TORCH

Tranexamic acid to prevent OpeRation in Chronic subdural Hematoma

A double-blind, placebo-controlled, multicentre, randomized controlled clinical trial

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Statement of compliance with Regulation (EU) 563/2014

Sponsor D. Verbaan
Title of the clinical trial TORCH: Tranexamic Acid to Prevent Operation in Chronic Subdural Hematoma EU CT Number 2024-514927-40-02

This clinical trial is conducted in full compliance with **Regulation (EU) No 536/2014**, as outlined in **CTR Annex I 17(a)**. All trial procedures adhere to the ethical and scientific requirements established by the regulation to ensure the protection of participants' rights, safety, and well-being, as well as the integrity and reliability of clinical trial data.

Date: 11-03-2025

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Role in the sponsor organization: Professor evidence-based neurosurgery

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CBG	**Medicines Evaluation Board; in Dutch: College ter Beoordeling Geneesmiddelen**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CRF	**Case Record Form**
CSDH	**Chronic Subdural Hematoma; in Dutch: chronisch subdural hematoom**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
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)**
NFU	**Dutch Federation of University Medical Centres; in Dutch: Nederlandse Federatie van Universitaire Medische Centra**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie 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; in Dutch: tranexaminezuur**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Chronic subdural hematoma (cSDH) is a relatively frequently occurring neurological disease, occurring mainly in the elderly. Surgical evacuation of the hematoma is an effective treatment, but is also associated with life-threatening risks. In these old, often frail, patients with multi-comorbidity, surgery also comes with significant risks for future cognitive functioning and, therefore, loss of independency. In five small retrospective series, tranexamic acid (TXA), an antifibrinolytic drug, showed a beneficial effect on the spontaneous resolution of the hematoma and, with that, the necessity for surgery. This randomised, placebo-controlled clinical trial aims to prove the efficacy of TXA.

Objectives: Primarily to evaluate the efficacy of TXA to prevent surgery for cSDH. Secondarily to evaluate the efficacy of TXA to reduce cSDH volume, to reduce neurological impairment (mNIHSS), to reduce the incidence of falling incidents, to improve cognitive functioning (MOCA), to improve performance in activities of daily living (Barthel and Lawton-Brody), to improve functional outcome (mRS), to improve the level of quality of life (SF-36 as the main secondary outcome parameter and the EQ-5D-3L), to reduce the mortality rate and to reduce the use of care and health-related costs (iMCQ and iPCQ).

Study design: Double-blind, placebo-controlled, multicentre, randomized clinical trial.

Study population: All patients, age 50 and above, diagnosed with cSDH for which a conservative treatment is selected as primary treatment strategy.

Intervention: During four weeks, the intervention group will receive oral TXA 500mg twice daily, the control group will receive a placebo twice daily. The TXA or placebo treatment is additional to standard care.

Main study endpoint: The number of patients requiring surgery within 12 weeks after start of treatment.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients will use the study medication twice daily for four weeks. Follow-up is at four, eight and 12 weeks with a standard CT-scan of the head, outpatient clinic visits and four patient-reported questionnaires (at baseline and at 12 weeks). In addition, a telephone interview is performed at two weeks and six months. The outpatient clinic visits are standard care; the third CT-scan, the questionnaires, the telephone interviews and extra clinical tests during the visits are extra for this study. Each patient may benefit from the study if the study medication proves effective in preventing surgery for cSDH, whereas the risk of potential side effects of the medication is slight (e.g. the risk of thromboembolic events is only 0.01-0.1%). Surgery remains a possibility for those patients in whom study medication is not effective.

1. INTRODUCTION AND RATIONALE

Chronic subdural hematoma (cSDH) is a frequently occurring neurological disease of the elderly [1,2] and common in daily neurosurgical practice. It consists of an extracerebral encapsulated collection of mostly liquefied old hematoma, located between the dura and arachnoid. The original small, and often asymptomatic, haemorrhage is caused by rupture of a bridging vein after, often minor, head trauma. Due to generalized cerebral atrophy, increased venous fragility [3], and the more frequent use of anticoagulation therapy, older people are more at risk of developing a cSDH.

During several weeks, the original hematoma is encapsulated by a membrane consisting of weak neocapillaries from where recurrent small bleedings occur. The pathophysiological mechanism is thought to be a problem in the local haemostasis due to fibrin degradation products of the original small hematoma that inhibit further haemostasis in the subdural space [4]. Together with an osmotic draw of water, owing to its high protein content, this results in growth of the hematoma. Therefore, it usually takes several weeks for the cSDH to grow and become symptomatic.

Signs and symptoms arise due to compression of brain tissue. These can be generalised, such as headaches, light-headedness, cognitive disturbances, apathy, somnolence, seizures, frequent falling and depression. Also focal deficits, such as dysphasia, motor weakness or sensory disturbances, can be symptoms of a cSDH.

The current incidence of cSDH is estimated to be 15/100,000 per year [5]. The number of patients with cSDH is expected to increase considerably in the near future due to the continuing growth of the elderly population, and the increase in the use of anticoagulation and anti-aggregation therapy [6]. By 2030, the incidence is expected to rise up to 20/100,000 per year [5], thus making cSDH the most common neurosurgical condition in adults. In The Netherlands, this comes down to 3,600 new patients each year.

Treatment

Treatment options are conservative and surgical. Conservative treatment currently consists of a wait-and-scan policy in which the patient is regularly monitored for neurological deterioration and growth of the hematoma on follow-up imaging. Anticoagulation and antiplatelet therapy is discontinued in low-risk patients, based on individual risk-benefit assessment and the discretion of the treating physician. If the clinical condition of the patient worsens, the indication for surgical evacuation of the hematoma is re-evaluated.

Spontaneous resolution of cSDH with a conservative treatment occurs in approximately 2.5% of patients, and is therefore relatively rare [7]. Of all patients diagnosed with cSDH in The Netherlands, about 50% is primarily treated conservatively [8]. Of these, around 75% still need an operation (own data). If the symptoms are serious or worsen over time, surgical evacuation of the hematoma is currently the designated therapy. This therapy is an effective treatment, but is also associated with life-threatening risks. In these old, often frail, patients with multi-comorbidity, surgery comes with significant risks for future cognitive functioning and, therefore, loss of independency. In a large series of 1205 patients, symptomatic recurrence after surgery was 9%, mortality 2% and unfavourable functional outcome 22% [9].

Outcome measurement

Studies evaluating quality of life and functional outcome with cSDH patients are scarce. The modified Rankin Scale (mRS) score is usually the only clinical outcome parameter [9]. A literature search for quality of life in cSDH results in only two clinical studies. The first used the postoperative mRS, Barthel Index and Sickness Impact Profile as outcome measurements [10]; the second used a pre- and postoperative Karnofski Performance Score [11].

Tranexamic acid

As hyperfibrinolysis is thought to play a role in the liquefaction and enlargement of cSDH, pharmaceutical options to block fibrinolysis have been explored in an effort to eliminate the necessity for surgery [12-18]. The use of tranexamic acid (TXA), an antifibrinolytic drug, has so far been reported in five small series. In the first retrospective series, a total of 21 patients were treated with TXA, of whom three after primary burr hole surgery. In none of these 21 patients, additional surgery was necessary [15]. The second, a prospective pilot study in 14 patients, showed a 41% reduction of cSDH after surgery, and an additional 91% residual volume reduction on CT after 90 days, during oral TXA treatment of 650 mg per day, for a mean (SD) duration of 90 (27) days, without recurrence, re-expansion, or any complicating venous thromboembolisms [16]. The third study, a case report series of three patients treated with 650mg TXA per day for one month after surgery for cSDH, showed no recurrences and thromboembolic complications [14]. The fourth, a case report of one patient successfully treated primarily with TXA, was recently published [17], and finally, in the abstract of a Asian article, the authors conclude that administration of Gorei-San, a Japanese herbal Kampo medicine, combined with TXA has the potential to prevent recurrences of cSDH [18].

