Title: Comparison of Fibrinogen Concentrate and Cryoprecipitate in Pediatric Cardiac Surgery Patients

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Parents' or Guardians' Permission for Your Child to Be in a Research Study

In this form "you" means the child in the study *and* the parent or guardian.

- ✓ If you are the parent or guardian, you are being asked to give permission for your child to be in this study.

In this form "we" means the researchers and staff involved in running this study at the University of Virginia.

Participant's Name_____

Medical Record # _____

What is the purpose of this form?

This form will provide you with information about this research study. You do not have to be in the study if you do not want to. You should have all your questions answered before you agree to be in this study. Please read this form carefully. If you want to be in the study, you will need to sign this form. You will be given a copy of this form.

Who is funding this study?

This study is being funded by Octapharma USA, a company that produces a clotting medication called fibrinogen concentrate.

Key Information About This Research Study

Principal Investigator:	Peggy P. McNaull , MD Department of Anesthesiology University of Virginia Medical Center Charlottesville, VA 22908 Tel: 434-924-2283
Sponsor:	University of Virginia Department of Anesthesiology
Support Source	Octapharma USA (121 River Street, Suite 1201 Hoboken, New Jersey 07030, USA, Tel: 201-6041130).

You are being asked to take part in a research study. You do not have to take part in this study. You should only agree to take part in this study after reading this consent form and discussing it with the study team. You may also discuss this with your family, friends, health care providers or others before you make a decision.

What problem is this study trying to solve?

During and after heart surgery it is very common to develop significant bleeding that could be life threatening. In order to prevent excessive bleeding and severe anemia (severe deficiency of red blood cells) that may be life threatening, patients often receive transfusion of clotting factors and /or blood. This blood and clotting factors are obtained from blood donors. While these clotting agents may be lifesaving, they are also associated with severe risks such as viral infections, respiratory complications (usually called TRALI – transfusion-related acute lung injury), weakening of the immune system and fluid overload (which could put a lot of stress on the heart, specifically in the context of open heart surgery). Over the last few years, new clotting agents (factor concentrates) have been developed to try and prevent the risks that are associated with transfusion of blood and clotting agents that are obtained from donors. These new agents have a much better safety profile and possibly have less complications, however, they have not been extensively tested and compared to the current available clotting treatments in children that undergo open heart surgery.

This study is being done to compare the new fibrinogen concentrate, Fibryga, to the existing fibrinogen supplement (cryoprecipitate) to determine whether similar clinical effects may be achieved. Cryoprecipitate is a concentrated blood component made from fresh frozen plasma (FFP). Cryoprecipitate contains specific protein molecules involved in blood clotting. If Fibryga provides a similar clotting profile to cryoprecipitate, its better safety profile (less infections, no lung complications, and no fluid overload) may make it a better treatment option over the currently available treatment.

Why would you want to take part in this study?

You might like to have your child take part in this study because he/she may be randomized to the fibrinogen concentrate group and if proven to have a similar clotting effect to the current available treatment (cryoprecipitate), the fibrinogen concentrate may offer less potential risks or complications than cryoprecipitate.

If your child is randomized to the currently standard treatment group (cryoprecipitate) he/she will receive the currently accepted standard of care.

Your child may not be helped by being in this study, but the information gained by doing this study may help others in the future.

Why would you NOT want to take part in this study?

You might not want to take part in this study because there is very little information in the USA about the use of fibrinogen concentrate in children that need heart surgery and therefore little information about potential complications. That being said, this agent is being routinely used in many countries in Europe (in adults as well as in children both in the context of heart surgery and in other clinical situations where there is congenital or acquired fibrinogen deficiency).

You also may not want to take part in this study because you cannot choose which clotting treatment your child receives. There are risks to both clotting agents, which are found later in this form.

What will I have to do if I take part in this study?

