Form FHS015: Research Protocol – Section C

Title:	**Postpartum hemorrhage reduction with oral tranexamic acid (PROTECT): a multicenter randomized controlled trial**
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Investigational product:	Tranexamic Acid (TA) oral solution
Indication:	Prophylactic medication for the prevention post-partum hemorrhage in vaginal delivery
Study Phase:	Phase III South Africa / Phase IV Sweden
Study sites Sweden:	Södersjukhuset, Stockholm Lund University Hospital, Lund Hudiksvall Hospital
Study Sites South Africa:	Mowbray Maternity Hospital, Cape Town Khayelitsha District Hospital, Cape Town

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List of abbreviations

TA	Tranexamic Acid
RCT	Randomized Controlled Trial
PPH	Postpartum Hemorrhage
Hb	Hemoglobin
IMP	Investigational Medicinal Product
EVF	Erythrocyte Volume Fraction (Hematocrit)
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
ITT	Intention to treat
PP	Per Protocol
AE	Adverse Event
SAR	Serious Adverse Reaction
AR	Adverse Reaction
RSI	Reference Safety Information
SUSAR	Suspected Unexpected Serious Adverse Reactions
SAE	Serious Adverse Event
CRF	Case Report File
MPA	Medical Products Agency (Läkemedelsverket)
RERB	Regional Ethical Review Board
SAPHRA	South African Health Products Regulatory Authority
CIOMS	Council for International Organizations of Medical Sciences

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1. Purpose of the Study

The main purpose of the study is to evaluate the effect of orally administered TA compared to placebo on rate of postpartum hemorrhage (PPH) >=500ml assessed by weight in vaginal deliveries.

Our secondary aims are:

- To evaluate the effect of orally administered TA compared to placebo on mean blood loss, pre-postpartal Hb difference ≥10 units, severe PPH (>=1000ml), and the need of blood transfusion
- To evaluate feasibility, i.e. adherence to administration of oral TA compared to placebo.
- To evaluate the acceptability of orally administered TA compared to placebo among women giving birth and providers
- To evaluate the safety of administration of oral TA compared to placebo
- To assess the effect of the intervention on PPH among the subgroup of women with anemia
- To assess the effect of the intervention on PPH according to time of administration in relation to delivery of the child.

2. Background

Severe PPH is the leading cause of maternal death worldwide especially in developing countries (1). Obstetric hemorrhage is one of the leading cause of preventable maternal deaths in South Africa according to the latest confidential inquiry on maternal deaths (2). The uterus and placenta are highly vascularized organs during pregnancy and labor which means that once bleeding starts it is often difficult to control. PPH increases maternal morbidity related to emergency interventions such as manual removal of the placenta, suturing of cervical or vaginal tears, embolization of uterine arteries, and hysterectomy as well as PPH-related complications such as anemia, postpartum

endometritis, venous thrombosis, and transfusion-related complications (3,4). Preventing PPH before onset is therefore of key importance.
Uterotonics such as oxytocin, ergometrine and misoprostol are often used to improve uterine contraction during PPH (1). TA is an anti-fibrinolytic agent which blocks plasminogen from binding to fibrin and in doing so, inhibits the break-down of blood clots. This means that hemorrhage is theoretically decreased regardless of its cause.

TA is a well-established and tested medication for treatment and prevention of heavy bleeding on the WHO list of essential medication (27). Intravenous TA (at doses 1-4g) reduces the rate of maternal deaths during diagnosed PPH but the prophylactic effect of intravenous TA on PPH after vaginal is still uncertain (4-9). A Cochrane review found a positive effect in rate of PPH but subsequent RCTs have shown conflicting conclusions.

TA is recommended by for treatment of PPH by the WHO but the effect of different forms of oral treatment in vaginal deliveries has been scarcely studied and is a stated research priority by the organization (10). Oral forms of TA exists as a tablet, an effervescent tablet, and as an oral solution of which the former two are routinely prescribed and available as over the counter medications in Sweden, though not in South Africa. Both the tablet and the solution forms of TA are low-cost, stable at room temperature and easy to administer which makes them especially applicable to both low resource delivery settings and home- births.

To prevent PPH, a therapeutic serum concentration of TA should coincide with the period immediately after delivery of the child, when the risk of PPH is greatest, meaning that TA should optimally be administered during the latter part of active labor. After oral administration to non-pregnant and pregnant individuals, maximum serum concentration of TA is attained after 60-180 minutes, uptake and clearance is linear and a serum-concentration of >10-mg/l provides near maximal inhibition of fibrinolysis and levels between 5mg/l to 10mg/l are enough to attain substantial effect on fibrinolysis in vitro (11-14).

The premises of the RCT are the following:

1) The effect of oral prophylactic TA on rate of PPH is insufficiently known

2) If oral TA is effective in preventing PPH, routine administration could reduce maternal morbidity significantly at low risk and expense.

3. Methodology

3.1 Study Design

This is a multicentre randomized placebo-controlled double-blinded phase IV study among 1000 women in Sweden and South Africa on the effect of oral tranexamic acid on PPH after vaginal delivery.

3.2 Characteristics of study population

The study will include 1000 women planned for vaginal delivery at three study sites in Sweden (n=500) and two study sites in South Africa (n=500) during the period March 2023 to December 2026.

3.2.1 Inclusion and exclusion criteria

Inclusion Criteria

- Women who are planned for vaginal delivery.
- Women ≥18 years old.

Exclusion Criteria

- Preterm labor before gestational week 36+0
- Ongoing treatment for venous thrombosis
- Known bleeding disorder (including prolonged APTT or high INR)
- History of seizures
- Known hypersensitivity towards TA,
- Inability to understand spoken and written English, Swedish,

IsiXhosa or Afrikaans (depending on the study site)

- Inability to understand the contents of the written information about the study.

3.3 Intervention

Our intervention consists of the oral self-intake of either 20 ml (2g) of oral solution of TA, or 20 ml placebo, at a time when an estimated that 3-4 hours remain until delivery. For a primipara this should approximate the time when the cervix is dilated 8 cm, for a parous woman it should approximate the time when the cervix is dilated 6 cm. Cervical dilatation is in Sweden routinely assessed every 2 hours during delivery until the cervix is fully dilated and then every 30min-1hr until delivery. In South Africa vaginal exams are performed 4-hourly until 7 cm dilatation and 2 hourly thereafter. Participation in the study should not entail any additional vaginal exams compared to clinical practice. Timing of administration and delivery will be recorded on a study protocol. Oral solution TA is a non-viscous, colorless, odorless, and orange-tasting liquid. Our placebo, which has been developed by APL is manufactured to be non-distinguishable in viscosity, appearance, odor, and taste. The reason we are using an oral solution instead of an equivalent dose of oral tablets (4 tablets á 500mg) is that TA tablets are quite large, and enclosed in the rubber-like coating used to disguise the investigational medicinal product (IMP) from the placebo, the size is prohibitively large to ask women to swallow during labor.

