UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: A Pediatric Trial Using Tranexamic Acid in Thrombocytopenia

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INTRODUCTION

We are seeking your permission to enroll you in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation. It describes, in words that can be understood by a lay person, the purpose, procedures, benefits, risks and discomforts of the study and the precautions that will be taken. No guarantee or assurance can be made as to the results of the study. Also, participation in the research study is completely voluntary. Withdrawing from the study will not affect your ability to seek routine care at this institution. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled.

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When "you, your, I, or me" is used in this consent form, it means your child. Parents will not be participants in this study.

Please take your time reading this form. After all of your questions have been answered, if you still wish to take part in the study, you will be asked to sign and date this Informed Consent Form.

If you have questions at any time during the research study, you should feel free to ask them, and should expect to be given answers that you understand and that are satisfactory to you.

Your doctor or another member of the study team will also be asked to sign this

Informed Consent Form. You will be given a copy of the signed consent form to keep.

You are not giving up any of your legal rights by volunteering for this research study or by signing this consent form.

This is a clinical trial, a type of research study. Clinical trials are studies designed to find better ways to treat diseases. Taking part in this study is entirely voluntary and in order to decide whether or not you wish to take part, you should understand enough about its purpose, procedures, risks (side effects), benefits (if any), costs and your rights as a participant to make an informed decision. This process is known as Informed Consent.

This consent form also describes the alternative procedures that are available to you/your child, and your right to withdraw from the study at any time. Please take time to read this consent carefully and ask questions if anything is not clear. Discuss it with your family doctor, friends, and relatives if you wish. Feel free to ask about anything that is not clear or request additional information. Take as much time as you want to decide whether or not you wish to take part. If you/your child agree to participate, you/your child will be asked to sign this form.

WHY IS THIS RESEARCH BEING DONE?

This research study is being done to find out how well tranexamic acid treatment works to prevent bleeding symptoms in pediatric patients who are receiving chemotherapy and/or blood or marrow transplant (BMT) to treat their cancer. We also want to find out what, if any, side effects are associated with this treatment. Children receiving chemotherapy or BMT are at high risk of bleeding. The risk of bleeding appears to be more than what can be explained by low platelet counts alone. It is not completely prevented with platelet transfusions. Tranexamic acid has been shown to decrease bleeding and decrease the need for blood product transfusions in patients with bleeding due to other causes. We do not know whether tranexamic acid will also help to prevent bleeding or the need for blood product transfusions in patients who are receiving chemotherapy or BMT. Therefore, we are asking you/your child to participate in a research study to look at the effects of tranexamic acid on your/your child's risk of bleeding during a period when their platelet counts are low. This study will involve about 10-20 patients who are receiving chemotherapy or BMT and have low platelet counts.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You / Your Child is being asked to take part in this research study because you have a risk of bleeding while you are receiving chemotherapy.

HOW LONG WILL YOU BE IN THIS RESEARCH STUDY?

If you/your child agree to take part in this study, you/your child will receive a "drug" through their IV three times per day over a period of up to 30 days.

HOW MANY SUBJECTS WILL TAKE PART IN THE RESEARCH STUDY?

We expect to enroll about 20 subjects at UPMC Children's Hospital of Pittsburgh.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

If you/your child agree to take part in this study, you/your child will receive a "drug" through their IV three times per day over a period of up to 30 days. The drug will either be tranexamic acid or a placebo. A placebo is a fake medication that looks like the study drug, made so that no one knows who is taking which medication. Tranexamic acid has been shown to help reduce bleeding due to other causes in patients who are not receiving chemotherapy. This drug helps to stabilize blood clots made naturally by the body and slows their breakdown. You or your child will randomly (by chance, like flipping a coin) be chosen to receive the drug or the placebo. Neither you or your doctor or study coordinator will know which treatment you are receiving. All of your other treatments will remain that same and you/your child can be assured, that you/your child will get the standard level of care for patients receiving chemotherapy.

