (e.g. cuff leak) requiring revision	◯ No ◯ Grade I ◯ Grade II

Discharge from NCCU

Date of Discharge from NCCU (YYYY/MM/DD) _____

Discharge destination
- ◯ Home
- ◯ Hospital
- ◯ Rehab-Center
- ◯ Long-term Care Facility
- ◯ Other

If Other, please specify _____

mRS at time of discharge from NCCU
◯ 0 ◯ 1 ◯ 2 ◯ 3
◯ 4 ◯ 5 ◯ 6

NIHSS at time of discharge from NCCU _____

Caregiver assessment on discharge of the patient from the NCCU: Questions should be answered by the patient's primary caregiver

Overall, I was satisfied with the ICU care the patient received
- ◯ strongly aggree
- ◯ agree
- ◯ disagree
- ◯ strongly disagree

I was personally involved in the ICU care of the patient
- ◯ strongly aggree
- ◯ agree
- ◯ disagree
- ◯ strongly disagree

To be able to make contact with the patient during the ICU stay was very important for me
- ◯ strongly aggree
- ◯ agree
- ◯ disagree
- ◯ strongly disagree

My overall impression of the patient after tracheostomy was
- ◯ much better
- ◯ better
- ◯ unchanged
- ◯ worse
- ◯ much worse
- ◯ not applicable

After the tracheostomy the patient was better able to make contact with me (as compared before)
- ◯ strongly agree
- ◯ agree
- ◯ disagree
- ◯ strongly disagree
- ◯ not applicable

After the tracheostomy the patient was more comfortable (as compared before)
- ◯ strongly aggree
- ◯ agree
- ◯ no opinion
- ◯ disagree
- ◯ strongly disagree

Hospital stay (after discharge from NCCU)

In-house death	◯ Yes ◯ No
if yes: Date of death (YYYY/MM/DD)	_____
if yes: Cause of death	_____
Date of Discharge from Hospital (YYYY/MM/DD)	_____
Discharge destination	◯ Home ◯ Rehab-Center ◯ Long-term Care Facility ◯ Other
If other, please specify	_____

NCCU day 1

NCCU day 1

Is patient able to make sustained eye contact and/or follow commands	◯ Yes ◯ No
Sedation scale	◯ Best RASS ◯ Best SAS
Best RASS	◯ Combative ◯ Very agitated ◯ Agitated ◯ Restless ◯ Alert and calm ◯ Drowsy ◯ Light sedation ◯ Moderate sedation ◯ Deep sedation ◯ Unarousable
Best SAS	◯ Dangerous agitation ◯ Very agitated ◯ Agitated ◯ Calm and cooperative ◯ Sedated ◯ Very sedated ◯ Unarousable
Mechanical ventilation for any part of 24 hours	◯ Yes ◯ No
Sedative infusion for any part of 24 hours	◯ Yes ◯ No
Vasopressor infusion for any part of 24	◯ Yes ◯ No
Antibiotica infusion for any part of 24 hours	◯ Yes ◯ No
Was patient extubated this day	◯ Yes ◯ No
if no, choose all that apply	☐ Unstable neurological condition ☐ Impaired respiratory automaticity ☐ Cardiopulmonary dysfunction ☐ Excessive secretions ☐ Inadequate airway protective reflexes ☐ Neuromuscular weakness ☐ Planned procedure ☐ Unable to safely reduce sedation ☐ Other (multiple answers possible)
- if other, please specify	_____

Follow Up

6-months telelphone interview performed ◯ Yes ◯ No

Reason
◯ Death
◯ Lost to Follow-up
◯ Withdrawal of informed consent
◯ Other

If Other, please specify _____

Date of death (YYYY/MM/DD) _____

Under what circumstances did the patient die
◯ Sudden, unexpected death due to a stroke-related neurological condition
◯ Sudden, unexpected death due to a stroke-related medical condition (e.g. aspiration pneumonia or a fall related to the stroke)
◯ Sudden, unexpected death due to an unrelated condition
◯ Died following WLST (hospice or palliative care) due to stroke-related disabiliy
◯ Died following WLST (hospice or palliative care) due to other medical conditions

