COMIRB
APPROVED
For Use
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Study Title: Control Of Major Bleeding After Trauma (COMBAT): *A prospective, randomized comparison of fresh frozen plasma versus standard crystalloid intravenous fluid as initial resuscitation fluid*

Principal Investigator: Ernest E. Moore, M.D.
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This study is sponsored by the Department of Defense's Telemedicine & Advanced Technology Research Center (TATRC).

This consent form may have words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.

Some people in this study cannot make decisions for themselves because of their injuries. If you have been asked to decide for someone else whether they should be in this study, please read this consent form carefully. In this form, we use the words "you" and "your." If you are deciding for someone else, the words 'you' and 'your' refer to that other person, not to you.

You were placed in this research study based on your injuries or condition. You were not able to consent for placement in this study when it began due to your injuries. You were placed in this study under exception to informed consent rules. These rules were created by the FDA (U.S. Food and Drug Administration) and written in the 21 Code of Federal Regulations Section 50.24. In order, to obtain a Waiver of Consent, Federal Regulations require that 1) The study must look at a life-threatening health problem that needs urgent treatment. 2)The patient cannot give informed consent to be in the study due to their condition. 3) Because the dangerous health problem needs to be treated quickly, the treatment being studied must be given before a legally authorized representative (LAR) can be contacted. 4) The treatment being studied must also have potential for helping the patient.

Before starting this study, the researcher met the requirements to do this type of research. The study team talked with community groups throughout the Denver area and tried to inform as many people as possible through the media, advertisements, and social media.

At the time of this consent, you have already been placed into a group. With your permission, we will continue to test your blood and record your clinical measures. No other treatments will be given to you, only standard medical care. When you were

placed in this study, you were in a life-threatening condition that needed care right away and could not give your permission due to your injuries. Placement into the study and treatment happened before you or a family member could give permission. We could not obtain your permission before the trauma happened. This study could only be done with an exception from informed consent.

You are now being told that you are a part of this study. This is the earliest time we could inform you of this study. From this point forward, anytime during the study, you may stop being a part of the study. You will not lose any benefits, normal care, and/or assistance if you decide to stop being in this study.

Study Description

Thawed plasma is given to severe trauma patients in the hospital as the standard of care to treat bleeding. The purpose of this study is to see if giving thawed plasma earlier in the ambulance to trauma patients will help slow or stop bleeding. Usually we give trauma patients plasma in the hospital, but we want to see if giving plasma in the ambulance will help to slow or stop their bleeding.

One form of thawed plasma that is given to trauma patients is called AB-FP24. This study looks to see if giving AB-FP24 to severe trauma patients in the ambulance will limit blood loss compared to giving plasma in the hospital.

Despite advances in science, patients continue to die from bleeding because their blood will not clot. Severely injured patients, who are in shock after trauma, often have bleeding that is hard to stop, known as coagulopathy. Normally, we have proteins in the blood to form a clot and stop bleeding. One reason that trauma patients continue to bleed is that these proteins in the bloodstream are used up from the trauma. Plasma is a part of donated blood that contains these proteins. Plasma is often given to slow or stop bleeding.

You would get the standard of care if you were not enrolled in the study. The current standard of care for severe trauma patients begins with giving salt water to replace blood that was lost. Then, in the hospital, blood transfusions, thawed plasma, and more salt water are given as needed to support the body and help the blood to clot. Salt water does not help clotting and only replaces lost blood.

The doctors conducting the study hope that thawed AB-FP24 that is given during the ambulance ride will slow down or stop bleeding in severe trauma patients. In this study, the thawed AB-FP24 is given as soon as possible after the severe injury. After the thawed AB-FP24, we would give salt water, blood transfusions and more thawed AB-FP24 in the hospital as needed.

You are being asked to continue in this research study because you were severely injured in a traumatic event and your heart rate and critically low blood pressure (both signs of severe shock) met the criteria to place you in the study.

