Tranexamic Acid for the Prevention of Obstetrical Hemorrhage After Cesarean Delivery: A Randomized Controlled Trial

Protocol

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1 Introduction

1.1 Study Abstract

Obstetrical hemorrhage is a common cause of maternal morbidity and mortality worldwide. The frequency and severity of hemorrhage is significantly higher after cesarean delivery than vaginal delivery. Recent evidence has emerged about the importance of the fibrinolytic pathway in the pathophysiology of hemorrhage in different clinical scenarios including trauma-associated bleeding, cardiovascular surgery, and obstetrical hemorrhage. Tranexamic acid (TXA) inhibits fibrinolysis and is used routinely to prevent hemorrhage in trauma cases and high risk surgeries. Randomized trials of TXA as a prophylaxis to prevent hemorrhage in cesarean delivery have been small and of mixed quality; however meta-analysis suggests that it is effective.

This protocol describes a randomized placebo-controlled trial of 11,000 women to assess whether tranexamic acid as prophylaxis lowers the risk of postpartum hemorrhage in women undergoing a cesarean delivery.

1.2 Primary Hypothesis

In women undergoing cesarean delivery, intraoperative intravenous administration of TXA reduces the need for red blood cell transfusion.

1.3 Purpose of the Study Protocol

This protocol describes the background, design and organization of the RCT and may be viewed as a written agreement among the study investigators. The Data and Safety Monitoring Committee (DSMC) and the Network Advisory Board review the protocol. Before recruitment begins, the protocol is approved by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network Steering Committee, and the Institutional Review Board (IRB) of each clinical center. Any changes to the protocol during the study period require the approval of the Steering Committee and the IRBs.

A manual of operations supplements the protocol with detailed specifications of the study procedures.

2 Background

2.1 Introduction

Globally, postpartum hemorrhage is the leading cause of preventable maternal mortality.[1] In 2007 in the United States, hemorrhage was the third leading cause of maternal death due to obstetric factors.[2] Current trends in the obstetrical population (e.g., rising obesity) and practice (e.g., cesarean delivery and labor induction) continue to contribute to the rise in postpartum hemorrhage and its associated maternal mortality.[3] In the United States, the current rate of cesarean delivery is 32% of all births,[4] with an estimated rate of postpartum hemorrhage of nearly 5% in scheduled and 7% in unscheduled cesarean deliveries.[5]

2.2 Hemorrhage and Fibrinolysis

As hemorrhage progresses, early coagulopathy may occur even before consumption of clotting factors or hemodilution take place. This mechanism of early coagulopathy has mainly been studied in trauma; however, obstetrical hemorrhage shares many of the mechanisms involved.[6] Tissue hypoperfusion results in up-regulation of thrombomodulin receptors in endothelial cells. Thrombomodulin receptors interact with thrombin resulting in activation of the protein C pathway. Protein C irreversibly inhibits factors Va and VIIIa and enhances fibrinolysis through inhibition of plasminogen activator inhibitor 1.[7] Similarly, endothelial ischemia results in increased local production of tissue plasminogen activator resulting in increased fibrinolysis. Conversion of plasminogen to plasmin results in lysis of fibrin clots with subsequent bleeding despite administration of commonly utilized blood products including fresh frozen plasma, platelets, and cryoprecipitate. TXA is a synthetic derivative of lysine that inhibits fibrinolysis by reversibly binding to the lysine receptor sites on plasminogen and plasmin. TXA prevents plasmin from binding to and degrading fibrin and has ten times the antifibrinolytic activity of the older analogue, ε-aminocaproic acid.[8]

2.3 Use of TXA

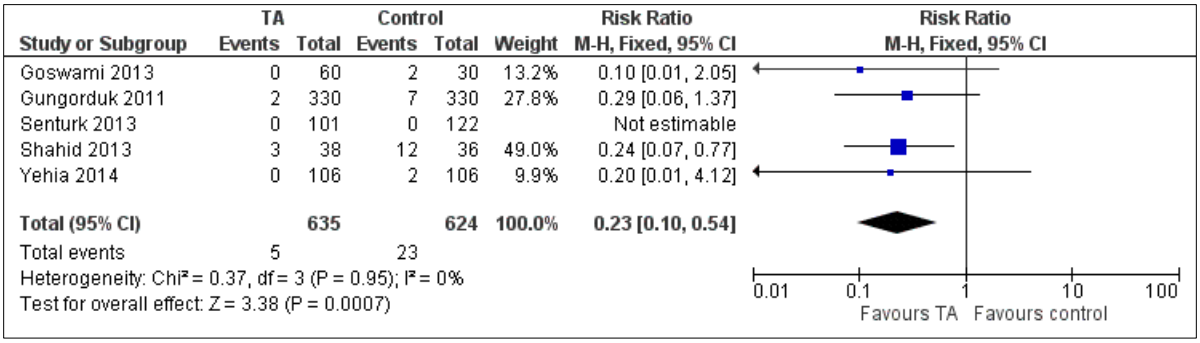
TXA is used routinely as prophylaxis in heart surgery requiring cardiopulmonary bypass, and in liver transplants. It is also part of massive transfusion protocols used in many trauma centers, as well as in some obstetrics units. A recent RCT found that trauma victims who received TXA within 3 hours of the injury had less severe bleeding and lower mortality compared with controls.[9] In this trial, TXA was administered empirically without the use of point of care testing (e.g., thromboelastography). Similarly, TXA has been effectively used prophylactically to prevent major surgical bleeding in cardiothoracic surgery, orthopedic procedures, and vascular surgery.[10,11]

Increased fibrinolytic activity has been documented in obstetrical hemorrhage secondary to uterine atony, placental abruption, and placenta accreta.[6] Following placental separation, levels of fibrinogen decrease dramatically while levels of plasminogen activators and fibrin degradation products increase as a result of increased fibrinolytic activity that may last for up to 10 hours post-delivery.[12,13] Small RCTs have demonstrated the efficacy of TXA in reducing blood loss at the time of cesarean delivery with no increase in thrombotic complications.[14,15]

A meta-analysis of relatively small RCTs comparing the use of intravenous TXA versus no TXA at the time of cesarean delivery concluded that TXA was associated with reduced blood loss.[13] The meta-analysis found a significant decrease in total blood loss, intra operative blood loss, postpartum blood loss, hemoglobin and hematocrit drop, and need for blood transfusion in patients who received TXA compared with controls. Another recent meta-analysis reported similar findings.[16] Other investigators have concluded that although TXA is effective in reducing postpartum blood loss, the effect on the incidence

of blood transfusions is unclear and requires further studies.[17,18] The results have not been consistent across trials as some did not find a benefit with the use of TXA.[19] Inconsistencies in the current literature are likely secondary to multiple factors including subjective assessment of blood loss, different definitions of postpartum hemorrhage, and lack of randomization and standardized protocols dictating drug administration.[20] Recently, a Cochrane review on the use of TXA in obstetric settings found that TXA was associated with a reduction in the need of blood transfusion among women undergoing cesarean delivery (RR 0.23, 95% CI 0.10 to 0.54, five trials, 1,259 participants) compared with placebo (Figure 1).[21] The authors conclude that there is evidence that TXA decreases postpartum hemorrhage and blood transfusions based on mixed quality studies. Furthermore, the effect of TXA on mortality and thromboembolic events requires further study.

Figure 1. Meta-analysis of Tranexamic Acid Trials with Outcome of Blood Transfusion



For the treatment of established postpartum hemorrhage, a recent randomized placebo controlled, international clinical trial found decreased mortality due to bleeding with the use of TXA.[22]

2.4 Safety of TXA

The use of TXA in non-obstetrical studies has not been associated with increased rates of thrombotic complications, and the available data regarding its use for the prevention of postpartum hemorrhage after a cesarean delivery suggest no increased risk in thrombotic complications.[23-26] The latter was also supported by the previously cited Cochrane review.[21]

The most common side effects of TXA include nausea, vomiting, and diarrhea, with less common side effects of allergic dermatitis, giddiness, hypotension, and changes in color vision. In patients with urologic bleeding, ureteral obstruction clots have been described.

At very high doses (50-100 mg/kg), TXA use has been associated with seizures in those undergoing coronary artery surgery.[27] However, even at these doses, as well as lower doses (20-40 mg/kg), there was no increased risk of thrombotic events.[9] This is particularly relevant to potential wide scale use at delivery as the rate of thrombosis in pregnancy has been estimated to be 4 to 5 times the rate in non-pregnant individuals, or roughly 1 to 2 per 1000 pregnancies.[28,29]

The half-life of TXA is 2 hours, and the antifibrinolytic effect may last up to 17 hours in tissues, and 7-8 hours in serum.[30] During delivery, the increase in fibrinolysis starts with placental separation, and has been described to last up to 10 hours post-delivery. Therefore, the administration of a single dose of TXA near the time of delivery should match the timing of increased fibrinolysis.

TXA is present in the mother's breast milk at a concentration of about a hundredth of the corresponding serum levels. When only one dose is administered, excretion of TXA is about 90% at 24 hours after intravenous administration of 10mg per kg body weight. (Cyclokapron [package insert]. New York, NY: Pharmacia & Upjohn Co., Pfizer; 2016). In a study of 21 women taking TXA while breastfeeding and 42 women in a control group, no increase in adverse outcomes were reported in the children exposed to TXA

through breastfeeding.[31] Furthermore, in a trial of 20,060 participants (10,051 receiving TXA), no thromboembolic events were reported in breast-fed babies in either group.[22]

2.5 Rationale for a Randomized Clinical Trial

Overall, the quality of the available trials assessing the efficacy of TXA in preventing excessive blood loss in obstetrics is limited (for example, unblinded trials), and most of the trials used a primary outcome of unclear clinical utility such as subjective estimated blood loss. The limited available data, however, point to potential benefit. Most studies report a decrease in estimated blood loss and some report a significant decrease in blood transfusion requirement. Of note, neither the non-obstetrical nor the limited obstetrical literature report an increase in thromboembolic complications with the use of TXA. It is clearly important to determine in a large well designed and executed randomized trial whether TXA at the time of cesarean delivery decreases the need for transfusion of blood products.

