NCT02578901

A-TREAT Consent Version 3.2

2016-06-24

[Insert University]

Patient or Legally Authorized Representative
Consent to take part in a research study:

A Randomized, Controlled Trial Evaluating the Safety and Efficacy of Tranexamic Acid in Patients with Hematologic Malignancies and Severe Thrombocytopenia

A-TREAT: American Trial Using Tranexamic Acid Therapy in Thrombocytopenia

Principal Investigator: [Insert Name]

[Insert contact**]**

[insert phone]

Subject Contact: **[**insert coordinator**]**

[insert contact]

[insert phone]

Emergency number (24 hours): [insert]

Researchers' statement

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to be in the study or not. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions, you can decide if you want to be in the study or not. This process is called "informed consent." We will give you a copy of this form for your records.

If you are a Legally Authorized Representative, the person that you are making medical decisions for is called your principal. We are asking you to decide if you want your principal to be in this research study or not. In the following form, "you" or "your" refers to your principal, and not the decision-maker. If your principal later is able to make decisions for (her) himself, (s)he will sign a new consent form.

We invite you to join this research study.

We invite you to join this research study because you have, or are expected to have, a very low platelet count, called thrombocytopenia, will be at an increased risk of bleeding, and are expected to require platelet transfusions. Up to 360 people will join this study.

Research is not the same as standard treatment or medical care. The purpose of a research study is to answer scientific questions.

Why are we doing this study?

Platelets are small cells in your blood that are important in helping your blood to clot. Many patients who are treated for blood disorders with chemotherapy, radiation, or bone marrow transplantation have low platelet counts. We have known since the 1960's that platelet transfusions help to prevent bleeding in patients with blood diseases who are being treated, and have low platelet counts. Earlier studies have shown that even when platelet transfusions are given, more than half of patients continue to have bleeding.

Because platelet transfusions alone do not prevent all bleeding, many doctors use drugs called antifibrinolytic agents to prevent or treat bleeding in patients with blood diseases who have low platelet counts. These drugs, such as Tranexamic Acid, stop bleeding by slowing down the breakdown of a clot that forms in an area of bleeding. There is evidence to suggest that Tranexamic Acid can be useful in the prevention and treatment of bleeding in patients with trauma, or undergoing surgeries such as open heart surgery, joint replacement, and liver transplantation. Some small studies suggest that antifibrinolytic agents, such as Tranexamic Acid, can also treat and prevent bleeding in patients with blood diseases and low platelet counts. These studies suggest that antifibrinolytic agents may also decrease the number of platelet

transfusions and red blood cell transfusions needed. However, in order to know how well these drugs work in treating bleeding related to low platelet counts in blood diseases, a larger study needs to be done comparing patients who are treated with an antifibrinolytic agent, Tranexamic Acid, with ones who are not.

There are 2 groups of participants in this study. We will give different treatments to each group, and then compare the results. One group will get the study drug, Tranexamic Acid, while the other group will get a placebo. A placebo looks like the drug being tested, but contains no active ingredient. Both groups will continue to get platelet and red blood cell transfusions when their doctors feel they are necessary. This study is a "blinded" study meaning that neither you nor your doctor and study team will know if you get the drug or the placebo. The purpose of having a blinded study is to make sure that both patients and doctors are able to look at all symptoms and events that occur during the study without bias. In the event of an emergency, the study team would be able to find out if you were receiving Tranexamic Acid or the placebo. This is how we hope to find out if adding Tranexamic Acid to standard care is good at preventing bleeding, and decreasing the number of blood and platelet transfusions that are required in patients with severe thrombocytopenia.

If you join this study, you would receive either Tranexamic Acid or a placebo. You would not get both. We will use a computer program to decide which treatment you will get. If you join this study, you would not be allowed to choose the treatment. You would have a 1-in-2 chance of receiving Tranexamic Acid.

What research tests, procedures, and treatments are done in this study?

If you decide to join this study, and meet the requirements needed for participation, the following tests, procedures and treatments will take place at various time points throughout the study:

- **Your Social Statistics (Demographics):** We will collect data about your birthdate, height, weight, gender, ethnicity, and race.
- **Medical History & Eligibility Exam:** You will be asked questions about your medical history. This includes conditions you have, medicines you are taking, and procedures (including transfusions) that you have undergone recently. All of the information that you provide will be confidential. You do not have to answer any questions that you do not want to, but then you might not be able to take part in this study. We will do an exam and look at your records to see if you are eligible to enroll. Altogether, this will take 30 minutes of time.
- **Urine & Blood Tests:** On the day of randomization, we will ask you for up to 6 teaspoons (30ml) of urine, collected in a cup, which will be tested in the laboratory. We will collect up to 4 teaspoons (20 ml.) of blood, throughout the duration of the study, for research, only if it has not already been collected for routine testing. We will need blood tests when you enroll, during pre-randomization, at randomization, and while you are taking the drug. It takes about 5 minutes for a blood draw or urine collection. These samples will be

tested for certain components to determine when you will begin study treatment, and to ensure it is safe for you to continue receiving study treatment.