Procedures

Since you were placed in this study, your care has been changed in the following ways:

Starting at the scene of injury, you received the usual treatment for shock that occurs following trauma, including finding your vital signs and protection of your airway and spinal cord. Since you were placed in the study, your care had the following differences:

1. Before patients get to the hospital, patients are given intravenous (I.V.) fluid into their veins to support blood pressure. Since you are in this study, you were given either salt water or thawed AB-FP24 as the first I.V fluid. To decide which treatment you would get, we used a method of chance. This method is like flipping a coin. You were randomized to either the standard (salt water solution) or experimental (thawed AB-FP24) group. You had an equal chance of being in either group.
2. If you were assigned to the standard group, you received salt water as the first fluid in the ambulance. You were then treated as all trauma patients are treated at the hospital. The doctors who saw you at the hospital may have decided to give you a blood transfusion or thawed AB-FP24. If you were transfused, you received donated blood products. If you need further blood products, you will be given donated blood products. This is the standard of care for all patients who come into the hospital after a severe injury.
3. If you were assigned to the experimental group, you received 2 units AB-FP24 as the first fluid in the ambulance. After the thawed AB-FP24, the doctors at the hospital may have decided that you needed a blood transfusion, salt water or more plasma. If you needed or continue to need blood transfusions or thawed AB-FP24, donated blood products were and will be given.
4. At the time of this consent, you have been assigned to the standard or experimental group. There will be no more differences in treatment between the two groups. For both groups, blood samples were collected in the ambulance, in the emergency room, 2, 4, 6, 12, 24, 48, and 72 hours after injury and on days 5 and 7 of your hospital treatment.
5. We also put body sensors on your skin. Participating in this study will permit us to use the data from additional body sensors that you wore in the first 24 hours at the hospital. The sensors (pulse oximeters) recorded information about how your body was responding to bleeding. You will also allow us to use data from your medical records about how you were treated for this hospital visit.

If you agree to continue to be in this study, we will continue to collect blood samples as scheduled above. The laboratory tests done as part of the study are the same for both the standard and experimental groups. We will collect blood samples up to 10 times during your hospital stay, but some of them are already done. The most

amount of blood drawn for any one sample for research only will be approximately 8 teaspoons, for a total of 75 teaspoons of blood.

The study continues for 28 days after your injury. As with any part of this study, you do not have to have your blood drawn and can withdraw from the study anytime. The portion of the study involving the body sensor devices is for 24 hours only.

Continuation in this study

If you continue to be in the study, we will continue to watch you closely and record pertinent information during your hospital course for 28 days after your injury or until you leave the hospital. If you are discharged before 28 days after injury, we will contact you 28 days after your injury to see how you are doing.

Other people in this study

Up to 224 people from your area will be entered in the study over 5 years.

Discomforts and risks

Transfusion risks: In this study, AB-FP24 was the product transfused. Type AB plasma is the universal donor type. This means that the plasma and the blood type of the patient getting the transfusion do not have to match. Fresh Frozen Plasma (FFP) is taken from donors and frozen within 8 hours. We use AB plasma, called AB-FP24, that is frozen within 24 hours. AB-FP24 is almost the same as AB-FFP and works for trauma patients who need the clotting proteins after severe injury.

After receiving any blood products, patients may have a small increased risk of infection. They may also have a small increased risk of a transfusion related reaction. Both the thawed AB-FP24 in the experimental group and all blood products given as the standard of care in the standard group have these small increased risks. Most patients with severe injuries will require thawed plasma without being in this study. After getting any sort of blood product, the risk of infection is:

- 1 in 1,467,000 chance of HIV infection (human immunodeficiency virus),
- 1 in 8,300,000 chance of hepatitis A infection,
- 1 in 282,000 chance of hepatitis B infection,
- 1 in 1,149,000 chance of hepatitis C infection,
- 1 in 4,000,000 chance of malaria infection, and
- 1 in 2,990,000 chance of getting a human T-cell lymphotrophic virus infection (A virus that can cause leukemia or lymphoma)

<u>Other risks of blood transfusion include:</u>

- Fever, chills, or hives (1.1% to 2.5%),
- hemolytic transfusion reactions that occurs when the immune system of the patient receiving the blood transfusion attacks the cells in the transfusion of donated blood (1:1,250,000),
- transfusion-related lung injury (8.1 per 100,000), and
- transfusion associated circulatory overload, which occurs with rapid transfusion of a large volume of blood (2-3 per 100).

