INFORMED CONSENT FORM

Title: Prevention of central venous catheter-associated thrombosis in critically ill children: A multicenter phase 2b trial.

NCT Number: 03003390

Date: August 25, 2017

COMPOUND AUTHORIZATION AND PARENTAL PERMISSION FOR PARTICIPATION IN A RESEARCH PROJECT
310 FR. 3a (2016-1)

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: Prevention of catheter-associated deep venous thrombosis in critically ill children
Principal Investigator: E. Vincent S. Faustino, MD, MHS
Funding Source: National Institutes of Health

Invitation to Participate and Description of Project

We are inviting your child to participate in a research study. The research study will see if giving a blood thinner called enoxaparin soon after a child has a central venous catheter (CVC) inserted will prevent blood clots from developing. Your child has been asked to participate because he/she has a CVC. The use of these catheters in sick children are associated with blood clots. Blood clots can cause swelling in the arms and legs. When there is a blood clot, it makes it harder for the people taking care of your child to use the CVC. Blood clots may cause infections. When blood clots form, it can go to the lungs, cause stroke, or lead to longer stays in the intensive care unit or even death.

We do not know if blood thinners, particularly enoxaparin, can decrease the chances of getting blood clots in children with CVC. We are doing this study to find out if this drug helps prevent blood clots.

In order to decide whether or not you wish your child to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This permission form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all parts of this research: the purpose and nature of the research study, the procedures that will be performed, the risks of the study drug, possible benefits, possible alternative treatments, your child's rights as a participant and other information about the research study. You should take whatever time you need to discuss the research study with your child's doctor and family. The decision to allow your child to participate or not is yours. Once you understand the study, you will be asked if you wish for your child to participate; if so, you will be asked to sign and date this form. If you do not sign this permission form, your child cannot take part in this study.

If you choose to allow your child to participate, you will be told of any significant new findings that develop during the time your child is in the study that may affect your willingness to allow your child to continue to participate.

Purpose

The purpose of this study is to find out if giving children a blood thinner called enoxaparin, shortly after getting a CVC, will prevent blood clots from happening. Even though doctors give this drug to children, we are not sure if it works.

The study drug that will be used in this research study, enoxaparin, is investigational in children. This means it has not been approved for use by the public by the United States Food and Drug Administration (FDA) in children. The safety and whether it produces positive results in children is not known even though enoxaparin is used in clinical practice; which means that some doctors give enoxaparin to children.

Enoxaparin is approved for use in adults by the FDA for the prevention of deep vein thrombosis (DVT), which may lead to pulmonary embolism (a blood clot in the artery in the lungs). Enoxaparin is also used to prevent blood clots in the leg in adult patients who are on bedrest or who are having hip replacement, knee replacement, or stomach surgery. It works by stopping the body from producing clots.

In this study, we will enroll 100 children in 6 children's hospitals (pediatric ICUs) across the country. It is expected that about 15 children will be enrolled in the research study at Yale University, Yale New Haven Children's Hospital.

Study Procedures

If you agree to allow your child to participate in this research study, your child will be randomly assigned to the treatment group or the control group but a computer system. If your child is assigned to the treatment group, the following tests and procedures will be done in the Pediatric Intensive Care Unit (PICU):

- Enoxaparin: Your child will have injections of enoxaparin 2 times a day (every 12 hours or so). These injections will be in your child's thigh or abdomen (depending on your child's age) under the skin until the end of your child's participation in the study.

- Anti-Xa Testing: Your child's blood will be checked using a test called anti-Xa after the third time they get enoxaparin (3rd dose) to make sure the correct amount is being given. Your child's doctor may change the dose of enoxaparin so that your child is getting the dose that they need. Blood (1/2 teaspoon) will be taken from the CVC for this test.

The following tests and procedures will be done if you agree to allow your child to participate regardless of treatment group assignment:

Ultrasound: Your child will have an ultrasound over the location where CVC is inserted. The ultrasound is being done for research purposes only and is not part of your child's clinical care. This will be done once at only one the following time points, whichever comes first.

