23.02.2025
Version 11

The Effect of Topical Tranexamic Acid on Postoperative Complications in Soft Tissue Plastic Surgery. A Multicenter Randomized Controlled Trial

The TRANOP Study

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Protocol Title:

A parallel-group treatment, Phase 4, prospective multicenter double-blind randomized 2-arm placebo-controlled low-intervention study to investigate the effect of single dose topical administration of tranexamic acid vs placebo onto surgical wound surfaces on postoperative re-bleeding, wound complications, seroma and thromboembolic events in male and female patients above 18 years of age undergoing plastic surgery.

Protocol Number: 270777

Protocol Version: 11
Compounds: Active drug: Tranexamic acid concentrate for infusion B02A A02
Placebo: Sodium Chloride 0.9% solution for injection B05X A03

Brief Title:

A study to investigate the effect of local application of tranexamic acid versus placebo (saline) onto a surgical wound on surgical postoperative complications in participants above 18 years of age undergoing plastic surgical procedures.

Working Title: The TRANOP Study

Study Phase: Phase 4

Sponsor Name:
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Participating Study Centers and Local Principal Investigators
To be provided after approval of study design/study protocol by national authorities.

Regulatory Agency Identifier Numbers:

Registry	**ID**
EudraCT	2022-001580-28
EU CT number	2023-510381-28-01
Regional Ethical Committee	2022/478778
CRISTIN	2574360
ClinicalTrials.gov	NCT06270407

Approval Date:

Sponsor Signatory:

Torbjørn Dahl, MD PhD	**Date**
Head of Clinic of Surgery, St Olav's University Hospital	

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*11-05-2022*
Amendments	Protocol Version 2 27-11-2022 has been re-structured to comply with protocol structure recommended by NorCrin. No amendments of content have been made. Protocol Version 3 16-02-2023 has been re-structured according to the response from the Norwegian Medicines Agency to protocol version 2. Protocol Version 4 15-03-2023 has been further re-structured according to the response from the Norwegian Medicines Agency to protocol version 3. Protocol Version 5 25-03-2023 has changed the wording of Appendix 7 to match the protocol section 6.4 Protocol Version 6 24-11-2023 has expanded its title on the front page. CTIS transition number added (page 3) Study funding has been defined (1.1) "Seroma needing intervention" is added as end point where study end points are defined (1.1, 1.2, 1.3, 2.1, 2.2, 3.1, 9.1, Appendix 2 and 3) "Former bariatric surgery" to registered variables (1.3, 3.2, 9 and Appendix 2 and 3). Blood transfusion as end point variable for postoperative bleeding is added (3.1, 9.1, Appendix 2 and 3). The word "patients" has been replaced with "wounds" (3.1, 6.3, 9.2). Study solution for single wound vs bilateral surgical procedures has been clarified (6.2, 8.1, 9.3.1, Appendix 6). Plans for final analyses and publications have been clarified (4.1, 9.3.2). Indications for performing an interim analysis has been modified. (9.3.3). Study Center candidates have been defined (10.1.10, Appendix 8) English versions of Appendices added for international collaboration Informed consent form has been updated regarding study dates and signature from study collaborator (Appendix 5) Protocol Version 7 05-02-2024 is updated in accordance with EU CTR 536/2014 (1.1), increasing data storage time to 25 years (10.1.8) and added language skills and capacity to consent as inclusion criteria (5.1, 5.2). Protocol Version 7 is corrected to minor typos and inconsistencies.

	Informed consent form has been updated regarding EU General Data Protection Regulation (GDPR) and patient information data (Appendix 5) Protocol Version 8 20-02-2024 has added ClinicalTrials.gov registration number. References to NoMA changed to "competent authorities" in preparation for adding more countries (List of abbreviations, 8.4.4, 10.1.7). Removed language skills as selection criterion (5.2). Protocol Version 9 15-04-2024 has corrected the list of participating centers to only include those with adequate training at the time of submission(10.1.10, Appendix 8). Protocol Version 10 27-12-2024 has added the working title "The TRANOP Study" and study logo. Registration number for CRISTIN (Current Research Information System in Norway) has been added. Edited 6.3 as randomization code is not kept with monitor to keep monitor blinded. Details regarding study organization, registration and storage of patient variables have been added to the consent form, and how to obtain consent has been clarified (Appendix 5, 5.1, 10.1.3 and 4). How to contact unresponding patients has been further clarified (7.3, 8.1, 8.2 and 10.1.3). Criteria for breaking of code have been clarified (8.4.4, Appendix 7), and action in case of adverse events have been specified (2.3.1, 8.4.2). Variables to identify screen failures and lost to follow-ups have been added to the eCRF (Appendix 2). Structure and layout of the final eCRF (Appendix 2) and Patient Questionnaire (Appendix 3) and procedures for obtaining study variables have been clarified (Synopsis, brief summary, 2.3, 3.2, 4.1, 4.4, 8.2, 8.4). A final signature page has been added. The changes in Protocol Version 10 have been deemed non-substantial. Helsinki University Hospital, Vejle and Odense Hospital and Tromsø University Hospital UNN have been added as collaborating study centers (Appendix 8) in preparation for submitting them via substantial modifications/additional member states in CTIS. Protocol Version 11 23-02-2025 has been amended as requested in Requests for Information (RFIs) in CTIS. Norwegian consent form V7 (Appendix 5) has been revised. The fact that the IMP ampoule number equals study ID number is clarified (6.2). The protocol is modified with regards to financing and the systems used for obtaining informed consent and study variables as to accommodate other research systems than the one used in Norway. Several sections revised for clarity (1, 3.2, 4.1, 4.4, 8.1, 8.2, 10.1). The study is a "low-intervention study". The term "low-intervention" is added to the protocol title.

Medical Monitor Name and Contact Information

Monitoring will be provided through the Clinical Research Unit at St Olav's University Hospital and their national and Nordic collaborators.

List of Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
eCRF	electronic Case Report Form
eForsk	Norwegian Electronic System for Health-Related Data Collection
GCP	Good Clinical Practice
ICF	Informed Consent Form
IMP	Investigational Medical Product
IRB/IEC	Institutional Review Board/Institutional Ethical Committee
KLINBEFORSK	Clinical therapy research in the specialist health services
REK	Regional Ethical Committee
SD	Standard Deviation
SoA	Schedule of Activities
SPC	Summary of Product Characteristics
SUSARs	Suspected Unexpected Serious Adverse Reactions
TXA	Tranexamic acid
Viedoc	Electronic Data Capture System, Internationally approved

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A parallel-group treatment, Phase 4, prospective multicenter double-blind randomized 2-arm placebo-controlled low-intervention study to investigate the effect of single dose topical administration of tranexamic acid vs placebo onto surgical wound surfaces on postoperative re-bleeding, wound complications, seroma and thromboembolic events in male and female patients above 18 years of age undergoing plastic surgical procedures.

Brief Title:

The effect of local application of tranexamic acid versus placebo on postoperative complications in plastic surgery.

Regulatory Agency Identifier Numbers

Registry	ID
EudraCT	2022-001580-28
Regional Ethical Committee	2022/478778
EU CT number	2023-510381-28-01
ClinicalTrials.gov	NCT06270407

Rationale: The antifibrinolytic drug tranexamic acid (TXA) reduces surgical bleeding. Approved administration is systemic (intravenously or orally), but local use of TXA onto surgical wounds is becoming increasingly common. This administration form is however still off-label, and large studies regarding potential adverse effects from local administration are lacking.

Objectives, Endpoints and Estimands: Our main objective is to investigate whether topical use of TXA onto a surgical wound surface affects the incidence of postoperative re-bleeding needing intervention within 10 days after surgery. Secondary objectives are to investigate whether the procedure affects the incidence of wound infection, wound rupture, postoperative seroma or thromboembolic events needing intervention within 30 days after surgery. Estimands are the occurrence or absence of such incidents within the defined time periods.

Overall Design: This will be a prospective randomized placebo-controlled double-blinded multicenter trial conducted in plastic surgery units which already have established single dose topical application of TXA onto surgical wounds before wound closure as a routine prophylactic procedure to reduce bleeding.

Study intervention: In surgeries where they would normally choose to apply TXA onto the wound surface, participating surgeons will utilize a numbered study ampoule for the single-dose topical application onto the surgical wound, diluting the vial and using the solution according to their

local practice. Intervention is therefore potential withdrawal of routine TXA treatment if the patient receives a placebo ampoule. In procedures where patients have two separate surgical wounds, each wound will constitute a study case and receive a separate study ampoule. The ampoule number constitutes study ID number. A paper study form will link study ID number to patient identification.

End points: The effect of TXA will be compared to a placebo (saline) on the following end points: Postoperative re-bleeding needing intervention such as re-operation, drainage or extra compression within the first 10 days after surgery, wound complications such as infection, wound rupture or seroma needing extra follow-up, re-operation, revision or antibiotics within 30 days after surgery, and any thromboembolic event needing medical treatment up to 30 days after surgery.

Study drug and manufacturing: A professional manufacturer will mask ampoules and manufacture ready-made randomized packages with identical ampoules containing either active drug or placebo in a 1:1 ratio.

Study size: We plan to include 1500 patients in each group. As each wound will constitute a case, number of cases will be higher as a proportion of patients will have two separate wounds.

Inclusion criteria: Patients aged 18 or above who are to undergo a plastic surgical procedure where the participating centers have established topical use of TXA, and who sign an informed consent form (ICF).

Exclusion criteria: If routine pre-surgical screening reveals a condition which would prevent the surgeon from routine administration of TXA (allergy to TXA).

Patient follow-up and registration of study data: Patients will be observed in accordance with prevailing routines for their surgery. Patients will receive an electronic web-based self-report study form on study variables and end points 30 days after surgery and may also receive a follow-up phone call 5-6 weeks after surgery to assure correctly registered study data and adverse events. Reported variables are defined as study site, age, sex, surgical procedure, BMI, smoking, co-morbidities, medication, perioperative anticoagulation, and any postoperative medical event for each wound up to postoperative day 30. Medical records may be screened when patient reported outcomes need clarification. Pseudonymised study data will be registered in web-based Case Report Forms (eCRFs/Viedoc® for final data analyses).

Timeline for trial participation: Participants will be screened for eligibility when enrolled for surgery. Participation is terminated after the transfer of study variables based on the self-report study form and/or medical journal and phone call to eCRF 5-6 weeks after surgery.