With these limited, however promising, data no definitive conclusion can be made regarding the role of TXA in the treatment of cSDH. Therefore, a prospective study evaluating the efficacy and safety of TXA is needed. Currently, two prospective trials (the TRACS study [19] and the TRACE study [20]) are running in an effort to answer this question. The first study, a phase IIb trial with the aim to provide preliminary data required to plan a larger phase III trial, excludes patients using anticoagulants [19]. These patients comprise a significant portion of the cSDH patient population, and therefore, the results of the TRACS study will be difficult to extrapolate to the future care of all cSDH patients. The second study (TRACE) is a randomised, observer blinded trial, investigating the value of treating cSDH patients with TXA after surgery [20]. This is a different patient population than proposed in our trial, in which we plan to include only patients in whom the primary treatment is conservative. Also, both trials are set up with a primary radiological outcome parameter and therefore potentially provide insufficient clinically relevant information.

Our phase III trial aims to investigate the efficacy and safety of TXA as an addition to a primary conservative treatment of cSDH, in an effort to prevent surgery for cSDH. Since surgical treatment under general anaesthesia and a hospital admittance of a minimum of two days is associated with significant morbidity, as described earlier [9], we assume that preventing surgery also prevents deterioration of patients' quality of life. To our knowledge, this trial is also the first in describing functional outcome and quality of life of cSDH patients in a prospective manner. Since the target population partially comprises patients with a depressed level of consciousness, and patients using anticoagulants and antiplatelets, these patient groups will be included in this trial as well.

2. OBJECTIVES

Primary objective

To evaluate whether patients with TXA treatment compared to placebo

1. need to undergo surgery for cSDH within 12 weeks after start of treatment less often.

Secondary objectives

To evaluate whether patients with TXA treatment compared to placebo

2. need to undergo surgery less often for cSDH within six months after start of treatment;
3. have a lower cSDH volume at four, eight and 12 weeks on follow-up CT scan of the head;
4. have less neurological impairment at four, eight and 12 weeks, measured with the modified National Institutes of Health Stroke Scale (mNIHSS) score;
5. have less falling incidents during the six month study period;
6. have a better cognitive functioning at four, eight and 12 weeks, measured with the Montreal Cognitive Assessment (MOCA) test;
7. have a better performance in activities of daily living at 12 weeks and six months, measured with the:
   a. Barthel Index scale;
   b. Lawton-Brody scale;
8. have a better functional outcome at 12 weeks and six months after start of treatment, measured with the modified Rankin Scale (mRS) score;
9. have less deterioration of quality of life at 12 weeks and six months after start of treatment, measured with the:
   a. Short Form Health Survey (SF-36) questionnaire (main secondary outcome parameter);
   b. five dimensional EuroQol (EQ-5D-3L) questionnaire;
10. have a lower mortality rate at 12 weeks and six months;
11. have less use of care and health-related costs during the six month study period, measured with the
    a. Medical Consumption Questionnaire (iMCQ);
    b. Productivity Cost Questionnaire (iPCQ).

3. STUDY DESIGN

Design

Double-blind, placebo-controlled, multicentre, randomized clinical trial. As this study will be a registry study, we consulted the Medicines Evaluation Board (CBG) for scientific advice and the CBG approved the design of this study (see attachment K1).

Duration

11 years

Setting

All patients, who are diagnosed with a cSDH and are referred to a neurosurgeon or neurologist dedicated to this study, are tested for eligibility for study participation. Referral is done either by a clinical transfer to a neurological/neurosurgical ward or a visit to the neurological/neurosurgical outpatient clinic. To ensure that all cSDH patients are referred, even without neurological symptomatology, this study will be promoted by notifying all referring neurologists and by an advertorial in the Dutch Journal of Medicine (paragraph 12.6). Treatment strategy, either primarily surgical or primarily conservative, will be decided on the basis of clinical and radiological parameters, in accordance with current standards. Inclusion will be performed after a definite conservative treatment is decided; if the patient meets the inclusion criteria; if the patient does not meet any of the exclusion criteria; and if informed consent is obtained. Follow-up is performed with frequent outpatient clinic visits, together with the standard conservative treatment and follow-up. Both mentally competent and patients with a depressed level of consciousness are eligible for inclusion. Also, high-risk patients using anticoagulation can be included into the study.

Justification of the design

As described in paragraph 6, safety and efficacy data of TXA in both intra- and extracranial bleeding patients is amply available to justify this phase III trial. Patients with major symptoms and/or a midline shift of >10mm caused by the cSDH, as defined in paragraph 4, are excluded from the study, since surgical treatment should not be withheld in these patients. Patients using anticoagulants are not excluded form study participation, because these patients comprise a large part of the target population, and therefore it would be difficult to extrapolate the results of this study to the total group of patients with cSDH.

Anticoagulation and/or antiplatelet use

Conform standard care, patients using this medication for indications with a low risk of thromboembolic complications are advised to discontinue use. Patients using anticoagulants for indications with a high thromboembolic risk are advised to continue the medication, next to the study TXA or placebo treatment. Concomitant use of TXA in patients treated with anticoagulation is not expected to lead to an increased risk of thromboembolism, as any prothrombotic effect of TXA is sufficiently mitigated by the anticoagulation itself. This is analogous to the continued use of oral contraceptive pills in women with recent venous thromboembolism who also use oral anticoagulation. While an oral contraceptive is associated with a 3-7 fold increased risk of venous thromboembolism in non-anticoagulated women, there is no risk increase at all in women treated with oral anticoagulation. Since the study is randomised and placebo-controlled, decisions of re-initiation of anticoagulant will nog be influenced by the intervention, allowing for an unbiased assessment of the effect of the investigated treatment. Concomitant use of TXA and anticoagulation for this study is endorsed by the CBG.

Inclusion protocol

If the patient is eligible for the study according to the in- and exclusion criteria, informed consent will be asked by the attending physician. If the midline shift is >5mm, then the judgement of a second independent neurologist/neurosurgeon (not involved in the execution of the study) is required. Study information will be provided in word and writing and ample time and opportunity will be given for inquiring about details of the trial and for consideration to participate. Inclusion is performed as soon as reasonably possible after the request for study participation. Once informed consent is provided, web-based randomisation will be done, after which administration of the study medication can be started. If a patient has a depressed level of consciousness, the legal representative will be asked to provide informed consent. As soon as the patient becomes mentally competent at a later instance during the 12 week follow-up period, he or she will be asked whether he or she agrees to continue the study participation and if so, to sign the informed consent form as well.

Flow chart

See appendix 14.1

Follow-up schedule

See appendix 14.2

4. STUDY POPULATION

4.1 Population (base)

Adult patients, age 50 and above, with cSDH, as diagnosed by a neurologist and neuroradiologist on CT-imaging of the head, are eligible for participation in the study. On CT-imaging, a cSDH is defined as a uni- or bilateral isodense or hypodense subdural collection, with or without some hyperdense compartments [29]. Inclusion criteria are described in paragraph 4.2.