  - After the CVC is removed, OR
  - Before your child is discharged from the PICU, OR
  - If your child's doctor detects a blood clot, OR
  - If your child's doctor decides to start blood thinners, OR
  - If your child develops a bleed that is causing other health problems, OR
  - If your child's platelet count drops because of enoxaparin, OR
  - At 28 days after insertion of the CVC.

- Blood Draws: We will draw about 5.4 mL of blood at 4 different times (4 teaspoons total for the entire study) during the study. The blood will be drawn for research purposes only. This will happen on the day of enrollment (when your child starts being in the study), 1 day after that, 4 days after insertion of the CVC and at the end of the study period. Blood will be drawn from the CVC or another catheter that is already inserted. Your child will not need to have a needle stuck in them to get this blood.

- Urine collection: We will collect 2-5 mL of urine at 4 different times (1.5- 4 teaspoons total for the entire study). The urine will be collected for research purposes only. This will happen at the same times that the blood for research is collected (see above).

Your child will be in the study until the CVC is removed. Your child could be in the study for up to 28 days.

If any of the following things happen, your child will be removed from the study because these medical problems will stop us from knowing if the study drug is working.

- He/she is discharged from the PICU
- He/she is diagnosed with a blood clot in the vein from the CVC
- He/she starts another mediation that helps prevent or to treat blood clots
- He/she is bleeding and it is causing other health problems
- His/her platelet count drops because of enoxaparin
- 28 days after the CVC is inserted

Your child will no longer be in the study if any of the events listed above occur. Your child will be followed for side effects for 30 hours after the last dose of enoxaparin is given.

Potential Risks

While in this study, your child may have side effects. Expected side effects are listed here. In addition to the risks listed below, there may be risks that are currently unknown. If significant new information becomes known to us during the time your child is on the study, we will tell you so you can decide if your child should stay in the study. Possible side effects that your child may experience during this study will be fully explained to you by the study staff. Please ask as many questions as you want so that you can understand the possible side effects of your child's treatment before you decide whether you want to allow him/her to be in this study. Please ask the study doctor or the study staff to explain any information or words that are not clear to you.

Risks associated with enoxaparin (the drug we are studying)

If your child is assigned to the treatment group, s/he will be given enoxaparin. Enoxaparin is a blood thinner commonly used in adults and children. Because it is a blood thinner, there is a possibility that your child may have some bleeding associated with the use of the drug. Based on the information that we have right now, less than 3 out of 100 sick children receiving enoxaparin had significant bleeding, which is the same in sick children who are not receiving any blood thinners. We try to lower the risk of bleeding by enrolling only those children that have lower tendency to bleed. We are also checking drug levels to make sure that bleeding is not likely to happen.

In addition to an increased risk of bleeding, there is an increased risk of thrombocytopenia which means low platelets in the blood which help blood clot and stops bleeding, anemia (low healthy red blood cells or hemoglobin), elevation of serum aminotransferase (which could mean the liver is not functioning well), diarrhea, and nausea.

Enoxaparin will be given as injections to the thighs or abdomen depending on your child's age twice a day. There may be some pain involved with the injection. We will do our best to minimize pain from the injection. There is also a very small chance that your child will have anemia from the blood draw or other reaction to the drug.

Other Risks

The following risks are associated with participation in the study regardless of treatment assignment.

Blood Collection
The risks of drawing blood from your child through a catheter may include light-headedness and fainting. Approximately 5.4 mL of blood will be taken four times (a total of 4 teaspoons for the entire study) during your child's participation for research purposes only. More will be taken as part of the routine care of your child.

Ultrasound
There might also be some discomfort to your child during the ultrasound procedure. We will do everything possible to reduce discomfort. There may be a slight pressure in the area when the ultrasound probe is passed over your child's body.

Loss of Privacy and Confidentiality
There is also a potential for loss of privacy and confidentiality. To lower this risk, we will assign your child a study number. All data collected for the study will be identified by this number, not your child's name or other information that could be linked to your child.