3 Study Design

3.1 Primary Research Question

This randomized trial will address the primary research question:

Does prophylactic administration of intravenous TXA at the time of cord clamping during cesarean delivery reduce the need for transfusion of packed red blood cells?

3.2 Secondary Research Questions

Secondary research questions that this study will address are:

- Does prophylactic administration of intravenous TXA at the time of cesarean delivery reduce:
    - transfusion of other blood products (fresh frozen plasma, cryoprecipitate, platelets, and other factor concentrates)?
    - additional surgical or radiologic procedures to abate bleeding?
    - perioperative estimated blood loss?
    - postpartum infectious complications?
- Is administration of prophylactic TXA at the time of cesarean delivery associated with thromboembolic complications?

3.3 Design Summary

The study is a randomized placebo-controlled trial of 11,000 women undergoing either a scheduled or unscheduled cesarean delivery. Participants will be randomized to receive either:

- TXA (1 gram) in 50 cc of normal saline administered intravenously immediately following umbilical cord clamping (or as soon as possible afterward) or
- 50 cc of normal saline as a placebo

Randomization will be restricted to allow a maximum of 50% scheduled cesarean deliveries compared with unscheduled.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

1. Scheduled or unscheduled cesarean delivery
2. Singleton or twin gestation

3.4.2 Exclusion Criteria

1. Age less than 18 years
2. Transfusion or planned transfusion of any blood products during the current admission because the primary outcome is already pre-determined and the need for transfusion will be unrelated to perioperative hemorrhage
3. Recent diagnosis or history of venous thromboembolism or arterial thrombosis because TXA is a risk factor for thromboembolism, and its use is contraindicated

4. Known congenital or acquired thrombophilias, including antiphospholipid antibody syndrome, because of the increased risk of thrombosis
5. Seizure disorder (including eclampsia) because TXA is a GABA receptor antagonist, and its use has been associated with postoperative seizures
6. Serum creatinine of 1.2 mg/dL or higher, or on dialysis, or with renal disease or a history of renal insufficiency, because TXA is substantially excreted by the kidney, and impaired renal function may increase the risk of toxic reactions.
7. Sickle cell disease, because of substantial use of perioperative transfusion unrelated to hemorrhage. Sickle cell trait is not an exclusion per se.
8. Autoimmune diseases such as lupus, rheumatoid arthritis, Sjogren's disease, and inflammatory bowel disease because of hypercoagulability and the increased risk of thrombosis or thromboembolism
9. Need for therapeutic dose of anticoagulation before delivery, because the risk of thrombosis may be increased with TXA
10. Treatment with clotting factor concentrates, because the risk of thrombosis may be increased with TXA
11. Presence of frank hematuria, because the risk of ureteral obstruction in those with upper urinary tract bleeding may be increased with TXA
12. Patient refusal of blood products because the primary outcome is then pre-determined
13. Receipt of TXA; or planned or expected use of TXA prophylaxis
14. Receipt of uterotonics, other than oxytocin, or planned or expected use of uterotonic prophylaxis
15. Active cancer, because of risk of thromboembolism
16. Congestive heart failure requiring treatment, because of risk of thrombosis
17. Symptomatic for COVID-19 infection within 14 days prior to delivery, regardless of whether viral testing was performed
18. History of retinal disease, because the risk of central retinal artery or vein obstruction may be increased with TXA
19. Acquired defective color vision or subarachnoid hemorrhage, since TXA is contraindicated
20. Hypersensitivity to TXA or any of the ingredients
21. No hemoglobin result available from the last 4 weeks, since it is necessary to measure the post-operative change in hemoglobin
22. Scheduled cesarean delivery and quota for scheduled deliveries already met. Quotas on the number of scheduled and unscheduled deliveries will be placed to ensure approximately equal distribution of scheduled and unscheduled cesarean deliveries.
23. Participating in another intervention study where the primary outcome includes postpartum bleeding or thromboembolism, or the study intervention directly affects postpartum bleeding or thromboembolism.
24. Participation in this trial in a previous pregnancy. Patients who were screened in a previous pregnancy, but not randomized, may be included.

3.5 Informed Consent

The study is double masked; neither the patient nor the clinical staff will be aware of the treatment assignment.

Each center will develop its own consent form(s) according to the requirements of its own institutional review board using the model consent form in Appendix B. Each center will also develop its own patient research authorization documents, as required by the HIPAA Privacy Rule, following the guidelines of its own institution. A copy of the signed consent form for the study will be provided to the patient.

Women who are not fluent in English will be enrolled by a person fluent in their language, if possible. Both verbal and written informed consent and authorization will be obtained in that language; if this is not possible the patient will be excluded.

3.6 Randomization Method and Masking

Consenting women will be assigned to TXA or placebo in a 1:1 ratio according to a randomization sequence prepared and maintained centrally by the Biostatistical Coordinating Center (BCC). The trial is double masked; neither the patient nor the clinical staff will be aware of the treatment assignment.

Simple randomization will be used to generate the randomization sequences because this is an extremely large trial and therefore the probability of imbalance is low. Randomization will be stratified by clinical site to assure balance between the two treatment groups with respect to anticipated differences in the hospital populations and possible differences in patient management.

4 Study Procedures

4.1 Screening for Eligibility and Consent

All women with a singleton or twin gestation are potentially eligible for screening. Women with a scheduled cesarean delivery may be screened before coming to the hospital to deliver. Women who plan to deliver vaginally should be screened once they arrive at the hospital expecting to deliver. Inclusion/exclusion criteria will be reviewed with the patient's chart.

If a patient appears to meet the criteria for the trial, she will be told about the study and asked for written informed consent to participate in the trial. Women who plan to deliver vaginally, but otherwise meet the study eligibility, may sign the informed consent document with the understanding that they will not be randomized unless a decision is made to perform a cesarean delivery. Consent for release of medical information will be obtained at the time of study consent.

Patients at risk for developing renal dysfunction will have serum creatinine measured, including women with preeclampsia and HELLP syndrome.

In response to concerns from the FDA, those women delivering at <34 weeks of gestation will discard their breast milk in the first 24 hours.

4.2 Randomization

At the start of the study, each center's designated research pharmacist will be given access to a secure internet website created by the BCC to determine treatment assignment. All other staff (research and clinical) will be blinded to the allocation scheme. The pharmacist will prepare identical-appearing IV infusion bags of TXA (1g [10cc] mixed with 40cc of normal saline) or placebo (50cc of normal saline only) according to the randomization sequence, ensuring that TXA is fully dissolved. The IV bag will be labeled with a unique study drug code and expiration date, and delivered to a secure refrigerated location convenient to L&D. The pharmacy and research staff will regularly confirm the supply of study drug remaining in L&D, and replenish as needed. Any unused infusion bags will be removed when expired.

When the patient is taken to the OR, she will be randomized by certified research staff by assigning the next infusion bag to her. The infusion will start immediately after cord clamping, and be run over at least 10 minutes. The infusion may not be given simultaneously with penicillin in the same line.

4.3 Baseline Procedures

In addition to information collected for eligibility, the following information will be obtained at randomization from a patient interview followed by a review of her chart:

- Demographic information: age, race, insurance status
- Medical history: pre-pregnancy weight, current weight, height, chronic disease history
- Obstetrical history including outcome of all prior pregnancies and history of vaginal bleeding in the current pregnancy
- Pre-randomization maternal and labor information

If not already done in the prior 4 weeks, hemoglobin and hematocrit levels will be obtained and recorded preoperatively.

4.4 Patient Management and Follow-up

Administration of uterotonics and management of obstetrical hemorrhage will be guided according to preferences and protocols of the participating centers. Vital signs and physical examinations will be obtained according to clinical practice at each site. Measures to prevent venous thromboembolism will also be per the practice at each site.

TXA without evidence of significant hemorrhage should not be given. Open label administration of TXA will be permitted if considered necessary by the clinician involved, however only as a second-line agent or when a transfusion is given. Furthermore, the dose should be no more than 1g. This amount of TXA would be in addition to the masked study drug, which by that time would have been already administered. A larger dose should not be given, since only 1 to 2 g has shown to be safe and effective in the treatment of postpartum hemorrhage.[22] The protocol subcommittee will monitor and review all cases of open-label use in the absence of transfusion, and will classify use as prophylactic or therapeutic.

Administration of blood products (packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets) will be at the discretion of the treating physicians and will be recorded. All transfusions will be assessed by review of the hospital medical record at discharge, or at 7 days if discharge is later. Physician orders, operative notes, nurses notes and physicians notes will be reviewed.

The primary surgeon and anesthesiologist will visually estimate intraoperative blood loss.

For any birth before 34 weeks gestation where the mother is planning to breastfeed, any breastmilk from the first 24 hours should be discarded. Feeding of infants born at later gestational ages will not be restricted at any time, or at earlier gestational ages after 24 hours. Evidence of thromboembolic events in the neonate will be recorded through discharge.

Postpartum maternal and delivery outcomes will be collected. Occurrence of medication adverse effects will be recorded by review of medical records through discharge, and a phone call if the patient is discharged before 7 days after delivery.

Women will be contacted 1-2 weeks after delivery to inquire about signs and symptoms of deep vein thrombosis and pulmonary embolism (chest pain, shortness of breath, unilateral lower extremity swelling and tenderness) as well as incisional issues (wound drainage, separation, redness, fever, chills, and incisional pain). Education on thrombotic complications will also be reinforced.