The trial is to be conducted in accordance with Good Clinical Practice (GCP) and in accordance with the Helsinki declaration on ethical principles on medical research in humans. The trial will follow EU Clinical Trial Regulation 536/2014 Clinical Trials on Medicinal Products for Human Use. The trial will be coordinated by the Clinical Research Unit and Section for Plastic and Reconstructive Surgery, Clinic of Surgery, St Olav’s University Hospital, Trondheim, Norway. Study nurses will be engaged for day-to-day patient recruitment and follow-up. Monitoring of the trial will be coordinated by the Clinical Research Unit at St Olav’s University Hospital. The study is funded through a national research grant from KLINBEFORSK (Clinical therapy

research in the specialist health services). Participating centers outside Norway will have separate agreements on funding and staffing in collaboration with local research authorities and the Sponsor.

1.2. Brief Summary:

Study objective: This is a study to investigate whether applying the drug tranexamic acid (TXA) onto a surgical wound surface may affect the incidence of surgical complications such as re-bleeding needing intervention, wound complications such as infection, wound rupture or seroma, or if it may increase the risk of blood clots.

Eligible patients: Patients undergoing plastic surgical procedures with wounds that would normally receive application of TXA to reduce bleeding after surgery.

Study intervention: Participants will receive a single local application of study drug onto their wound surfaces at the end of surgery. Study drug will be identical looking ampoules which contain either TXA or placebo (saline). In case of several separate wounds, each wound will constitute a study case and receive a separate ampoule. Neither participants nor study personnel will know the contents of the ampoules.

Study details: Any serious postoperative complication needing intervention, specifically re-bleeding, wound infection, wound rupture, or the occurrence of blood clots for the first 30 days after surgery will be registered for each wound through the following interventions:

-Distribution of an electronic self-report form to participating patients at postoperative day 30

-Follow-up phone call when needed to verify data after day 30.

-Screening of patient medical records when needed for clarification

The study is terminated for participants when all study variables from around Day 30 have been collected.

Number of participants: To assess the effect of TXA on the defined surgical complications compared to placebo, 1500 patients are needed in each group. Total number of cases will be higher as a proportion of patients will have more than one wound.

Data monitoring committee: A data monitoring committee consisting of a group of independent scientists will be appointed for this study to monitor the safety and scientific integrity of this human research intervention.

1.3. Schedule of activities (SoA)

The following table demonstrates the schedule of activities for a participant:

Procedure	**Screening (up to 30 days before Day 1)**	**Day of surgery**	**Day 1**	**Day of discharge**	**On demand out-patient contact**	**Day 30 Patient Self-report form**	**After Day 30: Final follow-up: Screening of medical record and phone call**
Informed consent	X						
Inclusion and exclusion criteria	X						
Study Site	X					X	X
Planned surgical procedure	X					X	X
Sex, age, height and weight	X					X	X
Former bariatric surgery	X						
Diabetes / Hypertension	X					X	X
Former thromboembolic event	X					X	X
Smoking status	X					X	X
Peri/postoperative anticoagulation		X	X	X		X	X
Randomization		X					
Study intervention		X					
AE review			X	X	X	X	X
SAE review			X	X	X	X	X
Re-bleeding within 10 days postoperatively warranting intervention					X	X	X
Within 30 days postoperatively: -Wound infection warranting intervention					X	X	X
-Wound rupture warranting intervention					X	X	X
-Seroma warranting intervention					X	X	X
-Any thromboembolic event					X	X	X

Procedure	Screening (up to 30 days before Day 1)	Day of surgery	Day 1	Day of discharge	On demand out-patient contact	Day 30 Patient Self-report form	After Day 30: Final follow-up: Screening of medical record and phone call
Registration of study data in eCRF and termination of participation							X

2. Introduction

2.1. Study Rationale

Topical (local) use of TXA in soft tissue surgical procedures has been shown by our study group and others to reduce surgical bleeding. The method has been adopted by the Norwegian plastic surgical community, and it is increasingly utilized internationally as this is a low-cost drug and a simple procedure. Various modes of topical delivery and drug concentrations are practiced. As topical use is expanding, sufficiently powered studies to evaluate the effect of topical TXA on postoperative complications are lacking. While we believe topical TXA may reduce re-bleedings, we need to know if it may increase other surgical complications. Study rationale is to investigate whether topical application of TXA[1] onto a surgical wound affects the incidence of postoperative re-bleeding, wound infection, wound rupture, seroma or thromboembolic events in plastic surgery procedures compared to the topical application of a placebo (saline)[2].

2.2. Background

The antifibrinolytic drug TXA has been shown to reduce both postoperative bleeding and transfusion needs in high-bleed surgery, which is typically surgery involving bony structures where bleeding is hard to control[3]. The drug is normally administered intravenously or orally. Due to unease regarding potential adverse effects such as thromboembolic events and seizures, systemic TXA has not been routinely administered in soft tissue surgery where bleeding is easier to control[4]. However, all reduction in bleeding is beneficial, both with regard to patient safety and discomfort, and use of medical resources. Of particular interest is the occurrence of postoperative re-bleedings warranting active intervention such as re-operation, aspiration, or active compression. Moreover, re-operations for hematomas and blood transfusions may be independent risk factors for thromboembolic events[5].

Topical application may provide sufficient drug concentration at the site of bleeding while minimizing the risk of systemic adverse effects[6]. Meta-analyses on topical use show a reduction in bleeding volume and transfusion needs comparable to iv use, but studies are mainly from orthopaedic joint replacement surgery and cardiac surgery, with few studies from soft tissue surgery[7-9]. Concentrations of TXA used for topical application ranges from 0.5 to 100 mg/ml[8].

Our group has demonstrated a 30-40% reduction of bleeding volume measured as drain production in breast surgery from moistening wound surface with 25 mg/ml TXA[10,11]. A review on the effect of topical use of TXA in soft tissue surgery suggests a significant reduction in hematomas needing surgical intervention from applying topical TXA[12]. However, significant re-bleedings are generally rare and few randomized studies on the effect of topical TXA report re-bleeding as an end point. No studies on the effect of iv or topical TXA have to date been powered to assess this variable as the primary outcome. It is, however, often reported as a secondary outcome in cardiac surgery, where iv TXA reduces the risk of re-exploration by approximately 50%[13].

Topical application of TXA results in very low systemic drug levels and should therefore pose a negligible risk of systemic adverse effects such as thromboembolic events[6]. However, the local

effect of topical TXA on tissue is inadequately explored[14]. Wound complications such as wound ruptures, wound infections and seromas are also rare occurrences and no study on topical use of TXA has been powered to assess whether topical TXA may increase the risk of local adverse events.

2.3. Benefit/Risk Assessment

TXA is an old drug and in the WHO list of essential drugs[15]. Topical use is widely published albeit mainly from orthopaedic and cardiac surgery[9]. Use is less common in soft tissue surgery, and publications have no standardized mode of application or drug concentration, as mode of delivery and concentration is often adapted to the wound surface area and anatomy of the respective surgeries[12]. While the plastic surgical community has widely adopted this method, evidence regarding use in soft tissue surgery is still limited and randomized studies are few and small. Other surgical fields may argue that evidence is still insufficient to widely adopt this method. Topical use is still off-label.

Documenting that the simple topical administration of TXA significantly reduces re-bleeding without increasing wound complications would be of great beneficial value both to patients and to society (shorter recovery, less drain time and less discomfort for the patient, less use of donated blood, less risk of secondary complications such as thrombosis, less outpatient visits). The methodology is low-cost and simple and may therefore be particularly of interest in health care settings with limited resources. However, should we discover that the procedure may increase the risk of surgical complications, we must reconsider the benefits versus risks.

In a previous study, we have documented that moistening of large wound surfaces with TXA 25 mg/ml results in very low systemic concentrations which render any risk of systemic affection of coagulation unlikely[6]. It is however unclear whether prolonged local exposure of tissue to high concentrations of TXA may affect healing[14]. In this study, participating centers will use topical application in accordance with local routine, both with regard to concentration and mode of drug delivery. The study investigates the effect of topical use of TXA per se and no standardized use will be introduced. The study will therefore only include study centers which have already established use of topical TXA.

2.3.1. Risk Assessment

As the intervention of this study is established practice at the participating units, patients would normally be exposed to topical TXA without any preoperative information. Intervention is withdrawal of treatment, which may deprive the patients of the reduction in bleeding the drug might provide. However, soft tissue surgery is conducted by many surgical specialties, and most have not introduced topical use of TXA as they are not aware of the method. Also, within the plastic surgical community, surgeons choose freely whether they want to utilize topical TXA as part of their surgery, and within a center which has adopted the method, surgeons may still choose to abstain. Therefore, study patients who do not receive topical TXA are still undergoing a standardized mode of surgery. The risk from not receiving TXA would equal the risk in most soft tissue surgery.

Patients are observed postoperatively according to normal surgical routine. Any allergic reactions will normally appear within this period. Should sudden unexpected serious adverse

effects (SUSARs) occur, or any other adverse effects, the patients should be treated as if they had received TXA.

Patients may receive a telephone follow-up after approximately 5-6 weeks which they would normally not receive. Detecting potential adverse effects/risks is the end point of this study.

Study personnel may screen the patient's medical journal and may see confidential information. Study data and ID-links will however be pseudonymized.

2.3.2. Benefit Assessment

Patients will receive a closer follow-up than they would normally have after receiving routine topical TXA treatment, as they will be actively asked to report any potential adverse effects and may also receive a telephone follow-up after 30 days.

2.4. Overall Benefit Risk Conclusion

Topical TXA is widely used and no increase in surgical complications have been reported so far[9]. We therefore consider the general risk of this procedure as very low. However, no studies have been powered to assess rare events. Patients in this study who do not receive TXA are expected to have a 30-40% larger postoperative bleeding volume compared to those who receive TXA, but we find this risk acceptable as most soft tissue surgery outside plastic surgery, and a significant fraction within plastic surgery, does not provide TXA at all. Soft tissue surgery has much less bleeding than surgery in bony structures. This is why intravenous use of TXA is established practice in high-bleed surgery such as joint replacement surgery, while soft-tissue surgery has not introduced intravenous use of TXA. Even with non-TXA-treated wound surfaces, soft tissue surgery generally does not have large volume bleeding.

As this prophylactic intervention is increasingly being used globally, evaluating postoperative complications in an adequately powered high quality study is necessary. If we find beneficial effects, we should promote this low-cost and simple measure further. If there are unforeseen adverse effects, this should be communicated. Topical use is still off-label, and large studies to clarify these questions are needed before topical use can become an approved mode of application and further promoted.

We therefore find benefits superior to risk for this study.