For more information about risks and side effects, you can ask the researcher during your visits or contact their office at 203-785-4651

Benefits

If you agree to allow your child to take part in this research study, we cannot guarantee that your child will receive any good results or benefits. However, there is a potential that your child will directly benefit from the study. S/he may have less risk of developing blood clots in the blood vessel where the catheter was inserted if s/he is assigned to the treatment group. This may result in shorter stay in the hospital. We hope the information learned from this research study may benefit other children at risk of blood clots in the future. The information your child will provide in this study will be used to design a bigger study with more children to determine whether enoxaparin can decrease the risk of blood clots from CVC in sick children.

Economic Considerations

You and your child will not be paid for taking part in this study. Tests and procedures that are done for your child's regular care (whether he/she is on this study or not) are called "standard of care". There will be no charge to you or your insurance provider for tests or procedures that are not standard of care, done only for research purposes. You and your insurance provider will not have to pay for the study drug enoxaparin, or the ultrasound. All other tests and procedures will be charged to you or your insurance provider in the usual way because they are standard care for your child's condition. This may include other tests and procedures not listed in this consent if your child's doctor feels it is necessary for his/her care, such as additional laboratory tests.

Alternatives

Blood thinners are currently the only potential treatment to prevent blood clots.

Another alternative is to provide no blood thinner or no treatment to prevent clots.

If you decide not to allow your child participate in the study, your doctor will decide if your child will receive blood thinners which will have nothing to do with the study. Currently there are no blood thinners approved for children to prevent blood clots from happening.

Talk to your doctor about your choices before you decide if your child will take part in this study.

Confidentiality and Authorization to collect, use and disclose Protected Health Information

For purposes of this study, Yale University, Yale-New Haven Hospital, and Dr. Faustino will use medical information collected or created as part of the study, such as medical records and test results, which identifies your child by name or in another way. Your permission to allow your child to participate in the study means you agree that Yale University, Yale-New Haven Hospital, and Dr. Faustino may obtain your child's medical information that they request for study purposes from your child's doctors and other health care providers from the past or during your child's participation in the study. The study doctor may need this information to watch, review and report on the safety of the study drug.

The protected health information that will be collected in this study includes: demographics (name, date of birth), medical history, physical examinations, routine lab tests, your child's medications (past and present), ultrasound scan results, blood and urine sample results and records about the study drug that your child received.

Any identifiable information (information that has your child's name on it) that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases such as HIV or hepatitis. When the results of the research are published or discussed in conferences, no information will be included that would reveal your child's identity unless your specific permission for this activity is obtained.

We understand that information about your child obtained in connection with your child's health is personal, and we are committed to protecting the privacy of that information. If you decide to allow your child to be in this study, the study staff will get information that identifies your child and his/her protected health information. This may include information that might directly identify your child, such as his/her name, date of birth, and medical record number**.** This information will be de- identified prior to providing it to Yale University, meaning we will replace your child's identifying information with a code that does not directly identify him/her. The study doctor will keep a link that identifies your child to his/her coded information, and this link will be kept secure and available only to the Principal Investigator or selected members of the study team. Any information that can identify your child will remain confidential.

The records for this trial will be stored in locked cabinets and/or offices and password protected computers. It is anticipated that records containing the information that links your child to his/her coded information will be maintained indefinitely, as there are no plans at this time to destroy these records at the end of the study.

Information about your child's study participation will be entered into his/her Electronic Medical Record (EMR). Once placed in the EMR, these results are accessible to all of your child's providers who participate in the EMR system. Information within your child's EMR may also be shared with

others who are appropriate to have access to your child's EMR (e.g., health insurance company, disability provider.)

Information about your child and his/her health which might identify he/she may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies and other government agencies in the United States and in foreign countries that watch over the study
- Representatives from Yale University and Yale New Haven Hospital
- Representatives from the Yale Human Research Protection Program, (the Institutional Review Board that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Representatives from the Yale Center for Clinical Investigation Quality Assurance may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.
- Your child's providers who are participants in the Electronic Medical Record (EMR) system
- Individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The study doctor Vincent Faustino and the Yale University study team
- The study funder (National Institutes of Health)
- The U.S. Food and Drug Administration (FDA). This is done so that the FDA can review information about the drug being used in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to your child in connection with this study.
- Laboratories and other individuals and organizations that analyze your child's health information in connection with this study, according to the study plan.
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study
- The people you have named as emergency contacts (if any) and the study team has not been able to reach you