Cause of death _____

Date of study termination / last contact (YYYY/MM/DD) _____

6-months telephone interview

Patient regained ability to consent to the study ◯ Yes ◯ No

if yes: Patient informed consent ◯ Yes ◯ No

if no: Patient data already collected can be used for analysis ◯ Yes ◯ No

Date of interview (YYYY/MM/DD) _____

Patient's destination
◯ Home
◯ Hospital
◯ Rehab-Center
◯ Long-term Care Facility
◯ Other

If Other, please specify _____

Is the patient able to participate in the evaluation
◯ Yes, directly
◯ Yes, through a proxy
◯ No, due to neurological impairment
◯ No, unwilling
◯ No, for other reason

If other reason, please specify _____

Is the primary caregiver able to participate in the evaluation
◯ Yes
◯ No, patient does not need caregiver
◯ No, unwilling
◯ No, for other reason

If other reason, please specify _____

Score of mRS 6 months after admission ◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6

EQ-5D questionnaire

Mobility
- ◯ I have no problems walking
- ◯ I have slight problems walking
- ◯ I have moderate problems walking
- ◯ I have severe problems walking
- ◯ I am unable to walk

Self-care
- ◯ I have no problems washing or dressing myself
- ◯ I have slight problems washing or dressing myself
- ◯ I have moderate problems washing or dressing myse
- ◯ I have severe problems washing or dressing myself
- ◯ I am unable to wash or dress myself

Usual activities
- ◯ I have no problems doing my usual activities
- ◯ I have slight problems doing my usual activities
- ◯ I have moderate problems doing my usual activities
- ◯ I have severe problems doing my usual activities
- ◯ I am unable to do usual activities

Pain/discomfort
- ◯ I have no pain/discomfort
- ◯ I have slight pain/discomfort
- ◯ I have moderate pain /discomfort
- ◯ I have severe pain/discomfort
- ◯ I have extreme pain /discomfort

Anxiety/depression
- ◯ I am not anxious/depressed
- ◯ I am slightly anxious/depressed
- ◯ I am moderately anxious/depressed
- ◯ I am severely anxious/depressed
- ◯ I am extremely anxious/depressed

EQ VAS (health state today) _____

Decannulation

Patient decannulated? ◯ Yes ◯ No

Date of decannulation _____

Late TT-related Adverse Events (from discharge to follow-up) - as reported

Recurrent / chronic infection at tracheostomy site ◯ No ◯ Grade I ◯ Grade II

Scarring / disturbed wound healing at tracheostomy site ◯ No ◯ Grade I ◯ Grade II

Tracheocutanous fistula ◯ No ◯ Grade I ◯ Grade II

Tracheal instability/tracheomalacia with respiratory insufficiency or disturbance of vocalization	◯ No ◯ Grade I ◯ Grade II
Clinically relevant tracheal stenosis	◯ No ◯ Grade I ◯ Grade II
Complicated change of cannula	◯ No ◯ Grade I ◯ Grade II
Need for surgical revision of stoma	◯ No ◯ Grade I ◯ Grade II

Serious Adverse Events

Any Serious Adverse Event	◯ Yes ◯ No

Patient Reported Outcome Questions

Is the patient currently suffering form persistent tracheostomy-related health conditions or symptoms?	☐ Wheezing ☐ Neck or throat pain ☐ Difficulty breathing ☐ Weak or impaired speech due to tracheal injury ☐ Other problems related to the tracheotomy (select ALL that apply)
Is the patient glad to be alive, in comparison to having been allowed to die immediately after the stroke?	◯ Yes, patient is glad to new be alive ◯ No, wish patient had been allowd to die ◯ Undecided ◯ Unable to answer
Is the patient satisfied wiht the outcome of care (current functional outcome), compared to having been allowed to die?	◯ Yes, satisfied with the outcome of care ◯ No, wish patient had been allowed to die ◯ Undecided ◯ Unable to answer
If the patient could go back in time and make the decision to consent for tracheostomy him/herself, would patient consent to undergo aggressive treatments, such as tracheostomy, again?	◯ Yes, if patient could go back in time he/she would again choose the aggressive treatments he/she received ◯ No, patient would not choose aggressive treatments, even knowing it would result in his/her death ◯ Undecided ◯ Unable to answer