Information on re-admissions, thromboembolic events, new onset seizure activity, and other peripartum complications will be collected during a patient telephone call or in person at a regular postpartum visit, 6 weeks after delivery by research nurses. If the patient's history is consistent with a thromboembolic event or taking anticoagulants, then the medical record will be obtained to confirm and assess the severity of the event.

4.4.1 Pharmacokinetics of TXA

A substudy will be conducted to measure TXA concentrations (across gestational ages) in maternal blood, neonatal blood and breast milk.

4.5 Adverse Event Reporting

Detailed information concerning adverse events will be collected and evaluated throughout the conduct of the protocol.

The NICHD Project Scientist and the BCC will be notified within twenty-four hours of any maternal death and seventy-two hours of any neonatal death by email/phone/fax, if the event occurred in a MFMU Network hospital. For any maternal or neonatal death occurring outside a MFMU Network hospital, the adverse event must be reported to the NICHD and the BCC within twenty-four hours of being notified.

Additionally, thromboembolisms and seizures (including eclampsia) will be reported within 24 hours of notification as serious adverse events. These and other adverse events deemed serious, unexpected and definitely, probably, or possibly related, will be immediately (within twenty-four hours of notification) forwarded by the BCC to the DSMC Chair, NIH representative, and any other DSMC member who requests notification. If a death is reported, a copy of the patient's medical record will be made.

Adverse events which do not qualify under the above definition must be reported to the BCC within 7 days of being notified. These adverse events will be collected and sent to the Chair, NIH representative, and any other requesting DSMC member on a monthly basis. The Chair decides whether the adverse event reports should be disseminated to the rest of the committee and whether a follow-up call or meeting is required. NICHD representatives may also request follow-up of specific events. All adverse events will be considered along with other interim safety data in the DSMC deliberations.

An FDA Investigational New Drug safety report will be completed for any suspected adverse reaction to the study medication, whether active or placebo. Serious unexpected suspected adverse reactions (SUSARs) that are fatal or life threatening will be reported by the BCC to the FDA within 7 days after the initial notification by the center. Other SUSARs will be reported to the FDA within 15 days.

The only indication for breaking the randomization code is when it is medically necessary to unmask the study drug assignment to be able to treat the patient.

4.6 Study Outcome Measures and Ascertainment

4.6.1 Primary Outcome

The primary outcome is maternal death or transfusion of packed red blood cells by discharge from the hospital or 7 days postpartum, whichever is sooner

4.6.2 Major Secondary Outcome

1. Estimated blood loss collected from anesthesia record and operative report

4.6.3 Secondary Outcomes

1. A composite of treatments and interventions in response to bleeding and related complications, within 7 days postpartum. Included are surgical or radiologic interventions to control bleeding and related complications, uterotonics other than oxytocin, open label TXA or other antifibrinolytics, and transfusion of any blood product. Treatments administered as prophylaxis are not included. [Individual components of the composite are described in more detail below.]
2. Maternal death or transfusion of packed red blood cells by 7 days postpartum
3. A composite of surgical or radiologic interventions to control bleeding and related complications within 7 days postpartum, or maternal death
4. A composite of maternal death, thromboembolic events (venous or arterial), ischemic stroke, myocardial infarction, new-onset seizure activity, or admission to the intensive care unit for more than 24 hours, within 6 weeks postpartum
5. Transfusion related acute lung injury (TRALI): defined as a ratio of partial pressure of oxygen to inspired fraction of oxygen below 300 within 6 hours of receiving a blood product with bilateral pulmonary edema on chest x-ray and no other cause
6. Transfusion of other blood products including fresh frozen plasma, cryoprecipitate, and platelets or administration of any factor concentrates by 7 days postpartum
7. Transfusion of 4 or more units of packed red blood cells by 7 days postpartum

8. Acute kidney injury: defined as an acute elevation of serum creatinine of ≥ 0.3 mg/dL during a period of 48 hours within 7 days postpartum
9. Thromboembolic events (venous or arterial), ischemic stroke, or myocardial infarction within 6 weeks postpartum since the majority of events occur within 6 weeks postpartum[32] (safety)
10. New-onset seizure activity within 6 weeks postpartum (safety)
11. Postpartum infectious complications within 6 weeks postpartum (e.g., endometritis, surgical site infection, pelvic abscess)
12. Admission to the intensive care unit for more than 24 hours
13. Maternal death within 6 weeks postpartum
14. Use of uterotonics other than oxytocin (e.g., prostaglandins, methergine) and quantity used in first 48 hours post delivery
15. Surgical or radiologic interventions to control bleeding and related complications within 7 days postpartum (e.g. laparotomy, evacuation of hematoma, hysterectomy, uterine packing, intrauterine balloon tamponade, interventional radiology)
16. Change in hemoglobin from before cesarean to lowest measured in first 48 hours postpartum
17. Maternal TXA-related side-effects (nausea, vomiting, dizziness)
18. Open label use of TXA or other antifibrinolytic
19. Length of stay after delivery
20. Re-admission within 6 weeks postpartum
21. Any transfusion-associated reactions within 7 days postpartum.

Central blinded chart reviews will be conducted by the protocol subcommittee to confirm the accuracy of the following diagnoses: transfusion related acute lung injury (TRALI), thromboembolic events, ischemic stroke, myocardial infarction, and new-onset seizure activity.

5 Statistical Considerations

5.1 Data Relevant to the Primary Outcome

Using data from the MFMU Network Cesarean Registry, the rate of packed RBC transfusion in the entire cohort of 57,169 women was 2.6%. The rate of packed RBC transfusion was 3.2% (762/23,486) in women undergoing primary cesarean and 2.2% (735/33,683) in those undergoing repeat cesarean.[33] When the analysis was limited to those who underwent cesarean without labor, the overall rate of blood transfusion was 2.4% (the rate of packed RBC transfusion for 1st, 2nd, 3rd and 4th cesarean were 4.05%, 1.53%, 2.26%, and 3.65%).[34]

In a more recent cohort (APEX study) consisting of a random sample of approximately one third of deliveries over a 3-year period, 29,343 women with a cesarean delivery did not meet trial exclusions, and had at least 2 hours from admission to delivery. The rate of RBC transfusion or death in this group of women was 2.8% (811/29,343). In the subset of the 29,343 women who had an unscheduled cesarean delivery the primary outcome rate was 3.5 % (584/16,859). Among those who had scheduled cesareans, the rate of packed red blood cells (RBC) or maternal death was 1.8% (227/12,484).

Based on these 2 large cohorts, the expected rate of the primary outcome in the women undergoing scheduled cesarean delivery is 1.5-2 % and in the women undergoing unscheduled cesarean delivery is 3.5%.

In the Cochrane review, the 95% range of the effect size of TXA was between 46% and 90% reduction in the need for blood products transfusion (RR 0.23, 95% CI 0.10 to 0.54, five trials, 1,259 participants compared with placebo).[21] For this study a relatively conservative effect size is used of 33-40%.

5.2 Sample Size and Power

The table below provides the sample size calculations needed to achieve 80-90% power to detect 30-40% difference in the primary outcome between women receiving TXA or placebo at time of their cesarean, using a two-tailed alpha of 0.05. The Poisson approximation to the normal distribution was used in the estimation of the sample sizes.

Table 1. Total Sample Sizes for TXA vs. Placebo for Various Primary Outcome Rates

Risk reduction (%)	Power (%)	Primary Outcome Rate in Placebo Group		
		1.5%	2.5%	3.5%
30	80	19,800	11,900	8,500
	85	22,700	13,600	9,700
	90	26,500	15,900	11,400
33.3	80	15,700	9,500	6,800
	85	18,000	11,000	7,700
	90	21,100	12,700	9,000
35	80	14,100	8,500	6,100
	85	16,200	9,700	7,000
	90	18,900	11,400	8,100
40	80	10,500	6,300	4,500
	85	12,000	7,200	5,200
	90	14,000	8,500	6,000

Since quotas will be issued to ensure approximately equal enrollment between scheduled and unscheduled cesareans, a sample size of 11,000 women (5,500 in the scheduled and 5,500 unscheduled) will achieve 85% power to detect a 33% reduction in primary outcome overall, assuming that the placebo rate is 2.5%.

The power to detect an interaction between treatment effect and scheduled versus unscheduled cesarean delivery (see Section 5.5.1) was estimated under the following assumptions: 1.5% outcome rate in the placebo group in the scheduled cesarean deliveries, 3.5% primary outcome rate in the placebo group in the unscheduled cesarean deliveries, no overall reduction in the primary outcome. With a sample size of 11,000, there is more than 85% power to detect an odds ratio for 3 for the interaction in a logistic regression and more than 75% if the odds ratio is 2.5.[35]

If there is a significant interaction between treatment effect and scheduled versus unscheduled cesarean delivery (Section 5.5.1) the effect of treatment within each group will be presented separately. There is more than 85% power to detect a 40% reduction in the primary outcome within the unscheduled cesarean deliveries and more than 75% power to detect a 50% reduction within the scheduled cesarean group.

For the major secondary outcome of estimated blood loss, the sample size calculation is based upon the Wilcoxon Rank Sum test, which depends on the specification of P(X>Y) where X is an observation from the TXA group and Y an observation from the placebo group. Under the null hypothesis this quantity is 0.5. In the APEX study mean blood loss was 800 with a standard deviation of close to 250. The distribution is approximately symmetric. Under the assumption of normality, but assuming a larger standard deviation of 300 to be conservative, there is ample power to detect P(X>0) of 0.477 or greater which corresponds to a median difference between the two groups of 25cc.

5.3 Feasibility

The feasibility of answering the primary research question will be addressed after the first 2000 patients (approximately 1000 placebo patients) have been randomized and the postpartum period completed. This is sufficient for a confidence interval half-width of no more than 1%, if the number of primary outcome cases observed is 25 or less. The primary outcome rate in the placebo group will be presented to the Data and Safety Monitoring Committee (DSMC) without any comparison by group. The DSMC will be charged with making a recommendation regarding potential revision of the sample size in addition to addressing the feasibility of answering the primary research question.