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

The study sponsor Yale University, people who work with the sponsor on the study, and government agencies and other groups that watch over research studies like this one may look at all your child's health information. Regulatory authorities may also require that the study doctor turn over to them copies of all your child's health information to make sure the study has been done the right way. They also want to make sure that your child's health information has been collected the right way, or for other reasons that are allowed under the law.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your child's information. The research staff at Yale University is required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your child's information in ways not mentioned in this form. Federal law does not protect your child against this,

but the laws of your state may provide additional protection. However, to better protect your child's health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

Authorized representatives of the FDA may need to review records of individual subjects. People from the FDA or other Health and Human Services agencies may see your child's name, but they are bound by rules of confidentiality not to reveal your child's identity to others.

The funder of this study, The NIH may see the research information we collect about your child if they come to monitor the conduct of this research study. This includes any persons that work for or are hired by the NIH. Researchers may also send the NIH your child's health information during the study or at the end of the study. When Yale University researchers send information about your child to the NIH, they will not send information that directly identifies him/her such as your child's name.

You have the right to review and copy your child's health information in your child's medical record in accordance with institutional medical records policies. You may also, under data protection laws, have the right to ask that any mistakes in your child's study-related health information be corrected. However, you will not be allowed to look at or copy your child's study related information until after the research is completed. This is because we want to wait until the study is over before we decide if the study drug worked well.

This authorization to use and disclose your child's health information collected during your participation in this study will never expire.

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 your child. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Your daughter will be asked to have a pregnancy test before starting this study. Only your daughter will be told the results. If she is pregnant, we will also advise her to get care for her pregnancy and to get the support of an adult. If your daughter is under age 13 and has a positive pregnancy test, we will report the pregnancy to the Department of Children and Families.

In Case of Injury

If your child is injured while on study, seek treatment and contact the study doctor as soon as you are able.

Yale University does not provide funds for the treatment of research-related injury. If your child is injured as a result of his/her participation in this study, treatment will be provided. You or your child's insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury is available.

You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Participation in this study is voluntary. You are free to choose not to allow your child to take part in this research study. Refusing to allow your child to take part in this research study will not lead to penalty or loss of benefits to which your child is otherwise entitled (such as his/her health care outside

the study, the payment for his/her health care, and his/her health care benefits). However, your child will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not sign this permission form and allow use of your child's information as part of this study.

Withdrawing from the Study:

If you decide to allow your child to participate in this research study, you are free to stop and withdraw your permission at any time. To withdraw your child from the study, you can call a member of the research team at any time and tell them that you no longer want your child to take part. They will make sure that proper procedures are followed to stop the study.

Withdrawing from the study will involve no penalty or loss of benefits to which you or your child are otherwise entitled. It will not harm your relationship with your child's doctors or with Yale University. We would still treat your child with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment.

You may request that the Sponsor destroy your child's blood and urine samples by contacting your study site. As long as it is possible to identify your child's samples (i.e., the samples have not been anonymized or the study site has not destroyed the key that links your child's name to the study ID), then the Sponsor will destroy the sample. However, if any analysis or research has already been performed on the samples, the Study Sponsor does not have to destroy the results of this analysis or research. If you request destruction of your child's sample(s), your child will not lose any benefits, medical treatment or legal rights to which he/she are otherwise entitled.

If you choose not to give your permission by not signing this document, or if you cancel your permission later, then your child will not be eligible to participate in this study and will not receive any treatment provided as part of the study. Unless and until you do cancel the permission, it will remain valid and effective.

Withdrawing Your Authorization to Use and Disclose Your Child's Health Information:

You may withdraw or take away your permission to use and disclose your child's health information at any time. You do this by telling the study staff or by sending written notice to the study doctor Dr. Vincent Faustino P.O. Box 208064 New Haven, CT 06520-8064. If you withdraw your permission, your child will not be able to stay in this study.

When you withdraw your permission, no new health information identifying your child will be collected after that date. Information that has already been collected may still be used and given to others as permitted in this document until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

<u>Questions</u>

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the permission form carefully – as long as you feel is necessary – before you make a decision.