3.3.1 Investigational medicinal product

The IMP, TA (product code SUB11214MIG**),** is a synthetic derivative of the amino acid lysine and has an antifibrinolytic effect by blocking lysine receptors on plasminogen, thereby preventing it from adhering to lysine molecules on the fibrin plug. This prevents plasminogen converting to its active form plasmin which inhibits the degradation of the fibrin plug.

TA is a commonly used drug and has in multiple studies proven efficient in preventing and decreasing blood loss in surgery, trauma, and obstetric care without

increased risk of thrombosis (15, 16). It is well tolerated with few serious side effects (17).

3.4 Outcomes

Primary endpoints

- Weight / volumetric estimated rate of PPH (≥500ml)

Secondary endpoints

- Pre-postpartum Hb difference equivalent to (g/L) ≥10 units
- Weight-estimated rate of severe PPH (≥1000ml)
- Mean blood loss (ml)
- Mean pre-postpartum Hb decrease (units)
- Rate of blood transfusion (%)
- Adherence to intervention/ feasibility (%)
- Rate of no to minor discomfort upon administration (acceptability)among participants
- Rate of no to minor discomfort upon administration (acceptability) among providers
- Rate of thromboembolic events up to 6 weeks postpartum (%)

	RCT PICO
P	Women ≥18 years old, planned for vaginal delivery at Södersjukhuset, Stockholm Skåne University Hospital, Lund, Hudiksvall Hospital, Hudiksvall, Mowbray Maternity Hospital, and Khayelitsha District Hospital during the period March 2023 to December 2025 (n=1000).
I	Two grams (20ml) oral TA at full cervical dilation (n=500)
C	20 ml oral, non-distinguishable, placebo at full cervical dilation (n=500)
O	Rate of PPH (≥ 500ml) between groups Hemorrhage in ml, estimated by weight

3.5 Recruitment and Enrollment

We will recruit women during a routine or planned antenatal visit after 35 gestational weeks, or after admission to the delivery ward before onset of labor. Potential participants will be approached and invited to partake in a non-committal brief information and screening regarding the study. If they are willing to participate and eligible, they will be included in the study after an informed consent process.

3.6 Randomization

Randomization will occur after a woman has been admitted to the labor ward. Participants will be randomized to receive either 20 ml of TA or 20ml of a placebo solution, equivalent to the IMP in appearance and taste.

The randomization sequence will be computer-generated by KTA (Karolinska Clinical Trial Alliance). Randomization will be 1:1 in permuted blocks of 10 to allow for block-sized deliveries to study sites. The placebo, an oral solution identical in appearance, taste, and volume to TA, will be developed and manufactured by Apotek Produktion och Laboratorier (APL) who will also supply the IMP. APL will perform the packaging, blinding, and marking of the IMP and placebo according to the randomization sequence sent them by KTA. The manufacturer and batch number of the drug administered for each participant will be recorded separately. All study sites will have a number to call in case unblinding is warranted. The sequence will be longer than 1000 to allow for differential rates of recruitment at the different study sites but recruitment will stop after the 1000th participant is included. The IMP/placebo flasks will delivered from APL to a central pharmacy location (Uppsala) and delivered in batches to each study site in Sweden. The IMP/placebo flasks for South Africa will be delivered in a temperature-validated transport by World Courier to Mowbray Maternity Hospital pharmacy in South Africa and from there delivered in blocks of 10 to Khayelitsha District Hospital Pharmacy. Participants, clinical staff, and the researchers themselves, will be blinded as to which treatment the woman receives. The study product is stable at room temperature. Randomization will occur by taking the next sequential flask of IMP/placebo and noting its number on the IMP log. In Sweden this will be performed by study-trained midwives. In South Africa, randomization and dosage and tracking of the IMP will be performed by a certified and GCP-certified pharmacist at each study site. The pharmacist may also "block-randomize" in advance, allowing for enrolment after the pharmacy has closed for

the day. A research assistant will bring the IMP to the study participant. After use, the IMP flasks will be returned to the pharmacy (South Africa) or to the delivery ward medicine room (Sweden), logged in the IMP log by the pharmacist or participating researcher, and stored until they have been monitored by the study monitor. All study procedures except those that form part of standard of care will be performed by GCP certified researchers or GCP certified delegated clinical staff.

3.7 Study Procedures

All study specific procedures will be performed by GCP certified study staff, or GCP certified clinical staff, that have been delegated these procedures by means of a delegation log, this includes the informed consent procedure, randomization and tracking the IMP, the administration of the IMP, and extraction of study data from medical records.

The intervention is intake of 20 ml IMP/placebo. The oral solution is stable at room temperature and can be placed on a table next to the participant. When between 2 and 3 hours of labor remains, the participant drinks the cup of 20ml liquid.

Participants will experience three study procedures that form part of (routine) standard of care which will be performed by clinical midwives.

1) A blood sample (hemoglobin, EVF, MCV, MCH, MCHC, LPC, TPC) in Sweden and hemoglobin only in South Africa, taken upon admission .
2) Measurement of blood loss volume weighing (1g=1ml) or calibrated drapes
3) A blood sample including (hemoglobin, EVF, MCV, MCH, MCHC, LPC, TPC) in Sweden, and hemoglobin only in South Africa, taken after 24 hours (or prior to discharge should discharge occur before 24 hours).

All study procedures including the measurement of the main outcome and most secondary outcomes will take place during the time the participant is admitted to the labor or postnatal ward.