If you chose to have your child participate in the study the following will occur:

- Results from routine blood work, including clotting tests, will be recorded from your child's medical records. These tests are routinely performed on every patient even if they do not participate in the study.
- On the day of surgery, your child will be randomly assigned to receive cryoprecipitate or Fibryga.
- Blood tests done as part of the surgery will show whether your child needs a clotting agent. If your child is identified as needing a clotting agent, your child will receive either Fibryga or cryoprecipitate, based on the group he/she has been randomized to, by IV infusion. Your child will NOT receive any fibrinogen supplementation if they do not show signs of fibrinogen deficiency, even if they enroll in the study.
- After receiving the study medication, a clinical assessment for bleeding (routinely performed by the surgeons) will be done and additional clotting tests will be taken to assess the effects of Fibryga/cryoprecipitate on the clotting system. These clotting tests are NOT routinely preformed currently and will only be done in those who participate in the study. The amount of blood needed for these tests will NOT be larger than 2 teaspoons.
- We will assess the amount of bleeding accumulated in the surgical drains for up to 48 hours after surgery. This information will be obtained from nursing documentation and from the medical chart.
- We will review and record the amount of blood and clotting factors that your child received in the operating room and in the ICU (up to 48 hours after the surgery) from your child's medical record.
- We will review and record postoperative complication information from your child's medical record for 30 days after surgery.

What is the difference between being in this study and getting usual care?

If your child were not taking part in this study:

- Your child would not receive Fibryga.
- Your child would not have the extra blood clotting labs done.
- Your child would not have his/her records reviewed and information collected for research purposes.

This is a research study about the use of a fibrinogen concentrate medication, Fibryga, in children having open heart surgery. Fibryga is a drug that is not approved by the U.S. Food and Drug Administration (FDA) for use in children having open-heart surgery. So far, Fibryga has been routinely used for over 20 years in many European countries both in patients having heart surgery

as well as patients with a rare genetic condition called congenital a/hypofibrinogenemia. In addition it has been approved in Canada and has been used there in >1000 people.

What other treatments may I receive if I decide to not take part in this study?

If you decide to not take part of the study, your child will be treated with cryoprecipitate, a clotting factor that contains fibrinogen.

How long will this study take?

Your child's participation in this study will last about 30 days.

What will happen if you are in the study?

If you chose to have your child participate in the study the following will occur:

- You will meet with a study coordinator or a research nurse for screening. This person will explain the study to you. This visit will happen during the pre-surgery clinic visit or on the day before surgery and will take up to 10-15 minutes.
- On the day of surgery you child will be randomized to the cryoprecipitate group (control group) or to the Fibryga group (interventional group). This randomization is similar to a coin flip and is done by special computerized software. It will determine whether your child will receive the study medication Fibryga, or the standard care with the blood component cryoprecipitate. Your child will receive either clotting agent ONLY if they have fibrinogen deficiency and exhibit clinically significant bleeding (this happens to about 85% of children after open heart surgery).
- After the separation from the heart-lung machine we will perform routine clotting tests (ROTEM, platelet count and fibrinogen level) to determine whether your child needs transfusion of clotting factors (most children, about 85%, have low fibrinogen levels at this point and need supplementation of fibrinogen). This is routinely done in all patients even if they do not participate in the study.
- If your child indeed needs supplementation of fibrinogen he/she will receive either the study medication (Fibryga) or cryoprecipitate based on whichever group they will be assigned to. Your child will NOT receive any fibrinogen supplementation if they do not show signs of bleeding and fibrinogen deficiency even if they enroll in the study.
- After the transfusion of the study medication or cryoprecipitate a clinical assessment for bleeding (routinely performed by the surgeons) will be done and additional clotting tests (ROTEM) will be taken to assess the effects of Fibryga/cryoprecipitate on the clotting system. These clotting tests are NOT routinely performed currently and will only be done in those who participate in the study. The amount of blood needed for these tests will NOT be larger than 2 teaspoons. The blood will be obtained through existing specialized intravenous lines that are routinely placed in all patients undergoing open-heart surgery. This means that no additional needle sticks are associated with the study.
- In the event that a second dose of fibrinogen supplementation is required (the bleeding continues with documented low fibrinogen level) your child will receive either the fibrinogen concentrate or cryoprecipitate based on the initial clotting therapy they were assigned to receive. If any additional fibrinogen doses are then needed (after the initial

two doses), cryoprecipitate will be administered to all subjects per standard of care (including those who received fibrinogen concentrate).