5.4 Interim Analysis

The DSMC meets in person at least once per year and more often if recommended by the committee. For this trial, the DSMC will conduct a six-monthly regular safety review of cumulative adverse events.

Before each of the annual meetings, a formal detailed report will be written by the Biostatistical Coordinating Center (BCC) which presents all baseline variables, protocol adherence, side effects, all adverse events reported, as well as center performance in terms of recruitment, data quality, loss to follow-up and protocol violations.

Once a sufficient number of patients have been accrued into the trial, the report will also include a formal interim analysis evaluating the primary outcome by treatment group. For this evaluation, a cohort of patients is chosen consisting of all patients randomized before a certain date so that the analysis cohort is unaffected by delayed outcome reports.

The main statistical issue relevant to interim analysis is the problem of performing multiple tests of significance on accumulating data. For this trial, the group sequential method of Lan and DeMets will be used to characterize the rate at which the type I error is spent.[36] This method is flexible with regard to the timing of the interim analyses.

Asymmetric stopping boundaries will be used for the Lan-DeMets procedure. The upper boundary which describes the stopping rule for benefit will be based on 1-sided type I error of 0.025 and the Lan-DeMets generalization of the O'Brien-Fleming boundary. The lower boundary will be based on a less stringent stopping rule: 1-sided type I error of 0.05 and the Lan-DeMets generalization of the Pocock-type boundary. If the primary outcome is significant or the trial is stopped early for benefit, the methods of Maurer and Bretz will be used to test formally the major secondary endpoint of estimated blood loss while controlling the familywise error rate.[37]

In addition, the BCC will continuously monitor potential cases of serious adverse events in the active arm during the trial (defined as maternal death or thromboembolism). If the number of such events that occur in the postpartum period meets the number in the table below, recruitment for the study will immediately halt until the DSMC has met and reviewed all of the data to determine whether the trial should continue. The numbers were calculated assuming a 0.1% background rate of one of these events occurring post-cesarean delivery in the general population. Assuming the observed event rate is larger than the background rate, for each N (number of patients recruited), the smallest number of events was calculated such that the probability of the observed event rate occurring given the background rate is less than 5 percent.

Table 2. Number of Events in TXA Group to Trigger DSMC review

Number of Patients in TXA Group	Number of Events
Up to 383	2
384 to 905	3
906 to 1537	4
1538 to 2239	5
2240 to 2992	6
2993 to 3782	7
3783 to 4601	8
4602 to 5443	9
5443 upwards	10

It is often useful to calculate conditional power given the observed data to date, and conditional on the future data showing the originally assumed design effect. If this conditional power is low (under 10 percent) the DSMC may consider termination for futility if the accrual rate is slow with confidence that the Type II error is not greatly inflated.[38]

It is recognized that any decision to terminate the study would not be reached solely on statistical grounds but on a number of complex clinical and statistical considerations.

5.5 Analysis Plan

All statistical analyses will be based upon the total cohort of patients randomized into the trial. Although data on some patients may be missing, all relevant data available from each patient will be employed in the analyses. Patients will be included in the treatment group to which they were randomly assigned regardless of compliance.

The primary analysis will consist of a simple comparison of binomial proportions. The relative risk and confidence interval will be reported. If the treatment groups are found to differ on a pre-treatment factor

known to be a risk factor for the outcome, the statistical analysis will adjust for these differences. An evaluation of treatment by center interaction will be included. An analysis adjusting by center also will be performed to ensure that center differences do not change the conclusion.

Loss to follow-up will be defined as no information regarding transfusion or maternal survival through seven days postpartum, or maternal discharge if sooner. Those defined as lost to follow-up will not be included in the primary analysis. It is expected that the loss to follow-up rate will be negligible.

Since many of the secondary endpoints are dichotomous variables like the primary outcome, standard statistical methods for rates and proportions will be appropriate. The Wilcoxon rank sum test will be used to compare continuous variables, and survival analysis methodology may be used to compare time-to-event variables.

In general, analyses of data will be conducted to address the primary and secondary research questions of the trial, and other interrelationships among elements of study data of interest to the investigators and of relevance to the objectives of the study.

5.5.1 Subgroup Analyses

If the two groups show a difference in the incidence of the primary outcome, interactions will be evaluated and subgroup analyses conducted to determine whether the effect prevails throughout particular subgroups of patients. Indeed, NIH guidelines require investigators to evaluate consistency between the genders and across racial subgroups. It should be noted, however, that subgroup analyses have been greatly abused, particularly when there is no overall treatment difference. There is a strong temptation to search for a specific subpopulation in which the therapy is nevertheless effective. Yusuf et al. concluded "the overall 'average' result of a randomized clinical trial is usually a more reliable estimate of the treatment effect in the various subgroups examined than are the observed effects in individual subgroups." [39] Thus subgroup analyses will be interpreted with care.

It is generally acknowledged that subgroup analysis that is pre-specified in the protocol has more validity than ad-hoc comparisons. The following factors will be considered for subgroup analysis, if there is a significant interaction between the factor of interest and the treatment effect.

- Race/ethnicity
- Category of cesarean delivery (scheduled and unscheduled)
- Category of cesarean delivery (primary and repeat)
- Body mass index (BMI) at delivery (obese versus non-obese)
- Gestational age at randomization (< 34, 34-36, and ≥ 37 weeks)
- Preoperative hemoglobin level
- Number of fetuses (singleton and twin)
- Length of labor (within unscheduled cesareans only).

6 Data Collection

6.1 Data Collection Forms

Data will be collected on standardized forms on which nearly all responses have been pre-coded. Each form is briefly described below:

- TX01 Screening Log.
- TX02 Eligibility and Randomization Form is completed for all patients randomized in the study.
- TX04 Baseline Form is completed for all randomized patients. This form includes detailed demographic and social data, medical and obstetrical history, current pregnancy complications, and labor data.
- TX04A Previous Pregnancy Outcome Form.
- TX08 Maternal Delivery Form documents delivery and operative information while patient is in the OR until discharge.
- TX08A Maternal Bleeding-Related Treatment Log documents uterotonics and blood products given during and after delivery.
- TX08B Maternal Postoperative Form documents maternal complications and interventions after transfer from the OR.
- TX08C Maternal complications and re-admissions through 6 weeks postpartum.
- TX09 Neonatal Outcome Form records date and time of birth, delivery data and status at delivery, for each fetus/infant.
- TX11 Patient Status Form documents loss to follow up/withdrawal status, last date of contact for lost to follow-up patients.
- AE12 Universal Adverse Event Form records serious and non-serious adverse events.
- TX13A 1-2 Week Follow-up Form records contact at 1-2 weeks postpartum and maternal complications and re-admissions between discharge and 7 days postpartum.

6.2 Web Data Entry System

For this protocol, web data entry screens corresponding to the study forms listed above will be developed and maintained by the staff of the BCC. Clinical center staff will enter data into the MySQL database located at the BCC through a web data management system (MIDAS). The data are edited on-line for missing, out of range and inconsistent values. A Users' Manual documenting this system is provided to the centers by the BCC.

6.3 Centralized Data Management System

Daily data conversions from the MySQL database create up-to-date SAS datasets. Data are reviewed weekly using edit routines similar to those implemented on-line during data entry, as well as additional checks for data consistency within or across forms. A database of resulting potential data problems is generated in MIDAS for initial review by BCC staff who then evaluate the comments keyed in association with edits on missing or unusual values. Valid edits will be flagged in MIDAS for resolution at the clinical centers.

At regular intervals, specialized data reviews comparing data availability and consistency across forms are run by the BCC staff on the entire database or on a specific subset of data. These reports are also submitted to the centers for correction or clarification.

An audit trail, consisting of all prior versions of each data form as entered in the computer for each patient, is maintained so that the succession of corrections can be monitored.

6.4 Performance Monitoring

The BCC will present regular reports to the TXA Subcommittee, the Steering Committee, and the Data and Safety Monitoring Committee. These include:

- Monthly Recruitment Reports - reports of the number of women screened and enrolled by month and by clinical center are provided monthly to the TXA Subcommittee and all other members of the Steering Committee. Weekly or bi-weekly reports are provided electronically if needed.
- Quarterly Steering Committee Reports - reports detailing recruitment, baseline patient characteristics, data quality, incidence of missing data and adherence to study protocol by clinical center, are provided quarterly to the TXA Subcommittee and all other members of the Steering Committee.
- Data and Safety Monitoring Committee Reports - for every meeting of the DSMC, a report is prepared which includes patient recruitment, baseline patient characteristics, center performance information with respect to data quality, timeliness of data submission and protocol adherence (in addition to safety and efficacy data). The reports also include adverse events, loss to follow-up and all outcome variables as described previously in this protocol.

7 Study Administration

7.1 Organization and Funding

The study is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). The study is conducted by the NICHD Maternal-Fetal Medicine Units (MFMU) Network, consisting of twelve clinical centers, the Biostatistical Coordinating Center (BCC) and the NICHD, and is administered under cooperative agreements between each of the centers and the NICHD. Each of the funded institutions is represented by a Principal Investigator. A complete description of the organization of the MFMU Network is provided in the MFMU Network Policy Manual.

7.1.1 Participating Clinical Centers

The participating Principal Investigators of the clinical centers have agreed to abide by the study protocol, to have comparable staff, facilities and equipment and to ensure the proper conduct of the study at each of their centers including: recruitment and treatment of patients as specified in the protocol, accurate data collection and the transmission of information to the Steering Committee.

7.1.2 Biostatistical Coordinating Center

The BCC is responsible for all aspects of biostatistical design, data management, interim and final statistical analyses, and preparation of publications based on the study results. The Principal Investigator of the BCC reports to the Steering Committee and the Data and Safety Monitoring Committee.