4. Data Collection Methods and monitoring

4.1 Measurement of outcomes

Our main outcome is PPH>500ml assessed both by weight and by pre to post Hb difference. Blood loss is difficult to measure and correlation between weight-assessed assessment and pre-postpartum Hb difference is relatively poor (17, 18). PPH is defined as blood loss ≥500ml by the WHO and is the primary outcome used in most studies on TA. For this reason, we use PPH ≥500ml as out main outcome but include two measurements of its occurrence. Weight assessed rate of PPH will be measured by weighing all blood- and blood-soaked linen/pads within 2 hours of delivery according to clinical routines in Sweden as well as newly implemented routines in South Africa as part of the E-Motive Trial (19). Subsequent bleeding, if beyond the ordinary, within 24 hours of delivery will be weighed and recorded by the midwife at the postpartum care ward and entered into clinical records as per routine care. Pre- postpartum Hb difference (g/L) will be measured by subtracting the Hb level taken 24 hours after delivery to that taken upon admission to the hospital, before onset of labor. A volume of 500ml represents ≈ 9% of a pregnant woman´s total blood volume. Assuming a mean Hb level of 114 in the third trimester, and an initial linear decrease in Hb, we stipulate that a ≥10 unit drop of Hb approximates the loss of 500ml of blood (20). Sweden diagnoses PPH only in cases of blood loss ≥1000ml (severe PPH) and there is an increasing consensus that this cut-off better correlates to clinical morbidity. We include rate of severe weight-assessed PPH, rate of blood transfusion, and mean weight-assessed blood loss as secondary endpoints measuring bleeding after delivery.

Hb will be measured in a blood sample taken at arrival to the delivery ward, hemoglobin level will be controlled 24 hours postpartum or directly before discharge if this occurs sooner. Biochemical analysis data will be extracted from digital or paper clinical records. Blood loss during delivery and up until two hours postpartum will be measured by weighing and recorded by the midwife in the delivery unit. Blood transfusions occurring within 24 hours, as well as thromboembolic events occurring within 6 weeks, will be extracted from clinical records. Time of IMP/placebo administration in relation to labor/delivery, suspected side-effects of the medication, as well as any difficulty taking the medication (adherence) will be recorded by the midwife

on study case report forms. Data pertaining to primary and secondary endpoints will be retrieved from participant clinical records, digital laboratory report, or study case report forms and recorded to study electronic case report forms (eCRFs) in RedCap. Data will be collected and entered into the database by either one of the investigators or experienced research assistants. In South Africa, the 6 week outcome rate of thromboembolism will be recorded by telephone follow-up.

4.2 Appropriateness of Intervention

The effect of prophylactic oral TA during labor has not been studied. Our intervention is a 2g stat dose of TA. Prophylactic oral treatment in pregnant woman is complicated as pharmacokinetics may be altered by physiological changes during pregnancy such as an increase in both plasma volume and renal clearance and by the fact that gastric emptying and gastrointestinal motility is decreased during labor, as well as by the unpredictable duration of labor.

Several trials on prophylactic intravenous treatment of PPH have used a 1g dose (8,9). A treatment study on PPH (500-800ml) tested intravenous doses of 4g (loading dose) plus 6g over 6 hours without adverse events (4). A recent RCT on non-pregnant volunteers suggest that the bioavailability of oral TA could be as low as 47% (22). Shakur-Still et al studied the pharmacokinetics of 4g of orally administered TA to pregnant women prior to planned cesarean delivery showing uptake similar to non-pregnant women taking about one hour to reach therapeutic serum concentration levels (13) whilst Muhunthan et al showed that mean time to maximum serum concentration of 10 mg/L in women receiving 2 g of oral TA one hour postpartum was 2,9 hours (1). This assessment is preliminarily supported by our pilot study on 40 laboring women showing uptake of 2 g of TA to therapeutic levels over 2-4 hours (unpublished data).

We therefore assess that a 2 gram dose is adequate for the oral form of TA in this study.

The study protocol adheres closely to clinical practice. No additional staff is provided by the study to ensure that the allocated treatment is given. This is to ensure that the feasibility of routine administration of TA can be assessed both from a provider and a participant perspective. Feasibility is not expected to differ between study groups and is

defined as the overall proportion of women successfully receiving and swallowing their allocated treatment at the timepoint planned in the study protocol.

TA is a well-tested product, available over the counter in Sweden, though not in South Africa, with mild and transient side-effects and no known increased risk of thromboembolic events (TE). Theoretically however the mechanism of action of TA could increase the risk of thromboembolism. Since the study tests the use of TA for a new indication (routine administration as a prophylaxis for PPH) we include the rate of TE as a secondary safety-related endpoint. Given an estimated baseline rate of TE in pregnancy of 1:1000, unchanged by the administration of TA, the expected rate of TE in both groups is 0-1 (21).

4.3 Measurement of background variables

Background-, pregnancy- and delivery- related variables will be retrospectively extracted from participant electronic or clinical records and entered into study electronic case report forms (eCRFs) by the investigator or research assistants. We will extract the following background and delivery-related variables from patient records:

Background variables:

- age at delivery
- BMI at start of pregnancy
- smoking
- reproductive history
- intercurrent diseases
- Pregnancy related diseases

Delivery data:

- gestational age
- fetal weight
- placental weight (if available)
- Apgar score
- Umbilical cord pH (if available)

4.4 Data analysis

Background, pregnancy, and delivery variables will be compared to demonstrate successful randomization using Fischer exact or Chi-square tests. Background data will be presented using a combination of the methods, as appropriate. Blood loss (ml) will be transformed to its natural logarithm to normalize the lognormal distribution and the geometric means corresponding to different groups will be compared using Student's T-test on the transformed (normal) variable. PPH ≥1000ml will be analysed using Chi^2 test or Fisher's exact test. Spearman's *rho* is planned for correlation assessments. Feasibility and safety outcomes will be presented descriptively as incidence rates per group. A p-value <0.05 or 95% confidence interval encompassing 1 will be considered significant.

Study groups will primarily be compared according to intention to treat (ITT) and secondarily per protocol (PP). The heterogeneity of study sites will be adjusted for in the final analysis. We plan a sub analysis per study site, per country as well as on the subgroup of women with prior history of severe PPH ≥ 1000ml, and women with anemia.

4.4.1 Sample size calculation

The baseline incidence of PPH≥ 500ml at the main recruiting site (Södersjukhuset, Sweden) is 39%. We assess that the smallest difference in treatment effect between TA and placebo groups would be an absolute decrease in PPH≥ 500ml of 9% (from 39% to 30%, relative treatment effect 23%). Using a 2- group Chi^2 test and 2-sided significance level we would require a sample size of 437 in each group to have 80% power to detect this decrease, or an equivalent decrease in rate of pre- postpartum Hb difference ≥ 10 units, with 95% confidence (from 39% to 30%). Based on baseline rates we assume that 8% of participants will be discontinued after randomization due to emergency caesarean section, and 1% of women will discontinue participation for other reasons. Our main outcomes are collected within 24 hours which will minimize loss to follow up. Accounting for this, we plan to randomize 500 women in each group, 1000 women in total.