In the Netherlands, 1,800 patients are diagnosed with cSDH each year [8]. Since this may be an overestimation, a conservative estimate of 1,000 newly-diagnosed patients per year may be realistic. Of these, approximately 50% is primarily treated conservatively [8], and therefore, in the Netherlands, 500 patients per year may be eligible for study participation. Using an existing network of Dutch hospitals and investigators currently collaborating in another prospective multicentre trial [21], 10 centres have signed a letter of intent and are willing to participate in this study, expecting a total of 275 patients to be eligible each year. Analysis of retrospective data of the Academic Medical Center confirms these numbers: of the 52 patients treated in 2015, 30 (58%) would have been eligible for study participation. Of these, 21 (70%) patients eventually needed surgery eventually (own data).

Also, the analysis of our retrospective data showed that all newly-diagnosed cSDH patients are referred to the neurosurgeon (own data). After assessment of the patient by the neurosurgeon, and after the decision is made to follow a primarily conservative treatment, eligibility for study participation is evaluated. If the patient is eligible, inclusion will be performed by the neurosurgeon.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age 50 years and above;
- On CT confirmed cSDH, performed 14 days before inclusion at the latest (for definition, see paragraph 4.1);
- Primary conservative treatment, based on clinical symptoms: Glasgow Coma Scale score >=14, mNIHSS score <=4 and a stable neurological deficit (no new, or progression of, symptoms between the assessment by the neurologist and the assessment by the neurosurgeon).

4.3 Exclusion criteria

A potential subject who meets any of the following criteria is excluded from participation in this study:

- Primary surgical treatment based on one or more of the following symptoms or parameters: medically intractable headache, midline shift >10mm (if >5mm, then judgement of second independent neurosurgeon is required), imminent death within 24 hours;
- Structural causes for subdural haemorrhage, e.g. arachnoid cysts, cortical vascular malformations and a history of cranial surgery <1year;
- Aneurysmal subarachnoid haemorrhage;
- Active treatment for deep vein thrombosis, pulmonary embolism or cerebral thrombosis (secondary prophylaxis is not considered to be active treatment);
- Active intravascular clotting or disseminated intravascular coagulation;
- Known hypersensitivity or allergy to TXA or to any of the ingredients;
- History of a blood coagulation disorder (hypercoagulability disorder);
- History of severe impairment of renal function (serum creatinine >500µmol/L);
- Anamnesis with signs of anaemia;
- History of epilepsy;
- History of inability to safely swallow oral medication.
- Inability to obtain informed consent from the patient or legal representative (when the patient has a depressed level of consciousness as described in paragraph 11.2), including language barrier;

4.4 Sample size calculation

In the Netherlands, approximately 50% of patients with cSDH is primarily treated conservatively [8]. Of these, 75% still need surgery (own data). Since oral TXA is an innovative treatment in these patients, little data is available concerning its efficacy. Until today, only five small studies concerning a total of 39 patients treated with TXA, have been published [14-18]: none of these patients required surgery after start of treatment. As this 100% reduction of surgery may well be an over-estimation of the true effect, a conservative estimate of 33% relative risk reduction was used in the sample size calculation (from 75% surgery in de placebo group to 50% surgery in the TXA group). A Fisher's exact test with a 0,05 two-sided significance level will have 80% power to detect the difference between a control (placebo) group proportion of 0,75 and a

treatment (TXA) group proportion of 0,50 when the sample size in each group is 64 (128 patients in total).
Due to hospital admission, general anaesthesia and (sometimes recurrent) surgery, deterioration of patients' quality of life (QL) is frequently noticed in our elderly target population. Therefore, we consider QL, measured with the SF-36, as an important secondary functional outcome indicator.

With a sample size of 64 patients per treatment arm we are also able the to detect a Cohen's *d* effect size (difference between the mean SF-36 scores of the control group and treatment group divided by the pooled SD) of 0,50. Although an effect size of *d* = 0,50 can be defined as 'moderate' [34], such a difference in mean QL scores may be clinically important.

Anticipating an attrition rate of about 8%, we will include 70 (64/0,92) patients in each group (140 patients in total).

Recently, the DSMB conducted an interim analysis of the first 60 patients. The advice of the DSMB was to increase the sample size to 554 patients. This advice was based on the fact that overall surgery rates are much lower than expected and therefore, the sample size calculation as performed before start of the study cannot be considered reliable. The DSMB suggested to perform the sample size calculation again using the original risk reduction of 33% but based on actual surgery rates, leading to a total sample size of 554 patients. Additionally, the DSMB will monitor safety data and sample size assumptions when follow-up is completed of the first 60 participants. After completion of follow-up of 105 participants a safety analysis will be performed, and after completion of follow-up of 200 participants a safety and efficacy analysis will be performed. . Since the latest efficacy analysis showed an effect of TXA on the primary outcome according to the DSMB, the Steering Committee decided to continue to 554 patients especially after ZonMW, Hersenstichting and a private subsidy provider secured the finances until 2029. A futility analysis will be performed after completion of follow-up of 300 patients.

TREATMENT OF SUBJECTS

4.5 Investigational product/treatment

In randomized patients, oral placebo or TXA 500mg twice daily will be administered for a period of four weeks (28 days), in addition to standard care. One capsule consists of a placebo substance or 500mg TXA. If surgery for the cSDH is necessary, administration of the study medication is stopped directly after surgery. Start of the treatment is within 7 days after inclusion.

4.6 Use of co-intervention (if applicable)

Not applicable.

4.7 Escape medication (if applicable)

Not applicable.

5. INVESTIGATIONAL PRODUCT

5.1 Name and description of investigational product(s)

Tranexamic acid (TXA, Cyklokapron®) is a registered compound for primary hyperfibrinolysis or fibrinogenolysis with a risk of bleeding, secondary fibrinolysis (menorrhagia, prostatectomy and bladder surgery, cervix conisation and tooth extractions with haemophilia A and B) and hereditary angioneurotic edema. TXA forms a reversible complex that displaces plasminogen from fibrin resulting in inhibition of fibrinolysis; it also inhibits the proteolytic activity of plasmin. In the Netherlands, oral administration is possible with tablets consisting of 500mg TXA.

TXA tablets will be overencapsulated by Tiofarma (Oud Beijerland, The Netherlands). See the Investigational Medicinal Product Details (IMPD) in attachment D2 for further details. Placebo capsules without active pharmaceutical ingredient will be developed by Tiofarma with similar appearance to TXA capsules. Information about the capsules can also be found in the IMPD.

5.2 Summary of findings from non-clinical studies

A summary of findings from non-clinical studies can be found in the Summary of Product Characteristics (SPC) in attachment D2.

5.3 Summary of findings from clinical studies

A summary of findings from clinical studies can be found in the SPC in attachment D2. Until today, five clinical series concerning the use of TXA in cSDH patients have been published:

- Kageyama et al [15] describe the primary treatment of 18 patients with TXA for cSDH. Also, three patients were treated with TXA after surgical treatment. No recurrences and complications were observed in all 21 patients. The used dosage of TXA was 750mg once a day for a median duration of eight weeks
- Stary et al [14] describe the treatment of three patients with TXA after surgery for cSDH. No recurrences and complications were observed in all patients. The used dosage of TXA was 650mg once a day for one month
- Tanweer et al [16] describe the treatment of 14 patients with TXA after surgery for cSDH. No recurrences and complications were observed in all patients. The used dosage was 650mg once a day for a median duration of 90 days
- Kutty et al [17] describe the primary treatment of one patient with TXA for cSDH. Resolution of the hematoma was observed and therefore no surgery was necessary.