- Once your child arrives in the ICU he/she will have another set of clotting tests to assess his/hers clotting system after surgery. These tests are routinely performed on every patient even if they will not participate in the study.
- We will assess the amount of bleeding accumulated in the surgical drains for up to 48 hours after surgery. This information is routinely recorded by the nurses and doctors in the ICU and will be collected from the medical chart.
- We will assess the amount of blood and clotting factors that your child will receive in the operating room (after separation from the heart-lung machine) and in the ICU (up to 48 hours after the surgery). This information is routinely documented both in the operating room and in the ICU and will be obtained from the medical chart.
- Follow up for postoperative complications such as infections, kidney injury, lung injury/prolonged ventilation, stroke/seizures, mortality, the duration of mechanical ventilation, the duration of stay in the ICU, the duration of hospitalization, thromboembolic complications (unwanted blood clots) will occur until 30 days after surgery or until discharge from the hospital (whichever happens first). This information will be obtained from the medical chart and will not involve direct contact with you or with your child.

SCREENING VISIT (will be combined with the preoperative clinic visit or will happen on the day before surgery in hospitalized patients)

If you agree to participate, you will sign this consent form before any study related procedures take place. Before you can start in the study, there will be a screening period. You will have tests and procedures during this time to make sure you are eligible and it is safe for you to participate. These include the following:

- A preoperative visit by a study coordinator or a research nurse to discuss this study. This will take up to 10-15 minutes.
- Review your child's medical history (routinely performed in all children regardless of study participation)
- Physical exam and vital signs (blood pressure, heart rate, etc). This is routinely performed for all patients regardless of study participation
- Standard blood tests (2-3 tablespoons) to check kidney and liver function, blood counts and routine clotting tests. All this blood tests are routinely performed before surgery regardless of study participation.

If these tests show that your child is eligible, he/she will be enrolled in the study.

RANDOMIZATION and STUDY TREATMENT

On the day of surgery, your child will be randomly assigned (like the flip of a coin) to 1 of 2 study treatment groups. Your child has an equal chance of being assigned to any one of the treatment

groups. Neither you nor your doctor can choose which treatment your child is assigned to. The team in the operating room will know which treatment your child will get, however, neither you nor the ICU doctors will know which study treatment your child received until the study is done. But if your child's doctors need to know, the people doing this study can find out. Your child will only receive the study medication if he/she is found to have clinically significant bleeding and low fibrinogen levels (happens in about 85% of children).

GROUP 1: *Fibryga.* If your child is assigned to this group, he/she will receive Fibryga at a dose of 70 mg/kg.

GROUP 2: *Cryoprecipitate.* If your child is assigned to this group, he/she will receive cryoprecipitate at a dose of 10-15 ml/kg. This is the current standard of care in the USA.

After the study drug is given, the surgeon will perform an assessment of bleeding. This step is routinely performed in all cases regardless of study participation. We will also send additional standard clotting tests to assess the effects of the clotting medications. These tests are routinely performed prior to separation from the heart-lung machine but here we will add an ADDITIONAL round of tests (not routinely done) only for the study participants.

If these tests show that bleeding is continuing and there is a low level of fibrinogen, your child will receive an additional dose of either Fibryga or cryoprecipitate based on which medication they were assigned to. In the event that the bleeding still continues after two doses of the clotting medication (unlikely), your child will receive a round of cryoprecipitate (if your child is assigned to the cryoprecipitate group, this will be a third dose) to achieve normal blood clotting.