This sample size will give us 80% power to detect an absolute decrease in severe PPH

(≥ 1000ml) of 5% assuming a baseline rate of 10.2%, and a 4% decrease in blood transfusion assuming baseline rate of 7%, using a 2-group Chi^2 test and 2-sided significance level, and a 3 unit difference pre-postpartum Hb (assuming a background Hb-difference of -8.9 gr/L and a standard deviation [SD] of 17gr/L) (23) using Student's *t*-test.

4.4.2 Handling of Dropouts or Missing Data

We expect low rates of missing data because all interventions and measurements are performed during the in-hospital period. Some women are expected to be discontinued because they will require an emergency cesarean section after randomization. Analysis will be performed both according to ITT and PP.

4.5 Research team qualifications and selection of study sites

The collaboration is based on local research capacity at five clinical study sites.
The study sites have been selected so as to include both primary and secondary level obstetric care. We have also selected units which have a focus on vaginal delivery and where the clinic staff are accustomed to, or motivated to learn, the standardized way in which blood loss is assessed in the study.

The principal investigator **Margit Endler, MD PhD** is a senior consultant at Södersjukhuset and an associate professor at Karolinska Institutet, Department of Women and Children´s Health and adjunct senior lecturer at the University of Cape Town. She is HPCSA certified. She has been principal investigator on two RCTs, both in South Africa. She has a PhD on the epidemiology and pathophysiology of retained placenta and postpartum hemorrhage. She will be principal investigator to the study and provide the scientific and medical management of study procedures.
Co-investigator and associate professor **Pelle Lindqvist, MD PhD** is a senior consultant and researcher at Södersjukhuset and is part of the collaborative Nordic Obstetric

Surveillance Study Group (NOSS) on placenta accreta spectrum disorders. He has an existing network at the Swedish study sites on the topic of postpartum hemorrhage.
Co-investigator **Gita Strindfors**, M.D, is a senior consultant in obstetrics at Södersjukhuset and a doctoral student. She is a member of the IS-PAS (International Society of Placenta Accreta Spectrum) and has worked clinically with this group of patients for the past five years. She will project manage the study as part of her PhD education.
Co-investigator **Lars Thurn, MD PhD** is a senior consultant and researcher at Lund´s University Hospital with a PhD on the topic of placenta accreta and postpartum hemorrhage. He will lead and coordinate the Lund study site.
Co-investigator **Zoltan Zavaczki, MD PhD** is head of the department of obstetrics at Hudiksvall hospital and twenty years of clinical experience. He will lead and coordinate the Hudiksvall study site.
Co-investigator **Chantal Stewart MD** is head of department at Mowbray Maternity Hospital (MMH)l in Cape Town Department and a specialist in high-risk pregnancy. She will lead and coordinate Mowbray study sites, MMH has approximately 12 000 deliveries per year.
Co-investigator **Christine Els MD** is head of the obstetric department at Khayelitsha District Hospital. The hospital has 3000 deliveries per year.
Co-Principal investigator for South Africa is Professor **Justus Hofmeyr, MD PhD** is a consultant gynecologist and obstetrician at the East London Hospital Complex, East London and a highly recognized expert in obstetrics. He has published 50 Cochrane systematic reviews and is an experienced lead researcher in the field of postpartum hemorrhage and other high risk obstetric disorders. He will act as consultant to the trial as a whole.
All research collaborators as well as research assistants will be GCP certified and receive GCP refresher courses if necessary.

4.6 Data Safety and Monitoring Plan

Adverse events (AEs) and serious adverse events (SAEs) will be continuously monitored during the trial. The research team will employ a professional monitor that

will assess whether any unexpected rate of adverse events or discrepancy between treatment effects are grounds for an early closure of the study**.** The monitor will á priori assess trial and data safety based on the protocol before initiation.

4.6.1 Display of Adverse Events

All adverse events occurring during after initiation of study treatments during the study period, irrespective of a relation with the study drug/device will be monitored and displayed in summary tables according to The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

Concurrent diseases that are reported at the time of inclusion will not be considered as adverse events, however any changes in symptoms or severity will be reported as an adverse even

i. Analysis of Adverse Events

Adverse events will be divided in severity categories and causality categories as listed below.

- Mild = the subject is aware of the event, but the event is easily tolerated
- Moderate = the subject experiences sufficient discomfort and the symptoms affect daily activities
- Severe = the subject experience significant impairment of functioning and the symptoms substantially affect daily activities

We draw a distinction between serious and severe AEs. The term severe is used to describe the intensity of the event but does not cause any of the serious effects of SAEs described below.

Further, the following definitions will be used to estimate the relation with adverse event and the IMP:

- Probable = clinically/biologically highly plausible and there is a plausible time sequence between the onset of the AE and the administration of the study drug. There is sufficient documentation to suspect a causal relationship
- Possible = clinically/biologically plausible and the relation cannot be rejected
- Unlikely = a causal relation is improbable, and another explanation is more likely
- Not possible to evaluate = relationship can be neither confirmed nor ruled out

The severity and causality categories will be displayed and listed in a fashion which enables comparison between the different treatment groups. We will also note whether there are signs of regional or background differences in experienced adverse effects. As we are examining the effect of one single dose, we don´t expect to be able to evaluate dose-response relationship.

4.6.3 Deaths, other serious adverse events (SAEs) and other significant adverse events

Death or other serious adverse events will be defined according to The ICH Guideline on Clinical Safety Data Management, Definitions and Standards for Expedited Reporting as:

“Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect”.

Serious Adverse Events (SAEs) will include all serious events independent of whether they have a suspected causal relationship to the IMP or not.

These will be listed separately and presented in summary tables and analyzed case by case. There will also be a separate objective individual event analysis in accordance with local clinical routine.

4.6.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Identification of and expedited reporting of SUSAR based on the RSI will be managed by the sponsor on regular basis.

4.6.5 Reporting of AEs, SAEs and SUSARs

Adverse Events (AEs)

- All adverse events the participant experiences (excluding known side-effect at expected severity) will be documented on the participant's paper case report file (CRF) following the participant by the midwife or doctor in charge during the delivery. The paper file will be collected by the principal study site investigator and transferred to the electronic participant CRF.
- Adverse events will be reported irrespective if the event has any relation with the study drug or not.
- Adverse events will be recorded in a separate CRF in the electronic study database RedCap and will define the suspected relationship to study medication, severity and expected outcome.
- AEs will be registered until the end of the study.