7.1.3 NICHD

In addition to its role as funding agency, the NICHD participates in the activities of the Network, including the development of protocols, administration and conduct of the studies and preparation of publications.

7.1.4 Network Advisory Board

Appointed by the NICHD, the members of the Network Advisory Board consist of a group of experts who are not affiliated with the research being conducted by the Network and represent the disciplines of maternal-fetal medicine, neonatology and biostatistics/epidemiology. The role of the board includes the review and prioritization of proposed studies, in addition to the identification of scientifically and clinically important questions and ideas that might be conducted by the Network. The NICHD Project Scientist convenes and attends the meetings.

7.2 Committees

7.2.1 Steering Committee

This committee consists of fifteen members. The Principal Investigator from each of the twelve clinical centers, the BCC, and the NICHD MFMU Network Project Scientist are all voting members. The Chair of the Steering Committee may vote to break a tie. The Chair, a person independent of the participating institutions, is appointed by NICHD. The Steering Committee has the responsibility for identifying topics for Network studies, designing and conducting study protocols and monitoring study implementation, recruitment and protocol adherence. The committee receives recommendations from the Data and Safety Monitoring Committee and the Network Advisory Board.

7.2.2 Protocol Subcommittee

The subcommittee consists of a chair (who is an investigator from one of the clinical centers), investigators from one or more other clinical centers, BCC staff, nurse coordinators, outside consultants

(if appropriate), and the NICHD MFMU Network Project Scientist. The Protocol Subcommittee is responsible for the preparation and conduct of the study, and reporting the progress of the study to the Steering Committee.

7.2.3 Publications Committee

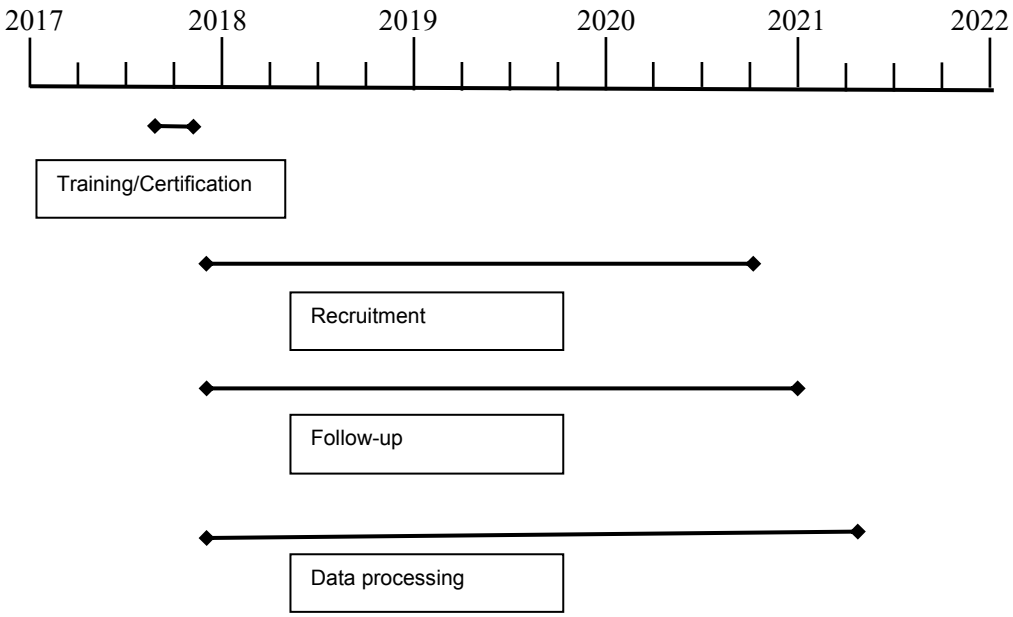
The Publications Committee is a standing committee of the Steering Committee. The functions of this committee are to develop publication policies and to review all manuscripts and abstracts prior to submission. The goals of this committee are fair and appropriate authorship credit and high quality publications.

7.2.4 Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee (DSMC), a group of individuals not affiliated with any of the participating institutions, was established by the NICHD. Before the trial can begin, the protocol must be approved by the committee. During the conduct of the study, the committee is charged with monitoring the emerging results for efficacy and safety, in addition to center performance and protocol adherence. Recommendations by the committee can include protocol modification, early termination for efficacy, or for unexpected safety problems. Recommendations are made to the NICHD and disseminated to the Steering Committee.

8 Study Timetable

Figure 2. Timetable



8.1 Training and Certification

During the study start-up period, preparation of the final case report forms, manual of operations, and randomization sequence, in addition to implementation of the data entry and management system will take place. Training with the nurse coordinators will be held before recruitment begins. Research pharmacists at each study site will also have to undergo training in preparation and dispensing of the blinded study medication. Each participating center must be certified to start the trial before recruitment at that center can begin. The certification requirements are designed to ensure that personnel involved in the trial are committed to the study and proficient in study procedures, and that the center has satisfied regulatory requirements. Each center is required to obtain IRB approval for the study before they are certified to begin the trial.

8.2 Recruitment and Data Collection Period

Approximately 160,000 women deliver in the MFMU Network annually. Using data from the APEX cohort, the rates of scheduled and unscheduled cesarean delivery were 12% and 20%, respectively. After excluding approximately 5% of women who would not meet eligibility criteria for the proposed trial, this leaves 18,240 eligible scheduled cesareans and 30,400 eligible unscheduled cesareans per year. For unscheduled cesarean deliveries it is assumed that only 20% are available for recruitment. This estimate allows for sufficient time for screening and consent (at least 2 hours) and that about 25% of unscheduled deliveries would be during normal office hours. Assuming only a third of eligible women consent to the

trial, approximately 2,000 women with unscheduled cesarean deliveries could be randomized annually. More scheduled cesarean deliveries are available for recruitment than unscheduled cesareans since the majority of scheduled deliveries are delivered during office hours, and there is more time for the screening and consent process. Since recruitment will be balanced between the two groups, approximately 4000 women can be randomized annually overall, which would mean that the trial could be completed in under 3 years.

8.3 Final Analysis

After a three-month period for completion of data entry for the trial and close-out of the primary outcome, the data set will be locked and made available for the primary and other main analyses.

Appendix A Design Summary

OBJECTIVE: To determine whether intraoperative tranexamic acid reduces the need for red blood cell transfusion in women undergoing cesarean delivery.

ORGANIZATION

Clinical Centers: Magee, UAB, Ohio State, Utah, Brown, Columbia, Case Western, UT-Houston, UNC, Northwestern, UTMB-Galveston, U Penn

Subcommittee: Luis Pacheco, MD (Chair)

DESIGN

Major Eligibility Criteria:
- Cesarean delivery
- Singleton or twin gestation

Groups:
- Tranexamic acid (TXA)
- Placebo

Random Allocation:
- Simple randomization; 1:1 allocation

Level of Masking:
- Double-masked

Stratification:
- Clinical site

Sample Size:
- 11,000

Assumptions:
- Outcome event=transfusion of packed RBCs or maternal death
- Placebo group event rate = 2.5%
- TXA group event rate = 1.67% (33% reduction)
- Type I error = 5% (two sided)
- Power = 85%

Interim Analysis:
- Lan-DeMets group sequential method

SCHEDULED EVALUATIONS / DATA COLLECTION

Pre-randomization:
- Hemoglobin and hematocrit
- Pregnancy, exposure and medical history
- Gestational age

Post-randomization:
- Delivery and post-operative data
- Hemoglobin and hematocrit 0-48 hours post-delivery
- Phone call to assess readmissions and treatments at 1-2 weeks postpartum
- Phone call to assess complications and treatments at 6 weeks postpartum

MANAGEMENT PROTOCOL

Both Groups:
- Study medication infused immediately after cord clamping, and run over 10 minutes

OUTCOME

Primary:
- Transfusion of packed RBCs or maternal death

Secondary:
- Composite of treatments for blood loss
- Estimated blood loss
- Transfusion of other blood products
- Transfusion-related morbidities
- Thromboembolic events
- Change in hemoglobin from baseline

TIMETABLE

Enrollment:
- November 2017 to October 2020

Data Collection:
- November 2017 to December 2020

Closeout/Analysis
- January 2021 to August 2021

Appendix B Sample Informed Consent Forms

B.1 Sample Informed Consent Form (without Common Rule 2018 changes)

Title of Research Study:

Tranexamic Acid for the Prevention of Obstetrical Hemorrhage After Cesarean Delivery: A Randomized Controlled Trial

Sponsor:

This research is being funded by the National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

Principal Investigator:

<<insert name>>

Investigator Contact Information:

<<insert information>>

Why am I being invited to take part in a research study?

You are invited to take part in a research study because you are carrying one baby or twins and you will be delivering soon. Only women who have a cesarean delivery will take part in the research study. Even if you are planning to have a vaginal delivery we are asking you now in case things change. For example, your obstetrician or midwife may decide with you that you need a cesarean delivery. Sometimes this decision happens quickly, so we are asking you now to make sure you have enough time to think carefully about whether you would like to take part in this study.

Please take your time and read this information carefully. You may talk about it with your family members and others if you wish. You should ask the research staff if you have any questions about this study, or if there is anything you do not understand. If you decide to take part in the study, you will be asked to sign this form.

Who can I talk to if I have questions?

If you have any questions, concerns, or complaints, you can talk to the research staff or to Dr. _____, who is in charge of the study here.

The Institutional Review Board (IRB) is a group of people who are responsible for making sure the rights of people taking part in research are respected. A representative of the IRB is also available to answer questions about your rights as a participant in this study or to answer your questions about an injury or other complication resulting from your participation in this study.

If you have questions or are hurt while taking part in this study, you should contact _____ at (___) ___-____.