Also, no complications were observed. The used dosage was 250mg three times a day for six weeks

- Wakabayashi et al [18] describe the treatment of 199 patients with Gorei-San, a Japanese herbal Kampo medicine, and/or TXA after surgery for cSDH. Recurrence rate in the TXA group was 10.9%; in the combination Gorei-San and TXA group 2.9%. Used dosage and complications were not available. The authors conclude that administration of Gorei-San with TXA has the potential to prevent recurrences.

5.4 Summary of known and potential risks and benefits

Opposed to what is commonly thought, TXA has no known prothrombotic effects. It is an anti-fibrinolytic drug that inhibits the action of plasmin. Importantly, several studies with TXA show no increase in fatal or non-fatal vascular occlusive events (1.7% TXA versus 2.0% placebo; RR (95% CI) 0.84 (0.68-1.0)) [23] or death or thrombotic complications (RR (95% CI) 0.92 (0.81-1.05)) [24].

The most common adverse events occur mainly in a short period after start of medication. Known adverse events in patients receiving TXA for various indications are: 1-10%: gastrointestinal: diarrhoea, nausea, vomiting, and TXA-associated seizures, which are dose-dependent and 1.4% (95% CI 0.2-2.5) [25] in the dose described for this study; 0.1% to 1%: allergic skin reactions; 0.01-0.1%: thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, thromboembolic stroke, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction), thrombocytopenia, prolonged bleeding time, dizziness, impaired (colour) vision and other visual disturbances. There are no known drug interactions with other drugs.

The association between long-term TXA use and venous thromboembolism is often debated. While numerous case reports of TXA-associated thromboembolism can be found, higher quality studies do not show an increased risk, as shown in the examples below. The most common indication for long-term TXA is intermittent use in women with menorrhagia. In a Swedish case-control study of 450 women with venous thromboembolism (cases) prevalence of TXA use was 2%. In 1505 control women, prevalence of TXA use for menorrhagia was 4%, leading to an OR (95% CI) of 0.55 (0.31-0.97), i.e. no increased risk of venous thromboembolism for women using TXA for menorrhagia [26]. Another study evaluated the effect of high dose (1 gram, 3 times daily) TXA on epistaxis in 135 patients with hereditary haemorrhagic telangiectasia [27]. There

were no thromboembolic events after a 3-month course of TXA (incidence 0%, 95%CI 0.0-2.8%).

5.5 Description and justification of route of administration and dosage

In previous studies using TXA for cSDH, a dosage of 650 to 750 milligrams a day was used for a period of one to three months. No thromboembolic complications were observed [14-18]. Also, for the treatment of epistaxis, a dosage of 3000 milligrams a day for 3 months was used without thromboembolic complications [27]. This study proposes the treatment of cSDH patients with 1000mg a day (500mg two times a day) for a period of 28 days.

The route of administration will be orally. Study participants therefore have to be able to swallow safely.

5.6 Dosages, dosage modifications and method of administration

See paragraph 6.5 for dosage details. The study drug will be dispensed only to eligible subjects under the supervision of the investigator or identified sub-investigator(s). No dose modifications will be performed in this study (see also paragraph 3, study design).

5.7 Preparation and labelling of Investigational Medicinal Product

The products (TXA 500mg and placebo capsules) will be manufactured by Tiofarma under Good Manufacturing Practice (GMP) license. Placebo and TXA will be packaged and labelled identically by Tiofarma to maintain the blind for the patients and investigators.

5.8 Drug accountability

The placebo and TXA will be transported to the pharmacy of the AMC by Tiofarma under GMP license. Management of the capsules (e.g. storage, drug accountability, dispense, transport to patients) will be performed by the pharmacy of the AMC according GCP guidelines and Dutch Law. Drug accountability and destruction of returned medication will be performed by the investigators. Destruction of not used capsules will be performed by the pharmacy of the AMC.

6. NON-INVESTIGATIONAL PRODUCT

Not applicable.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Primary study parameters/endpoints

1. Number of patients requiring surgery for cSDH within 12 weeks after start of treatment;

7.1.2 Secondary study parameters/endpoints

2. Number of patients requiring surgery for cSDH within six months after start of treatment;
3. Volume and percentage of volume reduction of cSDH at four, eight and 12 weeks on follow-up CT scan of the head;
4. Neurological impairment at four, eight and 12 weeks, measured with the modified National Institutes of Health Stroke Scale (mNIHSS) score;
5. Number of falling incidents during the six month study period;
6. Cognitive functioning at four, eight and 12 weeks, measured with the Montreal Cognitive Assessment (MOCA) test;
7. Performance in activities of daily living at 12 weeks and six months, measured with the
   a. Barthel Index scale;
   b. Lawton-Brody scale;
8. Functional outcome at 12 weeks and six months, measured with the modified Rankin Scale (mRS) score;
9. Quality of life at 12 weeks and six months, measured with the
   a. Short Form Health Survey (SF-36) questionnaire (main secondary outcome);
   b. five dimensional EuroQol (EQ-5D-3L) questionnaire;
10. Mortality at 12 weeks and six months;
11. Care and health-related costs during the six month study period, measured with the
    a. Medical Consumption Questionnaire (iMCQ);
    b. Productivity Cost Questionnaire (iPCQ).

7.1.3 Other study parameters

None.

7.2 Randomization, blinding and treatment allocation

Patients will be randomised to placebo or TXA in a 1:1 ratio using an online randomisation module (TENALEA Clinical Trial Data Management System) and random blocks of size 2, 4 and 6 stratified for anticoagulant and/or antiplatelet use (yes/no). Concealment of treatment allocation is ensured, and patients, treating physicians and endpoint assessors are unaware of the treatment assignment.

7.3 Study procedures

See appendix 14.2 for the follow-up schedule in a crosstable.

Inclusion, after signing informed consent form

- Assessment of baseline characteristics by physician:
  - patient characteristics: sex, age, use of antiplatelet and/or anticoagulation medication, history of trauma, characteristics of hematoma on CT (=standard care);
  - symptomatology: Glasgow Coma Score, mRS and mNIHSS score (standard care);
  - in and exclusion criteria (=extra for study);
- Assessment of baseline secondary outcome measurements by trial nurse (=extra for study)
  - assessment of MOCA, Barthel, Lawton-Brody;
  - filling in quality of life questionnaires (SF-36 and EQ-5D-3L) together with patient;
- Randomisation and handing out study medication (=extra for study);
- Handing out questionnaires for outcome assessment at week 4 (=extra for study);

Week 1: start medication (=extra for study)

- Start use of study medication within one week from inclusion, two times a day for 28 days.

Week 2 (± one week): assessment by telephonic interview (=extra for study)

- Assessment of drug compliance and (S)AEs by trial nurse (=extra for study).

Week 4 (± two week): first outcome assessment in outpatient clinic (=standard care)

- CT scan of the head without contrast (=standard care);
- During visit: check the filled in self-reported questionnaires (iMCQ and iPCQ) by trial nurse (=extra for study);
- During visit: evaluation if patient has had surgery (=extra for study);

- During visit: assessment of mNIHSS (=standard care), number of falling incidents, MOCA, mortality and (S)AEs by trial nurse (=extra for study);
- During visit: assessment of drug compliance. Drug accountability (=extra for study);
- During visit: assessment of mental competence (if patient has a depressed level of consciousness, =extra for study);
- Handing out questionnaires for outcome assessment at week 8 (=extra for study).