Serious Adverse Events (SAE)

- All SAEs that occur during the study will be reported to the sponsor on a separate SAE report form within 24 hours of the initial notification of the event. The initial notification to the sponsor will be made on a SAE-report form, by e-mail or telephone.
- At the time of initial reporting the investigator will provide the participant number, the personal number (Sweden) or patient record identification number (South Africa), birth date, description of the SAE and a preliminary assessment of causality.
- Supplemental information will be reported by the investigator to the sponsor

as soon as possible. If the SAE is fatal or life-threatening the investigator will report back with follow-up information to the sponsor within 5 days after the initial report

- If a reported SAE is present or ongoing when the participant completes the study the event will be followed for up to three months past the final visit or followed until final outcome is known or the condition is stable
- If the participant has a prolonged hospital stay or is re-hospitalized due to conditions related to the neonate (delayed breastfeeding, neonatal jaundice, weight decrease, or other condition) this will not be reported as an SAE

SUSARs

The sponsor will commit to reporting:

- Any SUSAR of the study drug which is life threatening or fatal will be reported to the South African Health Products Regulatory Authority (SAPHRA) as soon as possible and not later than 7 days after the responsible investigator has been aware of the event. The report will be sent to SAPHRA and the relevant Ethics Committee (HREC). Relevant follow-up information of the report will be sent within an additional 8 days (maximum of 15 days from initial report).
- A SUSAR of the study drug/device that is not life threatening or fatal should be reported as soon as possible but within a maximum of 15 days to SAPHRA and the HREC.
- All SUSARs will be reported to the SAPHRA on a Council for International Organizations of Medical Sciences (CIOMS)-form and also reported into the Eudra Vigilance Clinical Trial Module.

During the study, the sponsor will report all SAEs with a suspected relation to the study drug, and SUSAR, to the SAPHRA and HREC once a year. Moreover, a safety report concerning the participants included in the study should be

supplied together with a summary on a risk/benefit evaluation for the participants in the study. The sponsor will also inform all investigators about occurring SUSARs during the study period.

4.6.6 Unblinding

In case of serious adverse events the blinding will be broken to identify the medication given in the trial. In cases of severe postpartum hemorrhage non-respondent to uterotonic medication, 2 gram of TA (100mg/ml) is often given intravenously (administered at 1 ml/min) according to postpartum hemorrhage treatment guidelines and may be repeated once if bleeding continues after 30 minutes or restarts within 24 hours . This dose may also be administered for study participants if needed, without breaking the blinding. Assuming the participants received a maximum of 2g in the study this would result in a total dose of 4g over the course of several hours which is still below the high dose treatment used in other clinical settings (22). If doses beyond this are needed, the blinding will be broken to avoid the risk of overdose. The randomization sequence linking each participant to the product received will be stored in a locked cabinet at a central site (Södersjukhuset in Sweden, and Mowbray Maternity, South Africa) who operate on a 24hr basis. A number will be posted at the nurse´s station of each study site, as well as in the investigational binder located at each site, in case unblinding is necessary. The following reasons are pre-stipulated for unblinding:

- A severe adverse allergic reaction where the study medication received is believed to be the cause
- Ongoing postpartum hemorrhage where an additional 2 g of TA has been given but additional doses are indicated within 6 hours of study dose.

4.6.7 Stopping criteria

We will not a priori perform an interim analysis with unblinding of the data to assess

early closure of the trial. We do not expect the IMP to have a magnitude of effect such that it would be evident in a smaller sample size population than the one planned and that would warrant early closure of the study. We further have no reason to suspect a negative effect related to the IMP that would warrant stopping of the study for safety reasons.

Based on the long experience of using TA in clinical practice, and low rate of side effects, we do not expect new side effects or SAE associated to the IMP above the baseline incidence. We will monitor AEs and SAEs continuously. If SUSARS related to the medication occur repeatedly, or if SAEs occur at a rate higher than expected, the trial will be paused and we will ask the monitor to perform an unblinding and interim analysis of the data. If the SAEs are disproportionately related to the intervention arm, we will ask the monitor for advice on stopping the trial.

4.6.8 Study monitoring

We have appointed a monitor (KTA in Sweden and Marietjie Pretorius, UCT, in South Africa) that will ensure that the study is carried out according to the protocol and that data is collected, documented, and reported according to ICH-GCP and applicable ethical and regulatory requirements. Monitoring is performed as per the study's monitoring plan and is intended to ensure that the subject's rights, safety, and well-being are met as well as that data in the electronic database are complete, correct, and consistent with the source data.

The sponsor will be responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data and documents, and reports for the purpose of monitoring and auditing, and inspection by domestic and foreign regulatory authorities. The sponsor has also ensured that this is specified in the protocol as done above.

Each site will have a Site Initiation Visit by the assistant coordinating investigator to ensure the site is ready for study start, that appropriate documentation is in place, that the site competence is sufficient, and that source data is defined.

4.7 Data confidentiality

When women are randomized to the study, they will be automatically assigned a study ID by the Redcap data system. No identifying characteristics such as their name, address, telephone or unique personal identification number will be entered into the research database. All data from the study forms and participant records collected during the study will be registered in an pseudonymized form where participants are identified only by their study identification number. Paper forms will be stored in a locked cupboard at the university for the duration of the study period and then destroyed.

Data will be handled and saved in such a way that no one but the researchers involved has access to them. Data will be saved for 10 years. The log containing the link between the participant's personal data and study-ID will be protected by a code-key stored on a research specified computer to which only the main responsible researchers have access. Anonymized study data will be shared between the collaborating institutions University of Cape Town, Karolinska Institutet, Sweden, and Södersjukhuset (South General Hospital), Sweden. A collaboration agreement has been signed and certified between these three parties as well as a joint controller agreement regarding data transfer and analysis. Only pseudonymised data will be shared between institutions.

5. Description of Risks and Benefits

5.1 Potential risks and discomforts

The study procedures include taking two venous blood samples. Venous blood samples are often routinely taken during delivery or postpartum and involve minor discomfort and minimal risk of complications such as irritation or local inflammation at the site of the sampling. The

The safety profile of the IMP TA is described below. Every intake of a medicine not previously tried before involves the risk of an adverse reaction but it is in the case of TA assessed as very small.