3. Objectives, Endpoints and Estimands

3.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• Comparison between wounds receiving TXA versus placebo of the incidence of *postoperative re-bleeding* within the first postoperative 10 days	• Given one or several of the following occurrences, *re-bleeding* will be defined as "yes": Re-operation, surgical exploration or evacuation, aspiration, blood transfusion or external extra compression due to hematoma within the first postoperative 10 days.
Secondary	
• Comparison between wounds receiving TXA versus placebo of the incidence of *postoperative wound infection, postoperative wound rupture*, *thromboembolic events* and *possible adverse effects* within the first 30 postoperative days	Given one or several of the following occurrences, the following endpoints will be defined as "yes": • *Postoperative wound infection* Infection within the first 30 days requiring any of the following: Extra outpatient follow-up, re-operation, or revision or antibiotic treatment. • *Postoperative wound rupture* Wound rupture within the first 30 days requiring any of the following: Extra outpatient follow-up, re-operation, or revision. • *Thromboembolic events* defined as thrombophlebitis, deep venous thrombosis, pulmonary embolus, cerebral or coronary infarctions until 30 days postoperatively. • *Seroma* defined as the need for aspiration of fluids, or spontaneous evacuation of voluminous fluids, between 10 and 30 days postoperatively. • *Other possible adverse effects* causing contact with the health service until 30 days postoperatively.

3.2 Registration of endpoints and patient variables

Each wound receiving a study ampoule will be provided with a study ID and constitutes a study case. Patients with e.g. bilateral breast procedures will thus constitute two study cases. The paper study form (Appendix 1) provides the link between patient identification and study ID, and confirmation of type of surgery and application of the investigational medicinal compound (IMC). Paper study forms will be securely stored at the respective study centers while the link between patient identity and study ID will be conveyed to a central study register for storage on a secure server separate from pseudonymized individual electronic case report forms (eCRFs, Appendix 2).

Endpoints and patient variables will be registered by the following approaches:

- Web-based patient self-report form sent on postoperative day 30 (Appendix 3). In addition to the defined end points, the following pre/perioperative variables will be registered for all patients:
    - Study site
    - Patient age and sex
    - Surgical procedure
    - Patient height and weight
    - Former bariatric surgery
    - Use of nicotine
    - Preoperative diabetes or hypertension
    - Former thromboembolic event
    - Perioperative anticoagulation

- Phone call from study nurse after 5-6 weeks postoperatively to double-check and verify variable and end point data when needed for clarification of patient-reported data.

- Screening of patient medical record from the preoperative screening until postoperative day 30 when needed for clarification of patient-reported data. When conflicting data, the patient reported data will be registered unless misunderstandings or strong evidence suggests otherwise.

All patient variables and end points will be registered in a pseudonymized individual eCRF with encrypted and limited access using Viedoc® provided by the Clinical Research Unit at St Olav's University Hospital. Defined study staff with access to the eCRF system and the patient self-report forms will register participant data based on sufficient information from the patient self-report form and/or additional information obtained from phone call/medical journal when deemed necessary. Participant termination is defined as the day when all study variables from around Day 30 have been collected.

4. Study Design

4.1. Overall Design

- Prospective double-blind randomized parallel group 2-armed placebo-controlled study in plastic surgery centers who have established use of topical TXA as a prophylactic measure to reduce bleeding.
- Participants are patients above 18 years of age who are to undergo a plastic surgical procedure where a single dose topical TXA would normally be applied onto the surgical wound and who have consented to participation by signing an electronic ICF.
- Randomization 1:1 TXA:Placebo (saline), randomized ampoule packages produced by professional manufacturer (Smerud Medical Research International).
- Ready-made randomized identical study packages with Study IDs containing a randomized ampoule and study form will be provided when the surgeon asks for TXA. Each wound will receive a separate ampoule will be assigned the corresponding Study ID. Hence, patients with more than one wound will contribute more than one study case/ Study ID.
- Patients receive a web-based report form regarding variables and end points at 30 days postoperatively, and a follow-up phone call after day 30 postoperatively is placed when necessary for clarification.
- Patient records may be screened for clarification when unclear patient reported end points.
- Registration of pseudonymised patient variables and end points in web-based case report forms (eCRFs/Viedoc®)
- Analysis of outcome will be performed for the wound population overall, and separate analyses will be performed for the respective types of surgical procedures.

4.2. Scientific Rationale for Study Design

Topical use of TXA has been widely adopted as a preventive measure to reduce bleeding in plastic surgery. Numerous retrospective studies and unblinded prospective studies are emerging but are prone to bias. A double-blind prospective placebo-controlled randomized study provides the highest possible level of scientific evidence.

We want to conduct such a study in a population where routine topical application of TXA has already been introduced, and without a standardized mode of topical administration or drug concentration. In this population, the intervention will be potential withdrawal of the topical TXA they would normally receive. For the patient, this implies a withdrawal of the potential

benefits of TXA should they be in the placebo group. However, as most soft tissue surgery globally is still conducted without the use of TXA, depriving our study group of the drug is considered acceptable for the greater goal of documenting potential benefits or risks prior to further promotion of this method to reduce surgical bleeding.

All significant postoperative complications are endpoints.

As this simple, low-cost intervention is increasingly used, determining safety and effect in an adequately powered high-quality study is important.

Patient Input into Design

The User Representative Group at St Olav's University Hospital has provided a designated user representative for input and feedback. See Appendix 4 for the input from the user representative. The Regional Ethics Committee also has user representatives and will provide feedback on the study.

4.3. Justification for Dose

An undiluted ampoule of TXA contains 5 ml of 100 mg/ml, total 500 mg dose. The authors of the study protocol have published 20 ml of 25 mg/ml of TXA as a recommended diluted volume/concentration dose for topical application. However, publications internationally describe topical applications of concentrations ranging from 1 to 100 mg/ml[8], and participating Plastic Surgery Units will use and dilute the ampoule of study drug as they would normally do for the respective surgical procedures. The intervention is the use of topical TXA, but not a defined mode of topical use.

4.4. End-of-Study Definition

The end of the study is defined as the date of the last collection of study variables of the last participant in the study.

A participant is considered to have completed the study if the participant's variables have been transferred to the eCRF, based on sufficient data from the day 30 self-report web-based patient forms and/or medical record/phone call when deemed necessary for clarification.

5. Study Population

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1) They are to undergo a surgical procedure within the field of plastic surgery where the procedure involves use of topical TXA at the participating center.

2) They are over 18 years of age and capable of independently providing informed consent

3) They have received adequate information about the study and signed the informed-consent form (Appendix 5).

5.2. Exclusion Criteria

Patients with known allergy to tranexamic acid.

5.3. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study and to whom a designated study package/ID has been appointed, but who does not receive the study intervention. All eligible patients will be registered with regard to demography, screen failure details, eligibility criteria, and any SAE for final transparent reporting of all study participants + screen failures.

6. Study Interventions

Participating clinics routinely apply topical TXA to the wound surface, using one ampoule of 5 ml 100 mg/ml TXA and diluting and applying it according to prevailing routines at the respective clinics. Intervention is substituting the ampoules of TXA with study vials, which are randomized 1:1 to contain 5 ml of either TXA 100 mg/ml or saline 0.9%. TXA and saline ampoules have identical translucent glass with saline and TXA, respectively, both being clear fluids; blinding of labels and randomization will be done by a professional manufacturer (Smerud Medical Research International).

Table 1. Study Interventions Administered

Intervention Label		
Intervention Name	Tranexamic acid for injection[1] (Cyklokapron®)	Sodium Chloride 0.9%, solution for injection[2]
Intervention Description	Single dose topical application	Single dose topical application
Type	Active drug	Placebo (physiological saline)
Dose Formulation	Ampoule 5 ml	Ampoule 5 ml
Unit Dose Strength(s)	100 mg/ml tranexamic acid	0.9% NaCl
Dosage Level(s)	Single dose, ampoule diluted according to local practice	Single dose, ampoule diluted according to local practice
Route of Administration	Topical single application	Topical single application
Use	Prophylactic drug	Placebo comparator
IMP	Tranexamic acid ampoule for injection	0.9% NaCl ampoule
Sourcing	Pfizer Manufacturing Belgium NV MIA: 277 V Manufactures the tranexamic acid (Cyklokapron)	LABORATOIRES CHAIX ET DU MARAIS (France), MIA: 2022_261_1_3 Manufactures the placebo (sodium chloride 0.9%)
Packaging and Labeling	Smerud Medical Research International AS (Norway) MIA (IMP): 9769-1 Labels and releases the study drug treatment packs containing either the active drug TXA or placebo.	Smerud Medical Research International AS (Norway) MIA (IMP): 9769-1 Labels and releases the study drug treatment packs containing either the active drug TXA or placebo.

Table 2. Study Arm(s)

Arm Title	TXA arm	Placebo arm
Arm Type	Active drug (tranexamic acid)	Placebo (Saline)

Associated Intervention Labels	Single dose topical application of study drug according to study center routines for TXA application	Single dose topical application of study drug according to study center routines for TXA application

6.1. Preparation, Handling, Storage, and Accountability

A detailed description of the chemistry, pharmacology, efficacy, and safety (Summary of Product Characteristics, SPC) of the active drug and placebo ampoules to be used in the study are provided as reference links[1,2].

Manufacturing and distribution will be managed by Smerud Medical Research International.

1. Smerud Medical Research must confirm appropriate conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study will receive study intervention, and only authorized site staff will supply, prepare, or administer study intervention.
3. All study intervention will be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. Authorized site staff at participating study centers is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
5. The final disposition of unused study interventions is provided in the trial site study manual will be in accordance with drug disposition at the connected hospital pharmacies.

6.2. Assignment to Study Intervention

Randomized identical looking ampoules labelled with consecutive numbers will be produced by a pharmaceutical professional manufacturer (Smerud Medical Research International AS). Ready-made randomized sealed envelopes containing a numbered vial (Appendix 6) and an accompanying numbered study registration form (Appendix 1) according to computer-generated block randomization will be produced by the pharmaceutical professional manufacturer. For bilateral wounds, separately produced study packages for bilateral procedures containing two envelopes and randomized 1:1 TXA:Placebo will be used to ensure within-patient randomization.

All packages have unique numbers, identical to the ampoule number, which will constitute the study ID. Distribution of study packages to participating units will be coordinated by the

manufacturer. Eligible patients will be assigned study packages from a storage associated with the operation theatres. The randomization code identifying the study ID as either active drug or placebo will be available via the IMP manufacturer; otherwise, participants, all care givers and researchers will be blinded to the randomization.

6.3. Masking and blinding

Masking of study ampoules will be done by Smerud Medical Research International. See Appendix 6 for proposed masking procedure.