If you are enrolled and found to be pregnant and got thawed AB-FP24 from the study, there may be risks to the embryo or fetus. These risks are currently unclear.

The thawed plasma (AB-FP24) that is given in the experimental group is the same plasma that is given in the standard treatment. Again, the experimental group receives the AB-FP24 in the ambulance. The standard group receives salt water solution in the ambulance.

Venipuncture risk: In most cases, blood can be drawn from a line in your vein (I.V.) already placed as part of your standard medical care. In the event you do not have an I.V., blood will be drawn by placing a small needle in a vein in your arm to remove blood. Blood is typically drawn this way if there is no I.V. Risks related with drawing blood from your arm include slight pain, bruising, lightheadedness, and a very low risk of infection. In this study we will need to get about 75 teaspoons of blood from you over the entire study period. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

Risk of unplanned release of protected health information (PHI): There is also a risk that people outside of the study team will see your personal information. We will do all that we can to protect your personal information.

Risk of unexpected events: Your condition may not improve or may worsen while being a part of this study. You will be told of any major new findings that may affect your decision to remain in the study.

It is not expected that patients placed in this study will have a reaction to plasma transfusion. Plasma is usually given to severe trauma patients as the standard of care. This study focuses on the time period it is given.

Body Sensors Risks: There are no known risks to wearing sensors, but there may be some discomfort. The discomforts associated with a pulse oximeter may be felt if the sensor is on too tight. We can reapply the sensor so it doesn't feel too tight. It may leave small marks on your skin. These marks should go away after removing the sensor. We may use something sticky to keep the sensor on you which could make your skin itch. These sensors are made to be used on patients and don't bother most people's skin.

The study may include risks that are unknown at this time.

Benefits of the study

This study is intended to benefit you, but we cannot guarantee that your health will improve if you join this study or continue in this study. You have either received usual medical care or you have received the experimental treatment that includes early thawed AB-FP24. If you are in the experimental group, we hoped to decrease the amount of blood lost. In the end, we hoped to decrease the amount of blood products given to you. If you get less blood products, your risk of infection from donated blood may be lowered.

In both groups, we have tested your blood's ability to clot normally in the first 24 hours after your injury. We also monitored the amount of blood transfusions that you need. By doing these things, we may be able to treat you better by reducing the

amount of blood you lose. Other possible benefits include a decreased risk of organ failure and infection, a decreased number of days in the intensive care unit, and a decreased risk of death.

By taking part in this study, there is no guarantee that your health will improve. Also, there are risks as mentioned in the Discomforts and Risk section.

Wearing the body sensor devices is a procedure designed for the researchers involved in the study to learn more about how our bodies respond to bleeding. Allowing us to collect data is not designed to treat any illness or to improve your health. Also, there may be risks, as discussed in the section describing the discomforts or risks.

Alternative treatments

At the time of this consent, you have already been given the standard or experimental treatment. From now on, you will receive the standard treatment given to all trauma patients. However, we will continue to collect blood samples for up to 7 days after your admission to the hospital. We will collect clinical data up to 28 days after injury. As an alternative, you may refuse to continue follow up in this study. If you refuse to continue follow-up, you will still get the standard medical care.

Who is paying for this study?

The COMBAT Study is being paid for by the Department of Defense. The use of the body sensors is being paid by a separate grant to Flashback Technologies from the Department of Defense. The data gathered from this device may be used to develop a commercial product. Currently, this device is not approved by the FDA. The product would be based on technology invented by Dr. Moulton, a co-investigator of this project, and assigned to the Regents of the University of Colorado. Flashback Technologies Inc. has licensed the technology from the University of Colorado, and Dr. Moulton has an equity interest in Flashback Technologies. If a commercial product is developed, Dr. Moulton, Flashback Technologies Inc., and the University of Colorado could gain financially by selling the product.

One of the investigators in this study (Dr. Moore) as well as the University of Colorado own intellectual property that is related to this study. As this may represent potential or perceived conflicts of interest (COI), management plans have been put into place to minimize the possibility that any COI will influence the outcome of the study.