5.2 Risk classification

This is a phase IV trial in Sweden and Phase III in Southh Africa because we are using an unregistered administration form of TA. The medicinal product is however not new and not used in a new population or a new context but is used in a way that is not yet standard of care, i.e. as a routine prophylactic treatment for all women instead of select women. We are also using a mode of administration (oral solution) that is not currently used. The rationale is that most PPH occur in women without previous risk factors (7). Oral solution is described as equivalent in dose-efficacy to tablets or effervescent tablets (24). We estimate the risk entailed in the study however as greater than minimal simply because it involves (in the case of participants randomized to the IMP) intake of a medical product. The IMP, TA was developed in 1962 and has been used to treat bleeding since the late 1960´s. Oral TA, is available without prescription at pharmacies at a recommended dose of 1-1.5g three times daily. It´s safety profile for women during pregnancy is well-tested and as intravenous solution it is routinely used therapeutically, and prophylactically for high-risk women, in pregnancy and postpartum with very low to unknown frequency of serious side effects.

According to the Swedish Medicinal Information Service (FASS) and the Food and Drug Administration, common side effects constitute mainly of gastrointestinal problems such as nausea, vomiting, diarrhea, and abdominal pains but also headache and dizziness (between 1 and 10%). Less common side effects are transient allergic skin reactions (between 0.1% and 1 %). Rare side effects are impaired color perception and photopsia (between 0.01% and 0.1%) and extremely rare (so rare that the frequency cannot be calculated with current data) are thromboembolic events and seizures (24-26). A recent systematic review and Meta-Analysis concluded that TA, in addition to being effective in reducing PPH has an increased risk of causing minor side effects such as nausea and vomiting but does not seem to increase the risk of dizziness and photopsia (25) All research to date has shown that TA when used as prophylaxis or treatment for PPH in pregnant and puerperal women is not associated with an increased risk of thrombosis. The WOMAN trial (2017), a large RCT where 20 000 pregnant women were randomized to receiving TA or placebo as treatment for PPH, showed that there was no significant

difference between the groups regarding incidence of venous or arterial thromboembolic events (8). This was confirmed in the TRAAP-study (2018), where 4079 pregnant women received TA or placebo prophylactically immediately after the delivery of the child, no significant differences were seen regarding incidence of thromboembolic events (9). These studies confirm what has previously been reported for trauma patients (15). It is likely that there is a relationship between dose and adverse effects as most studies use a low dose regimen (1 g TA iv as loading dose and repeat dose of 1 g as slow infusion if continued hemorrhaging) but even when using high-dose regimen (loading dose 4 g over 1 hour, then infusion of 1 g/hour over 6 hours) as in the EXADELI-study there were no significant differences in the incidence of severe adverse reactions (SARs) (22). There is no reported increased risk of fetal malformations (24-26).

TA is listed on the World Health Organization´s List of Essential Medicines for the indication of treatment of postpartum hemorrhage (27).

Table 1. Frequency of undesirable effects at a dose of 4 g/day (MedDRA LLT):

Organ Class	**Frequency**		
	Common	***Uncommon***	***Not known***
	Adverse Reactions(ARs)		***Serious Adverse Reactions (SARs)***
Nervous system disorders	Dizziness, Headache		Convulsions
Gastrointestinal Disorders	Vomiting, Diarrhea, Nausea, Abdominal pain		
Skin and subcutaneous tissue disorders		Allergic skin reaction	
Eye disorder			Impaired color vision and other

			visual disturbances
Vascular disorders			Thromboembolic events

5.3 Minimizing risk

The study procedures themselves- intake of 20ml of TA and two blood samples are not expected to cause more than minor discomfort or risk and both interventions often occur as part of routine care for women in delivery. As Reference Safety Information (RSI), we will provide a detailed overview of the safety profile of the IMP (TA) to all investigators including the expected ARs and SARs listed in the Summary of Product Characteristics (SmPC) as detailed in the table below.

It will serve as the basis for expectedness assessments of 'suspected' SARs by the sponsor for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) and annual safety reporting. SAR being "all noxious and unintended responses to an investigational medicinal product related to any dose administered that at any dose results in death, is life- threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect". This may imply a reasonable possibility of a causal relationship between the event and the IMP, i.e., evidence to suggest a causal relationship.

This section will be regularly assessed and revised if the risk/benefit relationship of the therapeutic effect of TA to ARs/SARs should change.

5.4 Potential benefits

For participants receiving the IMP, participation may result in less PPH. The long-term aim of this project is to optimize intrapartum management of PPH in an effort to reduce morbidity. Reducing complications to PPH will reduce the need of hysterectomy, blood transfusion, and medication, length of hospital stay, sick leave, psychological sequelae

and medical costs. It would also benefit the new-born, reducing acute morbidity at birth and separation from the mother, and increasing immediate uptake of breastfeeding.

Should prophylactic oral TA prove to be effective in preventing PPH, it could be a critical treatment in both high and low resource settings due to its low cost, stability and easy administration. If orally administered TA proves equally efficient to intravenous TA in reducing blood loss postpartum this should be considered for inclusion in routine delivery care. By including low resource settings in other countries in the larger RCT we hope to help increase optimal management of vaginal birth in these and other countries. In low-income countries many women are anemic even before pregnancy due to malnutrition and concurrent diseases such as malaria, HIV and tuberculosis, it is therefore of utmost importance to prevent unnecessary bleeding during delivery. Oral TA compared to intravenous TA is widely available, easy to administer even by the woman herself, cheap, and stable at room temperature.

Strengthening research capacity in the participating study sites in both Sweden and South Africa is a peripheral but important benefit and many clinical staff will gain both theoretical (through GCP certification) and practical research competence.

5.5 Alternatives to participation

The alternative to participation in the study is standard delivery care. The quality of care received during labor or afterwards will not be affected by participation or non-participation. Individuals that chose not to participate will be assured that this will not affect their clinical care whilst in the hospital or afterwards.

5.6 Harm: benefit ratio

PPH is the leading cause of maternal death worldwide and entails both short- and long-term morbidity. TA is a well-tested product used to treat hemorrhage and heavy menstrual bleeding, has no known common severe side-effects, is routinely used to treat PPH, and is available over the counter in many settings. The purpose of clinical trial is to assess the effectiveness of its prophylactic use in women in labor. The risk-benefit calculus therefore poses the question if the potential benefits outweigh the

cost, resources and expected side effects related to routine use. Our assessment is therefore that even a small prophylactic effect would outweigh the expected risk of the intervention. The aim of this project is to optimize intrapartum management to reduce PPH-related morbidity. Reducing complications to PPH will reduce the need of hysterectomy, blood transfusion, and medication, length of hospital stay, sick leave, psychological sequelae and medical costs. It would also benefit the newborn, reducing acute morbidity at birth and separation from the mother, and increasing immediate uptake of breastfeeding.