Ask the primary caregiver (confidentially)

Although it would be best if the stroke had not occurred, are you pleased with the results of treatment?	◯ Yes, I am plesed with the results of treatment for this stroke ◯ No, I am unhappy with the results of treatment for this stroke ◯ I feel conflicted about the results of treatment for this stroke ◯ I cannot or choose not to answer the queston

If you could go back in time, would you again choose to have the patient undergo aggressive treatments such as were provided for the stroke?	○ Yes, if primary caregiver could go back in the time he/she would again choose the aggressive treatments the patient received ○ No, primary caregiver would not choose aggressive treatments, event knowing it would result in the patient's death ○ Undedided

Burden Scale for Family caregivers BSFC-s

	strongly agree	agree	disagree	strongly disagree
1. My life satisfaction hs suffered because of the care.	○	○	○	○
2. I often feel physically exhausted.	○	○	○	○
3. From time to time I wish I could "run away" from the situation I am in.	○	○	○	○
4. Sometimes I don't really feel like "myself" as before.	○	○	○	○
5. Since I have been a caregiver my financial situation has decreased.	○	○	○	○
6. My health is affected by the care situation.	○	○	○	○
7. The care takes a lot of my own strength.	○	○	○	○
8. I feel torn between the demands of my environmet (such as family) and the demands of the care.	○	○	○	○
9. I am worried about my future because of the care I give.	○	○	○	○
10. My relationships with other family members, relatives, friend and acquaintances are suffering as a result of the care.	○	○	○	○

Protocol violations

Any protocol violations	○ Yes ○ No
if yes: Specification	_____

Investigator's statement

I confirm that all data entered in this CRF is complete and accurate at the best of my knowledge _____

Abbreviations:

AIS	– acute ischemic infarction
DCS	– decompressive surgery
Fisher	– Fisher SAH CT grading scale
IAT	– intraarterial thrombolysis/therapy
ICH	– intracerebral hemorrhage
ICP	– intracranial pressure
IVT	– Intravenous thrombolysis
mRS	– modified Rankin Scale
NCCU	– neurocritical care unit
NIHSS	– National Institutes of Health Stroke Scale
PEEP	– positive end-expiratory pressure
SAH	– subarachnoid hemorrhage
SpO2	– peripheral capillary oxygen saturation
TT	– tracheostomy
WFNS	– World Federation of Neurological Surgeons (WFNS) subarachnoid hemorrhage grading

Definition adverse events (AE):

AE grade I: The AE can be managed by the treating intensivists themselves without additional invasive procedure or material, is transient and without further clinical consequences.

AE grade II: The AE requires consultation from other disciplines and/or further invasive procedures and/or is not transient and/or has lasting consequences i.e. precipitates clinical deterioration or is fatal. Some of these AE may fulfill the definition of a severe AE.

2. Form for SAE

SETPOINT 2

Serious Adverse Event (SAE)

Center ID ☐☐ Screening No. ☐☐☐ Year of birth ☐☐☐☐ SAE No.* ☐

* to be counted for each patient seperatly.

Dr. med. Wolf-Dirk Niesen
University Hospital Freiburg
Department of Neurology
Breisacher Str. 64
D-79106 Freiburg / Germany
Fax: +49 761 270-53900
wolf-dirk.niesen@uniklinik-freiburg.de

Sender: Investigator

(Name, Adress, Stamp)

Definition

Severe adverse events (SAEs) are any adverse events, related to the procedure or not, that occur after enrollment into the study with one of the following consequences:

- Death
- Life-threatening situation
- Prolonged hospital stay or re-admission to hospital
- Related prolonged deterioration of health

SAEs should be faxed to the SAE coordinator Dr. Niesen within 24h or at the latest the next working day.