Week 8 (± one week): second outcome assessment in outpatient clinic (=standard care)

- CT scan of the head without contrast (=standard care);
- During visit: check the filled in self-reported questionnaires (iMCQ and iPCQ) by trial nurse (=extra for study);
- During visit: evaluation if patient has had surgery (=extra for study);
- During visit: assessment of mNIHSS (=standard care), number of falling incidents, MOCA, mortality and (S)AEs by trial nurse (=extra for study);
- During visit: assessment of mental competence (if patient has a depressed level of consciousness, =extra for study);
- Handing out questionnaires for outcome assessment at week 12 (=extra for study).

Week 12 (± one week): third outcome assessment in outpatient clinic (=standard care)

- CT scan of the head without contrast (= extra for study);
- During visit: check the filled in self-reported questionnaires (SF-36, EQ-5D-3L, iMCQ and iPCQ) by trial nurse (=extra for study);
- During visit: evaluation if patient has had surgery (=extra for study);
- During visit: assessment of mNIHSS (=standard care), number of falling incidents, MOCA, Barthel, Lawton-Brody, mRS, mortality and (S)AEs by trial nurse (=extra for study);
- During visit: assessment of mental competence (if patient has a depressed level of consciousness, =extra for study).

Month 6 (± one month): fourth outcome assessment by telephone interview (=extra for study)

- evaluation whether patient has had surgery;
- assessment of Barthel, Lawton-Brody, mRS, mortality, number of falling incidents and (S)AEs;
- check the filled in self-reported questionnaires (via mail, SF-36, EQ-5D-3L, iMCQ and iPCQ);

- assessment of mental competence (whether patient has a depressed level of consciousness);
- contact general practitioner whether patient has deceased, to track down reason of demise.

Since a CT-scan and a neurological examination are necessary for the assessment of the outcome measures, study participants have to able to attend the outpatient clinic. If this is not possible, a research nurse will visit the participant at home for the clinical outcome assessment to minimise the occurrence of missing values. Correction for any unequally distributed missing values is described in the statistical analysis plan.

Since the study design is intention-to-treat, outcome assessment will continue according to the study protocol, even if the patient has had a surgical treatment during study participation. If surgery is deemed necessary by the treating physician, the use of the study medication will be discontinued.

7.4 Withdrawal of individual subjects

Subjects, or their legal representatives who approved the authorization for inclusion in the study, can leave the study at any time for any reason if they wish to do so without any consequences. This is in accordance with the WMO, article 6. Acquired patient data until that moment will be used for data analyses. Only if the patient wants to have the acquired data removed from the database, these data will not be used for the outcome analyses.

The investigator can decide to withdraw a subject from the treatment with the study medication for urgent medical reasons. A specific reason could be the occurrence of a Serious Adverse Event. Administration of TXA or placebo will be stopped, but the follow-up schedule for the outcome assessments will be continued.

If it is revealed after inclusion, that one of the exclusion criteria was present in a certain patient on admission, this patient will remain included in the study and this will be recorded as a protocol violation. Administration of TXA or placebo will however, be stopped. These patients will nevertheless remain included for the outcome assessments to ensure an adequate intention-to-treat analysis.

7.4.1 Specific criteria for withdrawal

None

7.5 Replacement of individual subjects after withdrawal

Subjects will not be replaced after withdrawal. An attrition rate of around 8% is anticipated.

7.6 Follow-up of subjects withdrawn from treatment

The reasons for withdrawal of each patient will be recorded. Further treatment and policy will be performed by the treating physician. The research group will strive to continue the follow-up assessments in accordance with practice of standard care.

7.7 Premature termination of the study

Reasons for premature termination of the study are not specified.

7.8 Data collection

Research data is collected in an electronic CRF using Castor EDC (www.castoredc.com).

Paper questionnaires are used for the SF-36, EQ-5D, iMCQ and iPCQ outcome measurements, which are filled in at home by the study participants themselves. These completed questionnaires are digitalized to Castor EDC by the investigators. During the outpatient clinic visit, the MOCA is assessed by the investigators using the official MOCA paper sheet, which is afterwards digitalized to Castor EDC by the investigators. The results of the mNIHSS, mRS, Barthel and Lawton-Brody are added to Castor EDC using *direct entry* during the outpatient clinic visit. Baseline patient characteristics, if a surgery has been performed, the number of falling incidents and mortality are registered in the medical records and added to Castor EDC after the outpatient clinic visit. Radiological data is also stored in the medical records; volume measurements are performed after the outpatient clinic visit and are then added to Castor EDC.

8. SAFETY REPORTING

8.1 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 a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

All (S)AEs will be handled as described in the CCMO AE flowchart. This flowchart is attached in appendix 14.3. (S)AEs will be reported during the 12 week study period. If the participant opts in for the optional six month telephonic outcome measurement, (S)AEs will be reported during the additional study period between 12 weeks and six months after inclusion as well.

8.2.1 Adverse events (AEs)

AEs are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product.

Since the largest part of thestudy period takes place at home, AEs will not directly be observed by the investigator or his staff. Getting knowledge of AEs depends on spontaneous reporting by the subject or other treating physicians to the investigator or his staff. The reported AE will be documented in the patients' medical file, triaged for being a possible SAE and, if so, handled as such.

During the study period, at each follow-up moment as described in paragraph 8.3, occurrence of AEs will be monitored. Each AE will be reported in the CRF. Follow-up of AEs is described in paragraph 9.4.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;

- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following:

- Hospital admission for the treatment of diseases that can be attributed to being an elderly patient, such as delirium, infections, constipation and an exacerbation of a pre-existent disease (excluding cSDH). These SAEs will be reported in a twice-yearly line listing until the follow-up of the last patient is completed;
- Hospital admission because of the necessity for surgical treatment of the cSDH. This SAE will be reported in a twice-yearly line listing, since this is the primary endpoint of our study.

Except for the abovementioned, the sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within seven days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of eight days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

Since the biggest part of the study period takes place at home, SAEs will not directly be observed by the investigator or his staff. Getting knowledge of SAEs depends on spontaneous reporting by the subject or other treating physicians to the investigator or his staff. The reported SAE will be documented in the patients' medical file.

During the study period, at each follow-up moment as described in paragraph 8.3, occurrence of SAEs will be monitored. Each SAE will be reported in the CRF. Follow-up of AEs is described in paragraph 9.4.

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

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

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

SUSARs can only be determined by a physician. Therefore, if a trial nurse suspects an SAE to be a SUSAR, the adverse event is presented to the investigator. The investigator judges whether the event must be assessed as a SUSAR.

The sponsor will report expeditiously the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials 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 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.

9.2.3.1 Unblinding procedure

The pharmacy will hold the unblinding codes. In case a SUSAR is suspected, the investigator/attending physician will email/fax an Unblinding Request Form (URF) to the Principal Investigator or delegated person and make every effort to contact the Principal Investigator to discuss options. In case unblinding is deemed

necessary, the Principal Investigator or delegated person will send the URF to the pharmacy who will reveal the treatment assignment for the individual subject to the local investigator by telephone and confirmed in writing. The local investigator will document the unblinding on the Unblinding Form (UF) and store it in the local investigator study file (ISF). The date, time and reason for unblinding will also be recorded in the source documents and in the subject's CRF.

If the blind is broken, the individual subject must be discontinued from the investigational medicinal product as soon as possible, when not already done so. The subject should be strongly encouraged to perform an end of study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

An independent physician, authorised for this task, will report the SUSAR to *ToetsingOnline* in order to maintain the blind for the Principal Investigator and other research team members. The Principal Investigator or delegated person will file the URF in the Trial Master File.