Exploring alternative routes of TA administration for PPH reduction is a stated research priority by the WHO. In low-income countries many women are anemic even before pregnancy due to malnutrition and concurrent diseases such as malaria, HIV and tuberculosis, it is therefore of utmost importance to prevent unnecessary bleeding during delivery. Even a small clinical effect and reduction of bleeding can make a big difference for survival and recovery in poor countries where many women have hemoglobin values as low as 50 to 60 g/L and little margin exists to life-threatening anemia.

Oral TA compared to intravenous TA is widely available, easy to administer even by the woman herself, cheap, and stable at room temperature. Intravenous TA is effective to treat and prevent PPH. Intravenous TA however may require refrigeration which is unrealistic in many clinical settings. Administration is done slowly and requires the insertion of a peripheral line which 1) requires the presence of a skilled provider, and 2) means that the provider cannot perform other crucial interventions such as uterine compression during the time it takes to insert the line. The cost of intravenous TA is a relative barrier to routine administration in high resource settings and an absolute barrier in low resource settings. One treatment dose (1-2g) intravenous TA costs at a minimum 46-92$, whereas 1-2g oral TA is available for as little as 1.6-3.2$ per treatment, an almost 30-fold price difference.

Should prophylactic oral TA be effective in preventing PPH, it could be of critical impact in both high and low resource settings. Oral compared to intravenous TA is

applicable to all birth settings, including home births. If oral TA is feasible and has similar efficiency to intravenous TA in reducing PPH, it should be considered for inclusion in routine delivery care.

6. Informed Consent

6.1 Informed consent process

Women will be included to the study after a private written informed consent procedure in a private space. The informed consent procedure will be led by research midwives, study investigators, or trained and experienced research assistants, all GCP certified. The ICF process will take place in the language of the participant´s choice limited to English, IsiXhosa and Afrikaans in the South African context. During this process women will be informed of the risks and benefits of the study and their rights as participants. Participants will be able to discuss participation with family, friends, or advisors before signing the consent form.

The ICP will occur at a participating study site atwhich the women has sought care, either for an antenatal check-up, or after admission to the delivery ward for induction or in the latency phase. Women will be recruited before onset of active labor so as to ensure they can take part, understand and consent during the ICP.

6.2 Capacity to consent and assessment of vulnerability

The study will not include minors, adults with intellectual disability or mental illness interfering with decision making. All participants will be able to give informed consent to participation. The study will not exclude participants of low socioeconomic status, prior- or pregnancy related health disorders as these are groups for whom the intervention may be particularly valuable. The research will take place at clinical facilities to which the participants have been admitted for labor or which they are anyway consulting for antenatal check-ups. All primary research procedures will take place within 24 hours of admission.

6.3 Comprehension of information

The ICP will be performed by two research assistants who are experienced in performing this role during clinical trials in the field of reproductive health in general. Their experience includes assessing participants ability to understand the content of the ICP by asking them to relay back what they have understood from the text. The ICP will be performed in the participant´s native or preferred language. The research assistant will at standardized points in the process pause to ascertain that the participant understands what is being read to her by having her summarize the main content in her own words.

6.4 Withholding information

Participants will be blinded to whether they received the IMP or the placebo but will be aware of the blinding. No other information regarding the study will be withheld from participants.

6.5 Consent and assent forms

The informed consent form will be available in Swedish for participants in Sweden, and translated into English, IsiXhosa and Afrikaans for participants in South Africa. The content of the consent forms will comply with the legal and ethical requirements detailed in the Standard Operating Procedure relating to Informed Consent.

6.6 Privacy and Confidentiality

Forms for collection of data about participants will not include names or addresses, only the participant's medical record number and her study ID number. Signed informed consent forms will record participants´ names and signatures only and will be filed separately from other study documents. Likewise, a locator form with the participant's name, study ID, South African ID number, medical record numbers, address, and phone number, will be filed separately from all other study documentation. South African ID numbers will be needed to follow-up on medical records or unscheduled clinical visits after the delivery, in facility records. All study forms will be kept in a locked cabinet at

the research office at UCT and no one outside of the core research team members will have access to these forms. Study documents will be archived securely in a locked cupboard, accessible to the investigators only, for ten years, and then shredded. Staff involved in data entry will not have access to any identifying information on the participants or facilities. All electronic data files will be password-protected. We will not advertise the study at the clinics or surrounding communities.

7. Reimbursement for Participation

Women recruited to the study will receive compensation for the inconvenience and time loss that the study procedures are expected to incur. Participants in South Africa will be compensated R150 upon discharge from the hospital, in the form of a food voucher, in line with the 2022 SAPHRA participant compensation model https://www.sahpra.org.za/wp-content/uploads/2022/01/SAHPGL-CEM-CT-02_v2-Guideline-for-CT-Participant-Time-Inconvenience-and-Expense-TIE-Compensation-Model.pdf. Swedish participants are not expected to incur any loss of income due to study participation will not receive any compensation.

8. Emergency Care and Insurance for Research-Related Injury

The research is conducted within the normal delivery health care system in Sweden and South Africa and does not include any procedures outside of routine perinatal care. Patients in Sweden who suffer from injury are insured through the Swedish Patient Insurance (LÖF) and may be offered compensation determined by the Swedish Patient Injury Act.

Patients in South Africa are covered by an no fault insurance policy to cover injuries incurred in research not sponsored by a pharmaceutical company.

9. What Happens at the End of a Study?

Oral tranexamic acid in tablet from which is assumed to be equivalent to the oral solution in dose-efficacy is available and part of routine treatment for PPH in

delivery wards. Because of its low cost, stability at room temperature it would be easily integrated into routine share should the treatment prove effective as a prophylactic treatment for PPH.

The study is taking place in public facilities and as such we will work directly with the staff and management of the facility to build their capacity and obtain their input on the study implementation. They will also be informed of the study results, and the study team will work with the facility and policy makers to consider how the results may be implemented. At the time of recruitment, we will inform participants when we anticipate having final results for the study, and we will encourage them to contact us at the contact numbers on the consent form so they can be informed about the study results if they wish to know them.