◯ Initial report ◯ Follow-up report

Date of report (YYYY/MM/DD) ☐☐☐☐/☐☐/☐☐

Patient data

Age (years) ☐☐☐ Sex ◯ male ◯ female

Randomization Number ☐☐☐

Randomized to ◯ Early tracheostomy ◯ Prolonged intubation

Type of SAE (e.g. septic shock, pulmonary embolism)

_____

_____

_____

Date begin of SAE (YYYY/MM/DD) ☐☐☐☐/☐☐/☐☐ Date end of SAE (YYYY/MM/DD) ☐☐☐☐/☐☐/☐☐

OR ◯ ongoing (at end of study)

Intensity ◯ mild ◯ moderate ◯ severe

Related to TT ◯ yes ◯ no

Result ◯ Recovered ◯ Improving ◯ Unchanged ◯ Deteriorated ◯ Died ◯ Unknown

Investigator's name (in block letters) _____

Date (YYYY/MM/DD) ☐☐☐☐/☐☐/☐☐ Signature _____

09.02.2016 Page 1 of 1

PROTOCOL SIGNATURE PAGE

Version 2.0 20 MARCH 2017

TRIAL ID: SETPOINT 2 Protocol Version 22FEB2017
Early Tracheostomy in ventilated Stroke Patients
University of Heidelberg
NCT02377167

Principal Investigator

I agree to conduct the trial in compliance with this protocol and to adhere to all regulations that govern the conduct of the study.

Signature _____ Date _____

Printed name _____

Institution _____

Sponsor

Signature_____Date _____
Julian Bösel, Heidelberg University Hospital

Summary of changes between the original (2015) and final (2017) clinical trial protocol of SETPOINT2

Pages refer to the final (2017) version

- Synopsis: Rates of pre-defined adverse events and serious adverse events after 6 months added (p.6)
- Synopsis: Correction of wrongly stated tracheostomy day in control group (synopsis p.6)
- Abbreviations: put in alphabetic order + some additions according to PCORI amendments (p.7)
- Screening: Passage „Every patient that has been admitted to the ICU for requirement of invasive ventilation due to the severity of his acute cerebrovascular disease should be screened for the study.“ added (p.15)
- Secondary outcomes: US sites cost analysis dropped (considered not feasible) (p.18)
- Secondary outcomes: Daily NCCU assessments (extubation trials, need of sedation or vasopressor infusions, evaluation of consciousness and sedation scores (RASS, SAS), time to first coma-free day, caregiver burden at discharge and at 6 months after discharge from ICU, patient and caregiver satisfaction with processes and results of care, time to first autonomous breathing, time to cessation of sedation/vasopressors/antibiotics added (p.18)
- DSMB: Change in roles stated (Jose Suarez switched to Tim Friede) (p.19)
- DSMB: Statement on responsibility charter and a form for regular reports added (p.19)
- SAEs: Statements as to the reaction and reporting by the safety observer (very critical incidents ASAP, regular reports after 33% and 50% trial enrollment) added (p.19/20)
- Data management: descriptions of eCRF, data security, pseudonymization, daily backup, server details, tracking system, etc. added (p.22)
- Statistical analysis: Cost comparison / resource utilization dropped(p.25)
- (e)CRF: Display of additional variables to the original (paper) CRF, including race, ethnicity, extubation trials, respirator weaning details, medication details, caregiver assessment on discharge, daily NCCU assesment (incl. sedation scores, infusions, physiologic deviations), patient reported outcome / caregiver reported outcome and satisfaction at 6 months, Burden scale for Family caregivers clarified (pp. 31-51)