8.2.4 Responsibilities for reporting (S)AEs

Investigators in participating centres have the responsibility to report (S)AEs in the CRF. (S)AEs should also be reported to the coordinating investigator/sponsor within 24 hours. The coordinating investigator/sponsor reports the SAEs to the accredited METC as described in paragraph 9.2.2 and 9.2.3.

8.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC.
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.

8.4 Follow-up of adverse events

All AEs 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. SAEs need to be reported till end of study participation.

8.5 Data Safety Monitoring Board (DSMB)

The DSMB consists of two members who are clinicians with medical expertise in neurology (dr. J. Horn, chair DSMB and dr. P.J. Nederkoorn). The DSMB also includes an epidemiologist (dr. J.A. Boogaards) experienced in the (statistical) methods for clinical research. All members are independent of the study.

The DSMB will act in an independent, expert and advisory capacity to monitor participant safety, and evaluate the overall conduct of the clinical trial. Further specifications on the responsibilities, the meetings, and the decision making of the DSMB are documented in the DSMB charter.

The advice(s) of the DSMB will only be sent to the Steering Group of the study. Should the sponsor decide not to (fully) implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

9. STATISTICAL ANALYSIS

Statistical analyses will be based on the intention-to-treat principle. Baseline assessments and outcome parameters 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 (25th – 75th 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. Where necessary we will use multiple imputations for handling missing data. In all analyses statistical uncertainty will be expressed in two-sided 95% confidence intervals. A two-sided p value less than 0.05 is considered statistically significant. We will not correct for multiple testing.

9.1 Primary study parameter

The difference in the proportion of patients requiring surgery for cSDH within 12 weeks after start of treatment will be analyzed using Fisher's exact test. In addition, logistic regression will be performed including treatment groups and the stratification variables (use of anticoagulation and/or antiplatelets, see also paragraph 8.2) as independent variables. The effect size will be expressed in an adjusted odds ratio.

9.2 Secondary study parameters

Differences in volume reduction of cSDH, neurological impairment (mNIHSS), and cognitive function (MOCA) between the treatment groups and over all time points will be analyzed using a linear mixed model with treatment group membership as a fixed-effect and an appropriate random-effect structure. Number of falling incidents and mortality rate during the 12 weeks follow-up will be analyzed using Fisher's exact test. ADL scores (Barthel Index and Lawton-Brody scale) and functional outcome score (mRS) at 12 weeks will be compared with the two-sample t-test or Mann-Whitney test, where appropriate. Differences in the mean changes in level of quality of life (SF-36) from baseline to 12 weeks (main secondary outcome) will be analyzed using the two-sample t-test. In addition, we will analyse these treatment effects by performing multivariable linear regression with 12-weeks observations as the dependent variable, and treatment groups, the baseline values and the stratification variables as the independent variables.

9.3 Economic evaluation

The economic evaluation will be performed from a societal perspective, set up as a cost-effectiveness analysis and a cost-utility. The rationale for this economic evaluation is that lower rates of surgery for cSDH following TXA treatment will result in major reduction in

costs for surgery, associated hospital admissions, and nursing home placement. Although conservative management and TXA treatment also incurs costs (medication, CT-scans and out-patient visits), these are not expected to offset this cost-reduction.

The incremental cost-effectiveness ratio will be expressed as the costs per case of surgery avoided, as well as a cost-to-benefit ratio, where downstream costs associated with surgery and subsequent health care use until 12 weeks, are estimated. In addition, a cost-utility analysis (CUA) will evaluate cost differences in relation to differences in quality-adjusted life-years (QALYs). This CUA will estimate costs per QALY, to allow comparison with other health-related interventions or programs. With a study horizon of 12 weeks, no discounting will be applied.

We will differentiate between direct medical costs (surgical procedures, CT-scans, pharmacological therapy, hospital stay, outpatient care, admissions to nursing home and other primary and paramedical health care following discharge), direct non-medical costs (travel to and from health care providers) and indirect costs (lost productivity due to absence from paid work). Health care utilisation during the index hospitalisation will be documented in the clinical report form. Health care and other resource use following discharge will be collected with the iMTA Medical Consumption questionnaire and the Productivity Costs Questionnaire [30] at 4, 8 and 12 weeks. Unit costs for health care use will be estimated according to the Dutch guideline for economic evaluation research [31]. Medication costs will be valued by market prices [32]. Health-related QoL will be collected at 12 weeks with the EQ-5D. Utility values for EQ-5D scores will be based on Dutch estimates [33]. Utility scores will be uniformly interpolated, assuming constant health state between subsequent assessments.

Cost-effectiveness will be evaluated by calculating the incremental cost-effectiveness ratios (Δcosts / Δeffects). Robustness of the results for uncertainty in parameter estimates and assumptions will be evaluated in sensitivity analyses, including UK valuation of health states.

9.4 Interim analysis

The DSMB will perform an interim analysis for safety when follow-up is completed of the first 35 and 105 included participants. Additionally, the DSMB will monitor safety data and sample size assumptions when follow-up is completed of the first 60 participants and 200

participants. A futility analysis after 300 patients will be performed. Further details are described in the DSMB charter.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version of 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts. Study monitoring will be performed in accordance with the ICH GCP guidelines.

10.2 Recruitment and consent

Patients with a cSDH will be referred as usual by their treating neurologist to a neurosurgeon in a participating centre. To ensure that all cSDH patients are referred to a neurosurgeon, even without neurological symptomatology, this study will be promoted by an advertisement in the Dutch Journal of Medicine (Nederlands Tijdschrift voor Geneeskunde) and TNN (Tijdschrift voor Neurologie en Neurochirurgie), and by notifying all referring neurologists. Referral can be done in two ways: outpatient or clinical referral.

- Outpatient clinic. Based on clinical and radiological parameters, the desired treatment strategy will be decided upon. If a conservative treatment is chosen, eligibility for study inclusion will be determined. The treating physician will provide eligible patients with spoken and written information about the study, together with the Informed Consent Form. If the patient wishes to participate in the study, the Informed Consent Form has to be signed in twofold before inclusion. There will be ample time between providing patient information and signing the Informed Consent Form. Inclusion is performed as soon as reasonably possible after the request for study participation. Treatment starts at home.
- Clinical referral. Most patients are referred clinically with an in-hospital consultation or transportation from an emergency department or neurology ward of a referring hospital to the neurosurgical ward of a participating centre. Just as described above, eligibility for inclusion will be determined by the treating physician and the Informed Consent Form will be signed before inclusion. Treatment starts at the participating centre and will be continued at the referring centre and/or at home.

Because cognitive impairment is a frequently occurring symptom of the disease, a significant portion of the eligible study subjects might be mentally incompetent at the moment of inclusion. In those cases, a legal representative will be asked to sign the Informed Consent Form. Since resolution of the cognitive impairment is frequently seen in the course of the conservative treatment, these study subjects can become mentally competent again. In those cases, informed consent will be asked from the study subject

him-/herself, as soon as possible. Evaluation of the mental competence will be done at each outpatient visit, as described in the follow-up schedule in appendix 14.2. If no informed consent can be obtained, the patient will not be included into the study and only standard care will be provided. Examples of this are a language barrier and a mental incompetent patient without any family to give informed consent. After signing the Informed Consent Form, treatment with the study medication must start within the next seven days. This 7-day time window is necessary for the delivery of the study medication to the participant. This delay is acceptable due to the chronic nature of the emergence of a cSDH and the nature of the therapeutic effect of TXA, which is expected to take several weeks for its effect.