If you have any questions about the informed consent process or any other rights as a research subject, please contact _____, at (____) ___-____. _____ .

Why is this research being done?

This research study is being done to find out if a drug called Tranexamic Acid will prevent severe bleeding (hemorrhage) after a cesarean delivery.

Whenever a woman has a cesarean delivery, there is some amount of bleeding. Occasionally (in less than 5 of every 100 births) there is severe bleeding that can place the mother's health at risk. When there is too much bleeding after a cesarean delivery, women are given medicines, blood transfusions, or possibly

need another surgery. Tranexamic acid is routinely used to lessen the chance of hemorrhage after major operations such as heart surgery. It works by making your blood clot sooner. It is not routinely used for cesarean sections. We are doing this study to see if this drug also works for women who are having a cesarean section.

How long will I be in the study?

You will start in the study when you are having your cesarean section and continue while you are still in the hospital. You will then receive a telephone call one week after your delivery, and another call at 6 weeks after your delivery. After the call at 6 weeks, your time in the study will be done.

We expect to continue the study until all participants have been enrolled and all of their information has been collected. However, the study may be stopped at any time by the researchers at this institution or by the National Institutes of Health. The researcher may also withdraw you from the study without your approval. One reason this may happen is because the researcher feels it is necessary for your health and safety.

How many people will take part in this research study?

Twelve centers across the country are participating in this research study. In all, we expect that 11,000 women will take part in the study. We expect about <<number >> women will take part here at <<insert hospital>>.

What happens if I agree to be in this research?

If you agree to take part in this study, you will first be asked to sign this form. Usually you will already have had a routine blood test called the CBC (complete blood cell count) in the last few weeks. But if you did not and you are getting a cesarean, then we will collect a small amount of blood (about a half teaspoon) for a test which will measure the hemoglobin (the part of the blood that carries oxygen throughout your body) and hematocrit (the proportion of red blood cells in your blood).

Next, and only if you are having a cesarean delivery, you will be randomized (like tossing a coin) and assigned either to tranexamic acid diluted in 50 cc (less than 2 ounces) of water with salt (saline) or to just the saline by itself. The tranexamic acid diluted in saline is known as the active treatment. The saline by itself, which has no medical value, is known as the placebo treatment. Both treatments look the same and neither you nor your doctor will know which one you are getting.

The tranexamic acid or saline solution will be given immediately after your baby or babies are born using the IV (intravenous) tube that you will already have in place. The dose will start when the umbilical cord is clamped and your blood supply is separated from the blood supply of your baby. It will take 10 minutes to give you the entire dose.

If you do not have a cesarean delivery, you will not be part of this study and you will not be randomly assigned to active treatment (tranexamic acid in saline) or placebo (saline alone).

No matter whether you get the tranexamic acid or the saline by itself, you will receive all other care and treatment that is usually given before and after a cesarean delivery. This care includes any other treatments to reduce the amount of bleeding or blood loss.

Please note: The following section does NOT apply to you if you have already reached 34 weeks of gestation.

If you deliver before 34 weeks you will not be able to breast feed your baby for the first 24 hours, and the breast milk will not be saved to feed your baby later. There is no evidence from previous studies that tranexamic acid at the dose you will receive would have any effect on your baby through your breast milk. However, because few women delivering very early have been included in the studies there is not very much information about very small babies. Therefore to be cautious, if your baby or babies are born

before 34 weeks we ask you not to breast feed for the first day of life. After one day, there will be very little if any tranexamic acid in your breast milk and you will be able to breast feed as usual.

If you deliver after 34 weeks you will be able to breastfeed your baby as usual.

The research staff will collect medical information about you and your baby or babies until you leave the hospital. One week after your delivery, the research staff will give you a phone call to see if you have had any problems since going home. Six weeks after your delivery, they will call you again or meet with you to find out if you needed any other treatment or have had any problems since going home. It is possible after this study is done, the researchers may want to contact you to do another follow-up study with you or your baby. We will ask your permission for this below.

What other choices do I have besides taking part in the research?

Participation in this research study is voluntary. You have the option not to be part of this study. If you do not take part,you will receive the routine treatment usually provided to women during and after delivery.

Your decision to participate or not to participate will not affect any other part of your care at this hospital. If you are currently expecting to have a cesarean delivery, your decision will not affect your ability to have the cesarean. If you expect to have a vaginal delivery, your decision will not affect the chance that you will need a cesarean.

Refusal to take part will not result in any penalty or loss of benefits to which you are entitled. Your decision to take part or not take part will not affect your legal rights, available remedies or the quality of health care that you will receive at this hospital.

What happens if I agree to be in the research, but later change my mind?

You can leave the study at any time. Your participation is completely voluntary. You may refuse to take part or you may stop taking part at any time without penalty or loss of benefits to which you are entitled. Your decision to leave the study will not affect your legal rights or quality of health care that you will receive at this hospital.

If you decide to leave the study, contact the research staff or the investigator so that the investigator can withdraw you. If you stop being in the study, all of the information that has already been collected about you as part of the research study will not be removed from the study database. No new information about you will be collected for study purposes unless the information concerns an adverse event (such as a bad reaction). You will be asked whether the investigator can collect information from your routine medical care.

Is there any way being in this study could be bad for me or my baby?

Tranexamic acid is not a new drug, and it is commonly used to prevent bleeding in major operations such as heart operations. If you receive tranexamic acid there is a chance of side effects such as nausea, vomiting, diarrhea, skin rash, giddiness, low blood pressure, or dizziness. There is a small chance of having a seizure but this has only been seen in other types of surgery at much higher doses than you would get in this study. It is possible that there could be an increased risk of a blood clot in a blood vessel (thrombosis) but this increased risk has not been seen in any studies. If you ever had thrombosis before, you will not be able to participate in the study. Because you get the medicine after cord clamping, the baby will not be exposed to it. However, a very small amount of tranexamic acid may pass to the baby through breast milk. There have been no reports of harm to babies who have been exposed to tranexamic acid through breast milk.

Saline is used routinely in IV fluids and there are no known risks of receiving the small amount of saline for this study.

You may experience discomforts associated with the blood draw to measure your hemoglobin (if required). This may include bruising, infection, fainting, or discomfort or pain at the insertion site of the needle.

There is a risk of improper release or misuse of your personal information. The chance of this happening is very small. We have many protections in place to lessen this risk.

Unknown Risks:

There may be risks from taking part in this study that are not known to the researchers right now. They may find out new risks while the study is going on. If this happens, the research staff will tell you the new information, whether it may affect you, and what, if anything, to expect.

What are the costs to me for being in this research study?

There will be no cost to you to take part in the research study. All study-related drugs and procedures will be provided at no cost to you or your insurance company.

The costs of your standard medical care will be billed to you or your insurance company in the usual manner.

Will I be paid for taking part in this study?

<insert center-specific language about reimbursement>

By signing this consent form, you acknowledge and agree that in the event that this research project results in the development of any marketable product, you will have no ownership interest in the product and no right to share in any profits from its sale or commercialization.

What happens if I believe I am injured because I took part in this study?

<this section may be modified by the center>

If you are hurt or believe your are injured while taking part in this study, you should contact _____ at (___) ___-____.

This medical institution and the NICHD have not made any provision for monetary compensation in the event of injury resulting from the research. In the event of such injury, treatment will be provided, but it is not provided free of charge. Since this is a research study, payment for any injury resulting from your participation in this research study may not be covered by some health insurance plans.

Will being in this study help me in any way?

If you decide to take part in this study, you may or may not directly benefit from your participation. However, your participation can potentially benefit other mothers in the future, or you if you become pregnant again.

Can I be removed from the research without my permission?

The person in charge of the study here may withdraw you from the study without your approval. One reason this may happen is because the researcher feels it is necessary for your health and safety. Another reason is if the entire study is stopped.

What if new information becomes available?

During the course of the study, we may find new information that could be important to you. This includes information that may cause you to change your mind about being part of the study. We will notify you if any significant new information becomes available which may affect your health, safety, or willingness to continue in this study.

What happens to my information collected for the research?

To the extent allowed by law, we limit your personal information to people who have to review it. We cannot promise complete secrecy.

You have the right to privacy. All information obtained from this study that can be identified with you will remain confidential within the limits of the law.

The medical information collected on you for this research study will come from your medical record and from information you give the research staff, such as your previous pregnancies, height, weight, and whether you drink or smoke. Other information collected about you includes marital status, your level of education, type of medical insurance, and current pregnancy complications. Data will be collected on your labor (such as when it starts) and delivery, and treatment you need after delivery. Information will also be collected on your baby at delivery and on your baby's hospital stay. If we lose track of you, study staff may collect information from the internet including social network sites in order to find your contact information.

The information collected for this research study will be entered into an electronic database at the data coordinating center (George Washington University Biostatistics Center in Rockville, Maryland). The database has information from all of the participants. Your information in the database will only be used for statistical analysis and may appear in scientific publications but will not identify you. The information sent to the data coordinating center does not include your name, address, social security number, hospital number, date of birth or any other personal identifiers. Instead, the data center will use a unique code for each person consisting of a number and the first letter of your first name. The key to the code linking the data and samples to you will be kept here in a locked file. Only the research study staff employed for this study at this hospital will have access to the key to the code.

The following individuals and/or agencies will be able to look at and copy your medical and research records:

- The investigator, study staff and other medical professionals who may be evaluating the study.
- Authorities from this institution, including the Institutional Review Board (IRB) which is a group of people who are responsible for making sure the rights of participants in research are respected. Members or staff of the IRB at this medical center may also contact you about your experience with this research. You do not have to answer any questions the representative(s) of the board may ask.
- The United States Food and Drug Administration (FDA) and/or the Office for Human Research Protections (OHRP).
- The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) which sponsors this study, including persons or organizations working with the sponsors, such as the data coordinating center, the George Washington University Biostatistics Center in Rockville, Maryland.