This is a double-blind study in which participants/care providers/investigators and outcomes assessors are blinded to study intervention. The randomization code identifying the study ID as either active drug or placebo will be available via the IMP manufacturer. When inclusion of patients is terminated, researchers will for the final analyses be given information on whether a wound has received treatment A or B. The identity of A and B will be disclosed when analyses are completed. The trial site study manuals will be provided with blind-breaking instructions (Appendix 7). In case of an emergency, the study site primary investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator's discretion, contact the sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention as they would have received TXA intervention in accordance with local routines for topical TXA application. Administration and any dilution of the study ampoule will be in accordance with local routine for TXA ampoules. However, when the patient has more than one separate wound, participating centers are instructed to use a separate study ampoule for each wound. The actual application of study drug will be confirmed in the paper study form (Appendix 1) by the designated surgery study site staff. Any non-compliance/failure to deliver the drug after the opening of a study package will be registered by the study site staff and will qualify as a screen failure. The patient will still be registered as a study participant and included for the intention-to-treat analyses, albeit not for the per protocol-analyses.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

As topical application of TXA is an already established routine intervention at the participating sites, a situation to warrant discontinuation of the trial as such is very unlikely. Should there be an obvious increase in the incidence of possible adverse events such as unexplained bleeding/wound complications or thromboembolic events, it may be a reason to break randomization codes before the study is finished to clarify whether TXA may be associated with the adverse events.

7.1. Discontinuation of Study Intervention

As intervention is a single dose application, discontinuation of study intervention is not relevant. Enrolled patients will either receive study intervention, or they will be registered as screen failures.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- Should the participant withdraw from the study before or at the time of receiving the day 30 self-report form or a final phone call, the participant will be permanently discontinued from the study.
- Should the participant withdraw their consent after final registrations have been transferred to the eCRF, the sponsor may continue to use the data collected in its pseudonymous form.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if the participant does not reply to the postoperative patient registration form or phone call, and if there is no information regarding postoperative period in the patient record. Study personnel will attempt to contact the participant both by mail and by phone call to ascertain whether the participant wishes to continue participation in the study and to obtain the study variables. Should the participant continue to be unreachable, the participant will be considered lost to follow-up and excluded from the per protocol statistical analyses. However, any documentation from the patient record regarding the first postoperative 30 days will be retrieved and constitute the basis for inclusion in the intention-to-treat analyses.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- Screening will be in accordance with prevailing preoperative routines at the study centers for procedures where local application of TXA is established.

8.1. Administrative Procedures

- From the planned operation registries at participating study centers, dedicated study personnel will identify procedures which would normally receive topical TXA. These patients will be reported to the central coordinating study personnel between 7-30 days prior to planned surgery.
- Eligible patients will be sent a consent form (Appendix 5) with information about the study and for identification of potential exclusion criteria (allergy to TXA). The consent form will be adapted to the local requirements of the respective countries and may therefore not exactly match the version in the study protocol.
- Study personnel will contact eligible patients prior to surgery to clarify questions before patients finally respond to the consent form.
- Eligible patients who consent to participate are reported back to the study center, and their status as eligible study patient will be noted in their preoperative paper package.
- If the surgeon decides to use topical TXA during the procedure, a ready-made, ready-randomized study package with study form and study ampoule containing a Study ID will be opened for each study wound. (Appendices 1 and 5).
- If a study package is opened, but the surgeon fails or decides not to administer the study drug, the patient will be included as a screen failure.
- The linking between study ID and patient identity will be conveyed to the coordinating study personnel.

8.2. Efficacy Assessments

- Study variables and end points are defined in an eCRF form/Viedoc® (Appendix 2) to be filled out based on patient-reported data via an electronic self-report study formand/or the patient’s medical record and/or via a final phone call to the patient.

- Distribution of electronic self-report study form (Appendix 3) on day 30 regarding postoperative complications (end points) and study variables will be conducted by study personnel.
- Screening of patient medical record with regard to end points and patient variables will be done by designated study personnel at participating units after day 30 when needed to clarify patient-reported outcomes or when patient-reported outcomes are lacking. Study personnel will complete the eCRF form/Viedoc® (Appendix 2) based on the patient's self-report form or/and medical record (Appendix 3).
- Telephone follow-up with the patient 5-6 weeks postoperatively may be done by study personnel to confirm or clarify registered data when needed.
- If a patient fails to complete the self-report study form, the information can be obtained by phone and the variables can be filled into the digital study form by study personnel. Also, if the data in the self-report form is unclear, despite a clarifying telephone interview with the patient, patient medical record will be screened for clarification. If attempts to reach the patient by phone and e-mail fail, the patient variables will be based on the medical record only and the study form will be completed by study personnel. The patient is then registered as lost to follow-up for the per protocol analyses, and data will be used in the "intention to treat"-analysis only.

Planned timepoints for all assessments are provided in the SoA.

8.3. Safety Assessments

All participating centers have already established routine use of topical TXA. Safety assessments include the registration of the defined end points of the study which constitute possible complications but no further assessments will be made beyond routine postoperative follow-up. Questionnaire and phone call to the patient includes a question regarding "other possible adverse effects or unwanted happenings" (Appendices 2 and 3). As the drug is widely used already, the most severe suspected reaction would be an allergic reaction. As this is a single dose administration and the patients undergo routine postoperative surveillance, an allergic reaction would be detected prior to discharge from the hospital.

Planned timepoints for all safety assessments are provided in the SoA.

8.4. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

Definitions:

- An Adverse Event (AE) is defined as any untoward medical occurrence in a study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- A Serious Adverse Event (SAE) is defined as any serious adverse event that, at any dose:
  - Results in death
  - Is life threatening
  - Requires inpatient hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability/incapacity
  - Is a congenital anomaly/birth defect
- As topical administration of TXA is off-label, any SAE considered to have a possible relation to study intervention but not described in the TXA Summary of Product Characteristics (SPC) would be considered a sudden unexpected severe adverse reaction (SUSAR). For full SPC for TXA, see the linked reference[1].

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

Collecting AE information is the purpose of the study and collection of this information is described in the SoA. The study has defined the following specified AEs as study endpoints: Postoperative re-bleeding, wound infection, wound rupture and thromboembolic events. However, information regarding any other medical occurrence/AE in the follow-up period will also be collected (Appendix 2 and 3). Occurrence of any SAE from the time of study intervention onwards will be recorded in the patient's medical record due to the nature of the event. All study centers will be instructed to promptly report SAEs according to Appendix 7.

8.4.2. Method of Detecting AEs and SAEs

All AEs and SAEs will be collected from the start of study intervention until the final collection of postoperative events as registered in the self-report form and, if necessary, the follow-up phone call at the timepoints specified in the SoA (Section 1.3) AEs will be recorded in the eCRF (Appendix 2), while SAEs additionally will be promptly reported in accordance with Appendix 7. The recorded answers from self-report form and/or phone call will be compared to the information found in the patient's medical record and further communication will be initiated if clarification is needed.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 7. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. All SAEs should be treated as if the patient has received TXA.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

Please see Appendix 3 for the questions included in the patient day 30 self-report form which also constitutes the checklist questions for the phone call interview 5-6 weeks postoperatively (Appendix 2).

8.4.3. Follow-up of AEs, SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and the defined AEs which constitute study endpoints will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). SAEs considered to be related to study intervention will be treated as SUSARs and will be reported as described in 8.4.4. Further information on follow-up procedures is provided in Appendix 7.

8.4.4. Regulatory Reporting Requirements for SAEs

Enrolled patients would normally receive topical TXA as routine treatment, and the study will register adverse events which are normally expected to occur in 2-5% of the surgeries involved. Should an obviously larger percentage of patients experience the adverse events defined as end points, it may be a reason to break code prematurely to investigate whether it is associated with active drug (TXA). Such a suspicion and the move to break code will be reported to the competent authorities.

If no increase is suspected, the objective of the study is to investigate adverse events, and the final results will be actively conveyed to the competent authorities.

Any SAEs reported to the sponsor will be filed and reviewed to evaluate whether the event is likely to be connected to the drug intervention, but not described as a known adverse event according to TXA SPC[1] section 4.8, and thus qualify as a SUSAR. The sponsor will report fatal or life-threatening SUSARs immediately and no later than 7 days via the EudraVigilance system (EVCTM) when an association is suspected. Any other SUSAR will be reported within 15 days.

8.4.5. Pregnancy

Screening for pregnancy is routine procedure before surgical procedures. The plastic surgical procedures involved are normally not offered to pregnant patients. As eligible patients would normally receive topical TXA and intervention is potential substitution with placebo, no extra screening of pregnancy due to this study will be conducted.

8.4.6. Cardiovascular and Death Events

As patients would normally be given topical TXA and intervention is possible substitution of TXA with placebo, any cardiovascular events or death will be registered and reported if indicated according to prevailing routines at the department.

8.5. Pharmacokinetics

The pharmacokinetics of topical application of TXA in abdominoplasties has been investigated in an earlier study[6]. The low systemic concentrations detected after topical application even onto large wound surfaces makes the likelihood of systemic effects such as potential systemic adverse events such as thromboembolic events very unlikely. No further pharmacokinetic analyses will take place in this study.

8.6. Pharmacodynamics

Drug administration is a single dose application at the end of surgery before wound closure. No pharmacodynamic analyses will be conducted.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not actively evaluated in this study. Should however the study suggest that topical TXA reduces or increases any form of postoperative intervention demanding health resources, the health economic aspect will be discussed in the planned publication although the use of medical resources is not measured.

9. Statistical Considerations

The following patient characteristics are variables which may also influence the risk of developing a postoperative complication: Type of surgery, sex, age, BMI, former bariatric surgery, smoking status, use of anticoagulation, former thromboembolic event, cardiac disease, hypertension, diabetes. Outcome data will be adjusted for these variables and significant variables will be included for logistic regression analyses of study outcome data.

Outcome data are categorical and binominal- the occurrence or absence of each of the surgical complications as previously defined (re-bleeding, wound infection, wound rupture, seroma formation and thromboembolic events).

9.1. Statistical Hypotheses

The primary objective is to demonstrate that topical application of TXA is superior to placebo (saline) in preventing postoperative bleeding needing intervention within the first 10 days after surgery. Thus, the null hypothesis to be tested in relation to the primary estimand is as follows:

- Null hypothesis: Re-bleeding needing intervention, defined as the dicotome variable occurrence or absence of one of more of the below defined events within the first 10 postoperative days, occurs with the same incidence in wounds treated with topical TXA versus topical placebo (saline). One or several of the following will qualify as case:
    - Re-operation
    - surgical exploration or evacuation
    - aspiration of hematoma
    - blood transfusion
    - external extra compression due to hematoma
- Alternative hypothesis: Re-bleeding as defined above occurs less often with TXA than placebo (saline)

The null and alternative hypotheses corresponding to the secondary estimands are as follows:

Secondary objective 1:

- Null hypothesis: Wound infection needing intervention, defined as the dicotome variable occurrence or absence of one of more of the below defined events with within the first 30 postoperative days, occurs with the same incidence in wounds treated with topical TXA versus topical placebo (saline). One or several of the following will qualify as a case:
    - Extra outpatient follow-up
    - Re-operation or surgical revision
    - Antibiotic treatment.

