This supplement contains the following items

1. Protocol
    a. Original protocol (first version receiving IRB approval) version 2.0, 20th July 2012, page 2-31
    b. Final protocol version 12.0, 14th December 2016, page 32-62
    c. Summary of changes, chronologically displayed in appendix, page 63-70
        i. Original protocol
        ii. Amendment 1
        iii. Amendment 2
        iv. Amendment 3
        v. Amendment 4
        vi. Amendment 5
        vii. Amendment 6
        viii. Amendment 7

    Protocol versions 8, 9 and 11 were submitted to the IRB but before final acceptance the protocol was changed. Only the accepted protocols by the IRB were listed.

2. Statistical analysis plan
    a. Original statistical analysis plan (SAP) as published in Trials, page 71-88

Original protocol, 1st version receiving IRB approval, version 2.0, 20th July 2012

ULTRA-EARLY TRANEXAMIC ACID AFTER SUBARACHNOID HEMORRHAGE

ULTRA

A prospective, randomized, multicenter study

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PROTOCOL TITLE Ultra-early tranexamic acid after subarachnoid hemorrhage

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Project leader	**Prof.dr. W.P. Vandertop**
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Laboratory sites	**n.a.**
Pharmacy	**None involved**

PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
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TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form (General Assessment and Registration form) is required for submission to the accredited Ethics Committee (ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
CCMO	Central Committee on Research Involving Human Subjects
CT	Computed tomography
CT-a	Computed tomography angiography
CV	Curriculum Vitae
DSA	Digital subtraction angiography DSMB Data Safety Monitoring Board
DCI	Delayed cerebral ischemia
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials GCP Good Clinical Practice
GCS	Glasgow Coma Scale
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
(S)AE	Serious Adverse Event
SAH	Subarachnoid hemorrhage
SDM	Substitute decision maker
SPC	Summary of Product Characteristics (in Dutch: officiële productinformatie IB1- tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TXA	Tranexamic acid
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen)

2. SUMMARY

Rationale: Approximately 50% of all patients with a subarachnoid hemorrhage (SAH) die due to the hemorrhage or subsequent complications. There are several major causes for this course, such as in-hospital rebleed in 21.5% which most frequently occurs within the first 6 hours after the primary hemorrhage ("ultra-early rebleed"). A major part of the patients with a rebleed die during hospital admission and when they survive, they develop more severe cognitive dysfunctions. Reducing the rebleeds by ultra-early administration of tranexamic acid (TXA) could be a major factor in improving the functional outcome after SAH.

Objective: Primary: To evaluate whether SAH patients treated by state-of-the-art SAH management with additional ultra-early and short term TXA administration have a significantly higher percentage of favourable outcome after six months (score 0-3 on the Modified Rankin Scale) compared to the group treated by up-to-date SAH management without additional TXA. Secondary: To evaluate whether: 1) TXA reduces in-hospital rebleeds and case fatalities; 2) TXA causes more ischemic stroke 3) TXA causes more complications (such as thromboembolic events, hydrocephalus, extracranial thrombosis or hemorrhagic complications) during treatment, admission and follow-up; 4) there is a difference in causes of poor outcome between groups; 5) there is a difference in discharge locations between groups; 6) there is an association between the time between hemorrhage and TXA administration and outcome; 7) TXA increases (micro)infarctions after endovascular treatment; 8) TXA reduces health-care costs between discharge and six months after hemorrhage; 9) TXA improves quality of life at six months after hemorrhage; 10) there are differences in rebleed rates and outcome between genders or groups with different WFNS scores at admission.

Study design: Multicenter, prospective, randomized, open label treatment with blind endpoint assessment.

Study population: Adult patients (18 years and older) included within 24 hours after SAH.

Intervention: Group one: standard treatment with additional administration of 1 g TXA intravenously in ten minutes, immediately after the diagnosis SAH, succeeded by continuous infusion of 1 g per 8 hours until a maximum of 24 hours. Group two: standard treatment with no TXA administration. Both groups undergo a standardized and validated interview at discharge and six months after hemorrhage to assess the modified Rankin Scale score, and both groups receive a questionnaire to evaluate health-care costs and quality of life.

Main study parameters/endpoints:

Primary: modified Rankin Scale score after six months, dichotomized into favourable and unfavourable outcome. Secondary: rebleed and case fatality rate, complications during the first six months after hemorrhage, (micro)infarctions at MR imaging after endovascular treatment, health-care costs from discharge until six months, quality of life at six months and differences in rebleed rates and outcome between genders or WFNS score at admission.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Subjects are randomly allocated to ultra-early TXA therapy or standard treatment. Complications are minor and the expected benefit is large compared with separate studies done with antifibrinolytic medications. In these studies, the safety of the use of these medications in this study population is confirmed.

In this patient group there are adequate, disoriented and comatose patients on admission, so a part of the

studied patients are incapacitated when undergoing the study. To extrapolate the conclusions of this study to clinical protocols it is necessary to include patients with a SAH in all different severity grades. Weighing carefully the benefits versus the burden and risks, it is assumed that patients will benefit from ultra-early TXA administration with minimal burden during therapy.

3. INTRODUCTION AND RATIONALE

Subarachnoid hemorrhage (SAH) accounts for 5% of all strokes and has an incidence of 6-7 per 100.000 person-years[1]. In 85% an intracranial aneurysm is found which is responsible for the hemorrhage, in 10% a perimesencephalic hemorrage is diagnosed and the remaining group includes other or unknown causes[2, 3]. SAH occurs at a fairly young age and carries a worse prognosis than other types of stroke.[4] Approximately 25% of all patients with aneurysmal SAH have a favourable outcome[5]. Nevertheless, these patients still have severe cognitive and functional dysfunctions[6]. The case fatality in SAH is 50% due to the initial hemorrhage or subsequent complications[1]. A frequent complication in patients with SAH is a recurrent bleeding from the aneurysm ("rebleed") which occurs in 4-12%[7-11] of patients that reach the hospital within the first 24 hours. The percentage of rebleeds increases to 21.5%[12] if the rebleeds presenting within the first six hours after the primary hemorrhage[9, 11] ("ultra- early rebleed") are also counted in. A rebleed is, next to the primary hemorrhage, still one of the major causes of death and disability in patients with SAH[13]. Functional dependency in this patient group is related to a lower quality of life and higher healthcare costs[14].

The prognosis of patients with SAH can be improved by decreasing the amount of rebleeds which can be accomplished by early aneurysm occlusion[15, 16]. However, in daily clinical practice, treatment can be delayed by a delay in diagnosis and transfer to a tertiary center. Therefore, despite several efforts to improve the logistic processes, ultra-early rebleeds still occur before the aneurysm is secured[15].

An alternative to reduce the number of rebleeds, other than by early aneurysm occlusion, is treatment with antifibrinolytic agents prior to aneurysm occlusion[17]. Long-term administration of antifibrinolytics has been extensively studied in the previous century. A Cochrane review concerning antifibrinolytic therapy for aneurysmal SAH found a reduction in rebleeds of approximately 40% with administration of antifibrinolytic therapy[17]. Nevertheless, no significant difference was seen in outcome, due to a concurrent increase in ischemic stroke as a result of the antifibrinolytic treatment. A limitation of the included studies is that the majority was performed over a decade ago when overall outcome after SAH was worse because of less accurate diagnostic methods, lack of nimodipine treatment and a minor role for endovascular treatment[1, 18]. Nowadays, diagnosis and treatment are performed earlier after the initial hemorrhage and administration of nimodipin, a calcium antagonist which is proven to reduce ischemic stroke, is standard. Recent studies combining these up-to-date treatment protocols with early, short-term antifibrinolytic therapy show better results compared to the earlier performed studies[8, 9, 19], with a tendency for improved functional outcome without an increase in ischemic stroke, as shown in a recent meta-analysis[20].

Although results from previous studies are promising, a randomized clinical trial in which TXA is administrated ultra-early (as soon as possible and at least within the first 24 hours after the primary

hemorrhage) and for a short time period has not been performed yet. Ultra-early TXA treatment is expected to reduce the amount of rebleeds as much as possible whilst the short- term administration in combination with early aneurysm occlusion might reduce the risk for the occurrence of ischemic stroke[20]. This should result in a better outcome for patients with SAH. Therefore, the goal of this study is to evaluate whether patients with ultra-early and short-term administration of tranexamic acid (TXA), as add-on to standard, state-of-the-art SAH management have a significantly better functional outcome at six months compared to patients treated by standard, state-of-the-art SAH management without additional TXA administration.

4. OBJECTIVES

Primary Objective:

- To evaluate whether a group of patients with SAH treated by standard, state-of-the-art SAH management with additional ultra-early and short-term TXA administration (TXA group) has a significantly higher percentage of patients with a favourable outcome after six months (score 0-3 on the Modified Rankin Scale[21]; mRS) compared to a group treated by standard, state-of-the-art SAH management without TXA administration (control group).

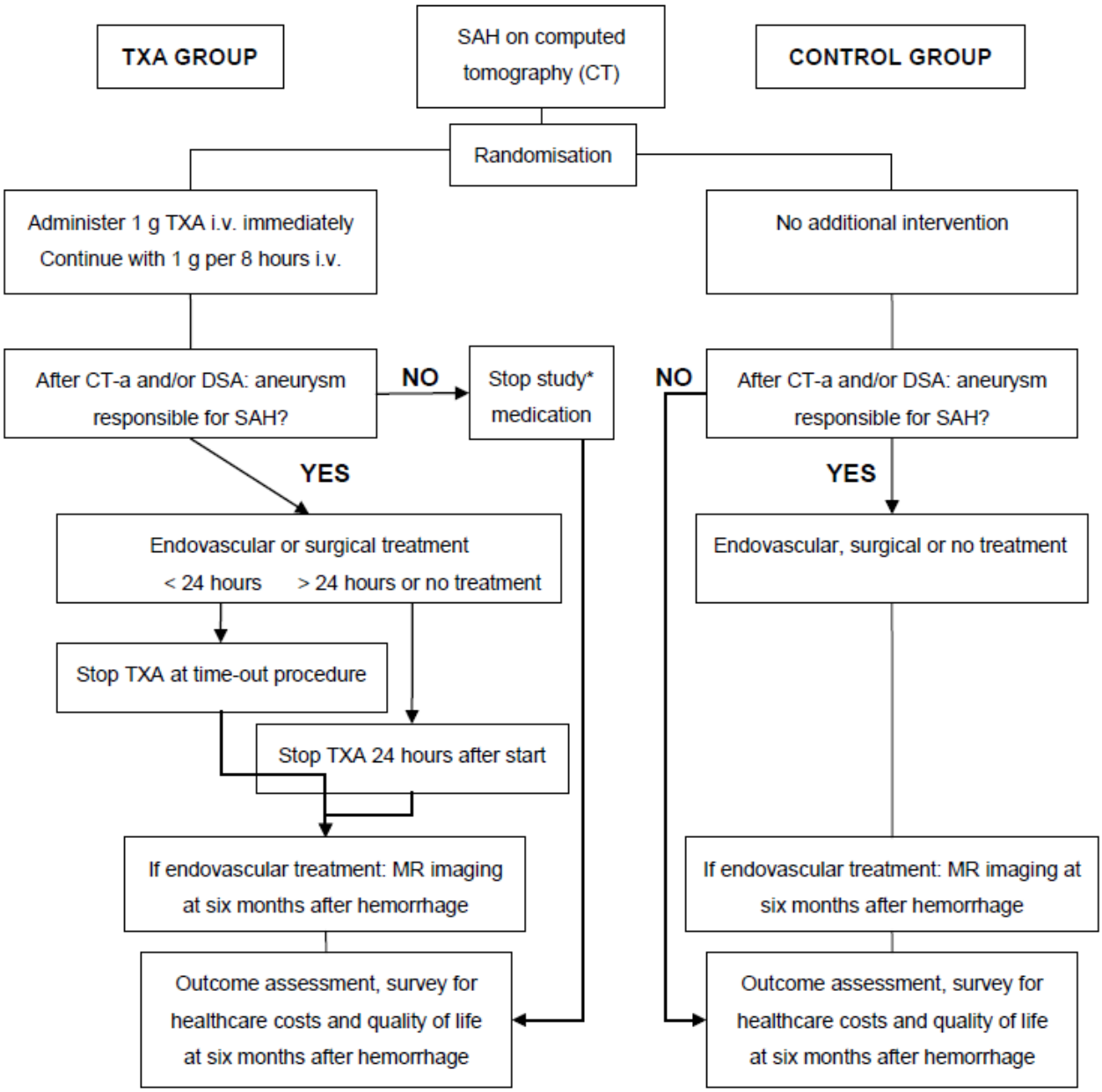
Secondary Objective(s):

- To evaluate whether there is a significant difference in case fatality rate between the TXA group and the control group at discharge and at six months after SAH
- To evaluate the cause of poor outcome
- To evaluate whether there is a significant difference in rebleed rate before or during aneurysm treatment between the TXA group and the control group
- To evaluate whether there is a difference in thromboembolic events during endovascular treatment between the TXA group and the control group
- To evaluate whether there is a difference in ischemic stroke rate between the TXA group and the control group
- To evaluate whether there is a difference in complications, such as hydrocephalus, extracranial thrombosis or hemorrhagic complications, during admission and after six months, between the TXA group and the control group
- To evaluate whether there is an association between favourable outcome and time from last hemorrhage to first TXA administration
- To evaluate whether there is a difference in discharge location, between the TXA group and the control group
- To evaluate whether there is a difference in (micro)infarctions on MR imaging at six months after endovascular treatment between the TXA group and the control group
- To evaluate whether there is a difference in health-care costs from discharge until six months after hemorrhage between the TXA group and the the control group

- To evaluate whether there is a difference in quality of life at six months after hemorrhage between the TXA group and the the control group
- To evaluate whether there is a significant difference in rebleed rate and favourable outcome between females and males and between groups with different World Federation of Neurological Surgeons (WFNS) scores at admission

5. STUDY DESIGN

A multicenter, prospective, randomized, open-label with blinded endpoint, trial will be performed in patients with a SAH (PROBE design: **P**rospective, **R**andomized, **O**pen label treatment with **B**lind **E**ndpoint assessment). With the calculated amount of included patients (950), the expected duration will be three years if all centers start inclusion at start of study. The following procedures will be performed during the study:



6. STUDY POPULATION

6.1 Population (base)

The research population are adult patients admitted with the diagnosis subarachnoi hemorrhage (SAH) as proven by computed tomography (CT) within 24 hours after the primary hemorrhage. The incidence of this type of hemorrhage is about 6-7 per 100.000 person-years[3]. It is expected that in the population admitted in The Netherlands about 80% of SAH is a result of a ruptured intracranial aneurysm[22]. Approximately 90% of SAH patients are admitted to a hospital within 24 hours after the hemorrhage (own data, not published). A bolus of the study medication will be administered as soon as possible after the diagnosis. The continuous infusion of the study medication will be cancelled immediately if after inclusion 1) no aneurysm appears to be present on CT-angiography (CT-a) or Digital Subtraction Angiography (DSA), 2) other intracranial pathology is responsible for the SAH, or 3) the aneurysm which is visualised is probably not responsible for the hemorrhage based on the bleeding pattern on CT. Patients, or their legally-appropriate substitute decision maker (SDM), will be approached to ask for the patients' participation in the study.

Due to the emergent intervention and the need to administer the medication as soon as possible an emergency procedure will be applied where consent is obtained after the administration of the medication (see 12.2). Patients or their legally appropriate SDM will be informed about the rationale of this study, possible risks and study burden as soon as possible after the emergency intervention. A member of the research team will provide the study information and will give eligible candidates, or their legally appropriate SDM, the study information letter. After the reflection period, patients or they SDM's will be asked to provide informed consent. If patients are primarily enrolled in the study after consent of an SDM and have become adequate enough to judge for joining the study, they will be informed by a study information letter as well with an additional question for informed consent.

6.2 Inclusion criteria

- Admission to one of the study centers or their referring hospitals
- CT-confirmed SAH with most recent ictus less than 24 hours ago

  Definition: subarachnoid hemorrhage is a bleeding pattern on computed tomography with hyperdensity in the basal cisterns and/or Sylvian or interhemipheric fissures or a intraparenchymal hyperdensity consistent with a hematoma from an anterior, a pericallosal, a posterior or a middle cerebral artery aneurysm.
- Age 18 years and older

6.3 Exclusion criteria

- No loss of consciousness after the hemorrhage with WFNS grade 1 or 2 on admission in combination with a perimesencephalic hemorrhage

  Definition: on CT examination presence of hyperdensities exclusively in the basal cisterns maximal extending to the proximal part of the Sylvian fissure or posterior part of the interhemispheric fissure, without evidence for intracerebral or intraventricular haemorrhage (except slight sedimentation)
- Bleeding pattern on CT compatible with a traumatic SAH
- Treatment for deep vein thrombosis
- History of blood coagulation disorder
- Pregnancy
- Severe renal (serum creatinin >150 mmol/L) or liver failure (AST > 150 U/l or ALT > 150 U/l or AF > 150 U/l or γ-GT > 150 U/l)
- Imminent death within 24 hours

6.4 Sample size calculation

The primary analysis at the end of the study is based on the difference in percentage of patients with good outcome (mRS 0-3) at six months after initial hemorrhage between patients with and without additional TXA intervention.

The overall favourable outcome in patients with standard, state-of-the-art SAH management without TXA was calculated by combining the results of the studies mentioned in this paragraph and the results from our own patients (293 consecutive patients, including angiogram-negative SAH, treated between 2008 and 2011) and was stated 69%.