FOLLOW UP:

We will follow your child in the ICU/Ward for 30 days after the surgery or until discharge from the hospital (whichever comes first) and record the following information from his/her medical record:

- Results of clotting tests after surgery.
- The amount of bleeding accumulated in the surgical drains for up to 48 hours after surgery.
- The amount of blood and clotting factors your child received in the operating room (after separation from the heart-lung machine) and in the ICU (up to 48 hours after the surgery).
- Information about any postoperative complications.

END OF STUDY:

After your child completes the study he/she will no longer receive the study medication. You and your child will be referred to the care of your primary cardiologist to resume your child's postoperative care

What are your responsibilities in the study?

You have certain responsibilities to help ensure your child's safety.
These responsibilities are listed below:

- You must bring your child to each study visit.
- You must be completely truthful about your child's health history.
- You should tell the study doctor or study staff about any changes in your child's health.
- Answer all of the study-related questions completely.

Blood Testing

There will be blood tests performed for the study. Fibrinogen will be collected in the OR while your child is on cardiopulmonary bypass. ROTEM blood test will be performed 10-20 minutes after the study medication is administered and upon admission to the ICU. It will involve taking no more than 2 teaspoons of blood and will not involve any needle sticks as your child will have specialized intravenous (IV) lines that allows for blood draws directly. This additional blood will be tested to see how your child's blood is clotting after receiving the study medication.

When these tests are done any left-over sample will be thrown away or they will be de-identified. This means there is no information that could be used by anyone to determine who the sample came from.

If you want to know about the results before the study is done:

During the study your study leader will let you know of any test results that may be important to your child's health. In addition, as the research moves forward, your study leader will keep you informed of any new findings that may be important for your child's health or may help you decide if you want your child to continue in the study. The final results of the research will not be known until all the information from everyone is combined and reviewed. At that time you can ask for more information about the study results.

What are the risks of being in this study?

Risks and side effects related to the drugs (both Fibryga and cryoprecipitate) administered in the study include:

CRYOPRECIPITATE

Likely

- fever
- decrease in blood pressure

Rare but serious

- viral infections

- respiratory complications (usually called TRALI – transfusion-related acute lung injury) weakening of the immune system
- fluid overload (which could put a lot of stress on the heart, specifically in the context of open heart surgery).
- allergic reaction
- excessive clotting that may result in unwanted blood clots in the blood vessels, the heart, the brain, or in surgical shunts or conduits

FIBRYGA

Likely

- fever
- weakness
- vomiting

Rare but serious

- allergic reactions
- excessive clotting that may result in unwanted blood clots in the blood vessels, the heart, the brain, or in surgical shunts or conduits

OTHER UNEXPECTED RISKS:

You may have side effects that we do not expect or know to watch for now. Call the study leader if you have any symptoms or problems.

FIBRYGA is made from human plasma. Products made from human plasma may contain infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent). Also, unknown infectious agents may be present in such products. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, by filtering the product through special virus-removing filters and by a process demonstrated to inactivate and/or remove certain viruses during manufacturing. Despite these measures, such products may transmit disease.

Could you be helped by being in this study?

Your child may or may not benefit from being in this study. Possible benefits for those randomized to Fibryga include avoiding some or all potential complications associated with the transfusion of donated blood or clotting factors (for example: increased risk for infections, human errors due to transfusion of the wrong agent, respiratory complications, etc).

For those randomized to the cryoprecipitate, your child is not expected to benefit from this study.

In addition, information researchers get from this study may help others in the future.

What are your other choices if you do not join this study?

Your child does not have to be in this study to be treated for his/her illness or condition. Your child will get the usual treatment even if you choose not to be in this study. The usual treatment would include: administration of cryoprecipitate, if significant bleeding occurs during/after surgery with a documented low level of fibrinogen.