- Alternative hypothesis: Wound infection as defined above occurs more often with TXA than placebo (saline)

Secondary objective 2:

- Null hypothesis: Wound rupture needing intervention, defined as the dicotome variable occurrence or absence of one of more of the below defined events with within the first 30 postoperative days, occurs with the same incidence in wounds treated with topical TXA versus topical placebo (saline). One or several of the following will qualify as a case:
    - Extra outpatient follow-up
    - Re-operation or surgical revision
- Alternative hypothesis: Wound rupture as defined above occurs more often with TXA than placebo (saline)

Secondary objective 3:

- Null hypothesis: Seroma needing intervention, defined as the dicotome variable occurrence or absence of one of more of the below defined events with within the first 30 postoperative days, occurs with the same incidence in wounds treated with topical TXA versus topical placebo (saline). One or several of the following will qualify as a case:
    - Active aspiration of seroma
    - Passive spontaneous drainage of a significant volume of seroma
- Alternative hypothesis: Seroma as defined above occurs more often with TXA than placebo (saline)

Secondary objective 4:

- Null hypothesis: Postoperative thromboembolic events, defined as the dicotome variable occurrence or absence of one of more of the below defined events with within the first 30 postoperative days, occurs with the same incidence in wounds treated with topical TXA versus topical placebo (saline). One or several of the following will qualify as a case:
    - Deep venous thrombosis
    - Pulmonary embolus
    - Cerebral or coronary infarction
- Alternative hypothesis: Thromboembolic events as defined above occurs more often with TXA than placebo (saline)

9.1.1 Multiplicity Adjustment

Not applicable

9.2. Analysis Sets

All wounds which have received the intervention will be included in all analyses. Analyses will also be stratified according to type of surgical procedures.

Screen failures will not be included for endpoint analyses.

9.3. Statistical Analyses

9.3.1. General Considerations

Plastic surgery often involves two symmetrical wounds in the same patient. Single study ampoules will be randomized 1:1 TXA:placebo in blocks of ten. Patients with two wounds will receive TXA to one wound and placebo to the other using separate packages with two ampoules with 1:1 randomization. Continuous patient characteristics data will be calculated as mean ± standard deviation (SD) and compared using independent samples t-tests. Categorical patient characteristics data will be calculated as frequency counts and percentages and compared using chi-square tests, but variables with ≤5 cases in one category will be analysed using Fisher exact tests.

Outcome data are categorical and will be calculated as frequency counts and percentages and compared using chi-square tests. Categorical outcome data will also be adjusted for significant variables using logistic regression with results given as odds ratios (ORs) with 95% confidence intervals (CIs). Logistic regression will be used to assess the impact of the flowing factors which may affect risk of complications: Patient age, BMI, study site, use of nicotine products, diabetes, former bariatric surgery, use of anticoagulants, former thromboembolic event, hypertension, and type of plastic surgical procedure. P-values < 0.05 will be considered statistically significant. Analyses will be performed per protocol, e.g. excluding screen failures and patients lost to follow-up. Analyses will also be repeated in accordance with the intention-to-treat principle, e.g. analysing all patients assigned a study number, including patients who failed to receive the intervention and lost-to follow up patients. IBM SPSS Statistics Version 26 will be used for statistical calculations.

9.3.2. Subgroup analyses

Of particular interest to surgeons are complication rates for specific procedures. Subgroup analyses will be performed with regards to the most common plastic surgical procedures defined as “abdominoplasty” and “breast reduction” where we will have several hundred included patients. Results from patients undergoing gender confirming breast surgery may be analyzed as a separate cohort and published separately.

9.3.3. Interim analyses

Should the study centers report concern regarding unexpected complication rates, an interim analysis may be performed by a statistician otherwise not connected to the study.

9.4. Sample Size Determination

In plastic surgery, 1-3 % of patients are re-operated due to postoperative re-bleeding and approximately 2-4% are re-operated due to wound infection or wound rupture, the rates for both hematomas and wound complications varying somewhat according to procedure[16]. A proportion of patients experiencing hematoma or wound complications will be managed conservatively. We therefore estimate that an average 4% of patients undergoing plastic surgery will experience early postoperative re-bleeding warranting compression, drainage, blood transfusion or re-operation (the primary endpoint), and another 4% will experience wound complications warranting wound revision or antibiotic treatment. In cardiac surgery, iv TXA has been demonstrated to reduce the risk of re-exploration by 50%[13] and a review from topical use in soft-tissue surgery suggested an 80 % reduced risk of hematoma warranting intervention[12].

For a reduction in hematomas to be clinically significant, we propose that the risk of hematoma in the intervention group should be half of the risk in the control group. Estimating a prevalence of hematoma in 0.04 in the control group and 0.02 of the intervention group, alpha of 0.05 and power 0.80, a sample size of 1136 patients in each group is needed[17]. We choose to include approximately 1500 patients in each group to ensure additional power.

The rationale behind the chosen sample size and statistical analyses has been discussed with and approved by statisticians at the Clinical Research Unit at St Olav's University Hospital.

10. Supporting Documentation and Operational Considerations

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
    - Applicable ICH Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure and other relevant documents will be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to ICH-E6(R2) guidelines (GCP), and Regulation 536/2014 for clinical trials.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- All potential participants identified from the operation waiting lists will at the latest two weeks prior to planned surgery be sent an invitation (Appendix 5) to participate in the study with written information and an invitation to be contacted by phone for further information by the investigator/the investigator's representative. In participating countries without access to digital communications, this invitation will be sent as a paper form.
- The investigator or the investigator's representative will contact the potential participant to explain the nature of the study, including the risks and benefits, and answer all questions regarding the study.
- Potential participants will be informed that their participation is voluntary. Participants will be required to sign a digital statement of informed consent that meets the requirements of local regulations, ICH guidelines, privacy and data protection requirements, and the requirements of the IRB/IEC.
- The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.
- A copy of the ICF will be provided to the participant.
- A list of participants who have agreed to participate will be conveyed to the surgical department of the participating centers. A note to provide a study package if the surgeons want to apply tranexamic acid onto the wound is linked to the patient's operations papers.
- If the patient does not reply to the invitation, then a maximum of two attempts to reach the patient by sms or e-mail can be made by the study personnel for clarification.
- Signing of informed consent forms must be in accordance with local regulations for medical research.

10.1.4. Recruitment strategy

Patients undergoing plastic surgical procedures where local application of TXA is established at participating centers will be identified from the operation lists by the designated study site investigators who will report eligible candidates to study personnel. No later than two weeks before surgery, the patient will receive a written ~~digital~~ invitation to participate in the study. The

patient can ~~digitally~~ consent to or decline participation. The patient can also request further information before making a decision. Study personnel will contact the patient by phone prior to surgery to clarify the patient's status and clarify questions from the patient.

10.1.5. Data Protection

- Participants will be assigned a unique identifier according to the study number/study form in their assigned drug study package (Appendix 1). While collecting data at the respective study centers, study ID and patient ID will be linked only until the data is registered and confirmed in a web-based case report form (eCRF/Viedoc®, Appendix 2) with Study ID only. Only the eCRFs are transferred to the sponsor; participant names or any information which would make the participant identifiable will not be transferred but kept with the investigator/investigator's representative on a secure separate digital server.
- The participant will be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure will also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant will be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites will specify responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6. Committees Structure

Monitoring of the study and the development of a monitoring plan will be provided by the Clinical Research Unit at St Olav's University Hospital (Appendix 9). Monitoring plans based on the Sponsor's original plan must be adapted to the specific rules of participating countries.

As the study recruits study patients who would normally receive tranexamic acid as an intervention and as end points is adverse events, close clinical monitoring of potential adverse events is less imperative but monitoring of consent and study process should be in accordance with any intervention study.

10.1.7. Dissemination of Clinical Study Data

Study status will be regularly reported to www.clinicaltrials.gov and the EU Clinical Trials Information System (CTIS).

Final results from this study will be published in a suitable peer-reviewed international medical journal and presented at national and international symposiums. Final results will also be made available via www.clinicaltrials.gov and the EU Clinical Trials Information System (CTIS).

Datasets will be kept available in secure digital storage for at least 25 years. Access to analyzable datasets through a secure system may be granted following an independent assessment of the scientific merit of a defined research question from a third party.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRFs provided by the Clinical Research Unit at St Olav's University Hospital/Viedoc®.
- The investigator or a designated representative is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.
- Guidance on completion of CRFs will be provided by the Clinical Research Unit at St Olav's University Hospital.
- The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) will be provided in a monitoring plan provided by the Clinical Research Unit at St Olav's University Hospital
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No

records may be transferred to another location or party without written notification to the sponsor.

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents which filed at the investigator's site include the patient's medical record and the paper study form from the randomized study packages (Appendix 1). Source documents filed at secure and approved research servers at the respective participating centers may include digital ICFs (Appendix 5) and patient self-report form after postoperative day 30 (Appendix 3), and a document linking patient identities to study ID. The eCRFs/Viedoc® (Appendix 2) based on the source documents must be stored on a separate secured server.
- Data entered into the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study and Site Start and Closure

Study site candidates and contact persons are listed in Appendix 8. Formal recruitment of study sites will commence when all digital systems and contracts are finalized and ready. Site start dates will be added consecutively as larger centers will be prioritized during start-up.

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment at a participating study site will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication Policy

- The results of this study may be published or presented at scientific meetings.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11. Appendices

11.1. Appendix 1 Paper Study Form

NO

Studie-ID_____ Navnelapp:

Tranexamsyre og postoperative komplikasjoner-studien

Ampullen skal brukes i henhold til lokal prosedyre for påføring av traneksamsyre på sårflate, og ampullens innhold skal bare brukes på ett sår. Ved to sår/bilateral prosedyre, bruk en studiepakke som inneholder to studiekonvolutter.

Type inngrep: _____

Sårets lokalisasjon:

_____ Hø ☐ Ve ☐

Påføring bekreftes:

Dato:_____ Navn: _____

Skjemaet skal oppbevares i egen studieperm.

EN

Study-ID_____ Patient ID:

Tranexamic acid and postoperative complications-study

Use the ampoule in accordance with local procedure for topical use of tranexamic acid onto the wound surface. The contents of the ampoule should only be applied to a single wound. In case of two/bilateral wounds, use a study package which contains two study envelopes.

Type of procedure: _____

Location of the wound:

_____ Right ☐ Left ☐

Confirming drug application:

Date:_____ Name: _____

Keep this form in the study binder.

11.2. Appendix 2 Case Report Form– questions for the eCRF

Study ID (number on ampoule):

Study Center (list of participants)

Year of operation:

Operative procedure:

-Abdominoplasty

Panniculectomy/mini-abdominoplasty without transposition of umbilicus

Abdominoplasty with transposition of umbilicus

Fleur-de-lis abdominoplasty

-Breast reduction

Breast reduction

Mastopexy

Gynecomastia

Anatomical side?