The total percentage of rebleeds in patients with standard, state-of-the-art SAH management without TXA was determined at 17%. Although two studies and a recent review evaluating ultra-early antifibrinolytic treeatment after SAH[8,9] reported a rebleed rate of approximately 12%, our own recent results showed a rebleed rate of 17.1%, which was supported by Guo et al. (rebleed rate of 21.5% in aneurysmal SAH)[12]. The differences in results may be due to the shorter interval between primary hemorrhage and diagnosis (the majority of rebleeds namely occurs within the first few hours) in our center compared to the studies reporting a lower rebleed percentage (own data, manuscript in preparation).

The percentage of patients with rebleeds who will have a favourable outcome with standard, state-of-the-art SAH management is 20% (0.17*0.20= 3.4% of the total group)9. Consequently, with an overall favourable outcome in 69% of the patients, the percentage of patients with a favourable outcome in patients without a rebleed is 79% (65.6/83= 0.79).

The reduction in rebleeds by ultra-early TXA administration is expected to be 77%, resulting in a rebleed percentage of 3.9% in the patients receiving TXA (0.17*0.77=13.1%; 17%-13.1%=3.9)8,9.

The percentage of patients with a rebleed and a favourable outcome is anticipated to improve from

20% to 30% in patients with TXA9. Summarizing, after TXA administration, 3.9% will have a rebleed, of which 30% will have a favourable outcome (0.039*0.3= 1.2%). The resulting patients without a rebleed will have a favourable outcome in 79%, which contributes 75.9% to the complete group with favourable outcome (0.961*0.79=75.9%).

With these premises we calculated an improvement of favourable outcome from 69% to 77.1% (75.9%+1.2%).

In conclusion, to be able to detect the difference of 8.1% with a power of 80% and alpha of 5%, approximately 470 patients have to be included in each group (940 patients in total). Taking into account some withdrawals, the amount to be included patients will be 950.

7 TREATMENT OF SUBJECTS

7.1 Investigational product/treatment

Eligible subjects are randomly assigned to immediate administration of TXA (1 g i.v.) after a diagnosis of SAH, as confirmed by CT-scan of the brain, continued by continuous infusion of 1 g per 8 hours to a maximum of 24 hours after start of medication. A maximum of 4 g TXA (1 g bolus + 3x 1 g continuous infusion) can be administered to one patient.

7.2 Escape medication

None.

8 INVESTIGATIONAL MEDICINAL PRODUCT

8.1 Name and description of investigational medicinal product

Tranexamic acid (Cyklokapron®) forms a reversible complex that displaces plasminogen from fibrin resulting in inhibition of fibrinolysis; it also inhibits the proteolytic activity of plasmin. Labelling of the investigational products will be done according to GMP annex 13. Eligible subjects are randomly assigned to immediate administration of TXA (1 g i.v.) after diagnosis SAH confirmed by CT, as soon as possible continued by continuous infusion of 1 g per 8 hours to a maximum of 24 hours after start of medication. If aneurysm treatment is initiated within 24 hours (approximately 80% of all patients) the medication infusion will be discontinued at the time-out procedure before start of aneurysm treatment (endovascular or surgical).

8.2 Summary of findings from clinical studies

- Immediate TXA administration after SAH is diagnosed reflects a tendency toward better outcome on the Glasgow Outcome Scale[9].
- In patients with a rebleed, TXA administration significantly reduces death from rebleed[9].
- Antifibrinolytic treatment reduces the risk of rebleeding (OR 0,55, 95% CI 0,42- 0,71)[17].
- Short-term TXA administration does not increase DCI significantly[9, 19].

- Short-term application of epsilon-aminocaproic acid does not result in an increase of ischemic complications, pulmonary emboli, vasospasm, ventriculoperitoneal shunt rates or differences in outcome in angiogram negative SAH[24].

8.3 Summary of known and potential risks and benefits

The most common adverse events occur mainly in a short period after start of medication. During this time subjects are continually monitored so it is expected that adverse events are diagnosed and treated adequately by the attending physician.
Standard care to prevent nausea, vomiting or hypotension is a part of the standard SAH protocol because patients with such a hemorrhage also often have such events.

Known adverse events of TXA are described below:

- >10%: gastrointestinal: diarrhea, nausea, vomiting
- 1% to 10%: cardiovascular: hypotension, thrombosis. Ocular: blurred vision
- <1% (limited to important or life-threatening): deep venous thrombosis, pulmonary embolus, renal cortical necrosis, retinal artery obstruction, retinal vein obstruction, unusual menstrual discomfort, ureteral obstruction

8.4 Description and justification of route of administration and dosage

In previously performed studies, safety is warranted with use of TXA intravenously up to 6 g per day [9, 19].

8.5 Dosages, dosage modifications and method of administration

- 10 ml (100 mg/ml) = 1000 mg dissolved in 100 ml NaCl 0,9% and administered intravenously in 10 minutes
- Start immediately after diagnosis SAH on CT and randomization
- Followed by continuous infusion of 10 ml (100 mg/ml) = 1000 mg dissolved in 500 ml NaCl 0,9% intravenously per 8 hours until a maximum of 24 hours
- The Study Drug will be dispensed only to eligible subjects under the supervision of the Investigator or identified sub-Investigator(s).

8.6 Drug accountability

Cyklokapron is registered in The Netherlands, available on prescription and widely used in different hospitals. Each participating center will ensure the availability of cyklokapron in their pharmacy. Accountability for the study drug is in accordance to GCP guidelines.

9 METHODS

9.1 Study parameters/endpoints

9.1.1 Main study parameter/endpoint

Clinical outcome assessed by the modified Rankin Scale score at six months.

9.1.2 Secondary study parameters/endpoints

1. If patient has deceased: date and cause of death
2. Cause of poor outcome

   Related to the primary hemorrhage, related to complications of hemorrhage, related to one of the reported adverse events or unrelated to hemorrhage. Assessed by a central reading committee
3. Possible or definite rebleed and time interval with first hemorrhage

   Definition: sudden neurological deterioration with change in vital parameters suggestive for rebleed (possible rebleed) and presence of more SAH on CT than in a previous investigation (definite rebleed).
4. Rebleed during endovascular or surgical treatment

   Definition: extravasation of contrast dye outside of the vascular wall or perforation of the microcatheter, microwire or coil through the aneurysm wall with of without a sudden change in vital parameters suggestive for rebleed. Rupture of aneurysm during aneurysm surgery.
5. Thromboembolic events during endovascular treatment

   Definition: reduced passage or stasis of contrast in an artery or slowed venous outflow without the aspect of vascular spasm. Evaluated by treating neuroradiologist.
6. Ischemic stroke (delayed cerebral ischemia)

   Definition: The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies[23].
7. Extracranial thrombosis

   Definition: Lower extremity deep venous thrombosis, upper extremity venous thrombosis, upper extremity arterial thrombosis or pulmonary embolism diagnosed after clinical suspicion.
8. Treatment for hydrocephalus (therapeutic lumbar puncture, lumbar or ventricular drainage or definitive shunt)

   Definition of hydrocephalus: gradual onset of deterioration of consciousness measured on the Glasgow Coma Scale with CT evidence of enlarged ventricles and no other explanation for deterioration.
9. Hemorrhagic complications (intra- and extracranial)

   Definition: on CT proven intracranial hemorrhage (intracerebral, intraventricular, subdural or epidural), increased or newly developed after the primary hemorrhage; any extracranial hemorrhage for which intervention is necessary; either with neurological deterioration or not.
10. Time interval from last hemorrhage to first TXA administration
11. Discharge location

Other hospital, nursing home, rehabiliation center or home

12. Infarctions on MR imaging at six months after endovascular treatment

    Definition: amount of hyperintensity signals in brain parenchyma on T2 weighted MR imaging.

13. Health-care costs between discharge and six months after hemorrhage

    Evaluated with a standardized questionnaire

14. Quality of life at six months after hemorrhage

    Evaluated with the EQ-5D questionnaire

15. WFNS grade at admission

    Dichotomized into 1-3 and 4-5

16. Gender

9.1.2 Other study parameters

1. Date of birth
2. Modified Rankin Scale score before admittance
3. Medication use (antihypertensives, antiplatelets, anticoagulation) before admittance
4. WFNS grading of SAH
5. Fisher grade
6. Date and time of SAH
   - if exact time is unknown, then approximation of time of hemorrhage
   - if patient is discovered with depressed consciousness, then the time of patient last seen well is used
7. Date and time of CT scan for diagnosis SAH
8. Date and time of first administration of TXA
9. Date and time of first continuous administration of TXA 10.Date and time of ending the administration of TXA 11.Total dose of administered TXA
12. Location of aneurysm 13.Type of aneurysm treatment
14. Date and time of time-out procedure for aneurysm treatment
15. If applicable: date and time of rebleed (or approximation of it) and whether this is confirmed by consecutive CT scans or based on a sudden change in vital parameters and neurological deterioration (see also 9.1.2.)

9.2 Randomisation, blinding and treatment allocation

When a patient is admitted directly to the study center, the on-line randomization procedure will be done immediately by the treating physician after confirmation of SAH on CT. When the subject is

allocated to administration of TXA, the bolus of TXA is given as soon as possible. After the bolus, continuous infusion of TXA is started as soon as possible.

In the majority of cases, about 80%, patients are first admitted to a referring center of the study center(s). In this case, when the diagnosis SAH is confirmed by CT, the treating physician contacts the neurology/neurosurgery resident at the center to which the patient will be transferred to. The resident will perform the on-line randomization as soon as possible. The result of the randomization will be communicated to the treating physician at the referring center and when the subject is allocated to TXA treatment, an order is given by the treating physician to administer the bolus as soon as possible. The continuous infusion is started as soon as possible after the bolus and at least before transport to the study center. In conclusion, when a subject is allocated to TXA treatment, the bolus of study medication will be administered as soon as possible through an already present venous catheter (conform standard protocol for SAH) followed by the start of continuous infusion as soon as possible.

Patients will be randomized, using permuted blocks and stratified for study center (i.e. equal number of patients in both trial arms per center), using the on-line randomization module (ALEA), where fictive patient initials, date of birth, date and time of hemorrhage and eligibility based on in- and exclusion criteria is considered before randomization. The study starts after the patient has been randomized. The study nurse who will evaluate the modified Rankin Scale score (mRS) at six months after the SAH will be blinded for treatment allocation. In this way, blinding of the primary endpoint measurement is established. This evaluation takes place at a later stage, and the data are not used in any way during treatment of the patient.

9.3 Study procedures

Patients are admitted to the intensive care unit, medium care or neurological/ neurosurgical ward in one of the study centers. The necessary data for the study are collected and imported in an on-line database by the treating physician of the study center, supported by the study coordinator. The CT-scan on which the diagnosis SAH was stated is evaluated by a neuroradiologist at the center where the treatment is performed.

The outcome assessment at six months after the hemorrhage is done by a trial nurse who is blinded for allocation and did not participate in the medical treatment of the included patients. The mRS score at six months is taken by a standardized and validated telephone interview with the patient or the legally appropriate SDM. This score is commonly used for outcome assessment in stroke trials. Additionally, a short questionnaire to assess the health-care costs and quality of life at six months after SAH is sent and patients or their legally appropriate SDM will be asked to return this to the study center.

If the patient has an unfavourable outcome (mRS 4-6), the most probable cause (i.e. related to the primary hemorrhage, related to complications of hemorrhage, related to one of the reported adverse events or unrelated to hemorrhage) is assessed by a Data Classification Committee (DCC). This

committee is composed of the investigators of the coordinating centre and the local investigator. The results of these evaluations will be made available to the DSMB. If the patient has deceased, the primary cause and date of death is recorded.
Prof. dr. W.P. Vandertop is responsible for all medical decisions related to this study.

9.4 Withdrawal of individual subjects

Subjects, or their legally appropriate SDM can refuse to participate in the study by not signing the informed consent. If the informed consent is not signed and patients are allocated to TXA administration, TXA will be cancelled immediately if it is still administered. Data from these patients will be destroyed immediately. Subjects, or their legally appropriate SDM who approved the authorization for inclusion in the study, can decide to exit the study at any time for any reason if they wish to do so, without any consequences. In these cases, the patient data are not used for primary or secondary outcome assessments. The investigator can decide to withdraw a subject from the study for urgent medical reasons. A specific reason for withdrawal would be the occurrence of a Serious Adverse Event.
When a patient has already received TXA and 1) no aneurysm appears to be present on DSA, 2) other intracranial pathology is responsible for the SAH, or 3) the aneurysm which is visualised is probably not responsible for the hemorrhage based on the bleeding pattern on CT, the continuous infusion of the medication will be cancelled immediately. These patients will be included for the outcome assessments to ensure an adequate intention-to-treat analysis.

9.5 Replacement of individual subjects after withdrawal

Subjects who are lost to follow-up cannot be included in the analysis of the primary outcome assessment. If possible, they will be included in the secondary endpoint assessment. Individual subjects will not be replaced after withdrawal. Our analysis will be according to the intention-to-treat principle and exclusion of these patients would lead to a selective patient sample.

10 SAFETY REPORTING

10.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

10.1.1 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational drug. All adverse events reported

spontaneously by the subject or observed by the investigator or his staff will be recorded.
A serious adverse event is any untoward medical occurrence or effect that at any dose results:

- in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

For the present study, an SAE is defined according to the definition above, during hospital admission. A life threatening SAE, or SAE with death as a result, must be reported within 7 days after the local investigator has been informed. Other SAEs must be reported within 15 days. The study coordinator is responsible for reporting and records SAEs at the internetsite of ToetsingOnline of the CCMO. This instance reports the SAE to the METC.
In this study, certain SAEs may occur that are expected in SAH patients irrespective of the kind of treatment. The expected SAEs are rebleed, severe hyponatriaemia, hydrocephalus, cerebral ischemia, pneumonia and nosocomial meningitis. These are recorded and reported to the METC every half year and not reported at the internetsite as described above.

10.1.2 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.
Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g.
Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product).
The investigator will report expedited the following SUSARs to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trial of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The investigator will report expedited all SUSARs conform protocol of the CCMO to the

competent authority, the Medicine Evaluation Board and the competent authorities in other Member States unless it is already reported to the EMEA Eudravigilance database (appendix).
The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

10.1.3 Annual safety report

In addition to the expedited reporting of SUSARs, the investigator will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study.
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

10.2 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

10.3 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) is an independent committee of trial experts, who will focus on both safety monitoring and analysis of effectiveness on unblinded data with an interim analysis after half of the patients were included. The DSMB consists of three members: 2 clinicians and 1 statistician/epidemiologist. A DSMB charter will be used with respect to the schedule and format of DSMB meetings and with respect to the format and timing of presenting data. The DSMB will perform ongoing safety surveillances, especially with regard to the occurrence of serious adverse events in terms of increased ischemic events and serious extracranial thombotic events, such as pulmonary embolism. The investigator will report the occurrences of these events to the chairman according to the charter.
The DSMB can recommend the Steering Committee of the ULTRA trial to terminate the trial when there is clear and substantial evidence of harm or to adjust the sample size.

10.4 Monitoring

Based on the guidelines for risk classification from the Dutch Federation of University Medical Centers (NFU) ("Kwaliteitsborging van mensgebonden onderzoek"), the risk analysis performed for this study resulted in a classification of "average risk". This classification is based on the low chance for complications with clinical consequences due to the use of TXA as described in paragraph 6.3, in a vulnerable patient population. Much experience is present with this medication because of many previously performed human-related studies. Additionally, the maximum dose of administered TXA in this study will be lower than the maximum dose in which safety has been warranted (see paragraph 8.4). Other described complications, such as increase in ischemic events and more thromboembolic events, are not expected to occur because of the short-term and minimal dose administration of TXA. This is supported by previous studies[8, 9, 19] and explained in more detail in paragraph 12.4.

Monitoring will be performed according to GCP and will be carried out by the Clinical Research Unit of the AMC using a predefined monitoring plan. The monitor will make several visits to the sites during the trial, in order to complete source data verification (SDV). Next to the 'regular' visits, the sponsor or investigators can ask for extra visits, performed by the monitor. By signing this protocol the investigators give consent and full cooperation to the monitor during the trial. The final statistical analysis will be performed by the investigators.

If inconsistencies are found during the monitoring, such as missing informed consents or protocol violations, this is reported back to the investigators. They will restore the inconsistencies if possible and report this to the monitor within one month after the monitoring.

11 STATISTICAL ANALYSIS

11.1 Descriptive statistics and analysis between randomization groups

Continuous data with a parametric distribution will be presented as mean with its standard deviation and continuous data with a non-parametric distribution will be presented as median with its interquartile range. Categorical data will be presented as proportions.

Group differences for continuous variables will be calculated by a mean difference with a 95% CI, using an independent t-test for continuous variables with a parametric distribution or Wilcoxon rank sum test for continuous variables with a non-parametric distribution. Group differences for categorical variables will be calculated using chi-square statistics. A 2 sided p-value < 0.05 will be considered significant.