A copy of your medical chart or your baby's medical chart also may be sent to research investigators at one of the other enrolling centers, the data coordinating center, or NICHD for review. If your chart is sent, all identifying information, such as your name, address, social security number, hospital number, and date of birth first will be removed.

The results of this research study will be provided to the sponsor, NICHD (and/or their representatives).

In addition, data from this study will be put in a public data set that will be available to other research investigators. This public data set will not contain any identifying patient data.

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.

Once the study is finished, you may request to have and review a copy of your personal health information collected during this study and placed in your medical record. This right to review and copy your personal health information only extends to information that is placed in your medical record; it does not extend to information that is placed in your research record.

This permission does not end unless you cancel it, even if you withdraw from the study. You can cancel this permission any time except where a healthcare provider has already used or released your health information, or relied on your permission to do something. Even if you cancel this authorization, the researchers may still use and disclose protected health information (PHI) they already have obtained about you as necessary to maintain the integrity or reliability of the research. However, no new PHI or new biological specimens will be collected from you after you revoke your authorization.

To cancel your authorization, you will need to send a letter to Dr. _____ of the _____ stating that you are canceling your authorization. This letter must be signed and dated and sent to this address:_____. If you are unable to write a letter ask one of the research staff to provide you with a letter that must be signed, dated, and sent to the above address. A copy of this cancellation will be provided to the Study Doctor and his or her research team. Not signing this form or later canceling your permission will not affect your health care treatment outside the study, payment for health care from a health plan, or ability to get health plan benefits.

Your protected health information will be treated confidentially to the extent permitted by applicable laws and regulations. Federal law may allow someone who gets your health information from this study to use or release it in some way not discussed in this section and no longer be protected by the HIPAA Privacy Rule.

By signing this form you authorize the Study Doctor and members of the research team to use and share with others (disclose) your PHI for the purpose of this study. If you do not wish to authorize the use or disclosure of your PHI, you cannot participate in this study because your PHI is necessary to conduct this study.

May we contact you about future studies that may be of interest to you?

There may be studies in the future that are or are not related to the research study you are consenting to participate in by signing this form. If this happens, to protect your confidentiality and respect your privacy, the research team would need your permission to contact you. If you agree to provide consent for contact for future studies, please initial in the appropriate space below.

____ Yes, you may contact me for future studies.

____ No, you may not contact me for future studies.

What else do I need to know?

The study is sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), which is part of the National Institutes of Health.

The results of the research study will be posted to www.clinicaltrials.gov within 13 months of completion of the study. You may review the results of the study at that time. If you have any questions regarding the study results, you may contact the research staff at the numbers provided to you in this consent form.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health (NIH). The researchers with this Certificate may not disclose or use information, documents, or biospecimens

that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIH or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it

Signatures

By signing below, you indicate that you have read this consent form, the study has been explained to you, your questions have been answered, and you agree to take part in this study. You do not give up any of your legal rights by signing this form. A copy of this consent form will be given to you.

_____	_____	_____
Signature of Participant	Printed Name of Participant	Date
_____	_____	_____
Signature of Person Obtaining Consent	Printed Name of Person Obtaining Consent	Date

A witness unrelated to the study is necessary if the participant can comprehend but cannot read (e.g., blind), or cannot sign (e.g., unable to use hands) the consent form.

_____	_____	_____
Signature of Witness	Printed Name of Witness	Date

Investigator Statement <this section is center-specific>

I certify that the research study has been explained to the above individual by me or my research staff including the purpose, the procedures, the possible risks and the potential benefits associated with participation in this research study. Any questions have been answered to the Individual's satisfaction.

_____	_____	_____
Signature of Investigator	Printed Name of Investigator	Date

B.2 Sample Informed Consent Form (with Common Rule 2018 changes)

Title of Research Study:

Tranexamic Acid for the Prevention of Obstetrical Hemorrhage After Cesarean Delivery: A Randomized Controlled Trial

Sponsor:

This research is being funded by the National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

Principal Investigator:

<<insert name>>

Investigator Contact Information:

<<insert information>>

Key Information

This research study is being done to find out if a drug called Tranexamic Acid will prevent severe bleeding (hemorrhage) after a cesarean delivery. If you agree to participate, you will be randomly assigned (like tossing a coin) to either Tranexamic Acid or placebo (saline). The study medication will be given immediately after your baby or babies are born using the IV (intravenous) tube that you will already have in place.

If you agree to participate, you will start in the study when you are having your cesarean and continue while you are still in the hospital. The research staff will collect medical information about you and your baby or babies until you leave the hospital. One week after your delivery, the research staff will give you a phone call to see if you have had any problems since going home. Six weeks after your delivery, they will call you again or meet with you to find out if you needed any other treatment or have had any problems since going home.

There are risks to this study that are described in this consent form. Uncommon risks of Tranexamic Acid include nausea, vomiting, diarrhea, skin rash, giddiness, low blood pressure, or dizziness. Rare risks include seizure and blood clot.

There are no known benefits from participating in this study. Participation in this research study is voluntary and if you do not take part, you will receive the routine care usually provided to pregnant women.

Why am I being invited to take part in a research study?

You are invited to take part in a research study because you are carrying one baby or twins and you will be delivering soon. Only women who have a cesarean delivery will take part in the research study. Even if you are planning to have a vaginal delivery we are asking you now in case things change. For example, your obstetrician or midwife may decide with you that you need a cesarean delivery. Sometimes this decision happens quickly, so we are asking you now to make sure you have enough time to think carefully about whether you would like to take part in this study.

Please take your time and read this information carefully. You may talk about it with your family members and others if you wish. You should ask the research staff if you have any questions about this study, or if there is anything you do not understand. If you decide to take part in the study, you will be asked to sign this form.

Who can I talk to if I have questions?

If you have any questions, concerns, or complaints, you can talk to the research staff or to Dr. _____, who is in charge of the study here.

The Institutional Review Board (IRB) is a group of people who are responsible for making sure the rights of people taking part in research are respected. A representative of the IRB is also available to answer questions about your rights as a participant in this study or to answer your questions about an injury or other complication resulting from your participation in this study.

If you have questions or are hurt while taking part in this study, you should contact _____ at (___) ___-____.

If you have any questions about the informed consent process or any other rights as a research subject, please contact _____, at (____) ___-____. _____ .

Why is this research being done?

This research study is being done to find out if a drug called Tranexamic Acid will prevent severe bleeding (hemorrhage) after a cesarean delivery.

Whenever a woman has a cesarean delivery, there is some amount of bleeding. Occasionally (in less than 5 of every 100 births) there is severe bleeding that can place the mother's health at risk. When there is too much bleeding after a cesarean delivery, women are given medicines, blood transfusions, or possibly need another surgery. Tranexamic acid is routinely used to lessen the chance of hemorrhage after major operations such as heart surgery. It works by making your blood clot sooner. It is not routinely used for cesarean sections. We are doing this study to see if this drug also works for women who are having a cesarean section.

How long will I be in the study?

You will start in the study when you are having your cesarean section and continue while you are still in the hospital. You will then receive a telephone call one week after your delivery, and another call at 6 weeks after your delivery. After the call at 6 weeks, your time in the study will be done.

We expect to continue the study until all participants have been enrolled and all of their information has been collected. However, the study may be stopped at any time by the researchers at this institution or by the National Institutes of Health. The researcher may also withdraw you from the study without your approval. One reason this may happen is because the researcher feels it is necessary for your health and safety.

How many people will take part in this research study?

Twelve centers across the country are participating in this research study. In all, we expect that 11,000 women will take part in the study. We expect about <<number >> women will take part here at <<insert hospital>>.

What happens if I agree to be in this research?

If you agree to take part in this study, you will first be asked to sign this form. Usually you will already have had a routine blood test called the CBC (complete blood cell count) in the last few weeks. But if you did not and you are getting a cesarean, then we will collect a small amount of blood (about a half teaspoon) for a test which will measure the hemoglobin (the part of the blood that carries oxygen throughout your body) and hematocrit (the proportion of red blood cells in your blood).

Next, and only if you are having a cesarean delivery, you will be randomized (like tossing a coin) and assigned either to tranexamic acid diluted in 50 cc (less than 2 ounces) of water with salt (saline) or to just the saline by itself. The tranexamic acid diluted in saline is known as the active treatment. The saline by

itself, which has no medical value, is known as the placebo treatment. Both treatments look the same and neither you nor your doctor will know which one you are getting.

The tranexamic acid or saline solution will be given immediately after your baby or babies are born using the IV (intravenous) tube that you will already have in place. The dose will start when the umbilical cord is clamped and your blood supply is separated from the blood supply of your baby. It will take 10 minutes to give you the entire dose.

If you do not have a cesarean delivery, you will not be part of this study and you will not be randomly assigned to active treatment (tranexamic acid in saline) or placebo (saline alone).

No matter whether you get the tranexamic acid or the saline by itself, you will receive all other care and treatment that is usually given before and after a cesarean delivery. This care includes any other treatments to reduce the amount of bleeding or blood loss.

Please note: The following section does NOT apply to you if you have already reached 34 weeks of gestation.

If you deliver before 34 weeks you will not be able to breast feed your baby for the first 24 hours, and the breast milk will not be saved to feed your baby later. There is no evidence from previous studies that tranexamic acid at the dose you will receive would have any effect on your baby through your breast milk. However, because few women delivering very early have been included in the studies there is not very much information about very small babies. Therefore to be cautious, if your baby or babies are born before 34 weeks we ask you not to breast feed for the first day of life. After one day, there will be very little if any tranexamic acid in your breast milk and you will be able to breast feed as usual.

If you deliver after 34 weeks you will be able to breastfeed your baby as usual.