If you are an employee of UVa your job will not be affected if you decide not to participate in this study. If you are a student at UVa, your grades will not be affected if you decide not to participate in this study.

Will you be paid for being in this study?

You will not get any money for being in this study.

By agreeing to be in this study, you are donating your child's blood for research, and giving up any property rights you may have in them. The results of this research using your child's donated materials may have commercial value. However, neither you nor your child will receive any payments.

Will being in this study cost you any money?

The following procedures/tests, which are being done for research purposes, will be provided at no cost to you or your child's health insurance:

- Rotem blood clotting tests, performed immediately after the administration of Fibryga/cryoprecipitate, and upon admission to the ICU. The study will pay for Fibryga.
- Cryoprecipitate will be billed to your/ your child's insurance as part of your child's usual care.

You and/or your insurance company must pay for any tests or care given beyond what is required in this study. In addition, you and/or your health insurance may also have to pay for other drugs or treatments that are given to help you control any side effects. You will have to pay for any costs not covered by your health plan. You may be responsible for any co-payments or deductibles. You may wish to ask your insurance company for an estimate of what these costs might be or if pre-approval is required.

You will be responsible for the cost of travel to come to any study visit and for any parking costs.

What if you are hurt in this study?

You do not give up any legal rights, such as seeking compensation for injury, by signing this form. If you feel you have been injured as a result of this study you may contact the Principal Investigator or the IRB (phone numbers are located near the end of this form). If you are hurt as a result of being in this study, there are no plans to pay you for medical expenses, lost wages, disability, or discomfort. The charges for any medical treatment you receive will be billed to your insurance. You will be responsible for any amount your insurance does not cover.

What happens if you leave the study early?

You can change your mind about being in the study any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services your child can normally get at the University of Virginia.

Even if you do not change your mind, the study leader (or the sponsor of this study) can take your child out of the study. Some of the reasons for doing so may include (but not limited to):

a) Your study physician is concerned about your child's health
b) The side effects of the treatment are too dangerous
c) New information shows the treatment will not work or is not safe for your child
d) The study sponsor closes the study for safety, administrative or other reasons

If you decide to stop being in the study, we will ask you to contact the Primary Investigator at the number listed below. Any data collected about you up until the time you leave the study must be kept in order to determine the results of the study.

How will your child's personal information be shared?

The UVa researchers are asking for your permission to gather, use and share information about your child for this study. If you decide not to give your permission, your child cannot be in this study, but can continue to receive regular medical care at UVA.

If you sign this form, we may collect any or all of the following information about your child:

- Personal information such as name and date of birth
- Your child's health information, if required for this study. This may include a review of your child's medical records and test results from before, during and after the study from any of your child's doctors or health care providers. This may include mental health care records, substance abuse records, and/or HIV/AIDS records.

Who will see your child's private information?

- The researchers to make sure they can conduct the study the right way, observe the effects of the study and understand its results
- People or groups that oversee the study to make sure it is done correctly
- The sponsor(s) of this study, and the people or groups it hires to help perform or review this research
- Insurance companies or other organizations that may need the information in order to pay medical bills or other costs of your child's participation in the study
- Tax reporting offices (if you are paid for being in the study)
- People who evaluate study results, which can include sponsors and other companies that make the drug or device being studied, researchers at other sites conducting the same study, and government agencies that provide oversight such as the Food and Drug Administration (FDA) if the study is regulated by the FDA.

- If you tell us that someone is hurting you or your child, or that you might hurt yourself or someone else, the law may require us to let people in authority know so they can protect you and others.

The information collected might be published in a medical journal. This would be done in a way that protects your child's privacy. No one will be able to find out from the article that your child was in the study.

Information obtained during this study may be used in future research. Your child's information may be shared with other researchers inside or outside of the University of Virginia. They will not be sent with information that could identify your child such as name, address or phone number.

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.

What if you sign the form but then decide you don't want your private information shared?