11.2 Interim analysis

The DSMB will perform an unblinded interim analysis on the primary outcome to assess the strength of the efficacy data when half of the patients are enrolled. The DSMB will also check the assumptions for sample size calculations. The DSMB can recommend the Steering Committee of

the ULTRA trial to:

- adjust the sample size
- early terminate the study when there is clear and substantial evidence of benefit, based on a significant(with alpha 1%) increase in favourable outcome (according to the Peto approach of interim analysis with alpha 5% at final analysis)
- early terminate the study when there is evidence of severe harm based on SAE reporting and case fatality
- early terminate the study in case accrual rates are too low to provide adequate statistical power for identifying the primary endpoint

The Steering Committee and the DSMB will agree on the approach to early termination (stopping rules) and the statistical methods used for efficacy evaluation beforehand.

11.3 Analyses on primary and secondary outcomes

The statistical analysis will be by “intention to treat”. The primary outcome analysis is an analysis evaluating the difference between the proportion of patients with favourable outcome (mRS score of 0 to 3 at six months) between the two randomization groups.

The secondary outcome analyses compare several variables between randomization groups: case fatality rate, rebleed rate before or during aneurysm treatment, thromboembolic events during endovascular treatment, rate of DCI, rate of complications with subdividing into types of complications, rate of (micro)infarctions at MR imaging, discharge location, health-care costs, quality of life, WFNS grade at admission or gender associated to rebleed rate and favourable outcome. Chi square statistics will be used to calculate an odds ratio, risk ratio, or risk difference. Adjustments for factors that differ at randomization will be made using regression or multi-level models.

12 ETHICAL CONSIDERATIONS

12.1 Regulation statement

This study will be conducted in full accordance with the principles of the "Declaration of Helsinki" (59th WMA General Assembly, Seoul, October 2008. http://www.wma.net/e/policy/b3.htm) and Medical Research Involving Human Subjects Act (WMO).

12.2 Recruitment and consent

This study evaluates the influence of an acute treatment in an emergency situation concerning a life-threatening disorder. The TXA treatment is intended to be administered as soon as possible after confirmation of the SAH to maximally reduce rebleeds (in our own database of 293 patients from 2008 until 2011, 39% of all rebleeds occur within two hours after the primary hemorrhage (manuscript in preparation)).

About two thirds of the patients have a decreased consciousness on admittance and are not able to give informed consent, and legally appropriate SDM’s are not always present at the ER.

Additionally, these patients are more prone for a rebleed because of the higher WFNS grading. By postponing the administration of the study medication until informed consent is given, rebleeds may occur which could be prevented by early treatment.

The emergency situation, the vulnerable patient group and the importance of the ultra-early administration allows an emergency procedure with obtaining a consent after start of medication in the above mentioned patient group.

Approximately one third of the patients arrive fully conscious (or with a legally appropriate SDM) and are theoretically capable of giving informed consent.
However, if these patients are asked for consent immediately, the ultra-early administration of TXA will be delayed compared to patients with a decreased consciousness, thus creating a bias between patients with and without the emergency procedure. Furthermore, a possible rebleed in patients who are clinically good after the first hemorrhage will result in a significant worse outcome. Therefore, TXA has to be administered as soon as possible after the diagnosis, and an emergency procedure with obtaining consent after start of medication in this group seems justifiable as well.
Therefore, in this study, TXA is administered as soon as possible after diagnosing SAH by CT and random allocation. There are no reported adverse events when TXA is administered for a short period[9, 20, 24]. Afterwards, as soon as possible at the study center, eligible subjects or their legally appropriate SDM will be notified by their treating physician that they have been included in the study. The investigator of the study will explain the rationale of the study and the study burden. An information letter and informed consent with the amendment that the patients' general physician will be informed of participation in the study will be given to eligible candidates or their legally appropriate SDM. The reflection period for signing the informed consent is as long as necessary. Participating patients can withdraw at any time from the study without prior notice or reason or can refuse participating by not signing the informed consent.

12.3 Objection by minors or incapacitated subjects

Due to the nature of the population studied, it is conceivable that in about 70% eligible subjects have a depressed level of consciousness and thus not be able to object themselves. In patients with a depressed level of consciousness, we will inform the SDM about this study and ask the SDM whether the patient would be willing to continue participating and sign the informed consent form on the patients' behalf. When patients are again capable for adequate judging, they will be informed about the study as written in 12.2.

12.4 Benefits and risks assessment, group relatedness

TXA is given by a bolus through an already present intravenous entry site, through which approximately 2 L NaCl 0,9% per 24 hours is administered (conform SAH protocol). Rapid infusion incidentally causes dizziness and hypotension, which is assumed to occur even less than normally because of the crystalloid infusion. If present, it will be rapidly diagnosed because the patient's parameters are

continuously monitored. A side effect is nausea, vomiting and diarrhoea, which generally occurs after SAH as well, so patients often receive medication for this purpose. In brief, by following the standard SAH protocol the extra burden by use of this medication is reduced to a minimum. Concerning risk evaluation, it was reported in a Cochrane review[17] that use of antifibrinolytic therapy (e.g. tranexamic acid) is associated with a higher incidence of DCI, without benefits in favourable outcome. A major drawback in the included studies is that the long-term administration of TXA caused an increase in DCI which negated the positive effects of a 40% reduction in rebleed rate. In addition, the majority of studies was performed before 1991 when outcome of SAH was worse because of less specialised institutes, lacking the use of nimodipine and less patients treated with endovascular methods[18]. More recently, studies have been done with improved treatment protocols and these tend to show better results than experienced in the past with no higher incidence of DCI[8, 9, 19]. Other risks associated with use of this medication are allergic skin reactions which can be treated adequately and sporadic thromboembolic complications[19].

At six months patients are invited for a telephone interview to evaluate the primary and secondary outcome assessments. A survey for the health-care costs and quality of life assessment will be sent to the patient with the question to fill it in and return it to the coordinating study center. When patients are unable to complete the telephone interview and/or questionnaire, a proxy will be asked. Weighing carefully the benefits versus the burden and risks, it is assumed that patients will benefit from ultra-early treatment with TXA with minimal burden during therapy.

12.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

12.6 Incentives

n.a.

13 ADMINISTRATIVE ASPECTS AND PUBLICATION

13.1 Handling and storage of data and documents

The data will be handled by the trial nurse who will have access to the source data and CT investigations.

Data are collected patient record forms and stored in a digital Case Record Form (CRF) based on Oracle Clinical. This data entry meets the needs of AMC Good Clinical Practice (GCP) Guidelines with a number and fictional initials for each patient and a double data entry process. Data will be archived for 20 years after end of study conform the directive of GCP. Every essential document will be preserved on paper or digital copies if no paper version is possible. It will be saved in cardboard archive boxes in the Academic Medical Center (AMC), location E2-170, with the name of the study, principal investigator, department, division and duration of archivation perceptible. Electronical data will be saved on a central server as "write once read many" (WORM) in consultation with an ICT administrator.

13.2 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority but will be recorded and filed by the sponsor.

13.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

13.4 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

13.5 Public disclosure and publication policy

Conform the CCMO statement on publication, this study will be proposed for publication within a year after the final outcome measurement, regardless of either positive or negative results.

This trial is registered at the international trial registry (www.clinicaltrials.gov), EudraCT database and Nederlands Trial Register (www.trialregister.nl) database. Results will be presented in an appropriate international, peer reviewed journal. Co- authorship will require a reasonable inclusion rate from participating centers.

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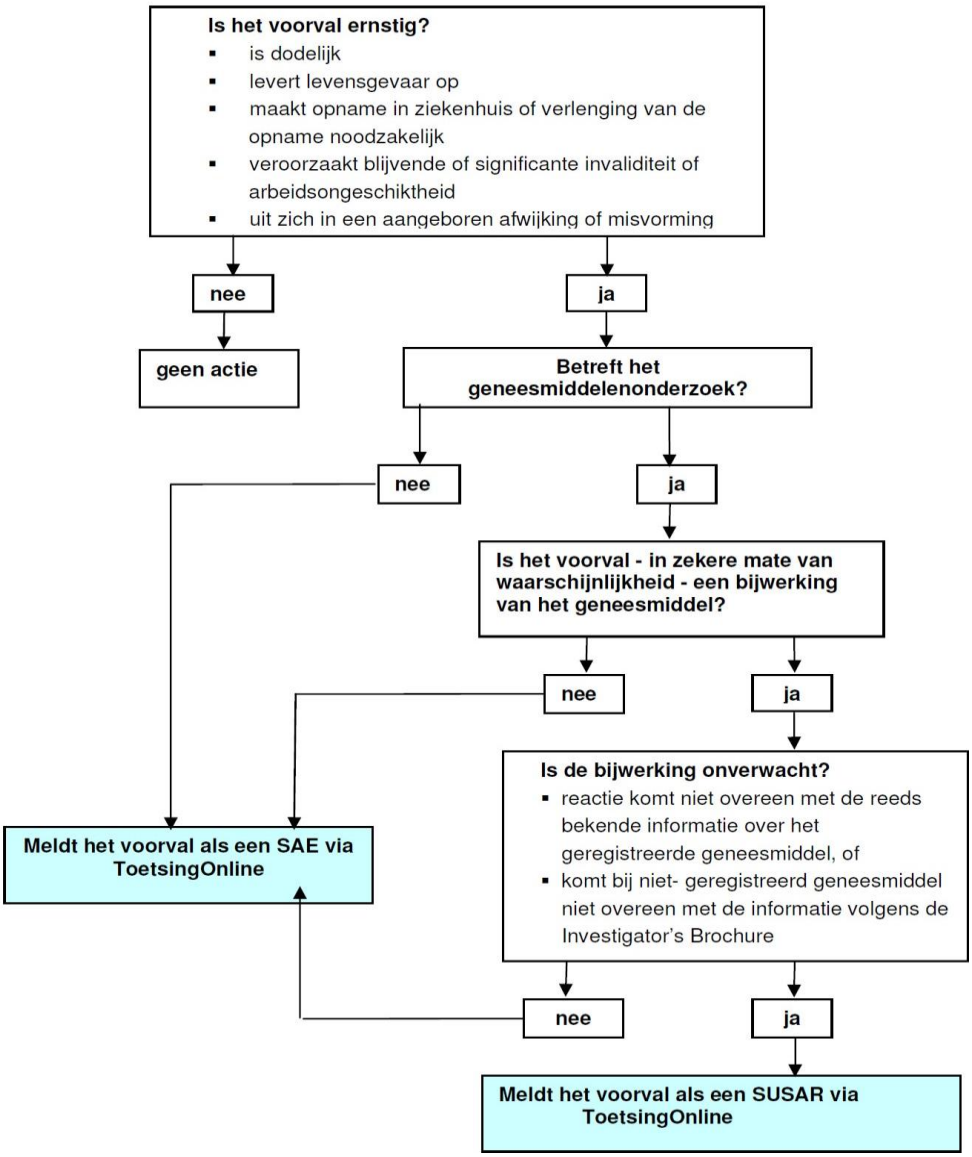
APPENDIX: Dutch Flowchart SAE and SUSAR procedures

Stroomdiagram bijwerkingen



Final protocol, version 12.0, 14th December 2016

ULTRA-EARLY TRANEXAMIC ACID AFTER SUBARACHNOID HEMORRHAGE

ULTRA

A prospective, randomized, multicenter study

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PROTOCOL TITLE Ultra-early tranexamic acid after subarachnoid hemorrhage

Protocol ID	**ULTRA**
Short title	**ULTRA**
Version	**12**
Date	**14/12/2016**
Project leader	**Prof.dr. W.P. Vandertop**
Coordinating investigator	**Dr. D. Verbaan, Academic Medical Center, Amsterdam**
Principal investigator(s) (in Dutch: hoofdonderzoeker/uitvoerder) ***Multicenter research: per site***	**Dr. D. Verbaan, Academic Medical Center, Amsterdam** **Prof.dr. W.P. Vandertop, VU University Medical Center, Amsterdam** **Prof. dr. G.J.E. Rinkel, University Medical Center Utrecht**
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Sponsor (in Dutch: verrichter/opdrachtgever)	**Academic Medical Center**
Independent physician(s)	**Dr. P. v.d. Munckhof, M.D., Ph.D., Academic Medical Center, Amsterdam**
Laboratory sites	**n.a.**
Pharmacy	**None involved**

PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
For non-commercial research, **Head of Department:** **Prof.dr. W.P. Vandertop**		
Principal Investigator: **Dr. D. Verbaan**		
Site investigator:		

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form (General Assessment and Registration form) is required for submission to the accredited Ethics Committee (ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
CCMO	Central Committee on Research Involving Human Subjects
CT	Computed tomography
CT-a	Computed tomography angiography
CV	Curriculum Vitae
DSA	Digital subtraction angiography
DSMB	Data Safety Monitoring Board
DCI	Delayed cerebral ischemia
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials GCP Good Clinical Practice
GCS	Glasgow Coma Scale
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
(S)AE	Serious Adverse Event
SAH	Subarachnoid hemorrhage
SDM	Substitute decision maker
SPC	Summary of Product Characteristics (in Dutch: officiële productinformatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TXA	Tranexamic acid
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen)

2. SUMMARY

Rationale: Approximately 50% of all patients with a subarachnoid hemorrhage (SAH) die due to the hemorrhage or subsequent complications. There are several major causes for this course, such as in-hospital rebleeding in 21.5% which most frequently occurs within the first 6 hours after the primary hemorrhage ("ultra-early rebleed"). A major part of the patients with a rebleed die during hospital admission and when they survive, they develop more severe cognitive dysfunctions. Reducing the rebleeds by ultra-early administration of tranexamic acid (TXA) could be a major factor in improving the functional outcome after SAH.

Objective: Primary: To evaluate whether SAH patients treated by state-of-the-art SAH management with additional ultra-early and short term TXA administration have a significantly higher percentage of favourable outcome after six months (score 0-3 on the Modified Rankin Scale) compared to the group treated by up-to-date SAH management without additional TXA. Secondary: To evaluate whether: 1) TXA reduces in-hospital rebleeds (and/or rebleed volumes) and case fatalities; 2) TXA causes more ischemic stroke 3) TXA causes more complications (such as thromboembolic events, hydrocephalus, extracranial thrombosis or hemorrhagic complications) during treatment, admission and follow-up; 4) there is a difference in causes of poor outcome between groups; 5) there is a difference in discharge locations between groups; 6) there is an association between the time between hemorrhage and TXA administration and outcome; 7) TXA increases (micro)infarctions after endovascular treatment; 8) TXA reduces health-care costs between discharge and six months after hemorrhage; 9) TXA improves quality of life at six months after hemorrhage; 10) there are differences in rebleed rates and outcome between genders or groups with different WFNS scores at admission.

Study design: Multicenter, prospective, randomized, open label treatment with blind endpoint assessment.

Study population: Adult patients (18 years and older) included within 24 hours after SAH.

Intervention: Group one: standard treatment with additional administration of 1 g TXA intravenously in ten minutes, immediately after the diagnosis SAH, succeeded by continuous infusion of 1 g per 8 hours until a maximum of 24 hours. Group two: standard treatment with no TXA administration. Both groups undergo a standardized and validated interview at discharge and six months after hemorrhage to assess the modified Rankin Scale score, and both groups receive a questionnaire to evaluate health-care costs and quality of life.

Main study parameters/endpoints:

Primary: modified Rankin Scale score after six months, dichotomized into favourable and unfavourable outcome. Secondary: rebleed number and volume, and case fatality rate, complications during the first six months after hemorrhage, (micro)infarctions at MR imaging after endovascular treatment, health-care costs from discharge until six months, quality of life at six months and differences in rebleed rates and outcome between genders or WFNS score at admission.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Subjects are randomly allocated to ultra-early TXA therapy or standard treatment. Complications are minor and the expected benefit is large compared with separate studies done with antifibrinolytic medications. In these studies, the safety of the use of these medications in this study population is confirmed.

In this patient group there are adequate, disoriented and comatose patients on admission, so a part of the studied patients are incapacitated when undergoing the study. To extrapolate the conclusions of this study to clinical protocols it is necessary to include patients with a SAH in all different severity grades. Weighing carefully the benefits versus the burden and risks, it is assumed that patients will benefit from ultra-early TXA administration with minimal burden during therapy.

3. INTRODUCTION AND RATIONALE

Subarachnoid hemorrhage (SAH) accounts for 5% of all strokes, and has an incidence of 6-7 per 100.000 person-years[1]. In 85% an intracranial aneurysm is found which is responsible for the hemorrhage, in 10% a perimesencephalic hemorrage is diagnosed and the remaining group includes other or unknown causes[2, 3]. SAH occurs at a fairly young age and carries a worse prognosis than other types of stroke.[4] Approximately 25% of all patients with aneurysmal SAH have a favourable outcome[5]. Nevertheless, these patients still have severe cognitive and functional dysfunctions[6]. The case fatality in SAH is 50% due to the initial hemorrhage or subsequent complications[1]. A frequent complication in patients with SAH is a recurrent bleeding from the aneurysm ("rebleed") which occurs in 4-12%[7-11] of patients that reach the hospital within the first 24 hours. The percentage of rebleeds increases to 21.5%[12] if the rebleeds presenting within the first six hours after the primary hemorrhage[9, 11] ("ultra-early rebleed") are also counted in. A rebleed is, next to the primary hemorrhage, still one of the major causes of death and disability in patients with SAH[13]. Functional dependency in this patient group is related to a lower quality of life and higher healthcare costs[14].

The prognosis of patients with SAH can be improved by decreasing the amount of rebleeds which can be accomplished by early aneurysm occlusion[15, 16]. However, in daily clinical practice, treatment can be delayed by a delay in diagnosis and transfer to a tertiary center. Therefore, despite several efforts to improve the logistic processes, ultra-early rebleeds still occur before the aneurysm is secured[15].