The research staff will collect medical information about you and your baby or babies until you leave the hospital. One week after your delivery, the research staff will give you a phone call to see if you have had any problems since going home. Six weeks after your delivery, they will call you again or meet with you to find out if you needed any other treatment or have had any problems since going home. It is possible after this study is done, the researchers may want to contact you to do another follow-up study with you or your baby. We will ask your permission for this below.

What other choices do I have besides taking part in the research?

Participation in this research study is voluntary. You have the option not to be part of this study. If you do not take part,you will receive the routine treatment usually provided to women during and after delivery.

Your decision to participate or not to participate will not affect any other part of your care at this hospital. If you are currently expecting to have a cesarean delivery, your decision will not affect your ability to have the cesarean. If you expect to have a vaginal delivery, your decision will not affect the chance that you will need a cesarean.

Refusal to take part will not result in any penalty or loss of benefits to which you are entitled. Your decision to take part or not take part will not affect your legal rights, available remedies or the quality of health care that you will receive at this hospital.

What happens if I agree to be in the research, but later change my mind?

You can leave the study at any time. Your participation is completely voluntary. You may refuse to take part or you may stop taking part at any time without penalty or loss of benefits to which you are entitled. Your decision to leave the study will not affect your legal rights or quality of health care that you will receive at this hospital.

If you decide to leave the study, contact the research staff or the investigator so that the investigator can withdraw you. If you stop being in the study, all of the information that has already been collected about you as part of the research study will not be removed from the study database. No new information about you will be collected for study purposes unless the information concerns an adverse event (such as a bad reaction). You will be asked whether the investigator can collect information from your routine medical care.

Is there any way being in this study could be bad for me or my baby?

Tranexamic acid is not a new drug, and it is commonly used to prevent bleeding in major operations such as heart operations. If you receive tranexamic acid there is a chance of side effects such as nausea, vomiting, diarrhea, skin rash, giddiness, low blood pressure, or dizziness. There is a small chance of having a seizure but this has only been seen in other types of surgery at much higher doses than you would get in this study. It is possible that there could be an increased risk of a blood clot in a blood vessel (thrombosis) but this increased risk has not been seen in any studies. If you ever had thrombosis before, you will not be able to participate in the study. Because you get the medicine after cord clamping, the baby will not be exposed to it. However, a very small amount of tranexamic acid may pass to the baby through breast milk. There have been no reports of harm to babies who have been exposed to tranexamic acid through breast milk.

Saline is used routinely in IV fluids and there are no known risks of receiving the small amount of saline for this study.

You may experience discomforts associated with the blood draw to measure your hemoglobin (if required). This may include bruising, infection, fainting, or discomfort or pain at the insertion site of the needle.

There is a risk of improper release or misuse of your personal information. The chance of this happening is very small. We have many protections in place to lessen this risk.

Unknown Risks:

There may be risks from taking part in this study that are not known to the researchers right now. They may find out new risks while the study is going on. If this happens, the research staff will tell you the new information, whether it may affect you, and what, if anything, to expect.

What are the costs to me for being in this research study?

There will be no cost to you to take part in the research study. All study-related drugs and procedures will be provided at no cost to you or your insurance company.

The costs of your standard medical care will be billed to you or your insurance company in the usual manner.

Will I be paid for taking part in this study?

<insert center-specific language about reimbursement>

By signing this consent form, you acknowledge and agree that in the event that this research project results in the development of any marketable product, you will have no ownership interest in the product and no right to share in any profits from its sale or commercialization.

What happens if I believe I am injured because I took part in this study?

<this section may be modified by the center>

If you are hurt or believe your are injured while taking part in this study, you should contact _____ at (___) ___-____.

This medical institution and the NICHD have not made any provision for monetary compensation in the event of injury resulting from the research. In the event of such injury, treatment will be provided, but it is not provided free of charge. Since this is a research study, payment for any injury resulting from your participation in this research study may not be covered by some health insurance plans.

Will being in this study help me in any way?

If you decide to take part in this study, you may or may not directly benefit from your participation. However, your participation can potentially benefit other mothers in the future, or you if you become pregnant again.

Can I be removed from the research without my permission?

The person in charge of the study here may withdraw you from the study without your approval. One reason this may happen is because the researcher feels it is necessary for your health and safety. Another reason is if the entire study is stopped.

What if new information becomes available?

During the course of the study, we may find new information that could be important to you. This includes information that may cause you to change your mind about being part of the study. We will notify you if any significant new information becomes available which may affect your health, safety, or willingness to continue in this study.

What happens to my information collected for the research?

To the extent allowed by law, we limit your personal information to people who have to review it. We cannot promise complete secrecy.

You have the right to privacy. All information obtained from this study that can be identified with you will remain confidential within the limits of the law.

The medical information collected on you for this research study will come from your medical record and from information you give the research staff, such as your previous pregnancies, height, weight, and whether you drink or smoke. Other information collected about you includes marital status, your level of education, type of medical insurance, and current pregnancy complications. Data will be collected on your labor (such as when it starts) and delivery, and treatment you need after delivery. Information will also be collected on your baby at delivery and on your baby's hospital stay. If we lose track of you, study staff may collect information from the internet including social network sites in order to find your contact information.

The information collected for this research study will be entered into an electronic database at the data coordinating center (George Washington University Biostatistics Center in Rockville, Maryland). The database has information from all of the participants. Your information in the database will only be used for statistical analysis and may appear in scientific publications but will not identify you. The information sent to the data coordinating center does not include your name, address, social security number, hospital number, date of birth or any other personal identifiers. Instead, the data center will use a unique code for each person consisting of a number and the first letter of your first name. The key to the code linking the data and samples to you will be kept here in a locked file. Only the research study staff employed for this study at this hospital will have access to the key to the code.

The following individuals and/or agencies will be able to look at and copy your medical and research records:

- The investigator, study staff and other medical professionals who may be evaluating the study.
- Authorities from this institution, including the Institutional Review Board (IRB) which is a group of people who are responsible for making sure the rights of participants in research are respected.

Members or staff of the IRB at this medical center may also contact you about your experience with this research. You do not have to answer any questions the representative(s) of the board may ask.

- The United States Food and Drug Administration (FDA) and/or the Office for Human Research Protections (OHRP).
- The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) which sponsors this study, including persons or organizations working with the sponsors, such as the data coordinating center, the George Washington University Biostatistics Center in Rockville, Maryland.

A copy of your medical chart or your baby's medical chart also may be sent to research investigators at one of the other enrolling centers, the data coordinating center, or NICHD for review. If your chart is sent, all identifying information, such as your name, address, social security number, hospital number, and date of birth first will be removed.

The results of this research study will be provided to the sponsor, NICHD (and/or their representatives).

In addition, data from this study will be put in a public data set that will be available to other research investigators. This public data set will not contain any identifying patient data. When the data set is shared, it will be done without obtaining additional permission from you.

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.

Once the study is finished, you may request to have and review a copy of your personal health information collected during this study and placed in your medical record. This right to review and copy your personal health information only extends to information that is placed in your medical record; it does not extend to information that is placed in your research record.

This permission does not end unless you cancel it, even if you withdraw from the study. You can cancel this permission any time except where a healthcare provider has already used or released your health information, or relied on your permission to do something. Even if you cancel this authorization, the researchers may still use and disclose protected health information (PHI) they already have obtained about you as necessary to maintain the integrity or reliability of the research. However, no new PHI or new biological specimens will be collected from you after you revoke your authorization.

To cancel your authorization, you will need to send a letter to Dr. _____ of the _____ stating that you are canceling your authorization. This letter must be signed and dated and sent to this address:_____. If you are unable to write a letter ask one of the research staff to provide you with a letter that must be signed, dated, and sent to the above address. A copy of this cancellation will be provided to the Study Doctor and his or her research team. Not signing this form or later canceling your permission will not affect your health care treatment outside the study, payment for health care from a health plan, or ability to get health plan benefits.

Your protected health information will be treated confidentially to the extent permitted by applicable laws and regulations. Federal law may allow someone who gets your health information from this study to use or release it in some way not discussed in this section and no longer be protected by the HIPAA Privacy Rule.

By signing this form you authorize the Study Doctor and members of the research team to use and share with others (disclose) your PHI for the purpose of this study. If you do not wish to authorize the use or disclosure of your PHI, you cannot participate in this study because your PHI is necessary to conduct this study.

May we contact you about future studies that may be of interest to you?

There may be studies in the future that are or are not related to the research study you are consenting to participate in by signing this form. If this happens, to protect your confidentiality and respect your privacy, the research team would need your permission to contact you. If you agree to provide consent for contact for future studies, please initial in the appropriate space below.

____ Yes, you may contact me for future studies.

____ No, you may not contact me for future studies.

What else do I need to know?

The study is sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), which is part of the National Institutes of Health.

The results of the research study will be posted to www.clinicaltrials.gov within 13 months of completion of the study. You may review the results of the study at that time. If you have any questions regarding the study results, you may contact the research staff at the numbers provided to you in this consent form.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health (NIH). The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIH or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it

Signatures

By signing below, you indicate that you have read this consent form, the study has been explained to you, your questions have been answered, and you agree to take part in this study. You do not give up any of your legal rights by signing this form. A copy of this consent form will be given to you.

_____	_____	_____
Signature of Participant	Printed Name of Participant	Date
_____	_____	_____
Signature of Person Obtaining Consent	Printed Name of Person Obtaining Consent	Date

A witness unrelated to the study is necessary if the participant can comprehend but cannot read (e.g., blind), or cannot sign (e.g., unable to use hands) the consent form.

_____	_____	_____
Signature of Witness	Printed Name of Witness	Date

Investigator Statement <this section is center-specific>

I certify that the research study has been explained to the above individual by me or my research staff including the purpose, the procedures, the possible risks and the potential benefits associated with participation in this research study. Any questions have been answered to the Individual's satisfaction.

_____	_____	_____
Signature of Investigator	Printed Name of Investigator	Date

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