Bilateral

Only right

Only left

-Mastectomy and breast reconstructions

Simple mastectomy

Mastectomy with direct reconstruction

Prosthesis reconstruction

Autologous reconstruction

Secondary breast reconstruction

Prosthesis only

Autologous tissue

Both autologous and prothesis

Breast-sparing mastectomy/oncoplasty

Anatomical side?

Bilateral

Only right

Only left

Transgender surgery

Mastectomy

Periareolar access

Inframammary access

Breast implant augmentation

Anatomical side?

Bilateral

Only right

Only left

-Other (free text)

Was liposuction performed in operated area? (Y/N)

Was a study package opened? Y/N

Was study drug applied to the wound? Y/N

Is the patient a «screen failure»? (Ampoule opened, but not applied. Further study data shall still be registered for «intention-to-treat-analysis) Y/N

Has the patient replied to the day 30 form? Y/N

Was the patient reached by phone? Y/N

Is there any information regarding the first postoperative 30 days in the medical record? Y/N

Is the patient “lost to follow-up”? (No postoperative info found) Y/N

Patient variables:

Sex: Male, Female, Female to male transgender, Male to female transgender

Year of birth

Height

Weight

Active smoker within the past year Y/N

Smoking the last month before the operation Y/N

Use of other nicotine substance Y/N

Use of other nicotine substances last month before the operation Y/N

Anticoagulants as regular medication (Y/N)

If yes: Warfarin

DOAC

LMWH

Surgery-related anticoagulation Y/N

Cardiac disease (Y/N)

Hypertension (Y/N)

Diabetes (Y/N)

Former thromboembolic event (Y/N)

Former bariatric surgery (gastric bypass/sleeve) (Y/N)

Complications after surgery:

If «yes» to any of the following, a sub-menu (indented text) will appear.

-Postoperative bleeding within the first 10 days? Y/N

Re-operation due to bleeding

Active evacuation of hematoma/aspiration/opening

Extra compression due to bleeding

Blood transfusion

-Postoperative wound rupture within first 30 days? Y/N

Re-operation due to wound rupture

Clinical wound rupture but conservative treatment

-Postoperative wound infection within first 30 days? Y/N

Re-operation due to wound infection

Antibiotics due to wound infection

Clinical infection but managed conservatively

-Need for seroma aspiration or spontaneous drainage of voluminous fluids between day 10-30? (Y/N)

Aspiration of seroma

Spontaneous drainage of large volume

-Postoperative thromboembolic event? Y/N

Superficial phlebitis

Deep venous thrombosis

Pulmonary embolism

Myocardial infarction

Cerebral infarction

Other postoperative complication or possible adverse effect/allergic reaction/other medical event? Y/N

Other? Free text description

11.3. Appendix 3 Questionnaire for participants in the study

NO

Spørreskjema til deg som har deltatt i studien

«Effekt av lokal traneksamsyre på komplikasjoner etter plastikkirurgi»

Vi spør om hendelser fra de første 30 dagene etter operasjonen. Du vil også motta en telefon angående informasjonen vi har registrert om deg.

Generell Helseinformasjon:

Operert på hvilket sykehus

Operasjonsdato:

Hvilket inngrep har du gjennomgått? (fritekst)

Høyde og Vekt

Røyer du til vanlig? J/N

Røyket du siste mnd før operasjon? J/N

Bruker du vanligvis annet nikotinprodukt, som snus, tyggegummi, e-sigarett, vaping? J/N

Brukte du annet nikotinprodukt siste mnd før operasjon? J/N

Bruker du blodfortynnende medisin til vanlig? (J/N) - om ja, navn på legemiddel og dose (fritekst)

Fikk du blodfortynnende medisiner eller sprøyter i forbindelse med kirurgi? J/N/vet ikke

Har du noen av følgende tilstander:

Hjertesykdom J/N

Høyt blodtrykk J/N

Diabetes J/N

Tidligere blodpropp J/N

Tidligere slankeoperert J/N

Eventuelle tilleggsopplysninger om tilstandene: Fritekst

Fikk du blødningskomplikasjoner etter inngrepet ditt? J/N

Om Ja:

Hvilke(t) sår fikk blødning (noen har flere operasjonssår) (fritekst)

Hvor mange dager etter inngrepet oppsto blødningen? (tall)

Ble det iverksatt tiltak pga stor blødning etter inngrepet? J/N

Om Ja, kryss av for hvilket tiltak som ble gjort:

-Jeg måtte opereres på nytt i narkose pga blødning

-Man måtte tømme blod /åpne såret, men uten at jeg måtte i narkose

-Man måtte legge på ekstra komprimerende bandasjer/plagg

-Jeg fikk blodoverføring

-Annet (rom for fritekst)

Har du fått sårkomplikasjoner som sårinfeksjon, oppsprekking av såret eller væskeansamling i sårhulen? J/N

Om ja:

Hvilke(t) sår fikk sårinfeksjon eller oppsprekking (noen har flere operasjonssår) Fritekst

Har det blitt iverksatt tiltak pga sårkomplikasjoner? J/N

Om ja, kryss av for hvilke tiltak som har blitt gjort:

-Jeg har fått antibiotika pga sårinfeksjon

-Jeg har måttet opereres på nytt/blitt sydd på nytt pga oppsprukket sår

-Jeg har måttet gå til ekstra kontroller pga såret, men man lar det gro av seg selv uten ny operasjon.

-De har måttet tappe væske fra såret/såret åpnet seg og mye væske tømte seg

Har du fått noen form for blodpropp etter operasjonen? J/N

Om ja, hvor fikk du blodpropp (fritekst)

Om ja, har du blitt satt på blodfortynnende behandling? J/N

Om ja, hvilken behandling har du fått? (fritekst)

Har du hatt noen allergisk reaksjon, bivirkninger eller andre komplikasjoner etter operasjonen? J/N

Om ja, hva skjedde? (fritekst)

EN

Questionnaire for participants in the study

«Effect of local tranexamic acid on complications after plastic surgery»

We enquire about events from these first 30 days. You may also receive a phone call to confirm the information we have registered.

General Health Information:

At what hospital was your operation?

Date of operation:

What surgical procedure did you undergo? (free text)

Your height and weight:

Are you a regular smoker? Y/N

Did you smoke the last month before the operation? Y/N

Do you regularly use any other nicotine product, like snuff, chewing gum, e-cigarettes, vaping? Y/N

Did you use such nicotine products the last month before the operation? Y/N

Do you use anticoagulants on a regular basis? Y/N (If yes, name of medicine and dose (free text)

Did you receive anticoagulants (injections or tablets) in connection with your surgery? Y/N/don't know

Do you have any of the following conditions:

Cardiac disease Y/N

High blood pressure Y/N

Diabetes Y/N

Previous thromboembolic event Y/N

Previous bariatric surgery Y/N

Any further information regarding your health condition: Free text

Did you have any bleeding complication after the procedure? Y/N

If yes:

Which wound had the bleeding? (some patients have several wounds) (free text)

How many days after the operation did the bleeding occur (number)

Was there any intervention because of the bleeding? Y/N

If yes, mark which intervention (one or several):

- I had to be operated again in general anesthesia due to the bleeding

-They evacuated the blood/opened the wound, but I did not need general anesthesia

-They applied extra compression onto the wound

-I had a blood transfusion

-Other intervention (free text)

Have you had one or more of the following wound complications: Wound infection, Wound rupture, or Accumulation of fluids in the wound cavity? (Y/N for each)

If yes:

Which wound(s) had wound infection, rupture or seroma (some have several wounds)? (free text)

Has there been intervention due to wound complications? Y/N

If yes, mar which intervention (one or several):

-I received antibiotics

-I had a new operation/new suturing of the wound

-I had extra outpatient controls but it healed by itself

-Fluids were aspirated/drawn from the wound, or spontaneously drained in large volumes

Have you had any thromboembolic event after the operation? Y/N

If yes, where was the blood clot? (free text)

If yes, did you receive anticoagulants to treat the blood clot? Y/N

If yes, what medication and dosage (free text)

Have you had any allergic reaction, side effects or any other complications after the operation? (Y/N)

If yes, what happened? (free text).

11.4. Appendix 4 Statement from user representative

Uttalelse fra brukerrepresentant/*Statement from user representative*

Studiet vil kunne være til almen nytte for å redusere blødning og komplikasjoner etter kirurgi, samtidig vil risiko for bivirkninger bli kartlagt i studie.

Jeg har fått informasjon om at TXA er et gammelt medikament som brukes intravenøst i all kirurgi med store blødninger, men er ikke rutinemessig bruk i kirurgi med mindre blødninger, da det er gjort lite for å avdekke bivirkninger.

Nå brukes det også i noen grad på kirurgiske sårflater lokalt, i litt konsentrert form og her er usikkerheten om det kan oppstå blodpropp.

Studien vil avdekke om denne behandlingsmåten er trygg. Påføring av TXA lokalt på kirurgiske sårflater er en rimelig og effektiv måte å lukke sårflaten på.

Anbefaler absolutt dette studiet, da det er grundig satt opp og hensyn tar veldig mange parameter i studiegruppen. Bra at noen tar tak i dette!

The study can be beneficial with regards to reducing bleeding and complications after surgery, and at the same time the risk of adverse effects will be mapped scientifically.

I have been informed that TXA is an old drug which is used intravenously in all surgery with large bleeding, but is not routinely used in surgery with less bleeding, as too little has been done to reveal adverse effects.

Now it is to some extent applied locally to surgical surfaces, in somewhat concentrated form and a question is whether thromboembolic events can occur.

The study will reveal whether this treatment is safe. Application of TXA locally onto surgical wound surfaces is a low-cost and effective way to close the wound surface.

Definitely recommend this study as it is thoroughly designed and takes into consideration very many parameters in the study group. Good that someone takes this on!

Trondheim, 4. oktober 2022

Tora Rømo

Brukerrepresentant/User representative

Brukerutvalget/User Board St Olavs Hospital

11.5. Appendix 5 Informed Consent Form

NO

Versjon 7, 19. februar 2025

VIL DU DELTA I FORSKNINGSPROSJEKTET

TRANOP-STUDIEN: PÅVIRKER TRANEKSAMSYRE PÅ SÅRFLATEN KIRURGISKE KOMPLIKASJONER?

1. FORMÅLET MED PROSJEKTET OG HVORFOR DU BLIR SPURT

Medikamentet traneksamsyre gitt intravenøst kan redusere blødning etter kirurgi. Plastikkirurger i Norge har begynt å bruke traneksamsyre direkte på sårflaten for å redusere blødning. Dette er en ny metode som ennå ikke er særlig utbredt innen kirurgi. Vi ønsker å undersøke hvorvidt slik påføring kan påvirke blødning, sårinfeksjon, sårtilheling og blodpropp. Du skal gjennomgå et inngrep hvor man ofte fukter sårflatene med traneksamsyre. Vi spør derfor om du er villig til å delta i denne studien hvor såret ditt enten fuktes med traneksamsyre eller narremedisin (placebo, saltvann). Studien ledes fra St Olavs Hospital i Trondheim, men plastikkirurgiske avdelinger i hele Norge deltar.