An alternative to reduce the number of rebleeds, other than by early aneurysm occlusion, is treatment with antifibrinolytic agents prior to aneurysm occlusion[17]. Long-term administration of antifibrinolytics has been extensively studied in the previous century. A Cochrane review concerning antifibrinolytic therapy for aneurysmal SAH found a reduction in rebleeds of approximately 40% with administration of antifibrinolytic therapy[17]. Nevertheless, no significant difference was seen in outcome, due to a concurrent increase in ischemic stroke as a result of the antifibrinolytic treatment. A limitation of the included studies is that the majority was performed over a decade ago when overall

outcome after SAH was worse because of less accurate diagnostic methods, lack of nimodipine treatment and a minor role for endovascular treatment[1, 18]. Nowadays, diagnosis and treatment are performed earlier after the initial hemorrhage and administration of nimodipin, a calcium antagonist which is proven to reduce ischemic stroke, is standard. Recent studies combining these up-to-date treatment protocols with early, short-term antifibrinolytic therapy show better results compared to the earlier performed studies[8, 9, 19], with a tendency for improved functional outcome without an increase in ischemic stroke, as shown in a recent meta-analysis[20].

Although results from previous studies are promising, a randomized clinical trial in which TXA is administrated ultra-early (as soon as possible and at least within the first 24 hours after the primary hemorrhage) and for a short time period has not been performed yet. Ultra-early TXA treatment is expected to reduce the amount of rebleeds as much as possible whilst the short-term administration in combination with early aneurysm occlusion might reduce the risk for the occurrence of ischemic stroke[20]. This should result in a better outcome for patients with SAH. Therefore, the goal of this study is to evaluate whether patients with ultra-early and short-term administration of tranexamic acid (TXA), as add-on to standard, state-of-the-art SAH management have a significantly better functional outcome at six months compared to patients treated by standard, state-of-the-art SAH management without additional TXA administration.

4. OBJECTIVES

Primary Objective:

- To evaluate whether a group of patients with SAH treated by standard, state-of-the-art SAH management with additional ultra-early and short-term TXA administration (TXA group) has a significantly higher percentage of patients with a favourable outcome after six months (score 0-3 on the Modified Rankin Scale[21]; mRS) compared to a group treated by standard, state-of-the-art SAH management without TXA administration (control group).

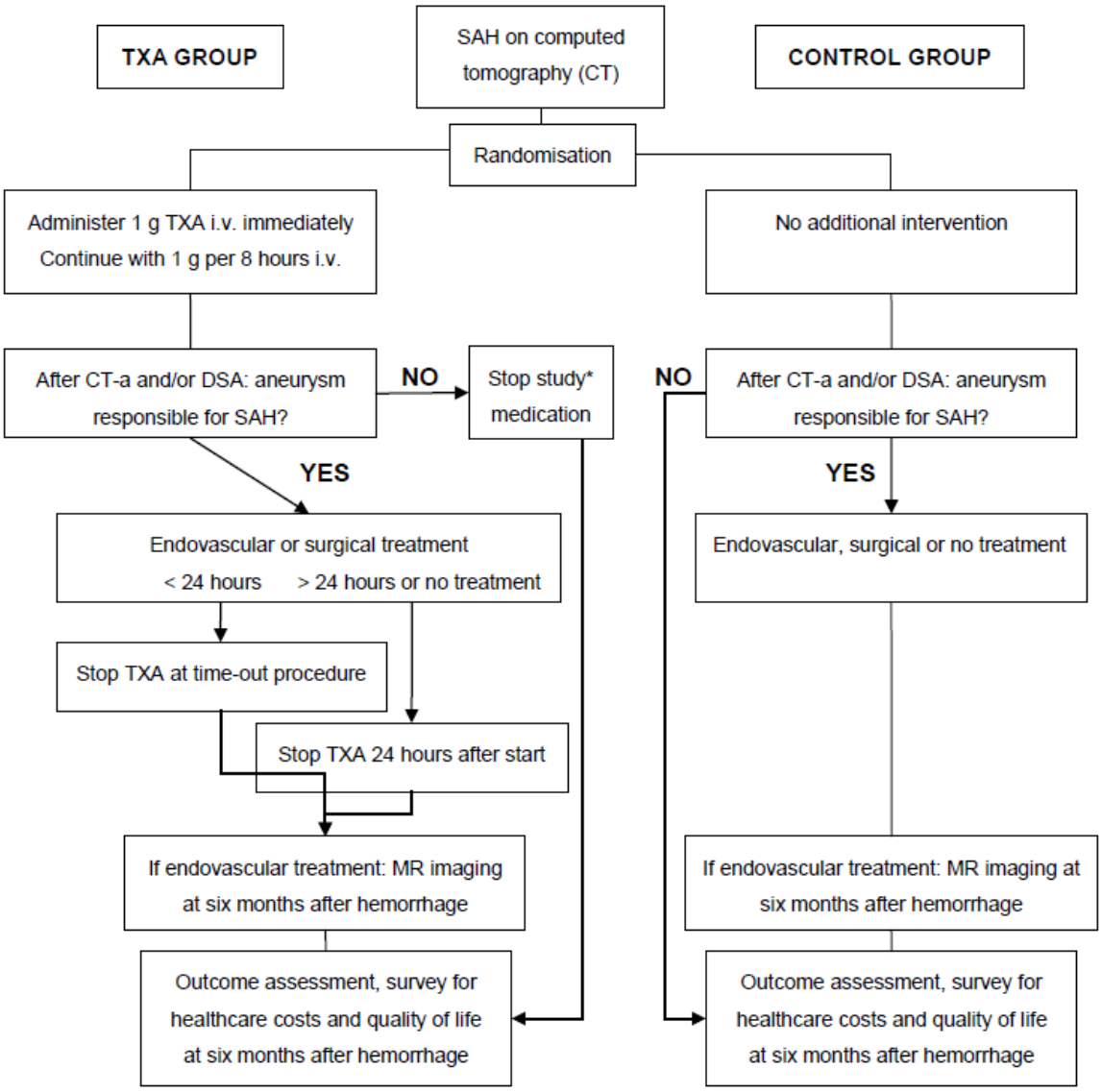
Secondary Objective(s):

- To evaluate whether there is a significant difference in case fatality rate between the TXA group and the control group at discharge and at six months after SAH
- To evaluate the cause of poor outcome
- To evaluate whether there is a significant difference in rebleed rate and volume before or during aneurysm treatment between the TXA group and the control group
- To evaluate whether there is a difference in thromboembolic events during endovascular treatment between the TXA group and the control group
- To evaluate whether there is a difference in ischemic stroke rate between the TXA group and the control group

- To evaluate whether there is a difference in complications, such as hydrocephalus, extracranial thrombosis or hemorrhagic complications, during admission and after six months, between the TXA group and the control group
- To evaluate whether there is an association between favourable outcome and time from last hemorrhage to first TXA administration
- To evaluate whether there is a difference in discharge location, between the TXA group and the control group
- To evaluate whether there is a difference in (micro)infarctions in number and volume on MR imaging at six months after endovascular treatment between the TXA group and the control group
- To evaluate whether there is a difference in health-care costs from discharge until six months after hemorrhage between the TXA group and the control group
- To evaluate whether there is a difference in quality of life at six months after hemorrhage between the TXA group and the the control group
- To evaluate whether there is a significant difference in rebleed rate and favourable outcome between females and males and between groups with different World Federation of Neurological Surgeons (WFNS) scores at admission

5. STUDY DESIGN

A multicenter, prospective, randomized, open-label with blinded endpoint, trial will be performed in patients with a SAH (PROBE design: **P**rospective, **R**andomized, **O**pen label treatment with **B**lind **E**ndpoint assessment). With the calculated amount of included patients (950), the expected duration will be three years if all centers start inclusion at start of study. The following procedures will be performed during the study:



*** if recent laboratory investigations revealed severe renal (serum creatinin >150 mmol/L) failure or pregnancy, study medication will also be stopped immediately**

6. POPULATION

6.1 Population (base)

The research population are adult patients admitted with the diagnosis subarachnoid hemorrhage (SAH) as proven by computed tomography (CT) within 24 hours after the primary hemorrhage. The incidence of this type of hemorrhage is about 6-7 per 100.000 person-years[3]. It is expected that in the population admitted in The Netherlands about 80% of SAH is a result of a ruptured intracranial aneurysm[22]. Approximately 90% of SAH patients are admitted to a hospital within 24 hours after the hemorrhage (own data, not published). A

bolus of the study medication will be administered as soon as possible after the diagnosis. The continuous infusion of the study medication will be cancelled immediately if after inclusion 1) no aneurysm appears to be present on CT-angiography (CT-a) or Digital Subtraction Angiography (DSA), 2) other intracranial pathology is responsible for the SAH, or 3) the aneurysm which is visualised is probably not responsible for the hemorrhage based on the bleeding pattern on CT. Patients, or their legally-appropriate substitute decision maker (SDM), will be approached to ask for the patients' participation in the study. Due to the emergent intervention and the need to administer the medication as soon as possible an emergency procedure will be applied where consent is obtained after the administration of the medication (see 12.2). Patients or their legally-appropriate SDM will be informed about the rationale of this study, possible risks and study burden as soon as possible after the emergency intervention. A member of the research team will provide the study information and will give eligible candidates, or their legally-appropriate SDM, the study information letter. After the reflection period, patients or they SDM's will be asked to provide informed consent. If patients are primarily enrolled in the study after consent of an SDM and have become adequate enough to judge for joining the study, they will be informed by a study information letter as well with an additional question for informed consent.

6.2 Inclusion criteria

- Admission to one of the participating study centers or the participating referring hospitals
- CT-confirmed SAH with most recent ictus less than 24 hours ago

  Definition: subarachnoid hemorrhage is a bleeding pattern on computed tomography with hyperdensity in the basal cisterns and/or Sylvian or interhemipheric fissures or a intraparenchymal hyperdensity consistent with a hematoma from an anterior, a pericallosal, a posterior or a middle cerebral artery aneurysm.
- Age 18 years and older

6.3 Exclusion criteria

- No proficiency of the Dutch or English language
- No loss of consciousness after the hemorrhage with WFNS grade 1 or 2 on admission in combination with a perimesencephalic hemorrhage

  Definition: on CT examination presence of hyperdensities exclusively in the basal cisterns maximal extending to the proximal part of the Sylvian fissure or posterior part of the interhemispheric fissure, without evidence for intracerebral or intraventricular haemorrhage (except slight sedimentation)
- Bleeding pattern on CT compatible with a traumatic SAH
- Treatment for deep vein thrombosis or pulmonary embolism
- History of a blood coagulation disorder (a hypercoagulability disorder)
- Pregnancy checked with a pregnancy test in women in their childbearing period
- History of severe renal failure (serum creatinin >150 mmol/L)

- Imminent death within 24 hours

Since a majority of the patients arrive at the hospital with decreased consciousness on admittance and the study is being executed based on the emergency procedure, exclusion criteria that cannot be determined on admittance are considered to be absent. These criteria will be checked later and if present, will be acted upon (see paragraph 9.4).

6.4 Sample size calculation

The primary analysis at the end of the study is based on the difference in percentage of patients with good outcome (mRS 0-3) at six months after initial hemorrhage between patients with and without additional TXA intervention.

The overall favourable outcome in patients with standard, state-of-the-art SAH management without TXA was calculated by combining the results of the studies mentioned in this paragraph and the results from our own patients (293 consecutive patients, including angiogram-negative SAH, treated between 2008 and 2011) and was stated 69%.

The total percentage of rebleeds in patients with standard, state-of-the-art SAH management without TXA was determined at 17%. Although two studies and a recent review evaluating ultra-early antifibrinolytic treatment after SAH[8, 9] reported a rebleed rate of approximately 12%, our own recent results showed a rebleed rate of 17.1%, which was supported by Guo *et al*. (rebleed rate of 21.5% in aneurysmal SAH)[12]. The difference in results may be due to the shorter time interval between primary hemorrhage and diagnosis (the majority of rebleeds namely occurs within the first few hours) in our center compared to the studies reporting a lower rebleed percentage (own data, manuscript in preparation).

The percentage of patients with rebleeds who will have a favourable outcome with standard, state-of-the-art SAH management is 20% (0.17*0.20= 3.4% of the total group)[9].

Consequently, with an overall favourable outcome in 69% of the patients, the percentage of patients with a favourable outcome in patients without a rebleed is 79% (65.6/83= 0.79).

The reduction in rebleeds by ultra-early TXA administration is expected to be 77%, resulting in a rebleed percentage of 3.9% in the patients receiving TXA (0.17*0.77= 13.1%; 17%-13.1%= 3.9%)[8, 9]. The percentage of patients with a rebleed and a favourable outcome is anticipated to improve from 20% to 30% in patients with TXA[9]. Summarizing, after TXA administration, 3.9% will have a rebleed, of which 30% will have a favourable outcome (0.039*0.3= 1.2%). The resulting patients without a rebleed will have a favourable outcome in 79%, which contributes 75.9% to the complete group with favourable outcome (0.961*0.79=75.9%).

With these premises we calculated an improvement of favourable outcome from 69% to 77.1% (75.9%+1.2%).

In conclusion, to be able to detect the difference of 8.1% with a power of 80% and alpha of 5%, approximately 470 patients have to be included in each group (940 patients in total). Taking into account some withdrawals, the amount to be included patients will be 950.

7. TREATMENT OF SUBJECTS

7.1 Investigational product/treatment

Eligible subjects are randomly assigned to immediate administration of TXA (1 g i.v.) after a diagnosis of SAH, as confirmed by CT-scan of the brain, continued by continuous infusion of 1 g per 8 hours to a maximum of 24 hours after start of medication. A maximum of 4 g TXA (1 g bolus + 3x 1 g continuous infusion) can be administered to one patient.

7.2 Escape medication

None.

8. INVESTIGATIONAL MEDICINAL PRODUCT

8.1 Name and description of investigational medicinal product

Tranexamic acid (Cyklokapron®) forms a reversible complex that displaces plasminogen from fibrin resulting in inhibition of fibrinolysis; it also inhibits the proteolytic activity of plasmin.

Eligible subjects are randomly assigned to immediate administration of TXA (1 g i.v.) after diagnosis SAH confirmed by CT, as soon as possible continued by continuous infusion of 1 g per 8 hours to a maximum of 24 hours after start of medication. If aneurysm treatment is initiated within 24 hours (approximately 80% of all patients) the medication infusion will be discontinued at the time-out procedure before start of aneurysm treatment (endovascular or surgical).

8.2 Summary of findings from clinical studies

- Immediate TXA administration after SAH is diagnosed reflects a tendency toward better outcome on the Glasgow Outcome Scale[9].
- In patients with a rebleed, TXA administration significantly reduces death from rebleed[9].
- Antifibrinolytic treatment reduces the risk of rebleeding (OR 0,55, 95% CI 0,42-0,71)[17].
- Short-term TXA administration does not increase DCI significantly[9, 19].
- Short-term application of epsilon-aminocaproic acid does not result in an increase of ischemic complications, pulmonary emboli, vasospasm, ventriculoperitoneal shunt rates or differences in outcome in angiogram negative SAH[24].

8.3 Summary of known and potential risks and benefits

The most common adverse events occur mainly in a short period after start of medication. During this time subjects are continually monitored so it is expected that adverse events are diagnosed and treated adequately by the attending physician. Standard care to prevent nausea, vomiting or hypotension is a part of the standard SAH protocol because patients with such a hemorrhage also often have such events.

Known adverse events of TXA are described below:

- 1% to 10%: gastrointestinal: diarrhea, nausea, vomiting
- 0.1% to 1%: allergic dermatitis
- unknown cardiovascular: arterial or venous thrombosis on each location; ocular: visual impairment

8.4 Description and justification of route of administration and dosage

In previously performed studies, safety is warranted with use of TXA intravenously up to 6 g per day [9, 19].

8.5 Dosages, dosage modifications and method of administration

- Bolus: 10 ml (100 mg/ml) = 1000 mg dissolved in 100 ml NaCl 0,9% and administered intravenously in 10 minutes
- Start immediately after diagnosis SAH on CT and randomization
- Followed by continuous infusion of 10 ml (100 mg/ml) = 1000 mg intravenously per 8 hours until a maximum of 24 hours
- The Study Drug will be dispensed only to eligible subjects under the supervision of the Investigator or identified sub-Investigator(s).

8.6 Drug accountability and logistics

Cyklokapron is registered in The Netherlands, available on prescription and widely used in different hospitals. If a patient is randomized to the TXA group, the treating physician (electronically) prescribes the TXA in their hospital according to standard procedures. TXA will be given from stock on the emergency department, or neuro (intensive) care unit. Charge numbers and expiry dates from the TXA are documented in the study CRF, as well as the initials from the person who administered the TXA. Each participating center will ensure the availability of cyklokapron in their pharmacy. Accountability for the study drug is in accordance to GCP guidelines, except for stock management. However, for financial purposes, each participating center needs to manage the administered TXA for all patients included in the ULTRA study treatment arm. Yearly, participating centers can send an invoice with respect to costs for TXA to the coordinating center.

9. METHODS

9.1 Study parameters/endpoints

9.1.1 Main study parameter/endpoint

Clinical outcome assessed by the modified Rankin Scale score at six months.