Payment for being in the study

You will not be paid to be in the study.

Cost to you

It will not cost you anything to be in the study and you will not be charged for laboratory tests done only for this study.

Continuing participation

Continuing to take part in this study is up to you. You have the right to choose not to continue in this study. If you decide to withdraw, you will not lose any benefits or rights. You will also still get the standard medical care given to all trauma patients. At this point, study treatments are done. Your continued participation would mean that blood samples will be collected from you if you are still in the hospital. Your clinical results would be monitored until 28 days after injury.

You were enrolled in the study under the federal rules for emergency research, 21 CFR Section 50.24. These rules require the study team to inform the public about the study and get feedback from the community before the study begins. People have the choice to "opt out" or not be placed in the study. They can do this by wearing a study bracelet or study necklace. This tells the ambulance crew at the time of your injury to not to place you into the study. Since this study is being done on severely injured patients, there is a chance these things may not be found on the patient. To the best of our knowledge, you were wearing neither a study bracelet nor a study necklace when you were enrolled in the study.

If you do choose to continue to be in the study, you have the right to stop at any time. The only treatment that you will lose is the care you are getting as part of this study.

If there are any new findings during the study that may affect whether you want to continue to participate, you will be notified about them.

Removal from this study

The study doctor may decide to take you out of the study without your permission. The infusion of the AB-FP24 may have been stopped if the study team found out you did not want to be enrolled, you refused blood products, or you had a major transfusion reaction. Also, the sponsor, Department of Defense's Telemedicine & Advanced Technology Research Center (TATRC), may stop the study at any time.

Injury from the study

If you have an injury while you are in this study, you should call Ernest E. Moore, MD immediately. His phone number is 303-602-1820. We will explore to see if the injury was due to the study. We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

If you have questions

You may have questions about your rights as a patient in this study. If you have questions, concerns, or complaints, you may call Ernest E. Moore, M.D. at (303) 602-1820. You will be given a copy of this form to keep.

You can also call the Institutional Review Board who approved this study (COMIRB) at 303-724-1055. COMIRB (Colorado Multiple Institutional Review Board) is a group of people not related to the study. They make sure the patients placed in the study have the lowest risk of harm from the study as possible.

A description of this study will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can access this website at any time.

You may also access a website specific to the COMBAT study. It will provide information as well as a forum for comments and questions. Links to this website will be accessible via the Denver Health website (http://denverhealth.org/COMBATStudy).

Optional Consent and Authorization for Data and Blood Banking for Future Research

Dr. Ernest E. Moore would like to keep some of the data and blood that is taken during the study but is not used for other tests. If you agree, the data and blood will be kept and may be used in future research to learn more about trauma related illnesses. The research that is done with your data and blood is not designed to especially help you. However, it might help people who have a traumatic injury in the future. Reports about research done with your data and blood will not be given to you or your doctor. These reports will not be put in your health records. The research using your data and blood will not affect your care in any way.

The choice to let Dr. Moore keep the data and blood for future research is up to you. No matter what you decide to do, it will not affect the care that you will receive as part of the study. If you decide now that your data and blood can be kept for research, you can change your mind at any time and contact Dr. Moore to let him know that you do not want your data or blood used any longer, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until Dr. Moore decides to destroy them.

When your data and blood are given to other researchers in the future, Dr. Moore will not give them your name, address, phone number or any other information that will let the researchers know who you are.

Sometimes data and blood are used for genetic research (about diseases that are passed on in families). Even if your data and blood are used for this kind of research, the results will not be told to you and will not be put in your health records. Your data and blood will only be used for research and will not be sold. The research done with your data and blood may help to develop new products in the future, but there is no plan for you to be paid.

The possible benefits of research from your data and blood include learning more about what causes illnesses in trauma patients, how to prevent them and how to treat them. The greatest risk to you is the release of your private information. Dr. Moore will protect your records so that your name, address and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any data or blood collection and storage by Dr. Moore.