You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form or complete the "Leaving the Study Early" part of this form and return it to the researchers. Then your child will no longer be in the study. The researchers will still use information about your child that was collected before you ended your child's participation.

A copy of this consent form will be put in your child's medical record. (This is not the same as the record of this research study.) This means that everyone who is allowed to see your child's medical records will be able to find out that your child is in this study. This is done so your child's regular doctors will know what your child received as part of this study. If your child has other health problems during the study, they will be able to treat your child properly.

Please contact the Principal Investigator listed earlier in this form to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your child's regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Peggy P. McNaull, MD
University of Virginia Health System, Department of Anesthesiology
Box 800710, Charlottesville, VA 22908 Telephone: 434-924-2283

What if you have a concern about this study?

You may also report a concern about this study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research
PO Box 800483
Charlottesville, Virginia 22908 Telephone: 434-924-9634

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the IRB-HSR Number (at the top of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

Signatures

What does your signature mean?

Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you have received this information and all your questions have been answered. If you sign the form it means that you agree to allow your child to join the study.

You will receive a copy of this signed document.

Parental/ Guardian Permission

By signing below you confirm you have the legal authority to sign for this child.

_____	_____	_____
PARENT/GUARDIAN (SIGNATURE)	PARENT/GUARDIAN (PRINT NAME)	DATE
_____	_____	_____
PARENT/GUARDIAN (SIGNATURE)	PARENT/GUARDIAN (PRINT NAME)	DATE

If you are unable to obtain parental permission from both parents/guardians, explain why not:

_____

Person Obtaining Consent

_____	_____	_____
PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT (PRINT)	DATE

Consent From Impartial Witness

If this consent form is read to the parent(s) because the parent(s) is blind or illiterate, an impartial witness not affiliated with the research or study doctor must be present for the consenting process and sign the following statement. The parent may place an X on the Parent Signature line above.

I agree the information in this informed consent form was presented orally in my presence to the parent(s) guardian(s) and the parent(s)/guardian(s) had the opportunity to ask any questions he/she had about the study. I also agree that the parent(s)/guardian(s) freely gave their informed consent for their child to participate in this trial.

_____	_____	_____
IMPARTIAL WITNESS (SIGNATURE)	IMPARTIAL WITNESS (PRINT)	DATE

Signature of Impartial Witness

If this consent form is read to the subject because the subject is blind or illiterate, an impartial witness not affiliated with the research or study doctor must be present for the consenting process and sign the following statement. The subject may place an X on the Participant Signature line above.

I agree the information in this informed consent form was presented orally in my presence to the **identified individual(s)** who has had the opportunity to ask any questions he/she had about the study. I also agree that the **identified individual(s)** freely gave their informed consent to participate in this trial.

Please indicate with check box the identified individual(s):

☐ Parent(s)/Guardian of the subject

_____	_____	_____
IMPARTIAL WITNESS (SIGNATURE)	IMPARTIAL WITNESS (PRINT)	DATE

Notification of My Child's Health Care Provider

Your child's health care provider will be notified of your child's participation in this study.

Leaving the Study Early

Signatures should be obtained in this section if the subject decides to leave the study early.

If you leave the study early the study leader will keep the data collected about your child up until the time you leave the study to help determine the results of the study.

Check one option below:

____ I am withdrawing my consent from the intervention or treatment part of this study but agree to continue to have follow up information about my child collected by the study team. The follow up information will be collected by:

- Obtaining information from my child's medical records

____ I am withdrawing my consent for this study. No additional information may be collected about my child including follow up information from my child's medical records.

Parental/ Guardian Permission

By signing below you confirm you have the legal authority to sign for this child.

_____	_____	_____
PARENT/GUARDIAN (SIGNATURE)	PARENT/GUARDIAN (PRINT NAME)	DATE

Person Obtaining Consent

By signing below you confirm that you have fully explained the implications of withdrawing from the study to the subject and have answered all their questions.

_____	_____	_____
PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT (PRINT)	DATE