Following analysis of study results, departmental heads provincial DOH structures will be invited to take part in the study findings with a view to initiating policy and program changes if supported by the study findings. We will ensure timely sharing and publication of results, and the data collected will ultimately be available for public use. Study findings will be made public through scientific meetings and peer-reviewed journals, as well as through a structured dissemination process with facility staff and policy makers.

Other pre-stipulated end-of-trial measures are the following:

- Within 90 days of completion of the study, the sponsor will report to the SAPHRA and the HREC that the study is completed as stated in the protocol.
- If the study will be ended and closed prematurely, the sponsor will report to the SAPHRA and the HREC within 15 days. The reasons for the decision shall be reported
- The EU-common form ”end of trial” shall be used and sent electronically to the SAPHRA
- The sponsor will also send a summarizing report to the EudraCT database within 12 months after the study has been closed.

10. References

1. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. The Lancet Global health. 2014;2(6):e323-33.
2. Moodley, J., Fawcus, S. & Pattinson, R.C. 2020, '21 years of confidential enquiries into maternal deaths in South Africa : reflections on maternal death assessments', Obstetrics and Gynaecology Forum, vol. 30, no. 4, pp. 4-7.
3. Fadel MG, Das S, Nesbitt A, Killicoat K, Gafson I, Lodhi W, et al. Maternal outcomes following massive obstetric haemorrhage in an inner-city maternity unit. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2019;39(5):601-5.
4. Ducloy-Bouthors AS, Jude B, Duhamel A, Broisin F, Huissoud C, Keita-Meyer H, Mandelbrot L, Tillouche N, Fontaine S, Le Goueff F, Depret-Mosser S, Vallet B; EXADELI Study Group; Susen S. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. Crit Care. 2011;15(2):R117.
5. Sentilhes L, Winer N, Azria E, Senat MV, Le Ray C, Vardon D, et al. Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. N Engl J Med. 2018;379(8):731-42.
6. Gilmandyar D, Thornburg LL. Surgical management of postpartum hemorrhage. Seminars in perinatology. 2019;43(1):27-34.
7. Novikova N, Hofmeyr GJ, Cluver C. Tranexamic acid for preventing postpartum haemorrhage. The Cochrane database of systematic reviews. 2015(6):Cd007872.
8. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet (London, England). 2017;389(10084):2105-16.
9. Sentilhes L, Winer N, Azria E, Sénat MV, Le Ray C, Vardon D, Perrotin F, Desbrière R, Fuchs F, Kayem G, Ducarme G, Doret-Dion M, Huissoud C, Bohec C, Deruelle P, Darsonval A, Chrétien JM, Seco A, Daniel V, Deneux-Tharaux C; Groupe de Recherche en Obstétrique et Gynécologie. Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. N Engl J Med. 2018 Aug
10. WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage. World Health Organization. 2017.
11. Picetti R, Shakur-Still H, Medcalf RL, Standing JF, Roberts I. What concentration of tranexamic acid is needed to inhibit fibrinolysis? A systematic review of pharmacodynamics studies. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2019;30(1):1-10.
12. Sindet-Pedersen S. Distribution of Tranexamic Acid to Plasma and Saliva After Oral Administration and Mouth Rinsing: A Pharmacokinetic Study. The Journal of

Clinical Pharmacology. 1987;27(12).
13. Shakur-Still H, Roberts I, Grassin-Delyle S, Chaudhri R, Geer A, Arribas M, Lamy E, Mansukhani R, Lubeya MK, Javaid K, Kayani A, Israr N, Mazhar SB, Urien S, Bouazza N, Foissac F, Prowse D, Carrington L, Barrow C, Onandia JG, Balogun E. Alternative routes for tranexamic acid treatment in obstetric bleeding (WOMAN-PharmacoTXA trial): a randomised trial and pharmacological study in caesarean section births. BJOG. 2023 Apr 5.
14. Muhunthan K, Balakumar S, Navaratnaraja TS, Premakrishna S, Arulkumaran S. Plasma Concentrations of Tranexamic Acid in Postpartum Women After Oral Administration. Obstet Gynecol. 2020 Apr;135(4):945-948.
15. Roberts I, Shakur H, Coats T, Hunt B, Balogun E, Barnetson L, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health technology assessment (Winchester, England). 2013;17(10):1-79.
16. McCormack PL. Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. Drugs. 2012;72(5):585-617.
17. Bedson R, Riccoboni, A. Physiology of pregnancy: clinical anaesthetic implications. Continuing Education in Anaesthesia Critical Care and Pain. 2014;14(2):69-72.
18. Anger H, Durocher J, Dabash R, Winikoff B. How well do postpartum blood loss and common definitions of postpartum hemorrhage correlate with postpartum anemia and fall in hemoglobin? PLoS One. 2019;14(8):e0221216. doi: 10.1371/journal.pone.. eCollection 2019.
19. The E-Motive Trial. University of Birmingham. https://www.birmingham.ac.uk/research/bctu/trials/womens/emotive/e-motive.aspx
20. Churchill D, Nair M, Stanworth SJ, Knight M. The change in haemoglobin concentration between the first and third trimesters of pregnancy: a population study. BMC pregnancy and childbirth. 2019;19(1):359.
21. https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/07/thromboembolism-in-pregnancy
22. Grassin-Delyle S SM, Lamy E, Urien S, Runge I, Foissac F, Bouazza N, Treluyer JM, Arribas M, Roberts I, Shakur-Still H. Pharmacokinetics of tranexamic acid after intravenous, intramuscular, and oral routes: a prospective, randomised, crossover trial in healthy volunteers. Br J Anaesth. 2022 128(3):465-72.
23. Lindqvist PG, Svensson PJ, Dahlbäck B, Marsál K. Factor V Q506 mutation (activated protein C resistance) associated with reduced intrapartum blood loss--a possible evolutionary selection mechanism. Thromb Haemost. 1998;79(1):69-73.
24. FASS. Tranexamsyra. https://www.fass.se/LIF/result?query=tranexamic%20acid&userType=0 (Swedish)
25. FDA. Tranexamic Acid N22-430S003 Clinpharm. PREA. https://www.fda.gov/media/86940/download
26. Xia Y, Griffiths BB, Xue Q. Tranexamic acid for postpartum hemorrhage prevention in vaginal delivery: A meta-analysis. Medicine (Baltimore). 2020;99(3):e18792.

27. World Health Organization. List of Essential Medicines. https://list.essentialmeds.org/recommendations/909

11. List of Appendix Material

The following appendix material is attached in addition to Sections A, B, and C,

- Funding/ grant application
- Consent and assent forms (English versions)
- Budget summary