If you/your child agree to participate in this study labs and information that will be collected when you/your child agrees to participate in the study include:

- Information from you/your child's medical record including height, weight, BMI, birth date, gender, ethnicity, race, diagnosis, current treatment, ABO blood type and current medications
- Blood will be taken to look at :
    - CBC - measures white blood cell, red blood cell and platelet counts ○ Creatinine -a marker of kidney function
    - A urine or blood pregnancy test for females of childbearing age ○ If you/your child has received Asparaginase >7 days but ≤14 days from consenting to this study then PT, PTT, INR and Fibrinogen (measures of the blood's clotting) will be checked
    - HLA Testing (if sent by your doctor)

If there is a period of time between enrollment on study and meeting the criteria to be randomized to either the study drug or placebo, the following information will be collected:

- Review of medical record to look for evidence of blood clots (weekly)
- CBC - measures white blood cell, red blood cell and platelet counts (daily)
- Information on other medications you/your child is receiving

You/your child will be randomly assigned to a treatment group when you/your child's platelet count is ≤50,000/uL. Information that will be collected when treatment group is assigned includes:

- Information from you/your child's medical record including platelet and red blood cell transfusions and information on blood clots
- You/your child will be interviewed and examined to evaluate for bleeding symptoms
- PT/PTT/INR/Fibrinogen/D-dimer– these labs evaluate the body's blood clotting system
- Urinalysis – to look for blood in the urine (if >72 hours from last)
- A urine or blood pregnancy test for females of childbearing age (if >72 hours from last)
- CBC -measures white blood cell, red blood cell and platelet counts
- Creatinine - a marker of kidney function

If there is a period of time between randomization on study and meeting the criteria to begin either the study drug or placebo, the following information will be collected: Review of medical record to look for evidence of blood clots (weekly)

- CBC - measures white blood cell, red blood cell and platelet counts (daily)
- Information on other medications you/your child is receiving

When you/your child's platelet count is ≤30,000/uL they will begin therapy with either the study drug or placebo for up to 30 days. After you/your child begin treatment with the study medication the following information will be collected:

- Information on platelet and red blood cell transfusions; information on blood clots, information on adverse effects potentially related to the study drug and current medications will be collected from you/your child's medical record (daily)
- You/your child will be interviewed and examined to evaluate for bleeding symptoms (daily)
- Urinalysis – to look for blood in the urine (on first day of study drug if >72 hours from last)
- CBC -measures white blood cell, red blood cell and platelet counts (daily)
- Creatinine - a marker of kidney function (daily)
- Bilirubin - to follow liver function (weekly)

Most of the lab tests described above are part of the routine testing that is standard care in patients receiving chemotherapy. As part of this study we will also be collecting blood samples to measure how well the study drug is working in the body by directly measuring the ability to break down blood clots. This will involve a small amount of additional blood (1-2 teaspoons) collected before beginning treatment and after several days of therapy. This will not involve any additional lab draws and will be collected when blood is being drawn for other purposes.

Some of this blood sample will be shared with researchers outside of this hospital so that the special testing measuring blood clot breakdown can be completed. These blood samples will be sent to the University of North Carolina Chapel Hill. Blood samples shared with other researchers will not have any information that will allow them to identify you. Blood samples sent to UNC Chapel Hill will be stored indefinitely for use in future testing. A portion of the blood samples will also be stored at the Children's Hospital of Pittsburgh for use in future research to measure clot breakdown. These blood samples will be stored indefinitely for use in future testing. Blood samples and information collected in this study may also be shared with colleagues within other institutions to help with future research. Information will be shared in such a way that those researchers will not be able to identify you.

You may request in writing that that samples no longer be used for research later on and any remaining samples will be destroyed.

Approximately one week and one month after study drug is discontinued we will collect information on bleeding/clotting events from you/your child's medical record and any information on adverse events potentially related to the study drug. You will be contacted

in person or by telephone to review any bleeding events, blood clotting events and any adverse events potentially related to the study drug if you/your child have been discharged from the hospital. If you/your child remain in the hospital we will speak with you there.

WHAT ARE THE BENEFITS TO BEING IN THE RESEARCH STUDY?

This study may or may not have a direct medical benefit to you. Any of your/your child's bleeding symptoms will be evaluated and monitored. Those patients who get the drug therapy may have a less risk of bleeding and less need for blood product transfusions. Over the long term, this medication may lower the exposure to multiple blood products and reduce both minor and major bleeding complications. Learning how this medication works in patients receiving chemotherapy may help us learn the reasons why patients receiving chemotherapy are at high risk of bleeding and be able to know which patients are at the greatest risk and help prevent these symptoms in the future.