9.1.2 Secondary study parameters/endpoints

1. If patient has deceased: date and cause of death
2. Cause of poor outcome

   Based on data from the patient file (AMC) or on imaging during admission and discharge letters (other treatment centers). Assessed by the Data Classification Committee. Causes of poor outcome are for instance: related to the primary hemorrhage, related to complications of hemorrhage, related to one of the reported adverse events or unrelated to hemorrhage.
3. Possible or definite rebleed and time interval with first hemorrhage

   Definition: sudden neurological deterioration with change in vital parameters suggestive for rebleed (possible rebleed) and presence of more SAH on CT than in a previous investigation (definite rebleed).
4. Rebleed during endovascular or surgical treatment

   Definition: extravasation of contrast dye outside of the vascular wall or perforation of the microcatheter, microwire or coil through the aneurysm wall with of without a sudden change in vital parameters suggestive for rebleed. Rupture of aneurysm during aneurysm surgery.
5. Rebleed volume
6. Thromboembolic events during endovascular treatment

   Definition: reduced passage or stasis of contrast in an artery or slowed venous outflow without the aspect of vascular spasm. Evaluated by treating neuroradiologist.
7. Ischemic stroke (delayed cerebral ischemia)

   Definition: The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies[23].
8. Extracranial thrombosis

   Definition: Lower extremity deep venous thrombosis, upper extremity venous thrombosis, upper extremity arterial thrombosis or pulmonary embolism diagnosed after clinical suspicion.
9. Treatment for hydrocephalus (therapeutic lumbar puncture, lumbar or ventricular drainage or definitive shunt)

   Definition of hydrocephalus: gradual onset of deterioration of consciousness measured on the Glasgow Coma Scale with CT evidence of enlarged ventricles and no other explanation for deterioration.
10. Hemorrhagic complications (intra- and extracranial)

    Definition: on CT proven intracranial hemorrhage (intracerebral, intraventricular, subdural or epidural), increased or newly developed after the primary hemorrhage; any extracranial hemorrhage for which intervention is necessary; either with neurological deterioration or not.
11. Time interval from last hemorrhage to first TXA administration
12. Discharge location

    Other hospital, nursing home, rehabiliation center or home

13. Infarctions on MR imaging at six months after endovascular treatment

    Definition: amount of hyperintensity signals in brain parenchyma on T2 weighted MR imaging.
14. Health-care costs between discharge and six months after hemorrhage

    Evaluated with a standardized questionnaire
15. Quality of life at six months after hemorrhage

    Evaluated with the EQ-5D questionnaire
16. WFNS grade at admission

    Dichotomized into 1-3 and 4-5
17. Gender

9.1.3 Other study parameters

1. Date of birth
2. Modified Rankin Scale score before admittance
3. Medication use (antihypertensives, antiplatelets, anticoagulation) before admittance
4. WFNS grading of SAH
5. Fisher grade
6. Date and time of SAH
   - if exact time is unknown, then approximation of time of hemorrhage
   - if patient is discovered with depressed consciousness, then the time of patient last seen well is used
7. Date and time of CT scan for diagnosis SAH
8. Date and time of first administration of TXA
9. Date and time of first continuous administration of TXA
10. Date and time of ending the administration of TXA
11. Total dose of administered TXA
12. Location of aneurysm
13. Type of aneurysm treatment
14. Date and time of time-out procedure for aneurysm treatment
15. If applicable: date and time of rebleed (or approximation of it) and whether this is confirmed by consecutive CT scans or based on a sudden change in vital parameters and neurological deterioration (see also 9.1.2.)

9.2 Randomisation, blinding and treatment allocation

When a patient is admitted directly to the study center, the on-line randomization procedure will be done immediately by the treating physician after confirmation of SAH on CT. When the subject is allocated to administration of TXA, the bolus of TXA is given as soon as possible. After the bolus, continuous infusion of TXA is started as soon as possible.
In the majority of cases, about 80%, patients are first admitted to a referring center of the study center(s). In this case, when the diagnosis SAH is confirmed by CT, the treating

physician contacts the neurology/neurosurgery resident at the center to which the patient will be transferred to. The resident will perform the on-line randomization as soon as possible. The result of the randomization will be communicated to the treating physician at the referring center and when the subject is allocated to TXA treatment, an order is given by the treating physician to administer the bolus as soon as possible. The continuous infusion is started as soon as possible after the bolus and at least before transport to the study center. In conclusion, when a subject is allocated to TXA treatment, the bolus of study medication will be administered as soon as possible through an already present venous catheter (conform standard protocol for SAH) followed by the start of continuous infusion as soon as possible. Patients will be randomized, using permuted blocks and stratified for study center (i.e. equal number of patients in both trial arms per center), using the on-line randomization module (ALEA), where fictive patient initials, date of birth, date and time of hemorrhage and eligibility based on in- and exclusion criteria is considered before randomization. The study starts after the patient has been randomized. The study nurse who will evaluate the modified Rankin Scale score (mRS) at six months after the SAH will be blinded for treatment allocation. In this way, blinding of the primary endpoint measurement is established. This evaluation takes place at a later stage, and the data are not used in any way during treatment of the patient.

9.3 Study procedures

Patients are admitted to the intensive care unit, medium care or neurological/ neurosurgical ward in one of the study centers. The necessary data for the study are collected and imported in an on-line database by the treating physician of the study center, supported by the study coordinator. The CT-scan on which the diagnosis SAH was stated is evaluated by a neuroradiologist at the center where the treatment is performed.

The outcome assessment at six months after the hemorrhage is done by a trial nurse who is blinded for allocation and did not participate in the medical treatment of the included patients. The mRS score at six months is taken by a standardized and validated telephone interview with the patient or the legally appropriate SDM. This score is commonly used for outcome assessment in stroke trials. Additionally, a short questionnaire to assess the health-care costs and quality of life at three and six months after SAH is sent and patients or their legally appropriate SDM will be asked to return this to the study center.

If the patient has an unfavourable outcome (mRS 4-6), the most probable cause (i.e. related to the primary hemorrhage, related to complications of hemorrhage, related to one of the reported adverse events or unrelated to hemorrhage) is assessed by a Data Classification Committee (DCC). This committee is composed of the investigators of the coordinating

centre and the local investigator. The results of these evaluations will be made available to the DSMB. If the patient has deceased, the primary cause and date of death is recorded. Prof. dr. W.P. Vandertop is, as co-PI with a medical background, responsible for the medical part of this study.

9.4 Withdrawal of individual subjects

Subjects, or their legally appropriate SDM can refuse to participate in the study by not signing the informed consent. If the informed consent is not signed and patients are allocated to TXA administration, TXA will be cancelled immediately if it is still administered. Data from these patients will be destroyed immediately, according to WMO (Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen)), article 6, clause 4. Subjects, or their legally appropriate SDM who approved the authorization for inclusion in the study, can decide to exit the study at any time for any reason if they wish to do so, without any consequences. In these cases, the patient data are not used for primary or secondary outcome assessments. The investigator can decide to withdraw a subject from the study for urgent medical reasons. A specific reason for withdrawal would be the occurrence of a Serious Adverse Event.

If it is revealed after inclusion, that one of the exclusion criteria was present in a certain patient at admittance, this patient remains included in the study and this is recorded as a protocol violation. Depending on the criterion, actions are undertaken. For instance, TXA may be stopped (perimesencephalic hemorrhage, traumatic SAH, treatment for deep vein thrombosis or pulmonary embolism, history of a blood coagulation disorder, pregnancy, history of severe renal failure). In case of no proficiency of the Dutch or English language, TXA will not be stopped but an interpreter has to be arranged to be able to perform the informed consent procedure (and the patient information has to be translated).

In patients who are correctly included and who already received TXA and 1) no aneurysm appears to be present on DSA, 2) other intracranial pathology is responsible for the SAH, 3) the aneurysm which is visualised is probably not responsible for the hemorrhage based on the bleeding pattern on CT, or 4) recent laboratory investigations reveal pregnancy or severe renal (serum creatinin >150 mmol/L) failure, the continuous infusion of the medication will be cancelled immediately. These patients will be included for the outcome assessments to ensure an adequate intention-to-treat analysis.

9.5 Replacement of individual subjects after withdrawal

Subjects who are lost to follow-up cannot be included in the analysis of the primary outcome assessment. If possible, they will be included in the secondary endpoint assessment. Individual subjects will not be replaced after withdrawal. Our analysis will be according to

the intention-to-treat principle and exclusion of these patients would lead to a selective patient sample.

10. SAFETY REPORTING

10.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending further review by the accredited METC. The investigator will take care that all subjects are kept informed.

10.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational drug. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose results:

- in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

For the present study, an AE is defined according to the definition above. Only AEs during the first hospital admission after ictus that are not related to the SAH must be reported.

For the present study, an SAE is defined according to the definition above, during hospital admission. The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. A life threatening SAE, or SAE with death as a result, must be reported within 7 days after the local investigator has been informed. Other SAEs must be reported within 15 days. The sponsor is responsible for reporting and records SAEs at the internetsite of ToetsingOnline of the CCMO. This instance reports the SAE to the METC.

In this study, certain SAEs may occur that are expected in SAH patients. The expected SAEs are rebleed, severe hyponatriaemia, hydrocephalus, cerebral ischemia, pneumonia,

nosocomial meningitis, Terson's syndrome, delirium, epilepsy, pneumocephalus, and perprocedural aneurysm rupture. These are recorded and reported to the METC every half year by line listing and not reported at the internetsite as described above.

10.2.1 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or severity is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product).

The investigator will report expedited the following SUSARs to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trial of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The investigator will report expedited all SUSARs conform protocol of the CCMO to the competent authority, the Medicine Evaluation Board and the competent authorities in other Member States unless it is already reported to the EMEA Eudravigilance database (appendix) .

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

10.2.2 Annual safety report

In addition to the expedited reporting of SUSARs, the investigator will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

10.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

10.4 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) is an independent committee of trial experts, who will focus on both safety monitoring and analysis of effectiveness on unblinded data with an interim analysis after half of the patients were included. The DSMB consists of three members: 2 clinicians and 1 statistician/epidemiologist. A DSMB charter will be used with respect to the schedule and format of DSMB meetings and with respect to the format and timing of presenting data. The DSMB will perform ongoing safety surveillances, especially with regard to the occurrence of serious adverse events in terms of increased ischemic events and serious extracranial thombotic events, such as pulmonary embolism. The investigator will report the occurrences of these events to the chairman according to the charter.
Each half year, a line listing will be reported to the METC, and a line listing and a safety evaluation will be reported to the DSMB. Based on these documents the DSMB will give an advice with respect to continuation of the trial based on this safety evaluation. The DSMB can recommend the Steering Committee of the ULTRA trial to terminate the trial when there is clear and substantial evidence of harm or to adjust the sample size.

10.5 Monitoring

Based on the guidelines for risk classification from the Dutch Federation of University Medical Centers (NFU) (“Kwaliteitsborging van mensgebonden onderzoek”), the risk analysis performed for this study resulted in a classification of “average risk”. This classification is based on the low chance for complications with clinical consequences due to the use of TXA as described in paragraph 6.3, in a vulnerable patient population. Much experience is present with this medication because of many previously performed human-related studies. Additionally, the maximum dose of administered TXA in this study will be lower than the maximum dose in which safety has been warranted (see paragraph 8.4). Other described complications, such as increase in ischemic events and more thromboembolic

events, are not expected to occur because of the short-term and minimal dose administration of TXA. This is supported by previous studies[8, 9, 19] and explained in more detail in paragraph 12.4.

Monitoring will be performed according to GCP and will be carried out by the Clinical Research Unit of the AMC using a predefined monitoring plan. The monitor will make several visits to the sites during the trial, in order to complete source data verification (SDV). Next to the 'regular' visits, the sponsor or investigators can ask for extra visits, performed by the monitor. By signing this protocol, the investigators give consent and full cooperation to the monitor during the trial. The final statistical analysis will be performed by the investigators.

If inconsistencies are found during the monitoring, such as missing informed consents or protocol violations, this is reported back to the investigators. They will restore the inconsistencies if possible and report this to the monitor within one month after the monitoring.

11. STATISTICAL ANALYSIS

11.1 Descriptive statistics and analysis between randomization groups

Continuous data with a parametric distribution will be presented as mean with its standard deviation and continuous data with a non-parametric distribution will be presented as median with its interquartile range. Categorical data will be presented as proportions.

Group differences for continuous variables will be calculated by a mean difference with a 95% CI, using an independent t-test for continuous variables with a parametric distribution or Wilcoxon rank sum test for continuous variables with a non-parametric distribution. Group differences for categorical variables will be calculated using chi-square statistics. A 2 sided p-value < 0.05 will be considered significant.

11.2 Interim analysis

The DSMB will perform an unblinded interim analysis on the primary outcome to assess the strength of the efficacy data when half of the patients are enrolled. The DSMB will also check the assumptions for sample size calculations. The DSMB can recommend the Steering Committee of the ULTRA trial to:

- adjust the sample size
- early terminate the study when there is clear and substantial evidence of benefit, based on a significant (with alpha 0.1%) increase in favourable outcome (according to the Peto approach of interim analysis with alpha 5% at final analysis)

- early terminate the study when there is evidence of severe harm based on SAE reporting, outcome, and case fatality
- early terminate the study in case accrual rates are too low to provide adequate statistical power for identifying the primary endpoint

The Steering Committee and the DSMB will agree on the approach to early termination (stopping rules) and the statistical methods used for efficacy evaluation beforehand.

11.3 Analyses on primary and secondary outcomes

The statistical analysis will be by "intention to treat". The primary outcome analysis is an analysis evaluating the difference between the proportion of patients with favourable outcome (mRS score of 0 to 3 at six months) between the two randomization groups.
A secondary analysis will perform an ordinal regression analysis according to a proportional odds assumption on the primary outcome. Furthermore, an as treated and per protocol analysis on the primary outcome will also be performed. The other secondary outcome analyses compare several variables between randomization groups: case fatality rate, rebleed volume and rate before or during aneurysm treatment, thromboembolic events during endovascular treatment, rate of DCI, rate of complications with subdividing into types of complications, rate of (micro)infarctions number and volume at MR imaging, discharge location, health-care costs, quality of life, WFNS grade at admission or gender associated to rebleed rate and favourable outcome. Independent samples t-test or Mann-Whitney U tests will be used for the group comparisons with respect to volume, whichever is appropriate. Chi square statistics will be used to calculate an odds ratio, risk ratio, or risk difference.
Adjustments for factors that differ at randomization will be made using regression or multi-level models.
For the interim analysis, a Chi-square test evaluating the difference in primary outcome between the groups based on intention-to-treat will be tested including all patients with a 6 months follow-up after randomization of 475 patients. Furthermore, Cochran-Mantel-Haenszel test will be performed as a secondary analysis to evaluate the difference in primary outcome between the groups corrected for the stratification factor treatment center.

12. ETHICAL CONSIDERATIONS

12.1 Regulation statement

This study will be conducted in full accordance with the principles of the "Declaration of Helsinki" (59th WMA General Assembly, Seoul, October 2008. http://www.wma.net/e/policy/b3.htm) and Medical Research Involving Human Subjects Act (WMO).

12.2 Recruitment and consent

This study evaluates the influence of an acute treatment in an emergency situation concerning a life-threatening disorder. The TXA treatment is intended to be administered as soon as possible after confirmation of the SAH to maximally reduce rebleeds (in our own database of 293 patients from 2008 until 2011, 39% of all rebleeds occur within two hours after the primary hemorrhage (manuscript in preparation)).

About two thirds of the patients have a decreased consciousness on admittance and are not able to give informed consent, and legally appropriate SDM's are not always present at the ER. Additionally, these patients are more prone for a rebleed because of the higher WFNS grading. By postponing the administration of the study medication until informed consent is given, rebleeds may occur which could be prevented by early treatment.

The emergency situation, the vulnerable patient group and the importance of the ultra-early administration allows an emergency procedure with obtaining consent after start of medication in the above-mentioned patient group.

Approximately one third of the patients arrive fully conscious (or with a legally appropriate SDM) and are theoretically capable of giving informed consent. However, if these patients are asked for consent immediately, the ultra-early administration of TXA will be delayed compared to patients with a decreased consciousness, thus creating a bias between patients with and without the emergency procedure. Furthermore, a possible rebleed in patients who are clinically good after the first hemorrhage will result in a significant worse outcome. Therefore, TXA has to be administered as soon as possible after the diagnosis, and an emergency procedure with obtaining consent after start of medication in this group seems justifiable as well.

Therefore, in this study, TXA is administered as soon as possible after diagnosing SAH by CT and random allocation. There are no reported adverse events when TXA is administered for a short period[9, 20, 24]. Afterwards, as soon as possible at the study center, eligible subjects or their legally appropriate SDM will be notified by their treating physician that they have been included in the study. The investigator of the study will explain the rationale of the study and the study burden. An information letter and informed consent with the amendment that the patients' general physician will be informed of participation in the study will be given to eligible candidates or their legally appropriate SDM. The reflection period for signing the informed consent is as long as necessary (during the admission period). Participating patients can withdraw at any time from the study without prior notice or reason or can refuse participating by not signing the informed consent.

If patients from whom their legally appropriate SDM signed the informed consent become mentally competent during hospital stay or during the follow-up period of the study, informed consent will be asked from the patients as well (called informed consent in the

second instance). The rationale of the study as well as the study will be explained, and an information letter and informed consent will be given or sent to the patients. Written or oral informed consent in the second instance are both considered appropriate, after consultation with the legal expert.