- **Pregnancy Test:** If you are a female who could potentially become pregnant, a urine or serum pregnancy test will be performed before you begin study treatment; this is done at enrollment and at randomization if it is more than 7 days after enrollment.
- **Bleeding & Clotting Assessments:** You will frequently be asked questions regarding episodes of bleeding or symptoms of blood clotting (thrombosis) that you may have experienced or are experiencing.
- **Eye tests:** No changes have been reported or noted in eye examinations in patients treated with Tranexamic Acid for weeks to months in clinical trials. However a small number of visual changes were reported in a study in Sweden. To better understand whether or not there are any risks, you will have an eye exam when you start taking the drug, weekly until two weeks after you finish the drug, and if we asked and you noted any changes in your vision. We will ask you to read a standard eye chart, look at an eye grid chart and a color vision chart. This will take about 10 minutes of time.

What Happens	Enroll	Between Enroll & Randomization	Randomization	Active Treatment w/Study Drug or placebo		End treatment	Follow-Up	
				Up to 30 days	If you have signs of bleeding	Stop drug or placebo	14- 21 days after stop drug or placebo	30 days after stop & 120 days after start drug or placebo
Demographic and Medical History	X							
Check your medical condition	X	X	X	Xa	X	X	Chart,Call & diary	Call
Pregnancy Test Females	X		X					
Urinalysis			X					
Blood tests	X	X- twice weekly	X	Xa		X	X	
EyeTests				X weekly			X-weekly to 14 days after	
Study Drug or placebo given				X				
Bleeding Diary & Review			X	X-daily	X	X	X-daily to 14 days after	

a- Twice weekly for outpatients, daily for inpatients

Treatment Procedures

If you have been screened and are deemed eligible for participation in the study the following treatment phases may apply to you:

- **Pre-Randomization:** This is the time between your initial study screening/enrollment visit and the date you are randomized to study treatment (either Tranexamic Acid or the placebo). You will not receive study drug during this time, however, your platelet count will be closely monitored so that when it reaches less than or equal to 50,000/μl you can be assigned to a study treatment.
- **Randomization to Start of Study Drug:** Once you have been assigned to a study treatment (randomization), either Tranexamic Acid or placebo, your platelet count will again be closely monitored. Once it reaches less than 30,000/μl the research team will instruct you when and how to begin taking study medication. The pharmacy team will receive your hospital ID, birthdate, gender, and treatment assignment, so that they can prepare for your treatment. After you are randomized, it is possible that if your medical condition changes, you may no longer qualify to receive the study drug, and then you will not receive it. For example if you have active bleeding or clotting. You will still be monitored according to the study schedule, just as if you had received the medication.
- **Active Study Treatment:** Per your randomized study drug assignment, you will begin taking 1.3 grams orally or 1 gram IV (in your vein) Tranexamic Acid or placebo 3 times a day (every 8 hours), though this dose may be decreased depending on your clinical condition. You will receive the drug every day for 30 days, or until your platelet count spontaneously rises above 50,000/μl without transfusion support, or two stable platelet counts at least 48 hours apart are above 30,000/μl without transfusion support . You may be on this study if you are an outpatient at SCCA, or if you are admitted to the University of Washington Medical Center as an inpatient. If you are staying in the hospital while participating in the trial, you might receive study drug orally or intravenously; this decision will be made by your study doctor and care team based upon your ability to swallow and/or absorb medication. The doctors and care team might change the drug administration from oral to IV or IV to oral. You may continue on this trial after you are discharged from the hospital if you can take the medication orally. If you are participating in this trial as an outpatient then you will only receive study drug via oral administration.