WHAT ARE THE RISKS FOR BEING IN THIS RESEARCH STUDY?

You may have side effects while on the study. As with any experimental procedure, there may be adverse events or side effects that are currently unknown. Side effects can go away shortly after drug administration is stopped, but some risks could be long-lasting, permanent, serious, life threatening, or even cause death. Everyone taking part in the study will be watched carefully for any side effects. You should talk to your study doctor about any side effects you have while taking part in the study.

Tranexamic acid is filtered by the kidneys and the dose should be adjusted in people with kidney disease.

Patients with bleeding in their upper urinary tract may develop clots that can block urine drainage and should not use this medication. Tranexamic acid has been reported in rare cases to be associated with blood clots. Patients who have a history of blood clots in the past or are on medications that promote blood clotting should not use this medication.

Tranexamic acid may be associated with GI upset, including nausea, vomiting or diarrhea but typically disappear when the dose is reduced or discontinued. Some people may also report symptoms of giddiness or dizziness with use.

Low blood pressure can occur when the medication is given too quickly by IV, and therefore there are rules about how quickly this can be given. Some patients may develop allergic skin reactions with use. There is a rare but potentially serious risk of allergic reaction leading to shock.

Seizures have been reported in association with the use of tranexamic acid, if you/your child has a history of seizures you will not be given this medication. In animal studies using dogs, cats and rats changes to the back of the eye affecting vision have developed

using doses that are 6-40 times the usual recommended human dose. No similar changes have been reported or noted in eye exams in human patients using tranexamic acid for weeks to months in other clinical trials. In animal studies using rats an increased risk of leukemia was seen in male mice using doses greater than the usual recommended human dose. There is no evidence of an increased risk of leukemia in human patients.

Breach of Confidentiality - There is a small risk of a breach of confidentiality occurring, which would entail the unauthorized or inappropriate sharing or release of your medical or research data. The research staff will take all necessary steps to ensure that this does not happen, including keeping your records in a locked file and using passwords for computer files.

ARE THERE REASONS I WOULD HAVE TO STOP BEING IN THE STUDY?:

You/your child will no longer take the study drug/placebo if any of the following should occur:

- It has been 30 days since you/your child first started taking the study drug/placebo
- You/Your child have an increase in your platelet count from a level of <30,000/uL to a level of ≥50,000/uL over two blood counts with no transfusions in between
- You/your child have a platelet count that remains consistently greater than 30,000/uL for over two days (>= 46 hours) without any intervening blood product transfusion or stem cell transplant
- You/your child becomes pregnant
- You/your child are prescribed tranexamic acid or other antifibrinolytic agent or other medication to promote blood clotting by the physician caring for them
- You/your child begins therapy with anticoagulation or antiplatelet therapy
- You/your child develops a blood clot
- You/your child develops a complete blockage of their central line requiring TPA therapy one more than one occasion
- You/your child develops visible blood in their urine
- You/your child stops making urine
- You/your child develops veno occlusive disease
- You/your child is discharged from the hospital

If these conditions occur and require the drug/placebo therapy to be discontinued, it will not be restarted even if any of the above conditions are no longer a concern for you/your child.

WHAT ARE THE ALTERNATIVES IF I CHOOSE NOT TO PARTICIPATE?

Participation in this research is voluntary. If you do not wish to take part in this research study, your doctor will discuss alternate treatment options with you, including their benefits and risks.

WILL I FIND OUT IF ANY NEW INFORMATION IS DISCOVERED DURING THIS RESEARCH STUDY?:

You will be promptly notified if, during the conduct of this research study, any new information develops which may cause you to change your mind about continuing to participate.

WILL THERE BE ANY COST TO ME TO PARTICIPATE IN THIS RESEARCH STUDY?

Some of the services you will receive and procedures you will undergo are being done only because you are participating in this research study. Examples of these "research-only" services include the study drug and the research blood work. The research-only procedures will be paid for by the study and will not be billed to you or your health insurance company.