In consultation with the legal expert, some exceptions that are possible on the abovementioned procedure are discussed and a solution is chosen based on both ethical and legal considerations as well as methodological considerations (diminishing of bias). If patients die before the informed consent procedure could be discussed and there is no legally appropriate SDM, no consent is necessary and patients remain included in the study as long as there is no clearly written objection in the chart from the patient against participation in scientific research projects.

If patients die and there is a legally appropriate SDM, but there has been no possibility yet to discuss the informed consent procedure, no consent is necessary and patients remain included in the study as long as there is no clearly written objection in the chart from the patient against participation in scientific research projects. In both cases, the reason to deviate from the standard procedure as well as the decision that the patient remains included in the study has to be written clearly in the chart.

12.3 Objection by minors or incapacitated subjects

Due to the nature of the population studied, it is conceivable that in about 70% eligible subjects have a depressed level of consciousness and thus not be able to object themselves. In patients with a depressed level of consciousness, we will inform the SDM about this study and ask the SDM whether the patient would be willing to continue participating and sign the informed consent form on the patients' behalf. When patients are again capable for adequate judging, they will be informed about the study as written in 12.2.

12.4 Benefits and risks assessment, group relatedness

TXA is given by a bolus through an already present intravenous entry site, through which approximately 2 L NaCl 0,9% per 24 hours is administered (conform SAH protocol). Rapid infusion incidentally causes dizziness and hypotension, which is assumed to occur even less than normally because of the crystalloid infusion. If present, it will be rapidly diagnosed because the patient's parameters are continuously monitored. A side effect is nausea, vomiting and diarrhoea, which generally occurs after SAH as well, so patients often receive medication for this purpose. In brief, by following the standard SAH protocol the extra burden by use of this medication is reduced to a minimum.

Concerning risk evaluation, it was reported in a Cochrane review[17] that use of antifibrinolytic therapy (e.g. tranexamic acid) is associated with a higher incidence of DCI, without benefits in favourable outcome. A major drawback in the included studies is that the long-term

administration of TXA caused an increase in DCI which negated the positive effects of a 40% reduction in rebleed rate. In addition, the majority of studies was performed before 1991 when outcome of SAH was worse because of less specialised institutes, lacking the use of nimodipine and less patients treated with endovascular methods[18]. More recently, studies have been done with improved treatment protocols and these tend to show better results than experienced in the past with no higher incidence of DCI[8, 9, 19]. Other risks associated with use of this medication are allergic skin reactions which can be treated adequately and sporadic thromboembolic complications[19].

At six months patients are invited for a telephone interview to evaluate the primary and secondary outcome assessments. A survey for the health-care costs and quality of life assessment will be sent to the patient with the question to fill it in and return it to the coordinating study center. When patients are unable to complete the telephone interview and/or questionnaire, a proxy will be asked.

Weighing carefully the benefits versus the burden and risks, it is assumed that patients will benefit from ultra-early treatment with TXA with minimal burden during therapy.

12.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

12.6 Incentives

n.a.

13. ADMINISTRATIVE ASPECTS AND PUBLICATION

13.1 Handling and storage of data and documents

The data will be handled by the trial nurse who will have access to the source data and CT investigations.

Data are collected patient record forms and stored in a digital Case Record Form (CRF) based on Oracle Clinical. This data entry meets the needs of AMC Good Clinical Practice (GCP) Guidelines with a number and fictional initials for each patient and a double data entry process. Data will be archived for 20 years after end of study conform the directive of GCP. Every essential document will be preserved on paper or digital copies if no paper version is possible. It will be saved in cardboard archive boxes in the Academic Medical Center (AMC), location E2-170, with the name of the study, principal investigator, department, division and duration of archivation perceptible. Electronical data will be saved on a central server as "write once read many" (WORM) in consultation with an ICT administrator.

13.2 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

13.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

13.4 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

13.5 Public disclosure and publication policy

Conform the CCMO statement on publication, this study will be proposed for publication within a year after the final outcome measurement, regardless of either positive or negative results. Results will be presented in an appropriate international, peer reviewed journal. Authorship will be granted using the Vancouver definitions and depending on personal involvement. The first, second and last author names will be decided by the principal investigator and project leader. After the first and second author, the steering group members, site investigators and additional names are mentioned in alphabetical order. Referral centres recruiting ≥ 30 patients and treatment centers recruiting ≥ 50 patients will be entitled to one name in the author list (site investigators). After the author list there will be added: "and the ULTRA-trial group" and a reference to an appendix with all sites, site investigators and number of patients enrolled. This trial is registered at the international trial registry (www.clinicaltrials.gov), EudraCT database and Nederlands Trial Register (www.trialregister.nl) database.

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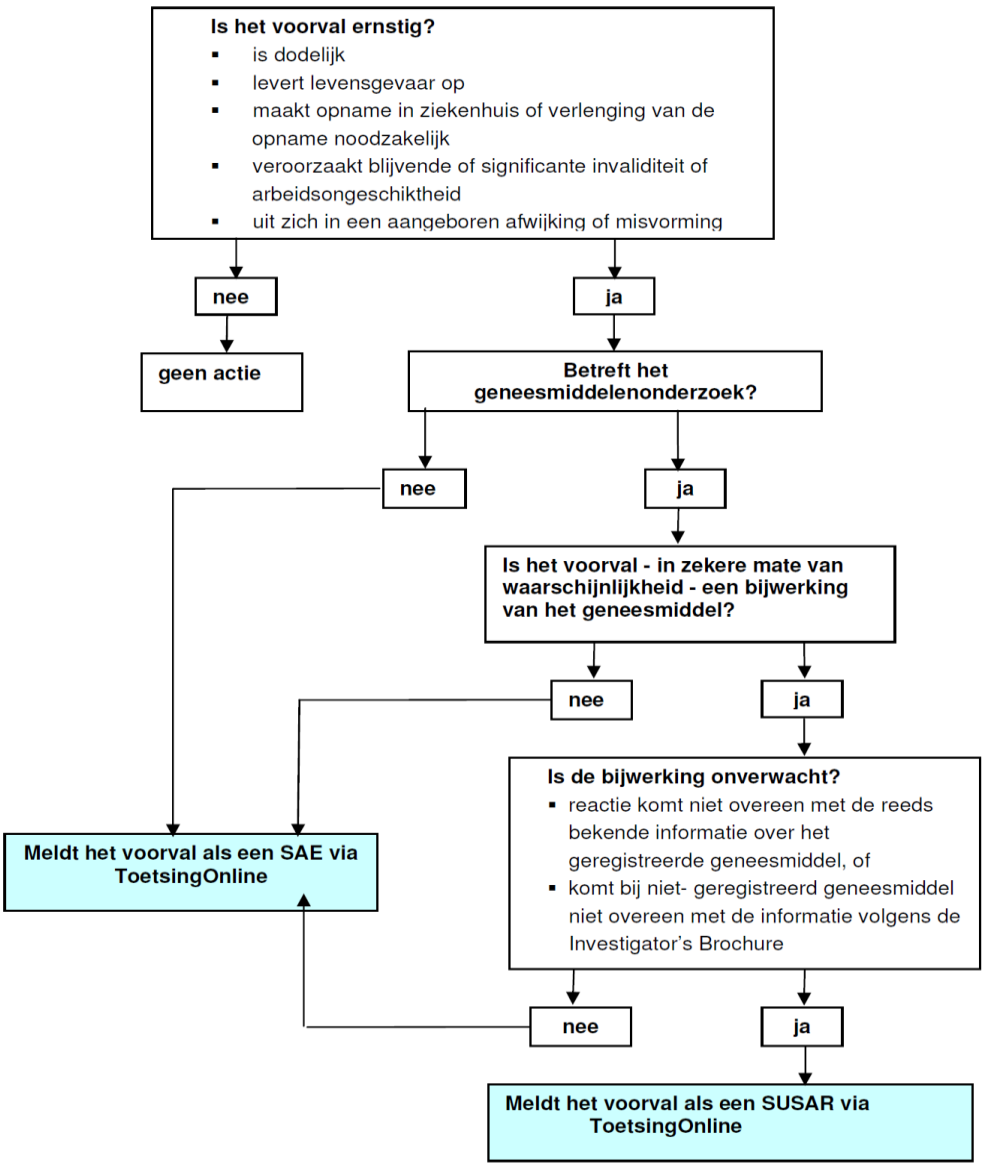
APPENDIX: Dutch Flowchart SAE and SUSAR procedures

Stroomdiagram bijwerkingen



SUBSTANTIAL AMENDMENT 1, PROTOCOL VERSION 3

Unsubstantial changes:

Amendment 1. Drs. R. Post was added to the list of co-investigator(s).

Substantial changes:

Amendment 2. Pulmonary embolism was added to the exclusion criteria.
Rationale of change: Tranexamic acid could potentially lead to an increased growth of a recently diagnosed pulmonary embolism.

Amendment 3. Hypercoagulability disorder was added to the exclusion criteria.
Rationale of change: Tranexamic acid could potentially increase the risk of thrombosis in patients with known hypercoagulability disorders.

Amendment 4. During the admission period was added in the sentence "The reflection period for signing the informed consent is as long as necessary".
Rationale of change: Patients with subarachnoid hemorrhage who are incapacitated on admission but recover during admission should be asked for informed consent.

Amendment 6. Added in paragraph 13.5 Public disclosure and publication policy the following text: "Results will be presented in an appropriate international, peer reviewed journal. Authorship will be granted using the Vancouver definitions and depending on personal involvement. The first, second and last author names will be decided by the principal investigator and project leader. After the first and second author, the steering group members, site investigators and additional names are mentioned in alphabetical order. Referral centres recruiting > 30 patients and treatment centers recruiting > 50 patients will be entitled to one name in the author list (site investigators). After the author list there will be added: "and the ULTRA-trial group" and a reference to an appendix with all sites, site investigators and number of patients enrolled."
Rationale of change: We added a guideline for rules for authorship following completion of the trial.

SUBSTANTIAL AMENDMENT 2, PROTOCOL VERSION 4

Substantial changes:

Amendment 1. Added under section 5. Study design to the footnote of the flow-chart we added the text:

"* if recent laboratory investigations revealed severe renal (serum creatinin >150 mmol/L) or liver failure (AST > 150 U/l or ALT > 150 U/l or AF > 150 U/l or gamma-GT > 150 U/l), study medication will also be stopped immediately"
Rationale of change: The flow-chart was published online and the footnote was added to specify when tranexamic acid treatment should be halted. Participating centers could use this flow-chart as a guideline for the study.

Amendment 2: Under inclusion criteria we added the word **participating** to study centers and **participating** referring hospital
Rationale of change: We added this to the inclusion criteria because there were some protocol violations in the beginning of the trial regarding inclusions from hospitals that were not participating in the trial.

Amendment 3. In the exclusion criteria section the word "History of " was added to exclusion criteria several renal and liver failure.
Rationale of change: Since ultra-early start with TXA treatment could substantially be delayed for over 30 minutes because in most participation centers for the results of the blood examinations took more time.

Amendment 4. Under section 9.4 Withdrawal of individual subjects the following was added
"4) recent laboratory investigations reveal severe renal (serum creatinin >150 mmol/L) or liver failure (AST > 150 U/l or ALT > 150 U/l or AF > 150 U/l or gamma-GT > 150 U/l)"
Rationale of change: see, amendment 1.

SUBSTANTIAL AMENDMENT 3, PROTOCOL VERSION 5

Amendment 1. Add new exclusion criteria: "No proficiency of the Dutch or English language"
Rationale of change: We added this criterion since patient information forms were only available in Dutch and English.

Amendment 2. Added under exclusion criteria the following text:
"Since a majority of the patients arrive at the hospital with decreased consciousness on admittance and the study is being executed based on the emergency procedure, exclusion criteria that cannot be determined on admittance are considered to be absent. These criteria will be checked later and if present, will be acted upon (see paragraph 9.4)."
Rationale of change: In our trial we wanted to randomize patients as soon as possible after the diagnosis of subarachnoid hemorrhage was confirmed by CT, even though some exclusion criteria

could still be unknown. If afterwards it turned out that patients still complied with one or more of the exclusion criteria, the tranexamic acid administration was immediately stopped, but patients remained in the study.

Amendment 3. 9.3 Study procedures
Assess the health-care costs and quality of life at **three** and six months after SAH
Rationale of change: to correctly interpret the health-care cost and improvement of quality of life questionnaire we added an additional measurement point in time.

Amendment 4. 9.4. Withdrawal of individual subjects
"If it is revealed after inclusion, that one of the exclusion criteria was present in a certain patient at admittance, this patient remains included in the study and this is recorded as a protocol violation. Depending on the criterion, actions are undertaken. For instance, TXA may be stopped (perimesencephalic hemorrhage, traumatic SAH, treatment for deep vein thrombosis or pulmonary embolism, history of a blood coagulation disorder, pregnancy, history of severe renal or liver failure). In case of no proficiency of the Dutch or English language, TXA will not be stopped but an interpreter has to be arranged to be able to perform the informed consent procedure (and the patient information has to be translated)."
Rationale of change: see amendment 2.

Amendment 5. 12.2 Recruitment and consent Added following text: "In consultation with the jurist, some exceptions that are possible on the abovementioned procedure are discussed and a solution is chosen based on both ethical and legal considerations as well as methodological considerations (diminishing of bias). If patients die before the informed consent procedure could be discussed and there is no legally appropriate SDM, no consent is necessary and patients remain included in the study as long as there is no clearly written objection in the chart from the patient against participation in scientific research projects. If patients die and there is a legally appropriate SDM, but there has been no possibility yet to discuss the informed consent procedure, no consent is necessary and patients remain included in the study as long as there is no clearly written objection in the chart from the patient against participation in scientific research projects. In both cases, the reason to deviate from the standard procedure as well as the decision that the patient remains included in the study has to be written clearly in the chart."
Rationale of change: Within the procedure of the urgent procedure protocol, we found it unethical to have caregivers trying to obtain informed consent from next of kin after their loved-one had died, during a period of maximal grief.

SUBSTANTIAL AMENDMENT 4, PROTOCOL VERSION 6

Amendment 1. Under the paragraph 10.2 Adverse and serious adverse events
The following SAE were added to the list: **"**Terson's syndrome", "delirium", "epilepsy", "pneumocephalus", and "perprocedural aneurysm rupture' that may be reported with a line listing every half year
Rational of change: Because of the frequency of occurrence of these disease-related adverse events participating treatment centers were unable to report this within 24 hours, and by adding this to our protocol, centers could report aforementioned, commonly occurring, adverse events every half year to the DSMB by a listing.

SUBSTANTIAL AMENDMENT 5, PROTOCOL VERSION 7

Unsubstantial changes

Amendment 1. The words **"**by line listing" were added to clarify the changed paragraph in 10.2 adverse and serious adverse events

Amendment 2. In paragraph 10.4 DSMB the following sentence was added "Each half year, a line listing will be reported to the METC, and based on this listing, the DSMB will give an advice with respect to continuation of the trial based on this safety evaluation."
Rational of change: Phrases have been added to clarify the procedure to be followed. Previous text was not entirely clear on some points.

SUBSTANTIAL AMENDMENT 5, PROTOCOL VERSION 10

Unsubstantial changes

Amendment 1. The words "and logistics" were added to the table of contents of paragraph 8.7
Amendment 2 . The study coordinator replaced with "sponsor"
Amendment 3. Prof. dr. W.P. Vandertop is, as co-PI with a medical background, responsible for the medical part of this study.
Amendment 4. The exclusion criteria of Pregnancy was revised into:
"Pregnancy checked with a pregnancy test in women in their childbearing period"
Rationale of change: Phrases have been added to clarify the procedure to be followed.
Amendment 5. In paragraph 9.4 Withdrawal of individual subjects, we added the word "pregnancy"
Rational of change: see, amendment 4.
Amendment 6. Under paragraph 10.2 we added the following text: "The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events".

Rationale of change: This was added because of updated regulations of the central committee on Research involving Human Subjects

Amendment 7. The section 10.1 temporary halt for reasons of subject safety was changed into: "In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending further review by the accredited METC. The investigator will take care that all subjects are kept informed."

Radionale of change: see amendment 6.

Substantial changes

Amendment 9. The following sentences were added to Paragraph 8.7

"If a patient is randomized to the TXA group, the treating physician (electronically) prescribes the TXA in their hospital according to standard procedures. TXA will be given from stock on the emergency department, or neuro (intensive) care unit. Charge numbers and expiry dates from the TXA are documented in the study CRF, as well as the initials from the person who administered the TXA." Accountability for the study drug is in accordance to GCP guidelines ", except for stock management. However, for financial purposes, each participating center needs to manage the administered TXA for all patients included in the ULTRA study treatment arm. Yearly, participating centers can send an invoice with respect to costs for TXA to the coordinating center."

Rationale of changes: In order to start ultra-early treatment with TXA, and since the design of our trial was open labelled, we used the locally available TXA from the stock in the emergency department and specified how accountability of the study drug should be monitored. Phrases have been added to clarify the procedure to be followed.

Amendment 9. The sentences "For the present study, an AE is defined according to the definition above. Only AE's during hospital admission that are not related to the subarachnoid haemorrhage must be reported" were added to paragraph 10.2 adverse and serious adverse events.

Rationale of change: Due to the large number of, commonly occurring, AE in our trial we reduced the number or AE that had to be reported after approval of the METC.

SUBSTANTIAL AMENDMENT 6, PROTOCOL VERSION 12

Unsubstantial changes

Amendment 1. In paragraph 9.4 Withdrawal of individual subjects the follow text was added**:** "according to WMO (Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen)), article 6, clause 4."