10.3 Objection by minors or incapacitated subjects

Minors are excluded from the study. A significant part of the study subjects might be incapacitated at moment of inclusion. In those cases, a legal representative will be asked to provide informed consent on behalf of the study subject. However, as stated in the WMO, mentally incompetent study subjects cannot be forced to undergo a treatment against their will. If resistance to the treatment is suspected, this will be evaluated according the Code of Conduct: *The expression of objection by incapacitated (psycho)geriatric patients in the context of the WMO* [28]. If objection by the study subject is obvious, treatment will be stopped.

10.4 Benefits and risks assessment, group relatedness

Since the current study is a therapeutic research, every study subject benefits extensively if the study medication indeed prevents the need for surgery. Each patient is also at risk since he or she is exposed to the potential side effects of the medication. The most frequently occurring side effects are mild and temporary: 1-10%: gastrointestinal: diarrhea, nausea, vomiting, and TXA-associated seizures, which are dose-dependent and 1.4% (95% CI 0.2-2.5) in the dose described for this study; 0.1% to 1%: allergic skin reactions; 0.01-0.1%: thrombocytopenia, prolonged bleeding time, dizziness, impaired (color) vision and other visual disturbances. As stated in the Summary of Product Characteristics (attachment D2), the risk of thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, thromboembolic stroke, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction) is only 0.01-0.1%. Therefore, this study is classified as a moderate risk according to the NFU criteria for human research.

The potential benefit, namely the prevention of a second surgery, is greater than the burden and risk of the temporary use of the study medication and its potential side effects.

It is important to also include mentally incompetent study subjects, since those cover the majority of the patient population.

10.5 Compensation for injury

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

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.6 Incentives (if applicable)

None

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

The executing investigator will set up a Trial Master File at the beginning of the study. The list of essential documents will be in accordance with the GCP-guidelines. The essential documents that make up the file will be stored in a secure but accessible manner. All essential documents will be legible and accurate. For each included patient a digital Case Record Form (CRF) will be completed. The CRF consists of a sequential set of instructions with provision for data recording. All randomized patients are identified by a Patient Identification Number (PIN). The investigators will ensure that patients' anonymity is maintained. On screening forms, digital or paper CRF's or other documents, patients will only be identified by a PIN. The subject identification code list will be safeguarded by the investigator. Data will be stored for 25 years.

11.2 Monitoring and Quality Assurance

Academic Medical Center's Clinical Research Unit (CRU) will provide independent monitoring. An independent monitor will monitor the study data according to Good Clinical Practice (GCP). In a selection of patients Informed Consent will be checked. Additionally, there will be an onsite monitoring source data verification. The intensity for this verification is related to the risk analysis of the trial. Details will be described in a study-specific Monitor Plan.

11.3 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.

11.4 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.

11.5 Temporary halt and (prematurely) 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.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

The sponsor will notify the Member States where the trial is conducted when the trial ends, specifying whether it was completed or terminated early.
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.

11.6 Public disclosure and publication policy

To ensure that all cSDH patients are referred to a neurosurgeon, even without neurological symptomatology, this study will be promoted by an advertorial in the Dutch Journal of Medicine (Nederlands Tijdschrift voor Geneeskunde) and TNN (Tijdschrift voor Neurologie en Neurochirurgie), and by notifying all referring neurologists.

The study will be registered in an international trial registry (http://www.clinicaltrials.gov). After completion of the study, the authors aim to publish the results in high-impact peer-reviewed journals and present the results in the usual international fora of relevant specialist societies, regardless of either positive or negative results. 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. Besides the first, second and last author, the steering group members and additional names are mentioned in alphabetical order. Participating centres including ≥ five patients, will be entitled to one name in the author list.After the author list the

following sentence will be added: “on behalf of the TORCH-trial group” and a reference to an appendix with all sites, site investigators and number of patients enrolled.

The trial results will be reported in CTIS within 12 months of the end of the trial. The end of the trial is defined as the last participants last visit (6-month telephonic interview). The sponsor will ensure that trial results are submitted to CTIS and participants in compliance with the CTR timelines. A layperson-friendly summary of the results will be uploaded to CTIS in the same timeframe. If the 12-month deadline for reporting trial results in CTIS cannot be met due to scientific reasons, the sponsor will provide a detailed justification, outlining the necessity for additional time, and will ensure that the results are uploaded without undue delay. Participants that signed for receiving trial results will receive a copy of the lay summary through email or post within 12 months after uploading the results to CTIS.

In addition, if this study shows that TXA significantly prevents surgery for cSDH and, with that, improves quality of life in elderly patients, steps will be taken to register cSDH as a new indication for TXA. Together with the registration, the use of TXA can be incorporated in the clinical guideline for the treatment of cSDH.

11.7 Statement of compliance with Regulation (EU) 2016/679 (GDPR)

Sponsor D. Verbaan
Title of the clinical trial TORCH: Tranexamic Acid to Prevent Operation in Chronic Subdural Hematoma EU CT Number 2024-514927-40-02

The sponsor declares that data have been and will be collected and processed in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR).

Date: 17-01-2025

Name and surname: Dagmar Verbaan, professor evidence based neurosurgery

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

Since decades, TXA is a widely-used drug that reduces clot breakdown, by inhibiting plasmin, which is involved in fibrinolysis. TXA is effective in various clinical settings, in both intra- and extracranial bleeding. Opposed to what is often thought, TXA does not have procoagulant effects, and does not lead to increased thrombin generation and fibrin formation. As hyperfibrinolysis is thought to play a role in the liquefaction and enlargement of cSDH, the use of TXA is being explored in an effort to reduce the occurrence of recurrent cSDH and thus to eliminate the necessity of (repeat) surgery. So far, only five small and mostly retrospective series have reported the use of TXA for cSDH (described in paragraph 6.3). In all of the treated patients, no surgery was needed after the start of TXA, no thromboembolic complications were mentioned and the mortality was zero. Together with extensive experience in treating patients with TXA for other indications, in which no increased risk of thromboembolic complications is seen (described in paragraph 6.4), treating cSDH patients with TXA is expected to be safe and promising.

The used treatment duration is similar compared to the duration in the four previous performed studies. Treatment dosage however, is approximately 25% higher than used in these studies. This is chosen, because the mean weight of the Dutch population is estimated to be somewhat higher than that of the Asian, in whom these previous studies were performed. Also, a higher daily dose, does not increase the risk of complications, as described in paragraph 6.4. Finally, only pills of 500mg TXA are available in the Netherlands, so only a daily dose of 500mg or 1000mg is possible.

Since cSDH patients often are mentally incompetent due to cognitive impairment as a symptom of the disease, acquiring informed consent for study participation can be challenging. The acquisition procedure of informed consent is described under Ethical Considerations in paragraph 10. Our staff is well experienced with this category of patients. This is because of the nature of the neurosurgical specialty in which we often treat mentally incompetent patients. Also, we are currently running a prospective multicentre trial [21], in which already over 650 patients, often mentally incompetent patients, are included.

Using an existing network of Dutch hospitals and investigators currently collaborating in an other prospective multicentre trial [21], 10 centres have signed a letter of intent and are

willing to participate in this study, expecting a total of 275 patients to be eligible each year.

There are no known interactions between TXA and other drugs, except thrombolytic medication. Therefore, patients receiving active treatment for deep venous thrombosis, pulmonary embolism, cerebral thrombosis and other hypercoagulability diseases are excluded from the study, since those patients are expected to be more at risk to develop thromboembolic complications.