Because you are also a patient at a UPMC facility, some of the services you will receive and procedures you will undergo during this research study are considered to be "routine clinical services" that you would have even if you were not participating in this research study. Examples are the routine blood draws, and any supportive care, treatment, or other medications ordered by your physician. These services will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or coinsurance that are a normal part of your health insurance plan. If you do not have health insurance, you will be responsible for those costs. To obtain more detailed information about what routine clinical services your health insurance is likely to pay for, contact a UPMC financial counselor. A member of the research team can provide you with this contact information.

WILL I BE PAID TO BE IN THIS RESEARCH STUDY?

You will not be paid for your participation.

Your data or specimens used in this research study may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products. You will not retain any property rights, nor will you share in any money that the investigators, the University of Pittsburgh, or outside agencies may receive.

WHAT WILL HAPPEN IF I AM INJURED WHILE IN THIS RESEARCH STUDY?

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation.

HOW WILL MY INFORMATION BE KEPT PRIVATE AND CONFIDENTIAL?

Any information about you obtained from this research will be kept as confidential (private) as possible. All records related to your involvement in this research study will be stored in a locked environment. You will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

DISCLOSURE OF IDENTIFIABLE MEDICAL INFORMATION:

This research study will involve the recording of current and/or future identifiable medical information from your hospital and/or other (e.g., physician office) records. The information that will be recorded will be limited to information concerning treatment of your cancer. This information will be used to determine your eligibility for this study and to follow your progress once you are enrolled in the study.

This research study will result in identifiable information that will be placed into your medical records held at Children's Hospital of UPMC. The nature of the identifiable information resulting from your participation in this research study that will be recorded in your medical record includes the results of lab and scan results, response to study treatment including adverse events (side effects).

ACCESS TO IDENTIFIABLE INFORMATION:

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

- University of Pittsburgh Research Conduct and Compliance Office
- U.S. Food and Drug Administration (FDA)
- UPMC hospitals or other affiliated health care providers.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

USE AND DISCLOSURE OF IDENTIFIABLE INFORMATION:

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for an indefinite amount of time.

ACCESS TO MEDICAL INFORMATION RESULTING FROM PARTICIPATION:

In accordance with the UPMC Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider.

VOLUNTARY AUTHORIZATION:

Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your doctor may be involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

WITHDRAWAL OF CONSENT TO PARTICIPATE:

You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable medical record information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

If you decide to withdraw from study participation after you have received the study drug, you should participate in described monitoring follow-up procedures directed at evaluating the safety of the study drug.

It is possible that you may be removed from the research study by the researchers as described earlier in this consent form. The study doctor may also stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study procedures, or if the study is stopped.

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VOLUNTARY CONSENT

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

By signing this consent, I am giving permission to the study doctor, Dr. McCormick to use and share personal health information from my medical record to conduct this research study.

A copy of this consent form will be given to me.

_____
Printed Name of Subject

_____ _____
Subject Signature (if 18 years of age) Date/Time
_____ Printed Name of Parent/Guardian

_____ _____
Parent/Guardian Signature Date/Time

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____
Name of Person Obtaining Consent (Print) Role in Research Study

_____ _____
Signature of Person Obtaining Consent Date/Time

CHILD ASSENT (Children age 12 and older)

This research has been explained to me, and I agree to participate.

_____ _____

Signature of Child-Subject Date/Time

VERIFICATION OF EXPLANATION

I certify that I have carefully explained the purpose and nature of this research to

_____ in age appropriate language.

Name of Child

He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she provided affirmative agreement (i.e., assent) to participate in this research.

_____ _____

Signature of Person Obtaining Assent Date/Time

CONSENT FOR CONTINUED RESEARCH PARTICIPATION

I understand that I am currently participating in a research study. I further understand that consent for my participation in this research study was initially obtained from my authorized representative as a result of my inability to provide direct consent at the time

that this initial consent was requested. I have now turned age 18 and I am able to provide direct consent for continued participation in this research study.

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given.

I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable. By signing this form I agree to participate in this research study.

By signing below, I agree to continue my participation in this research study. A copy of this consent form will be given to me.

_____ _____

Participant's Signature Date/Time

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____

Name of Person Obtaining Consent (Print) Role in Research Study

_____ _____

Signature of Person Obtaining Consent Date/Time