Biomarker Research

A biomarker is a biological substance from your body, the cells of your body, that is useful for measuring or predicting a disease or your child's response to the study medicine. We will perform research on your child's samples to see if there is a way to predict how children respond to treatment with the study drug enoxaparin.

Below is a list of bio specimen samples that we will collect in this study:

Blood: We will draw about 5.4 mL of blood at 4 different times (4 teaspoons total for the entire study). Blood will be drawn from a catheter that is already inserted. Your child will not need to have a needle stuck in them to get this blood.

- The day of enrollment (when your child starts being in the study)
- 1 day after that
- 4 days after insertion of the catheter
- At the end of the study

At any **one** of the time points specified above, additional 0.5 mL of blood will be drawn.

Urine: We will collect 2-5 mL of urine at 4 different times (1.5- 4 teaspoons total for the entire study). This will happen at the same times that the blood for research is collected (see above)

These samples are intended for research purposes only. These blood samples will be sent to and stored at research Laboratories at Yale University under the direction of Dr. E. Vincent Faustino and Saint Louis's Children's Hospital under the direction of Dr. Phillip Spinella. Both of these doctors are Investigators on this study.

The urine samples will be sent to and stored at Yale University.

Optional Future Storage/Genetic Testing of your Child's Specimens

You are invited to allow these blood and urine samples (called specimens) and related information to be stored (banked) for future research. This may help researchers in the future learn more about how to prevent blood clots from developing in children with CVC.

The storage of the blood and urine samples is optional: This means that the choice to allow us to store these samples is up to you. You may choose not to let us store and use your child's samples, and his/her care will not be affected by this decision. Your child will still be able to participate in this study if you do not agree to allow these samples to be stored for future use.

If you decide that your child's samples can be kept for future research, you may change your mind at any time. To withdraw your child's samples from the study, you can call a member of the research team or you may write to the Principal Investigator using the contact information on page one of this form at any time and tell them you do not want your child's samples used any longer.
Your child's samples will be destroyed if it is still possible to identify them.

When your child's specimens and information are stored, we are careful to try to protect his/her identity from discovery by others. Your child's samples and information will receive a unique code. Other researchers will only receive coded samples and information, and will not be able to link the code to your child. Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information.

Using your child's specimens for research will probably not help him/her. We do hope the research results will help other children in the future.

There is a risk that your child's information could be misused. The chance of this happening is very small. We have protections in place to lower this risk. There can also be a risk in uncovering genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Very rarely, health or genetic information could be misused by employers, health insurance companies, and others. There is a federal law called the Genetic Information Nondiscrimination Act (GINA) that, in general, makes it illegal for health insurance companies, group health plans, and most employers (except those with fewer than 15 employees) to discriminate against your child based on his/her genetic information. However, it does not protect him/her against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance in the future.

Your child's specimens and information will only be used for research and will not be sold. There is a possibility that this research may lead to development of products that will be commercialized. If this happens, there is no plan to share any financial gain with you or your family or child.

Research results will not be returned to you or your child's doctor. If research results are published, your child's name and other personal information will not be given.

Please indicate your choice below by checking yes or no:

- ☐ Yes, I agree to allow my child's blood and urine samples and information to be stored and used for future, unspecified research of any kind.

- ☐ No, I do not agree to allow my child's blood and urine samples and information to be stored and used for future research.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to allow my child to participate in the project as described above. The study, the details of my child's involvement, risks inconveniences have been explained. My signature also indicates that I have received a copy of this permission form.

By signing this form, I give permission to the researchers to use and give out information about my child for the purposes described in this form. By signing this permission form, I have not given up any of the legal rights that my child otherwise would have as a subject in a research study. By refusing to give permission, I understand that my child will not be able to participate in this research.

_____
Name of Child (print name)

_____
Parent Name (print name)

_____ _____
Parent Signature Date

_____ _____
Signature of Person Obtaining Permission Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale University Privacy Officer at (203) 432-5919.

If you have further questions about this project or if you have a research-related problem, you may contact Dr. Faustino at (203) 785-4651.

If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.