Substantial changes:

Amendment 2. In the objective section of the summary we added "and/or rebleed volumes" to secondary objectives that TXA reduces in-hospital rebleed volumes
Rationale of change: New computer software became available to perform these volume calculations, therefore, this was added as a secondary objective.

Amendment 3. In Main study parameters/endpoints. "Number and volume" was added to the secondary objective concerning rebleedings.
Rationale of change: see amendment 2.

Amendment 4. Under paragraph 4. Objectives, subparagraph secondary objective(s). We changed the text in the secondary objective: To evaluate whether there is a significant difference in rebleed rate **and volume** before or during aneurysm treatment between the TXA group and the control group
Rationale of change: see amendment 2

Amendment 5. Under paragraph 4. Objectives, subparagraph secondary objective(s). We changed the text in the secondary objective: To evaluate whether there is a difference in (micro)infarctions in **number and volume** on MR imaging at six months after endovascular treatment between the TXA group and the control group
Rationale of change: see amendment 2

Amendment 6. Under paragraph 6.3 Exclusion criteria. We removed the exclusion criteria a history of severe liver failure (AST > 150 U/l or ALT > 150 U/l or AF > 150 U/l or γ-GT > 150 U/l)
Rationale of change: Tranexamic acid is degraded by the kidneys, not the liver and was therefore removed as an exclusion criteria. This is in accordance to the Summary of Product Characteristics of tranexamic acid, as published by the European Medicines Agency (https://www.ema.europa.eu/en/documents/referral/antifibrinolytic-medicines-article-31-referral-annex-iii-tranexamic-acid_en.pdf)

Amendment 7. Under paragraph 8.3 Summary of known and potential risks and benefits. The known adverse events of TXA are described below section was changed into:

- 1% to 10%: gastrointestinal: diarrhea, nausea, vomiting
- 0.1% to 1%: allergic dermatitis
- unknown cardiovascular: arterial or venous thrombosis on each location; ocular: visual impairment

Rationale of change: This section was updated since there was a updated version of the SmPC of tranexamic acid as published by the European Medicines Agency

Amendment 8. Under paragraph 9.1.2 secondary study parameters/endpoints. We added the following definition under cause of poor outcome: "Based on data from the patient file (AMC) or on imaging during admission and discharge letters (other treatment centers). Assessed by the Data Classification Committee. Causes of poor outcome are for instance: related to the primary hemorrhage, related to complications of hemorrhage, related to one of the reported adverse events or unrelated to hemorrhage."
Rationale of change: Clarification of the sources from which the information is obtained and the definitions

Amendment 9. We added the secondary endpoint Rebleed volume to paragraph 9.1.2
Rationale of change: See, amendment 2

Amendment 10. Under paragraph 9.4 liver failure was removed
*Rationale of change***:** see amendment 6

Amendment 11. The bold sentences and words were added under paragraph 11.3 Analyses on primary and secondary outcomes
A secondary analysis will perform an ordinal regression analysis according to a proportional odds assumption on the primary outcome. Furthermore, an as treated and per protocol analysis on the primary outcome will also be performed. The **other** secondary outcome analyses compare several variables between randomization groups: case fatality rate, rebleed **volume and** rate before or during aneurysm treatment, thromboembolic events during endovascular treatment, rate of DCI, rate of complications with subdividing into types of complications, rate of (micro)infarctions **number and volume** at MR imaging, discharge location, health-care costs, quality of life, WFNS grade at admission or gender associated to rebleed rate and favourable outcome. **Independent samples t-test or Mann-Whitney U tests will be used for the group comparisons with respect to volume, whichever is appropriate.** Chi square statistics will be used to calculate an odds ratio, risk ratio, or risk difference. Adjustments for factors that differ at randomization will be made using regression or multi-level models.
For the interim analysis, a Chi-square test evaluating the difference in primary outcome between the groups based on intention-to-treat will be tested including all patients with a 6 months follow-up after randomization of 475 patients. Furthermore, Cochran-Mantel-Haenszel test will be performed as a secondary analysis to evaluate the difference in primary outcome between the groups corrected for the stratification factor treatment center.

Rationale of change: During the trial, the statistical analysis plan was written. Based on the statistical analysis plan we added the pre-specified analysis to the protocol.

Amendment 12. The following text was added to paragraph 12.2 Recruitment and consent:
"If patients from whom their legally appropriate SDM signed the informed consent become mentally competent during hospital stay or during the follow-up period of the study, informed consent will be asked from the patients as well (called informed consent in the second instance). The rationale of the study as well as the study will be explained and an information letter and informed consent will be given or sent to the patients. Written or oral informed consent in the second instance are both considered appropriate, after consultation with the legal expert."
Rationale of change: If patients were not able to sign written consent, a temporary oral consent could suffice after consultation with the legal authorities under strict conditions. In a second instance, written consent was obtained.

ULtra-early TRranexamic Acid after Subarachnoid Hemorrhage (ULTRA) trial: Statistical analysis plan

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Keywords
Statistical Analysis Plan – ULTRA - Subarachnoid hemorrhage – Tranexamic Acid

ABSTRACT

Background:

Recurrent bleeding from an intracranial aneurysm after subarachnoid hemorrhage (SAH) is associated with unfavorable outcome. Recurrent bleeding before aneurysm occlusion can be performed occurs in up to one in five patients, and most often happens within the first six hours after the primary hemorrhage. Reducing the rate of recurrent bleeding could be a major factor in improving clinical outcome after SAH. Tranexamic acid (TXA) reduces the risk of recurrent bleeding but has thus far not shown to improve functional outcome, probably because of a higher risk of delayed cerebral ischemia (DCI). To reduce the risk of ultra-early recurrent bleeding, TXA should be given as soon as possible after diagnosis and before transportation to a tertiary care center. If TXA is given short, i.e. less than 24 hours, it may not increase the risk of DCI. The aim of this paper is to present in detail the statistical analysis plan (SAP) of the ULTRA trial (**ULtra-early TRranexamic Acid after Subarachnoid Hemorrhage)**, which is currently enrolling patients and investigates whether ultra-early and short-term TXA treatment in patients with aneurysmal SAH (aSAH) improves clinical outcome at six months.

Methods/design:

The ULTRA trial is a multicenter prospective, randomized, open, blinded endpoint (PROBE) parallel group trial, currently ongoing at eight tertiary care centers and seventeen of their referral centers in The Netherlands. Participants are randomized to standard care or to receive TXA at a loading dose of 1 gram, immediately followed by 1 gram every eight hours for a maximum of 24 hours, in addition to standard care, as soon as the SAH is diagnosed. In the TXA group, TXA administration is stopped immediately prior to treatment (coil or clip) of the causative aneurysm. Primary outcome is the modified Rankin Scale (mRS) score at six months after SAH, dichotomized into good (mRS 0-3) and poor (mRS 4-6) outcome, assessed blindly to treatment allocation. Secondary outcomes include case fatality at discharge and at six months and causes of poor clinical outcome. Safety outcomes are recurrent bleeding, DCI, hydrocephalus, per procedural complications and other complications such as infections occurring during hospitalization. Data analyses will be according to this pre-specified SAP.

Trial registration

The trial has been registered at the Netherlands Trial Register on 25 January 2012 (NTR3272, https://www.trialregister.nl/trial/3122) and ClinicalTrials.Gov (NCT02684812, https://clinicaltrials.gov/show/NCT02684812) on 17 February 2016.

Keywords

Subarachnoid hemorrhage, Intracranial aneurysm, Tranexamic acid, Clinical outcome, Recurrent bleeding, Statistical analysis plan

Background

Subarachnoid hemorrhage (SAH) accounts for 5% of all strokes and has an incidence of 7.9 per 100.000 person-years(1). Only 25% of all patients with aneurysmal SAH have a favorable outcome, and even then, most of these patients still have severe cognitive dysfunctions and functional disabilities(2). The case fatality in SAH is approximately 35% due to the initial hemorrhage or subsequent complications. A frequent complication and one of the major causes of death and disability is a recurrent bleeding from the aneurysm, which occurs in 4-12% of patients who reach the hospital within the first 24 hours(3-9). The percentage of recurrent bleeding increases to 17%, if the recurrent bleedings presenting within the first six hours after the primary hemorrhage ("ultra-early recurrent bleeding") are also counted in(7, 10). In daily clinical practice, aneurysm treatment is often postponed by either a delay in diagnosis or by transfer to a tertiary treatment center(11-13). Therefore, despite several efforts to improve the logistic processes, ultra-early recurrent bleeding still occurs before the aneurysm is secured. A strategy additional to early aneurysm occlusion to reduce the number of recurrent bleedings, is treatment with antifibrinolytic agents prior to aneurysm occlusion. Results from previous, non-randomized studies using early and short-term administration of antifibrinolytics showed reduction of recurrent bleeding without an increase in delayed cerebral ischemia (DCI)(3, 6, 14, 15). The only randomized controlled trial of early (< 48 hours) and short-term (< 72 hours) TXA treatment confirmed a reduction in recurrent bleeding, but did not assess the occurrence of DCI and was underpowered to show an effect on clinical outcome(3). We therefore performed a sufficiently powered randomized clinical trial in which (TXA) is administrated ultra-early (as soon as possible and at least within the first 24 hours after the primary hemorrhage) and for an ultra-short time period (<24 hours) in to reduce the risk for the occurrence of DCI. The ULTRA trial is a multicenter, phase III, randomized, controlled, open-label, blinded end-point (PROBE) trial, performed in eight tertiary care centers and seventeen of their referral centers in the Netherlands (see appendix for list of participants). We published the ULTRA trial protocol previously (16), and now describe the statistical analysis plan (SAP).

Objectives

The primary aim of the ULtra-early TRanexamic Acid after subarachnoid hemorrhage (ULTRA) trial is to evaluate whether ultra-early and short-term TXA treatment improves clinical outcome after six months in patients with a SAH.

Methods/design

Trial protocol development and conduct

The ULTRA trial is registered at the Netherlands Trial Register (NTR3272; date of registration 25 January 2012) and Clinicaltrials.gov (2012-000343-26; registered on 17 February 2016). The ethics committee of the Amsterdam University Medical Centre (Amsterdam UMC, the Netherlands) approved the trial protocol on 6 September 2012, starting with two treatment centers and one referral center. Six

treatment centers and sixteen referral centers joined the study at a later date. The local accredited ethics committee of each participating hospital approved the local feasibility of the study protocol. During the course of the study, the accredited ethics committee approved three amendments with respect to changes in the in- and exclusion criteria. The study was conducted according to the principles of the Declaration of Helsinki, Dutch legislation regarding medical research involving human subject(17-20) and good clinical practice (GCP) guidelines(21). Since the majority of patients will not be able to give informed consent at admission, the informed consent procedure for this study is delayed in a so-called emergency procedure as described previously (16). All study sites were monitored by an independent clinical research associate of the Amsterdam UMC Clinical Research Unit (Amsterdam, the Netherlands). An independent data and safety monitoring board (DSMB) monitored the study's progress, with a special focus on safety (see below). The trial will be reported according to the Consolidated Standard of reporting Trials (CONSORT) guidelines(22).

In- and exclusion criteria are described in the previously published study protocol (16). Adult patients with a SAH, diagnosed by non-contrast computed tomography (CT) within 24 hours after the last hemorrhage, were included. During the trial, 'no proficiency of the Dutch or English language' and 'treatment for pulmonary embolism' were added to the exclusion criteria, whereas severe liver failure was removed from the exclusion criteria after consultation with the vascular internists. All changes were submitted as protocol amendments to the accredited ethics committee and approved.

Randomization and data collection

Patients are randomly allocated in a 1:1 ratio to either receive ultra-early TXA treatment or standard care, stratified by treatment center. TXA is administered as a loading dose of 1 gram, immediately followed by 1 gram every eight hours for a maximum of 24 hours, in addition to standard care, as soon as the SAH is diagnosed. In the TXA group, TXA administration is stopped immediately prior to treatment (coil or clip) of the causative aneurysm. To ensure allocation concealment, the randomization sequence was generated by using GCP compliant ALEA® ((https://nl.tenalea.net/amc/ALEA/) randomization software. Randomization was controlled in each treatment center and web-based, using a dedicated, password-protected, SSL-encrypted website. Data management was implemented according to GCP guidelines. Patients data until hospital discharge and six months follow-up data are entered via an electronic case record form in a central GCP proof web-based database to facilitate on-site data entry (Oracle Clinical®, Redwood Shores, CA, USA, OpenClinica LCC and collaborators, open source software, version 3.6, Waltham, MA, USA, www.OpenClinica.com and Castor Electronic Data Capture, Ciwit BV, Amsterdam, The Netherlands, 2018, www.castoredc.com). Security is guaranteed with login names, login codes and encrypted data transfer.

Primary outcome

The primary outcome is clinical outcome at six months measured with the modified Rankin Score (mRS) by a standardized and validated telephone interview, performed by a trained research nurse who was

blinded to treatment allocation(23, 24). The mRS is dichotomized into good (mRS 0-3) and poor (mRS 4-6) outcome (25) (23).

Secondary outcomes

Secondary outcomes include mRS score dichotomized into good (mRS scores 0-2) and poor (mRS 3-6) outcome, ordinal mRS score at six months, case fatality at discharge and at six months, causes of poor outcome (directly related to primary SAH, related to a complication of the SAH, related to a complication of treatment, related to another complication).

Safety

Safety outcomes were classified as follows:

1. Complications of SAH (recurrent bleeding, hydrocephalus, DCI)
2. Complications of treatment (per procedural thromboembolic complication, Infarct related to procedure, per procedural rupture)
3. Other complications (extra cranial thrombosis (deep venous thrombosis, pulmonary embolism), hemorrhagic complications, severe hyponatremia, pneumonia, meningitis, urinary tract infection, epilepsy, delirium, and Terson's syndrome)
4. Suspected unexpected serious adverse drug reactions (SUSARs); and
5. Other serious adverse events (SAEs)

Investigators recorded all SAEs during first hospital admission after ictus and reported any adverse event during first hospital admission after ictus that was not related to SAH.

Although there are more secondary endpoints, this statistical analysis plan will focus solely on the clinical (mRS scores, and case fatality) and safety (complications of SAH, complications of treatment, other complications, SUSARs, and other SAEs) secondary endpoints.

Statistical methods specified in the study protocol

Sample size calculation

As described in the study protocol(16) the primary endpoint analysis of this study is based on the difference in percentage of patients with good outcome (mRS score 0 to 3) at six months after SAH between patients with and without TXA treatment. It is expected that TXA administration will increase the proportion of patients with a good outcome from 69% to 77.1%.

This expected difference between the TXA, and Standard Care group was estimated using the results of renowned SAH studies and our own data (293 consecutive aneurysmal SAH patients, added with angiogram-negative SAH patients, treated at the AMC between 2008 and 2011). Of all SAH patients,

who reach the hospital, 69% have a good outcome (own data). In our data we find a recurrent bleeding rate of 17%, which is consistent with numbers reported in previous studies (11% to 22%)(3, 6, 8). For patients with recurrent bleeding, an estimated 20% will have a good outcome. Consequently, the percentage of patients with a good outcome without recurrent bleeding is 79%. In the TXA group, the reduction in recurrent bleeding is expected to be 77%(3, 6), which reduces the rate of recurrent bleeding to 3.9%. Furthermore, TXA is anticipated to improve the percentage of good outcome in patients with recurrent bleeding from 20% to 30%(3). Therefore, in the TXA group, 3.9% will have recurrent bleeding, of which 30% will have a good outcome.A two-group chi-square test with a 0.05 two-sided significance level will have 80% power to detect the difference between a Standard Care group proportion of 0.69 and a treatment group proportion of 0.771 (odds ratio of 1.513) when the sample size in each group is 470 (940 patients in total). Taking some withdrawals into account, a total of 950 patients will be included.

Originally proposed analyses

In the previously published protocol (16), the originally proposed analyses are described, focusing on the intention-to-treat (ITT) analysis. In the paragraphs below, the final and further detailed SAP is presented, including as-treated (AT) and per-protocol (PP) analysis because use of open-label TXA may modulate possible treatment effects.

Interim analysis and safety reporting

A data safety monitoring board (DSMB) was installed for this study to protect patients and advise the principal investigator in protection the safety, validity and credibility of the trial. Members include a clinically experienced neurologist/epidemiologist, an intensivist and a statistician. The members were not involved in the trial and had no competing interests. The tasks, responsibilities and working procedures of the DSMB were described in a charter.

The DSMB performed ongoing safety surveillances (every six months), especially with regard to the occurrence of SAEs in terms of increased ischemic events and serious extra cranial thrombotic events, such as pulmonary embolism. Every six months, the DSMB receives a report, prepared by an independent statistician, that includes data by treatment groups on primary outcome, predefined safety outcomes, other SAEs, and SUSARs. The DSMB also checks the assumptions for sample size calculations, without performing statistical analysis. Additionally, the DSMB performed one interim analysis of unblinded effectiveness data during the study. This interim analysis was performed after inclusion of 475 patients in the trial, to assess the strength of the efficacy data when half of the patients are enrolled.

The DSMB can recommend the Steering Committee of the ULTRA trial to:

• adjust conduct, design, or sample size

• terminate the study prematurely when there is clear and substantial evidence of benefit

The justifications for a recommendation to terminate the study due to clear benefit will be based on pre-specified stopping boundaries for the primary endpoint of the study (the score on the mRS at six months). As a stopping rule the Haybittle-Peto(26, 27) method will be used: interim efficacy analyses 1 (n = 475): p = 0.001; final efficacy analyses (n = 950): p = 0.05.