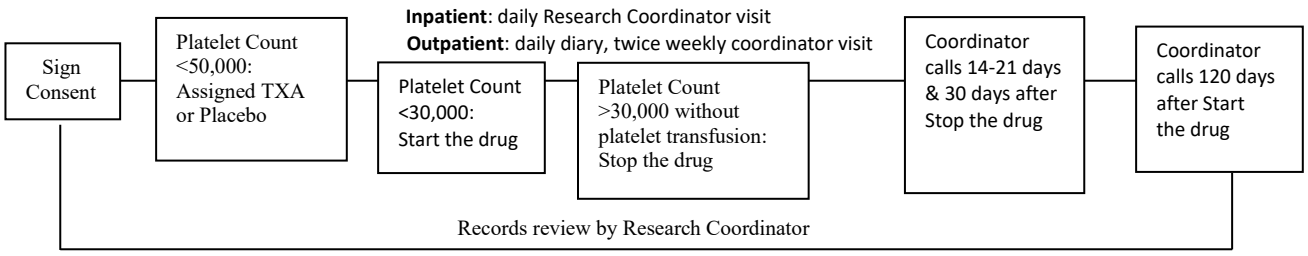
  The only person who will know if you are receiving Tranexamic Acid or the placebo will be the pharmacist preparing your drug for dispensing; the study team and your doctors will only be told whether you are receiving Tranexamic Acid or the placebo in the case of an emergency.
- **Daily Study Diary:** If you are participating in this trial, and not staying in the hospital, you will be asked to complete a daily diary that will help the study team keep track of how you are feeling, whether or not you are experiencing bleeding (and the type and severity of such episodes), if you are taking the

correct dose of study medication at the right times, and any other symptoms that you might report. Your will start filling out your diary when you are randomized, whether or not you receive the drug. This should take 10-15 minutes of time.

After you have finished taking the study drug (either Tranexamic Acid or a placebo) you will enter the **follow-up** portion of the study:

- **14-21 days after last dose of study drug:** Your status will be followed daily for 14 days after you stop taking the study drug. If you are in the hospital the research staff will perform a daily review of your medical chart. If you are not in the hospital then you will be asked to complete a daily study diary (see below), and the study staff will review your medical chart. You will be contacted in person or by telephone by a member of the research team so that they can follow-up on your health status after stopping the drug.
- **Daily Study Diary:** If you are participating in the follow-up portion of the study, and are not staying in the hospital, you will be asked to complete a daily diary that will help the study team keep track of whether or not you are experiencing any episodes of bleeding (and the type and severity of each episode). This should take 10-15 minutes of time.
- **30 days after last dose and 120 days after study drug is started:** You will be contacted in person or by telephone by a member of the research team so that they can follow-up on your health status after stopping study drug. This should take 10-15 minutes of time.

  Up to 120 days after starting study drug: The research team will continue to review your medical chart to follow up on your health status.



How long would you stay in this study?

If you join this study, you would stay in this study for approximately 120 days.

You would receive Tranexamic Acid or placebo for up to 30 days. After that, you would be followed closely for 14 days and then have a quick check-in with the study team at 30 days after stopping and 120 days after starting study drug.

Doctors could take you out of this study at any time. This would happen if:

- They think it is in your best interest not to continue in the study.

- You are not able or willing to follow study procedures.
- The whole study is stopped.

If you withdraw from the study for any reason, previously collected information would remain in the study records and would be included in the analysis of results. This information could not be removed from the study records.

What are the side effects (risks)?

Tranexamic Acid could cause side effects we do not know about yet. We carefully watch everyone in the study for side effects.

If you join this study, we would tell you if we discover new side effects that could affect you.

Below are possible side effects of Tranexamic Acid. Side effects may be mild or very serious. Medicines could be given to help lessen side effects. Many side effects go away soon after you stop taking Tranexamic Acid. In some cases, side effects can last a long time or never go away. The risk of death is low.

Likely side effects (greater than 10% of patients) of Tranexamic Acid are:

- Headache
- Abdominal Pain
- Back Pain
- Muscle Pain
- Nasal/Sinus symptoms (including congestion, sinus swelling and pain)

Less likely side effects (1% to 10% of patients) of Tranexamic Acid are:

- Fatigue
- Anemia
- Joint Pain
- Muscle Cramps/Spasms

Rare but serious side effects (less than 1% of patients) of Tranexamic Acid are:

- Allergic Reaction: *symptoms can include difficulty swallowing or breathing, itching, rash, facial flushing, or swelling. This can be life-threatening- Dial 911, seek immediate medical attention, and call the 24 hour number above.*
- Cerebral Thrombosis or Stroke: *a blood clot in a blood vessel in your brain. Symptoms include severe headache, abnormal vision, weakness of the face or limbs and/or seizure. This can be life-threatening- Dial 911, seek immediate medical attention, and call the 24 hour number above.*