12.2 Synthesis

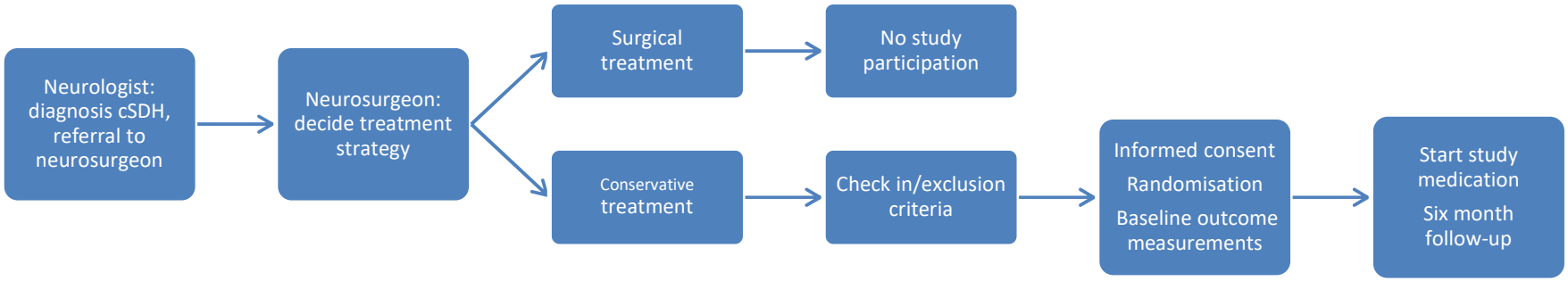
Together with two other currently running prospective trials (the TRACS study [19] and the TRACE study [20]), the current study is set up to investigate the value of treating cSDH patients with TXA. This study differs from the TRACS study, because it does not exclude patients using anticoagulants, who comprise a significant portion of the cSDH patient population. The results of the TRACS study are therefore expected to be difficult to extrapolate to the daily care of cSDH patients. Different from the current study, the TRACE study only investigates the value of treating cSDH patients with TXA after surgery, to prevent recurrence.

Since no data is yet available, the potential benefit of the treatment is yet uncertain. Based on the five earlier mentioned studies, a beneficial effect is expected.

The most important potential risk is that of a thromboembolic event, which can be life threatening and/or cause permanent damage to the patient. However, according to the Summary of Product Characteristics, the risk of thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, thromboembolic stroke, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction) is only 0.01-0.1%. In concordance, previous studies show no increased risk of developing such a complication. According to the NFU-criteria for human research, the current study has a moderate risk, because of the minimal risk of developing complications with potentially severe damage. Therefore, a DSMB is gathered to monitor the safety of the study.

13. APPENDICES

13.1 Flowchart inclusion

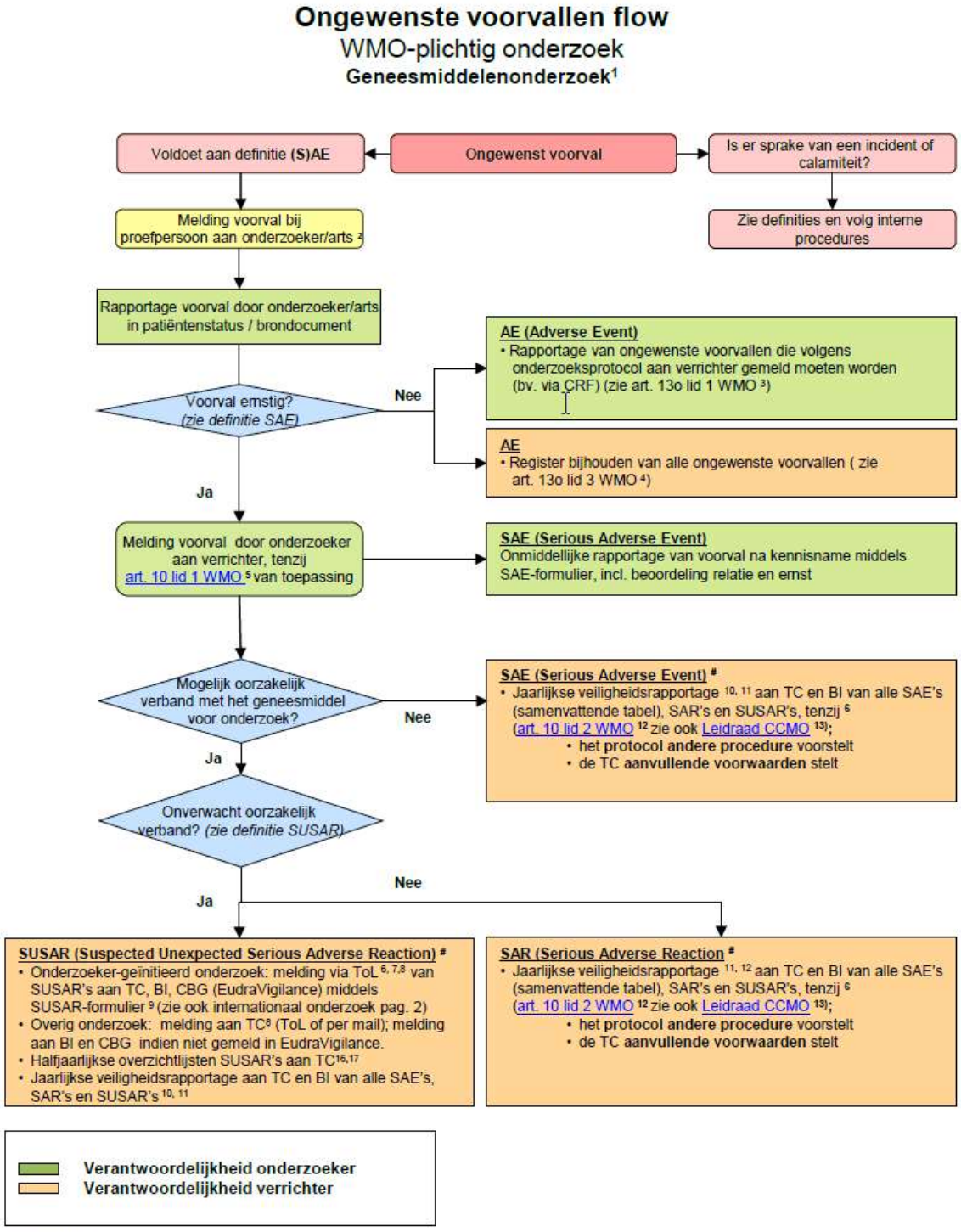


13.2 Follow-up schedule

	Inclusion ‡	Day 1: start medication	Week 2: telephonic interview ¶	Week 4: outpatient visit ¶	Week 8: outpatient visit ¶	Week 12: outpatient visit ¶	Month 6: telephone interview (optional)¶
Baseline data							
Inclusion and exclusion criteria	X						
Baseline characteristics	X						
Treatment							
TXA or placebo treatment		X	X	X			
Primary outcome							
1. Surgery for cSDH?			X	X	X	X	
Secondary outcomes							
2. Surgery for cSDH?							X
3. cSDH volume	X			X	X	X	
4. mNIHSS	X			X	X	X	
5. Falling incidents				X	X	X	X
6. MOCA	X			X	X	X	
7a. Barthel	X					X	X
7b. Lawton-Brody	X					X	X
8. mRS	X					X	X
9a. SF-36	X					X	X
9b. EQ-5D-3L	X					X	X
10. Mortality				X	X	X	X
11a. iMCQ				X	X	X	X
11b. iPCQ				X	X	X	X
Other							
Evaluation of mental competence	X			X	X	X	X
(S)AEs			X	X	X	X	X

‡ By physician, ¶ By trial nurse

13.3 Flowchart (S)AEs



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