• terminate the study prematurely when there is evidence of severe harm

The justifications for a recommendation to terminate the study due to clear harm will be based on data showing a notably increase of (serious) adverse events (including case fatality) in the intervention group. No pre-specified formal statistical stopping rule for safety is formulated.

• terminate the study prematurely in case accrual rates are too low to provide adequate statistical power for identifying the primary endpoint

If one or more of these situations occurred, the clinical relevance of the results will be incorporated into the decision whether to end the trial prematurely.

Statistical analysis plan

Overall principles

The database will not be unlocked until data regarding efficacy and safety from all patients have been included in the database, after data verification and validation are performed and after the SAP has been submitted for publication. The data analysis will start after the six months' follow-up data of the last included patient has been obtained. Analysis of the primary outcome will be performed according the ITT principle. Given the possible bias of open-label TXA treatment, primary outcome analysis will also be done in an AT population and a PP population to check the robustness of the main analysis, irrespective of the presence of statistical significance in the overall analysis. Secondary outcomes will be analyzed in the ITT population, except for the main secondary outcome, mortality at discharge and at six months, which will be analyzed in the ITT, AT, and PP population. Safety outcomes will be analyzed in the ITT and AT population. Statistical analyses will be done by the investigators of the ULTRA trial group (see Acknowledgements section). Statistical uncertainty will be expressed in a two-sided 95 % confidence interval (CI). Statistical analyses are performed using the SPSS Statistics Software (IBM Corporation, New York, United States, version 25).

Handling of missing data

In case of missing data, every attempt will be undertaken to retrieve the data. Because lost to follow-up is expected to be very low (< 1% missing data on the primary outcome), outcome data will not be imputed. We will state which data are missing and calculate frequencies using the total number of patients with available data. When a patient is lost to follow-up missing his/her 6-months mRS score, this patient cannot be included in the analysis of the primary outcome. If possible, these patients will be

included in the secondary outcome analyses. When a patient has withdrawn consent, we will use all available data up until withdrawal of consent(28).

Definition of analysis sets (Appendix 1)

Intention-to-treat population

All randomized patients will be analyzed in the treatment group to which they were originally allocated, irrespective of non-adherence or deviations from protocol.

As-treated population

Patients will be analyzed in groups according to treatment received, irrespective of allocated treatment at randomization, thus creating a group that received at least one dose TXA (intervention) and a group that did not (control). The patients will still be included in the AT analysis if there was a protocol violation (e.g. TXA administration not according to study protocol, or not meeting inclusion or exclusion criteria).

Per-protocol population

In the PP population, patients allocated to the Standard Care group who did not receive TXA will be included, as well as patients allocated to the TXA group who received TXA (at least one dose). The patients will still be included in the PP analysis if there was a protocol violation.

Statistical analyses

Patient flow

The flow of participants will be displayed in the Consolidated Standard of Reporting Trials (CONSORT) Flow diagram (Figure 1), including the total number of randomized patients and then showing per treatment group the numbers receiving allocated treatment, withdrawing consent, and lost to follow-up.

Protocol deviations

When a patient is randomized but does not adhere to inclusion or exclusion criteria, this is considered a protocol deviation regarding eligibility. When a patient is allocated to the Standard Care group but does receive TXA, or when the patient is allocated to the TXA group but medication administration is not according to the protocol, this is considered a protocol deviation with respect to administration of medication.

Protocol deviations will be line-listed in an appendix.

Baseline characteristics

The baseline characteristics of all participants in each treatment group according to allocation will be outlined in a table without formal statistical testing. The table will describe the following variables: age,

sex, World Federation of Neurosurgical Societies (WFNS) score, Fisher grade on non-contrast CT on initial (baseline) scan, medication use prior to SAH (antiplatelet therapy, anticoagulants, antihypertensive drugs), location of aneurysm and treatment modality. Baseline variables will be summarized using simple descriptive statistics. Continuous, normally distributed variables will be expressed as means and standard deviations; continuous, non-normally distributed and ordinal variables as medians (25^{th}-75^{th} percentiles) and categorical variables as counts and percentages. Normality of data will be explored by a normal Q-Q plot and tested by the Shapiro-Wilk test.

Primary outcome

The main statistical analysis will be based on the intention-to-treat principle. The occurrence of the primary outcome, dichotomized mRS score at six months (good versus poor as mRS 0 to 3 versus mRS 4 to 6, respectively), will be compared between the two treatment groups. The distribution of the mRS scores in both treatment groups will be depicted in a histogram. Treatment effect will be expressed in a difference in proportions with corresponding 95% CI, and an odds ratio (OR) estimate, with corresponding 95% CI. Additionally, we will analyze the treatment effect on the dichotomized mRS score, using multivariable logistic regression, adjusting for the stratification variable (treatment center) and, if necessary, clinically relevant baseline imbalances. Effect size will be expressed as an adjusted OR (aOR). The crude and adjusted analyses will also be performed in both the AT and PP populations.

Sensitivity analyses

Dichotomized mRS score is chosen as primary outcome because results from the analysis are straightforward and easy to interpret. However, it is also clear that the cut-off is arbitrarily chosen and information is lost by dichotomization. Ordinal analysis of outcome data is becoming increasingly more common in acute stroke trials, as it increases statistical power(29).

"Sensitivity analyses play a crucial role in assessing the robustness of the findings or conclusions based on primary analyses of data in clinical trials. They are a critical way to assess the impact, effect or influence of key assumptions or variations—such as different methods of analysis, definitions of outcomes, protocol deviations, missing data, and outliers—on the overall conclusions of a study."(30)

Therefore, two sensitivity analyses will be performed: first, the dichotomized mRS using the cut-off frequently used in stroke (good outcome: mRS scores 0-2) will be analyzed using the same analysis as described by the primary outcome; second, the ordinal mRS score will be analyzed using an ordinal regression model on the total range of the mRS, under the assumption of proportional odds. If the assumption of ordinal regression does not hold, we will perform sliding dichotomy analysis(31).

When the lost to follow-up rate is >10%, a third sensitivity analysis will be performed. Data will be analyzed according to a worst case scenario, i.e. patients lost to follow-up in the treatment group will have the worst possible outcome and patients in the Standard Care group will have the best possible outcome**.**

Secondary outcomes

The secondary outcome analyses will compare case fatality at discharge and at six months, causes of death or poor outcome at six months and all safety outcomes between treatment groups. The statistical analysis will also be based on the ITT principle. Treatment effect will be expressed in a difference in proportions with corresponding 95% CI, and an odds ratio (OR) estimate, with corresponding 95% CI. The analyses for the main secondary outcome, mortality at 30 days and at six months, will also be performed in both the AT and PP population. The analyses for the safety outcomes will also be performed in the AT population.

Trial status

Initially, two treatment centers started recruitment between July 2013 and February 2014, and six additional treatment centers started recruitment between April 2014 and September 2016. A total of 17 referral centers started recruitment between July 2013 and November 2018. All participating centers are in the Netherlands. Currently, we enrolled 935 patients.

Abbreviations

a**SAH aneurysma** subarachnoid hemorrhage **TXA** Tranexamic acid, **DCI** delayed cerebral ischemia, **SAP** statistical analysis plan, **PROBE** prospective randomized open blinded endpoint, **mRS** modified Rankin Scale, **GCP** good clinical practice, **CONSORT** consolidated Standard of Reporting Trials, **CT** computed tomography, **WFNS** World Federation of Neurosurgical Societies **SUSAR** Suspected Unexpected Serious Adverse Reaction, **AE** Adverse Event, **IIT** intention to treat, **AT** as treated, **PP** per protocol, **DSMB** Data Safety Monitoring Board

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Authors´ contributions

RP, conception and design, acquisition of data, statistical analysis and interpretation of data, drafting the article, critically revising the article, reviewed submitted version of manuscript, approved the final version of the manuscript

MRG, conception and design, critically revising the article, reviewed submitted version of manuscript, approved the final version of the manuscript

BAC, critically revising the article, reviewed submitted version of manuscript, approved the final version of the manuscript

GJER, conception and design, critically revising the article, reviewed submitted version of manuscript, approved the final version of the manuscript

WPV, conception and design, critically revising the article, reviewed submitted version of manuscript, approved the final version of the manuscript

DV, conception and design, critically revising the article, re-viewed submitted version of manuscript, approved the final version of the manuscript

Competing interests

The authors declare that they have no competing interests.

Ethical approval and consent to participate

We obtained research ethics committee approval before patients were enrolled from: the Academic Medical Centre Ethics Committee (MEC NL39577.018.12) in The Netherlands on 6 September 2012; The trial was conducted according to the principles of the Declaration of Helsinki and national laws, such as the Medical Research involving Human Subjects Act (WMO) in The Netherlands. Potential participants or their legal representatives were provided with written information in their native

language explaining the trial, consequences of participation, and a statement saying participation was voluntary and refusal to participate would not change medical treatment. Collaborating clinicians at each hospital site recruited participants and obtained written informed consent from the participant or their legal representative.

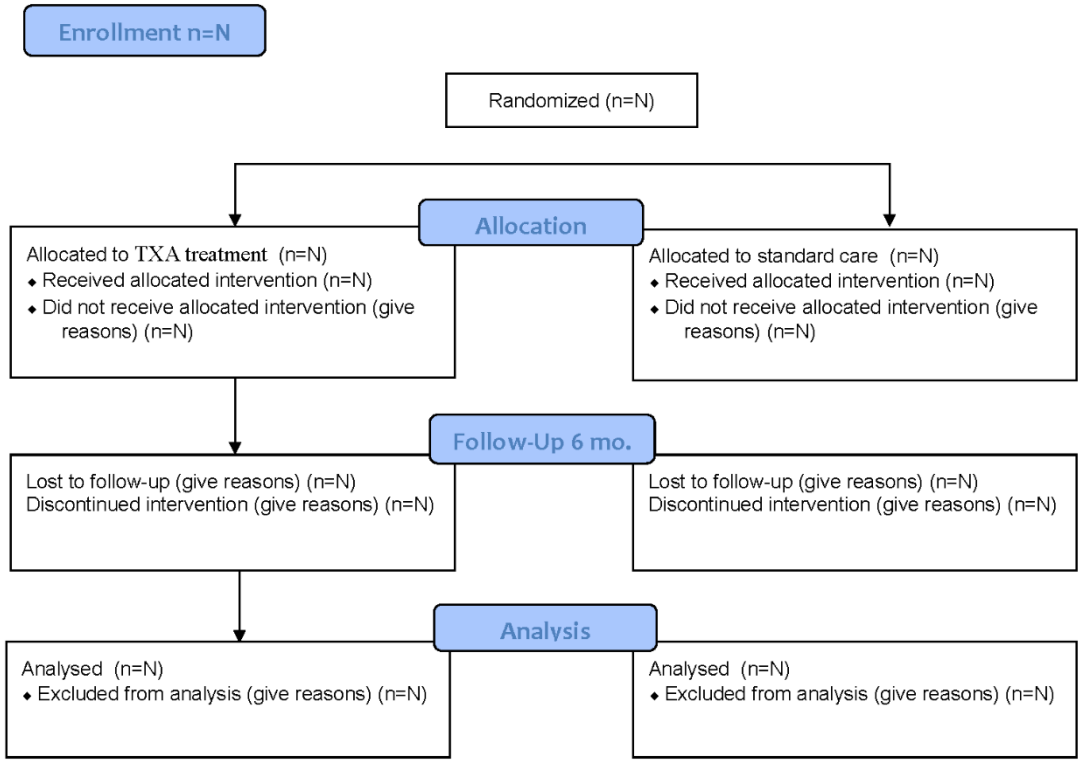
Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Figure 1. Trial allocation profile (CONSORT)



Appendix 1. Definition of population analysis sets

Analysis population	**TXA Group**	**Standard Care Group**
Intention to treat ('as randomized')	Patients randomized to TXA group: • Including all protocol deviations	Patients randomized to standard care group: • Including all protocol deviations
As treated ('actual treatment')	Patients who received TXA (at least one dose), regardless of allocated treatment at randomization: • Including patients who received TXA as described according to protocol • Including patients who received TXA not following protocol (protocol deviation) • Including patients with other protocol deviations	Patients who did not receive TXA, regardless of allocated treatment at randomization: • Including patients who received standard care as described according to protocol • Including patients who received standard care not following protocol (protocol deviation) • Including patients with other protocol deviations
Per protocol	Patients randomized to TXA group who received TXA (at least one dose): • Including patients who received TXA as described according to protocol • Including patients who received TXA not following protocol (protocol deviation) • Including patients with other protocol deviations	Patients randomized to Standard Care group who did not receive TXA: • Including patients who received standard care as described according to protocol • Including patients who received standard care not following protocol (protocol deviation) • Including patients with other protocol deviations

***TXA* Tranexamic acid**

Table 1. Baseline characteristics of participants prior to randomization

	TXA Group *(N = XXX)*	**Standard Care Group** *(N=XXX)*
Age (years), *mean (SD)*	NN. N (NN.N)	NN. N (NN.N)
Female, *n (%)*	NNN (X)	NNN (X)
WFNS		
I, *n (%)*	N (X)	N (X)
II, *n (%)*	N (X)	N (X)
III, *n (%)*	N (X)	N (X)
IV, *n (%)*	N (X)	N (X)
V, *n (%)*	N (X)	N (X)
Fisher Grade Score		
II, *n (%)*	N (X)	N (X)
III, *n (%)*	N (X)	N (X)
IV, *n (%)*	N (X)	N (X)
Medication prior to SAH		
Platelet inhibitor, *n (%)*	N (X)	N (X)
Anticoagulation, *n (%)*	N (X)	N (X)
Antihypertensive, *n (%)*	N (X)	N (X)
None, n (%)	N (X)	N (X)
Location of aneurysm		
Anterior circulation, *n (%)*	N (X)	N (X)
Posterior circulation, *n (%)*	N (X)	N (X)
None, *n (%)*	N (X)	N (X)
Treatment modality		
Endovascular, *n (%)*	N (X)	N (X)
Clipping, *n (%)*	N (X)	N (X)
None, *n (%)*	N (X)	N (X)

Data presented as mean (range), n (%), or median (IQR), unless noted otherwise. WFNS = World Federation of Neurosurgical Societies. *Stratification variable.

Figure 1. Primary outcome (mRS score at 6 months)

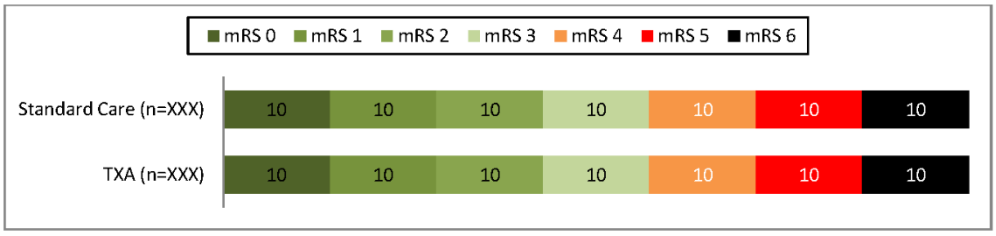


Table 2. Primary outcome (mRS score at 6 months) and secondary outcomes

	IIT			
	TXA Group	Standard Care Group	OR (95% CI)	aOR (95% CI)
mRS 0-3	XX	XX	XX (XX-XX)	XX (XX-XX)
Mortality at 30 days	XX	XX	XX (XX-XX)	XX (XX-XX)
Mortality at six months	XX	XX	XX (XX-XX)	XX (XX-XX)

Table 3. Sensitivity analysis

	IIT			
	TXA Group	**Standard Care group**	**OR (95% CI)**	**aOR (95% CI)**
Excellent outcome (mRS 0-2)	NN (X %)	NN (X %)	X.XX (X.XX–X.XX)	X.XX (X.XX–X.XX)
Ordinal shift mRS) **mRS0** **mRS1** **mRS2** **mRS3** **mRS4** **mRS5** **mRS6**	NN (X %)	NN (X %)	X.XX (X.XX–X.XX)	X.XX (X.XX–X.XX)

Data are n (%), mean (SD) or median (IQR). OR=odds ratio, NA=not applicable.

Table 4: Safety outcomes occurring during hospital admission

	IIT		
	TXA group *(n=xx)*	**Standard care group** *(n=xx)*	**OR(95% CI)**
Any SAE, *n* (%)	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Recurrent bleeding	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Hydrocephalus	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Delayed Cerebral Ischemia	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Trombo-embolic complications during treatment Coiling, *n (%)*	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Infarct related to procedure Clipping, *n (%)*	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Procedural rupture Coiling, *n (%)* Clipping, *n (%)*	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Extracranial thrombosis	NN (X)	NN (X)	X.XX (X.XX–X.XX)
- DVT	NN (X)	NN (X)	X.XX (X.XX–X.XX)
- PE	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Hemorrhagic complication	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Severe hyponatriemia	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Pneumonia	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Meningitis	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Urinary tract infection	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Epilepsy	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Delirium	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Terson´s syndrome	NN (X)	NN (X)	X.XX (X.XX–X.XX)
SUSARs	NN (X)	NN (X)	X.XX (X.XX–X.XX)
Other	NN (X)	NN (X)	X.XX (X.XX–X.XX)

DVT deep venous thrombosis, **PE** Pulmonary embolism

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