- Deep Vein Thrombosis: *occurs when a blood clot forms in the veins of the body (usually in the legs). Symptoms include swelling and/or pain that can often feel like cramping or a general soreness when it begins. This can be serious-call the 24 hour number above, and seek immediate medical attention by calling your SCCA care team.*
- Pulmonary Embolism: *occurs when a blood clot travels to your lungs and blocks the arteries. Symptoms include shortness of breath (typically occurs suddenly and gets worse with exertion), chest pain (may feel like a heart attack and become worse when you breathe deeply, cough, eat or bend; often it will get worse with exertion and will not go away during rest) and/or cough (coughing may produce bloody sputum). This can be life-threatening- Dial 911, seek immediate medical attention, and call the 24 hour number above.*
- Diarrhea
- Nausea and/or Vomiting
- Renal Cortical Necrosis: *kidney damage caused by a lack of blood flow to the kidneys characterized by tenderness and/or swelling of the kidneys.*
- Seizure
- Ureteral Obstruction: *blockage in one, or both, of the tubes going from the kidney to the bladder characterized by pain, fever, nausea, vomiting and/or infection. This can be life-threatening- call the 24 hour number above and seek immediate medical attention by calling your care team.*
- Visual Disturbances: For sudden changes or loss of vision (including impaired color vision) *seek immediate medical attention by calling your SCCA care team and the 24 hour number above.*

Interactions with Other Drugs

Tranexamic Acid affects blood clotting and it may interfere with treatments designed to prevent clotting. We have reviewed your medical record and current treatments to ensure that you are not receiving treatment that affects clotting or other similar treatments that you should not receive while receiving Tranexamic Acid. If your physician decides that you require treatment that affects blood clotting, we will discontinue your use of the study drug. Estrogens and progesterone hormones (used in birth control pills or hormone replacement) are sometimes given to patients like yourself to prevent vaginal bleeding. Estrogen and progesterone may increase the risk blood clots (thrombosis) and this may also be a risk of treatment with Tranexamic Acid. It is possible treatment with both Tranexamic Acid and these hormones will lead to an increased risk of blood clotting. We will be assessing the development of any adverse blood clots during this therapy.

Reproductive Risk

Tranexamic Acid is classified as Category B risk to the fetus in pregnancy. This means that there was no harm to the fetus in animal studies. However there have not been enough studies in humans to know that the drug is completely safe in pregnancy. Therefore you should not enroll in this study if you are pregnant, and we will ask you to have a pregnancy test if one

has not been done when you enroll and before you start the drug. If you thought that you were not pregnant and this test showed that you were pregnant, this may or may not cause you distress. Males and females should use contraception while taking the study drug, and for 30 days after stopping the study drug to prevent pregnancy in themselves or their partner. You should not consent to be enrolled in this study if you are unwilling to use contraception to prevent pregnancy. If you become pregnant while enrolled in this study you should notify your physician and a member of the study team as soon as possible, stop taking the study drug, and you will be referred to qualified medical personnel for follow-up. We will obtain information from your medical record about the outcome of your pregnancy. You may not join this study if you are breast feeding. If you are pumping breast milk and disposing it (not giving it to your infant), then you may join the study.

Blood draw risk

Most blood draws are not done for research, but are done for routine care. Therefore, there is little additional risk. Having your blood drawn could cause mild pain, and bruising at the site. There is a rare risk of infection. You could feel faint or light headed during the procedure. If you have a central venous line, such as a Hickman, PICC, or Port-a-Cath, blood draws will be done through this line whenever possible.

Protecting Privacy as an Individual and the Confidentiality of Personal Information

Government or university staff sometimes review studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm. Reviewers include:

- Researchers involved with this study.
- Institutional Review Boards (IRB), including the University of Washington IRB. An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- Staff at [name]
- US National Institutes of Health, National Heart Lung and Blood Institute,, Office for Human Research Protections, Food and Drug Administration, and other regulatory agencies as required.
- Your participation in this study will be noted in your [name] medical record.
- An appointed board, called a Data Safety Monitoring Board (DSMB), will be following the information on safety for Tranexamic Acid in this study.

To protect your privacy, we assign you a unique study ID number. Only a few study staff members know the link between your name and your study ID number. We make every effort to safeguard your private information by storing paperwork in locked files, and using computer password protection. There is limited access to both paper and computer files.

We will do our best to keep personal information confidential. But we cannot guarantee total confidentiality. Personal information may be given out if required by law. For example, workplace safety rules may require health workers to contact you

about lab tests. Or a court may order study information to be disclosed. Such cases are rare.

We will not use personal information in any reports about this study, such as journal articles or presentations at scientific meetings.

What are the benefits?

We do not know if Tranexamic Acid would help prevent bleeding or the need for transfusions in patients with low platelet counts. It is possible that if you receive Tranexamic Acid you will experience less bleeding and will require fewer platelet and red blood cell transfusions. We hope the information we learn will help treating people with thrombocytopenia in the future.