2. HVA INNEBÆRER PROSJEKTET FOR DEG?

~~Dersom du er villig til å delta i prosjektet, går operasjon som planlagt.~~ Din operasjon vil gå som planlagt uansett om du ønsker å delta i studien eller ikke. Dersom kirurgen ønsker å fukte sårflaten med traneksamsyre, vil kirurgen få en kamuflert ampulle som enten inneholder traneksamsyre eller saltvann. I etterkant av operasjonen vil vi registrere hvorvidt du får noen komplikasjoner de første 30 dagene. Vi kommer i tillegg til å registrere alder, høyde, vekt, type kirurgisk inngrep, røyking/snus, medikamenter og andre relevante sykdommer. Vi kommer til å sende deg et digitalt skjema 30 dager etter operasjonen hvor vi spør om dette, og ved behov vil vi gå gjennom pasientjournalen din fra operasjonstidspunkt til 30 dager etter operasjon for å registrere eventuelle mulige bivirkninger og hendelser. Du kan også få en telefon et stykke etter 30 dager for å sikre at vi har registrert riktige opplysninger. Alle disse opplysningene oppbevares i et sikkert digitalt forskningsregister (eForsk) hvor bare helsepersonell tilknyttet studien har tilgang.

3. MULIGE FORDELER OG ULEMPER

Ved å delta i denne studien bidrar du til å øke kunnskap om hvorvidt man bør rutinemessig bruke traneksamsyre på sårflater. Bruk av traneksamsyre på sårflater er en relativt ny metode, og det meste av kirurgi i verden foregår uten traneksamsyre. Ved din plastikkirurgiske avdeling er metoden innført, og det er opp til kirurgene å bestemme om de ønsker å bruke medikamentet i forbindelse med et inngrep. Dersom du

har sagt deg villig til å delta i studien og kirurgen ønsker å bruke medikamentet, så er det en 50% sjanse for at såret ditt bare får saltvann i stedet for traneksamsyre. Du kan dermed gå glipp av den blødningsreduserende effekten, men også slippe eventuelle bivirkninger. Det er imidlertid til nå ikke beskrevet noen alvorlige bivirkninger ved lokal bruk av medikamentet.

4. FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE DITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Det vil ikke ha noen negative konsekvenser for deg eller din behandling hvis du ikke vil delta eller senere velger å trekke deg. Hvis du sier ja til å delta i studien, har du, etter EUs personvernforordning (GDPR), rett til å få innsyn i hvilke opplysninger som er registrert om deg. Vi registrerer informasjonen som nevnt i punkt 2. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene. Dersom du trekker deg fra studien~~, vil det ikke samles inn flere opplysninger fra deg.~~ før du har fylt ut det digitale skjemaet 30 dager etter operasjon, så vil det ikke samles inn opplysninger fra deg og du slettes fra deltakelse. Dersom du trekker deg etter at dette skjemaet er sendt inn, vil informasjonen være videreført i avidentifisert form og dersom du da trekker deg vil likevel de avidentifiserte opplysningene bli brukt i analysene. ~~Opplysninger som allerede er innsamlet vil ikke bli slettet og vil kunne inngå i det videre forskningsarbeidet i denne studien.~~ Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte prosjektleder (se kontaktinformasjon på siste side).

5. HVA SKJER MED OPPLYSNINGENE OM DEG?

Opplysningene som registreres om deg skal kun brukes slik som beskrevet under formålet med prosjektet og vil brukes frem til studieslutt desember 2028.

Alle opplysningene vil registreres i forskningssystemet eForsk, som bare studiepersonell har tilgang til og som er sikkert knyttet opp mot Helsenorge.no. Opplysningene vil deretter overføres til forskningssystemet Viedoc for endelige analyser, og der vil opplysningene være avidentifisert- dvs de blir behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. Kun personell som har ansvar for studien har tilgang til eForsk mens innsamling av pasientopplysninger pågår. Ved studieslutt vil tilgangen lukkes for deltakende sykehus, og kun sentralt studiepersonale ved St Olavs Hospital (prosjektleder Kjersti Ausen og koordinerende studiesykepleier) vil ha videre tilgang til eForsk. Det er kun sentralt studiepersonale som på noe tidspunkt har tilgang til Viedoc. En kode i Viedoc er koblet til den registrerte informasjonen i eForsk. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene. Du kan klage på behandlingen av dine opplysninger til Datatilsynet og institusjonen sitt personvernombud. Opplysningene vil bli lagret frem til 2053 for kontrollformål på et sikkert dataområde ved St Olavs Hospital

Du har rett til å få informasjon om resultatene av studien. Uansett utfall, vil et sammendrag av studieresultatene tilpasset allmennheten gjøres tilgjengelig via EU-portalen Clinical Trials Information System (CTIS) innen ett år etter studieslutt.

.6. FORSIKRING

Alle som deltar i studien er dekket via legemiddelansvarsforsikringen (LAF).

7. GODKJENNINGER

~~Legemiddelverket og Regional komité for medisinsk og helsefaglig forskningsetikk har gjort en forskningsetisk vurdering og godkjent prosjektet~~ Etisk komité for klinisk utprøving av legemidler og medisinsk utstyr (REK KULMU) og Direktoratet for medisinske produkter (DMP), har vurdert studien (EU CT nr 2023-510381-28-01) og har gitt forhåndsgodkjenning. St Olavs Hospital og prosjektleder Kjersti Ausen er ansvarlig for personvernet i prosjektet. Vi behandler opplysningene basert på Lov om medisinsk og helsefaglig forskning.

8. KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet eller ønsker å trekke deg fra deltakelse, kan du kontakte studiesykepleier på Klinisk Forskningspoliklinikk, tlf. 72829970, mail: TRANOP@stolav.no, eller prosjektleder Kjersti Ausen, tlf 72826622, mail: kjersti.ausen@stolav.no

Dersom du har spørsmål om personvernet i prosjektet, kan du kontakte personvernombudet ved ansvarlig institusjon St Olavs Hospital: personvernombudet@stolav.no

Nederst ber vi deg svare på om du samtykker til å delta i studien eller ikke. Dersom du samtykker, kommer vi til å ringe deg for å høre om du trenger mer informasjon om studien. Etter samtalen, og når som helst senere, kan du trekke deg fra studien. Se kontaktinformasjon over.

Dersom du ikke samtykker til å delta i studien, så kontakter vi deg ikke, og du slettes fra vår oversikt av mulige studiekandidater.

~~Dersom du ønsker mer informasjon fra oss før du bestemmer deg, må du svare nei på samtykke, og skrive inn telefonnummeret i rubrikken under, så skal vi kontakte deg.~~

~~Om du føler du har fått tilstrekkelig informasjon, kan du bare svare på samtykkespørsmålet uten å gi oss telefonnummeret.~~

~~Dersom du ønsker mer informasjon, oppgi telefonnummer du kan nås på: TLF _____~~

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE PERSONOPPLYSNINGER BRUKES SLIK DET ER BESKREVET

☐ Jeg samtykker ☐ Jeg samtykker ikke

Mitt tlf nr: _____

EN

[Logo for relevant study center and St Olavs/NTNU] Version , 6, Dec 27th 2024

WILL YOU PARTICIPATE IN THE RESEARCH PROJECT

DOES TRANEXAMIC ACID ONTO THE WOUND SURFACE AFFECT SURGICAL COMPLICATIONS?

1. THE PURPOSE OF THE PROJECT AND WHY WE ASK YOU

The drug tranexamic acid given intravenously can reduce bleeding after surgery. Plastic surgeons have started using tranexamic acid directly onto the wound surface to reduce bleeding. This is a new method which is not yet very common in surgery. We want to investigate whether such application can affect bleeding, wound infection, wound healing or thrombosis. You are to have surgery where the wound is often moistened with tranexamic acid. We therefore ask if you are willing to participate in this study where your wound may be moistened with either tranexamic acid or placebo (saline, salt water). The study is led by St Olav's University Hospital in Trondheim, Norway, but plastic surgical units from several locations in Scandinavia participate.

2. WHAT DOES THE PROJECT MEAN FOR YOU?

The surgery will go as planned, regardless of whether you consent to participation in the study. If the surgeon wishes to apply tranexamic acid to the wound surface, the surgeon will be given a camouflaged ampoule which contains either tranexamic acid or saline. After the surgery we will register whether you experience any complications within the first 30 days. We will also register age, height, weight, type of surgery, smoking/nicotine use, drugs and other relevant health conditions. We will send you a digital form 30 days after the surgery where we ask for these data, and we may also go through your medical record for the period from the surgery until 30 days thereafter to register any possible adverse effects of events. You may also receive a phone call after the first 30 days to ensure we have registered the correct information.

3. POSSIBLE BENEFITS AND DISADVANTAGES

By participating in this study you are contributing to increased knowledge of whether tranexamic acid should be routinely used on wound surfaces. Applying tranexamic acid onto wound surfaces is a fairly new treatment, and most surgery globally is performed without using tranexamic acid. The surgeons at the department where your procedure takes place have introduced the method, and it is up to the surgeons to decide whether they want to use the drug in connection with a procedure. If you have agreed to participate in the study and the surgeon wants to apply tranexamic acid to the wound surface, there is a 50% chance that your wound will receive only placebo

(saline) instead of tranexamic acid. You can therefore miss the assumed effect on bleeding, but you will also miss potential adverse effects. However, no serious adverse effect has been described after using the drug locally onto a wound surface.

4. VOLUNTARY PARTICIPATION AND POSSIBILITY TO WITHDRAW YOUR CONSENT

Participation in this project is voluntary. If you wish to participate, then sign the consent on the last page. You can at any time and without giving any reason withdraw your consent. If you do not consent to participation, or decide to withdraw your consent later, this will in no way negatively affect you or the treatment you receive. If you agree to participate in the study, you have the right, under the EU General Data Protection Regulation (GDPR), to access the information that has been registered about you. We register the information mentioned under section 2. You also have the right to have any errors in the data we have registered corrected. You also have the right to access the security measures used in the processing of the data. If you withdraw from the study before filling out the digital form 30 days after your surgery, no further data will be collected from you. If you withdraw after having submitted this form, the information will have been transferred to an anonymous version and this de-identified data can still be used in the analyses. If you later wish to withdraw or have questions regarding the project, you may contact the project administrator (see contact information on the last page).