You have other choices besides this study.

You do not have to join this study. You are free to say "yes" or "no". Your regular medical care would not change if you decide to say "no".

You have other choices for treatment. Each of these choices has risks and benefits. You should talk to your doctor or healthcare provider about these choices.

Other choices may include:

- Standard Treatment, which may/may not include TXA or another antifibrinolytic agent
- Another Research Study
- No Treatment

Enrollment in this study may exclude you from other research studies.

Would we pay you if you join this study?

There is no payment for being in this study.

Would you have extra costs if you join this study?

If you join this study, you or your insurance company would have to pay for the costs of standard treatment in this study such as:

- Cost of platelet transfusions and the people and equipment used to give you the platelet transfusion
- Cost of standard lab tests that may be done to monitor your health while you are receiving study treatment

- Cost of people and equipment used to give you the study drug (if you receive the drug intravenously)

You would **not** be billed for:

- Study Medication (Tranexamic Acid or placebo)
- Pregnancy test (females of childbearing potential)
- Laboratory tests which are only done for research purposes related to this study

What if you get sick or hurt after you join this study?

For a life threatening problem, call 911 right away or seek help immediately. Contact your study doctor when the medical emergency is over or as soon as you can.
It is important that you promptly tell the researchers if you believe that you have been injured because of taking part in this study. You can tell Dr [Insert name] in person or call her at [Insert number] or the 24 hour number listed at the top of this form.
She will treat you or refer you for treatment.
The costs of the treatment may be billed to you or your health insurance just like other medical costs, or it may be covered by the [name] discretionary Human Subjects Assistance Program (HSAP), depending on a number of factors. The researcher may request HSAP coverage by following established procedures. If you wish to request HSAP coverage yourself, contact the researcher or the [name]Human Subjects Division at [phone]. Ask the researcher if you would like information about the limits and conditions of the HSAP. The [name] does not normally provide any other form of compensation for injury. However, the law may allow you to seek payment for injury-related expenses if they are caused by malpractice or the fault of the researchers. You do not waive any right to seek payment by signing this consent form.

You would not lose any legal right to seek payment for treatment if you sign this form.
You or your insurer will be billed for treatment of problems or complications that result from your condition or from standard clinical care.

Your rights

- You do not have to join this study. You are free to say “yes” or “no”.
- If you get sick or hurt in this study, you do not lose any of your legal rights to seek payment by signing this form.
- During the study, we might learn new information that you need to know. For example, some information may affect your health or well-being. Other information might make you change your mind about being in this study. If we learn these kinds of information, we would tell you.
- If you join this study, you would not have to stay in it. You could stop at any time (even before you start). Your regular medical care would not change.

You would have no penalty for stopping, but it would be better not to join the study if you think that you would change your mind later.

- If you decide to drop out, we would want you to tell the study doctor. The doctor could tell you about the effects of stopping Tranexamic Acid. You and the doctor could talk about the follow-up care and testing that would help the most. Before you leave the study, the doctor might ask you to continue in the follow-up part of the study
- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Your responsibilities

If you join this study, you would have some responsibilities.

- Follow the schedule of study visits and procedures.
- Takes study medications as directed.
- If an outpatient participant, fill out the daily diary.
- Tell us about side effects.

Source of funding

This study is funded by a grant from the National Heart Lung and Blood Institute /National Institutes of Health.

For more information

If you have questions or concerns about this study, you could talk to your doctor anytime. Other people you could talk to are listed below:

If you have questions about:	**Call:**
This study (including complaints and requests for information)	[phone] [name] Principal Investigator [phone] [name], Clinical Research Nurse
If you get sick or hurt in this study	[phone][name], Principal Investigator
Your rights as a research participant	[phone] Human Subjects Division
Your bills and health insurance coverage	[phone] Patient Financial Services,

Emergency number [insert]

Signatures

Subject's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, or if I have been harmed by participating in this study, I can contact one of the researchers listed on the first page of this consent form. If I have questions about my rights as a research subject, I can call the Human Subjects Division at [phone]. I give permission to the researchers to use my medical records as described in this consent form. I will receive a copy of this consent form.

Printed name of subject	Signature of subject	Date

When subject is not able to provide informed consent:

Printed name of representative	Signature of representative	Date

Relationship of representative to subject

Copies to: Researcher
Subject
Subject's Medical Record (if applicable)

Researcher's statement

I have discussed the research study, including procedures and risks, with the person signing above. A copy of the signed consent form will be given to the participant.

_____
Printed Name of Person Conducting the Informed Consent Discussion

_____ _____
Signature of Person Conducting the Informed Consent Discussion — Date