5. WHAT HAPPENS WITH YOUR INFORMATION?

Your registered information will be registered only as described under the purpose of the project and will be used until the end of the study end in December 2028. Your identified data will be stored securely …. (specify method for identified material for the respective countries)

All data will be further processed without name and national identity numbers or other directly recognizable data in the digital research system Viedoc. A code links you to your data through a list of names. This means that the data is de-identified. The list that can link your name to the code will only be stored at the medical centre/hospital and only personnel responsible for the study have access to this list. The data will be stored until 2053 for control purposes. You are entitled to access to information regarding what data has been stored and to correct any errors in stored information. You are also entitled to information regarding security measures regarding the data handling. You can complain regarding the handling of your data to the National Data Protection Authority and the Data Protection Officer at the medical institution.

All data will be processed without name or date of birth or other directly identifying information (= coded data). A code will link you to your information through a list of names. It is only the project leader Kjersti Ausen and coordinating study nurses who have access to this list. At the termination of the research project, the information will be kept for 25 years at a secure data area at St Olav's University Hospital.

The results from the study will be published in an international medical journal. The results and a summary understandable to a lay person will also be made available through the Clinical Trials in the European Union (CTIS) database.

6. INSURANCE

All participants in the study are covered through the drug research responsibility insurance (LAF) (Change according to country rules).

7. APPROVALS

(Replace with local authority in other country) The Norwegian Medicines Agency and the Regional Ethical have approved the project (EU CT nr 2023-510381-28-01). St Olav's University Hospital and project manager Kjersti Ausen are responsible for the patient confidentiality of the project. We treat all information based on Law on medical and health-related research.

8. CONTACT INFORMATION

(Replace with local authority in other country) If you have questions regarding the project or wish to withdraw your participation, contact Kjersti Ausen, phone +47 92249693, mail: kjersti.ausen@stolav.no, or local contact (fill out:)

If you have questions regarding the privacy and confidentiality of the project, you can contact the Data Protection Officer at the medical institution: (address for participating centers).

I CONSENT TO PARTICIPATION IN THE PROJECT AND THAT MY PERSONAL DATA IS USED AS DESCRIBED

Place and date	Signature of participant
	Participant's name in capital letters

Confirmation on providing information to the participant

I confirm that I have informed the participant about the study.

Name: ---------- Date: ----------

Signed by project collaborator

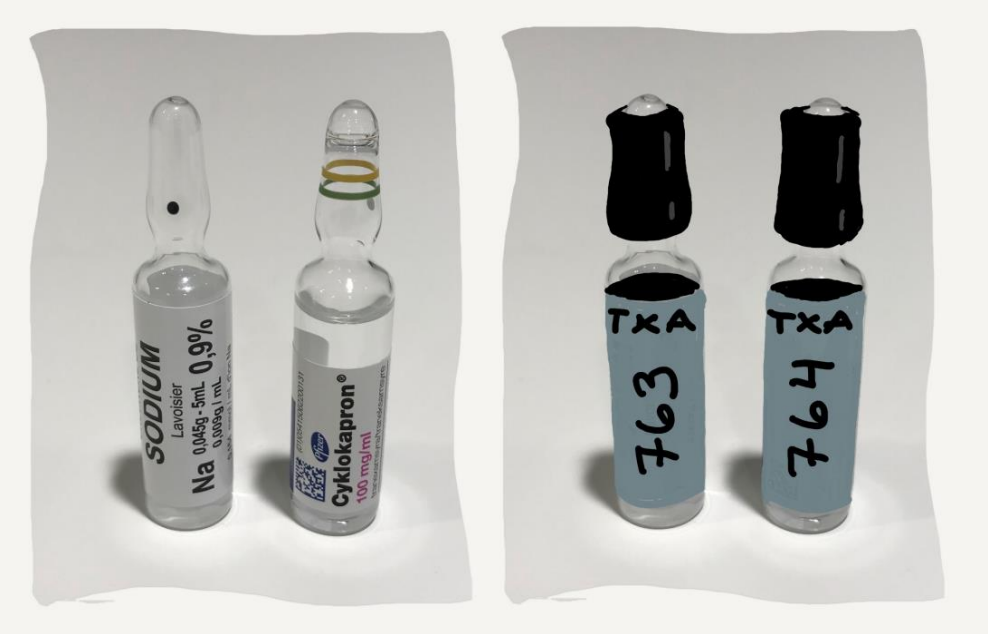
Study role

11.6. Appendix 6 Masking and Blinding of Study Drug

We have identified identically shaped ampoules containing traneamic acid (Cyklokapron, Pfizer) and 0.9% NaCl (Lavoisier, France). For an ideal blinding we should have had a production of saline ampoules with yellow and green ring identical to the Cyklokapron-ampoule. We are investigating this possibility.

The picture illustrates the solution we also think is satisfactory. The ampoule top part is camouflaged with a tight-fitting black tube which preserves the breaking point on the neck of the ampoule. The ampoules will be re-labeled with study-specific labels (text will be in accordance with Regulation 546/2014, annex VI). Randomized study envelopes will be provided in packages of two, with a 1:1 TXA:Placebo randomization, enabling a within-patient randomization in bilateral procedures.

Randomization, blinding, labelling, shipment of ampoules and keeping of the randomization code will be done by Smerud Medical Research International AS.



11.7. Appendix 7 Instructions for breaking of code

NO

Instruksjoner for rapportering av mulig bivirkning, uventet og alvorlig medisinsk hendelse og ved behov for bryting av blinding

Rapportering av mulig bivirkning: Mindre alvorlig mulig bivirkning skal dokumenteres i journal.

Rapportering av kritisk medisinsk hendelse:

Følgende regnes som kritisk medisinsk hendelse:

-Plutselig død

-Livstruende hendelse

Dersom det oppstår en kritisk medisinsk hendelse hos en studiedeltaker, skal man behandle pasienten som om pasienten har fått traneksamsyre. Studieansvarlig på studiestedet selvstendig ansvar for å bestemme hvorvidt det er behov for å bryte koden. Se instrukser under for bryting av randomiseringskode. Studieledelsen skal informeres i ettertid.

Rapportering av uventet eller alvorlig medisinsk hendelse:

Følgende regnes som uventet eller alvorlig medisinsk hendelse:

-Hendelse som krever sykehusinnleggelse eller forlenget sykehusinnleggelse

-Hendelse som fører til varig eller signifikant funksjonsnedsettelse.

Ved uventede eller alvorlige medisinske hendelser skal dette rapporteres til studieledelsen innen 24 timer etter at studiestedet har fått kjennskap til hendelsen. Man må også sikre at

pasienten får adekvat medisinsk oppfølging til hendelsen er avklart. Pasienten skal behandles som om vedkommende har fått traneksamsyre. Studieledelsen vurderer sannsynlig relasjon til studieintervensjonen og bestemmer evt videre rapportering.

Kontaktpersoner studieledelse:

Lokal studieansvarlig: Navn, tlf
Nasjonal studieansvarlig: Kjersti Ausen tlf 92249693, mail kjersti.ausen@stolav.no
Nasjonal studiesykepleier: Kirsti Sørås, tlf 72829970, mail forskningsposten@stolav.no

Instruksjoner for bryting av randomiseringskoden hos en pasient før inklusjon av alle pasienter er avsluttet

Randomiseringskoden kan brytes på dagtid ved å kontakte Smerud Medical Research International AS, tlf +47 2327 2000, og referere til TRANOP-studien samt pasientens studienummer.

Studien har ikke mulighet for akutt avblinding utenfor kontortid.

Dersom det oppstår et akutt behov for å få vite hvorvidt pasient har fått aktivt medikament eller saltvann som studiebehandling, skal pasienten behandles som om pasienten har fått traneksamsyre. Dersom man likevel mener at randomiseringskoden bør brytes, bør studieledelse konsulteres, men lokal studieledelse kan selvstendig kontakte Smerud Medical Research International AS.

Lokal studieansvarlig: Navn, tlf
Nasjonal studieansvarlig: Kjersti Ausen tlf 92249693, mail kjersti.ausen@stolav.no
Nasjonal studiesykepleier: Kirsti Sørås, tlf 72829970, mail forskningsposten@stolav.no

EN

Instructions for reporting possible adverse effect, sudden and serious medical event and in need of breaking of code.

Reporting possible adverse effect: Less serious possible adverse effect shall be documented in the patient's medical journal.

Reporting of critical medical event:

The following defines a critical medical event:

-Sudden death

-Life-threatening event

In case of a critical medical event in a study participant, the patient should be treated as if having received tranexamic acid. The study site primary investigator has an independent responsibility to decide whether the event warrants breaking of code. See Instructions for breaking of code. The Sponsor should be informed at the earliest convenience.

Reporting of an unexpected or serious medical event:

The following defines as an unexpected or serious medical event:

-An event causing hospitalization or prolonged hospitalization.

-An event leading to permanent or significant loss of function.

In case of unexpected or serious medical events, this should be reported to the Sponsor within 24 h after the study site received knowledge of the event. Study site must ensure that the patient receives adequate medical follow-up until the event has been resolved. The patient should be treated as if having received tranexamic acid. The Sponsor will assess the likelihood of the event being related to the study intervention and will decide on further notifications.

Contact information Study :

Study Site Primary Investigator: Name, Phone..
International Study Manager: Kjersti Ausen, phone +47 92249693, mail kjersti.ausen@stolav.no.

International Study Nurse: Kirsti Sørås, Phone+47 72829970, mail forskningsposten@stolav.no

Instructions for breaking randomization code prior to inclusion of all patients

Breaking of code is available during office hours by contacting Smerud Medical Research International AS, phone +47 2327 2000, refer to the TRANOP study and patient ID.

This study does not offer breaking of code outside of office hours.

In case of acute need of knowing whether a patient received active drug or saline as study treatment, the patient should be treated as if the patient received tranexamic acid. If local study staff still feel a need for breaking code, central study staff should be consulted but local study staff are allowed to independently contact Smerud Medical Research International AS.

Local primary investigator: (Name, phone)
International Study Manager: Kjersti Ausen, phone +47 92249693, mail kjersti.ausen@stolav.no.
International Study Nurse: Kirsti Sørås, Phone+47 72829970, mail forskningsposten@stolav.no

11.8. Appendix 8 Study Site Candidates

Public Departments of Plastic Surgery with established use of topical TXA

Helse SørØst		
Hospital	**Primary contact**	**Contact Info**
Vestre Viken	Malgorzata Gosciewska	malgorzata.gosciewska@gmail.com
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Hospital		
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Denmark		
Hospital		
Vejle and Odense Hospitals	Tine Engberg Damsgaard	Tine.M.Engberg.Damsgaard@rsyd.dk

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13. SIGNATURE PAGE:

Signatures to be added upon study initiation at the respective sites.

National Primary Investigator and primary investigator for St Olavs University Hospital:

Kjersti Ausen _____ (date) _____(sign)