The data and blood collected from you during this study are important to this study and to future research. If you join this study:

- The data or blood are given by you to the investigators for this research and therefore no longer belong to you. However, if you take back your permission to use your data and blood, we will no longer use your data or blood in research.
- Both the investigators and any sponsor of this research may study your data and blood collected from you.
- If data or blood are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or IRB approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to get any financial benefit from the creation, use or sale of such a product or idea.

Storage of Data and Blood

Please read each sentence below and think about your choice. After reading each sentence, circle "yes" or "no." If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and future use of your data and blood, you may still take part in the study.

I give my permission for my data and blood to be stored in a central tissue bank at DHMC for future use by the study investigators:

1. I give my permission for my data and blood to be kept by Dr. Moore for use in future research to learn more about how to prevent, detect, or treat trauma-related illnesses.

☐ **Yes** ☐ **No** **_____Initials**

2. I give my permission for my data and blood to be used for research about other health problems (for example: causes of heart disease, osteoporosis, diabetes).

☐ **Yes** ☐ **No** **_____Initials**

3. I give my permission for my study doctor (or someone he or she chooses) to contact me in the future to ask me to take part in more research.

☐ **Yes** ☐ **No** **_____Initials**

Who will see my research information?

The University of Colorado Denver and the hospital(s) it works with have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- The Children's Hospital

- Denver Health and Hospital Authority

The Children's Hospital of Colorado shares a medical record system with the Barbara Davis Center and PedsConnect; therefore, it is also possible that your information could be viewed by healthcare professionals at these organizations.

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the University of Colorado Denver and its affiliate hospitals may not be covered by this promise.

We will do everything we can to keep your records a secret. It cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Primary Investigator, at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Ernest E. Moore, MD
655 Broadway, Suite 365
MC 1655
Denver, CO 80203
(303) 602-1820

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information.

- Federal offices such as the Food and Drug Administration (FDA) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team.
- Officials at the institution where the research is being conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research
- Representatives of the U.S. Army Medical Research and Materiel Command, who are authorized to review research records as part of their duty to protect human research volunteers. Research records will be stored in a way to protect your information and keep it confidential.

- Naval Medical Research Center to test samples without information that can identify you.
- Officials identified by the DoD, called the research monitor, who are in charge of making sure that we follow all rules for research.

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator. To ensure proper evaluation of test results, your access to these study results may not be allowed until after the study has been completed.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.).
- Portions of any previous and current Medical Records that are related to this study, including but not limited to Diagnoses, History and Physical, laboratory or tissue studies, radiology studies, procedure results, and clinical measures
- Hospital stay and Research Test records
- Blood samples and the data with the samples.

What happens to Data and Blood that are collected in this study?
Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data and blood collected from you during this study are important to this study and to future research. If you join this study:

- The data and blood are given by you to the investigators for this research and so no longer belong to you.
- Both the investigators and any sponsor of this research may study your data or blood collected from you.
- If data or blood are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or IRB approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

The investigator (or staff acting on behalf of the investigator) will also make *all*

or some **of the following health information collected from the body sensors about you available to:**

- Flashback Technologies
- The Department of Defense

This information may include a limited data set consisting of:

- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records
- Waveform data collected by the body sensors

NOTIFICATION OF PARTICIPATION AND OPTION TO CONTINUE

The investigator has placed you in this study without your consent using a process called, "Exception from Informed Consent Requirement for Emergency Research" (21 Code of Federal Regulations Section 50.24). These rules give us guidelines to study life-threatening health problems in human subjects who cannot give informed consent because of their life-threatening medical condition. These medical conditions require a treatment to be given to the patient before informed consent can be obtained from the patient or a legally authorized representative.

☐ **Option #1: I have been informed of the details of this study, have had the opportunity to ask questions about this study and have my questions answered. I choose to continue my participation in this research study and authorize the continued release of my medical records as stated in this consent.**

Initials_____

☐ **Option #2: I have been informed of the details of this study, have had the opportunity to ask questions about this study and have my questions answered. I choose to withdraw from this study and do not agree to any further data collection.**

Initials_____

HIPAA Authorization for Optional Additional Study Procedures

In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. If choose to continue to be in this study, I will get a signed and dated copy of this consent form.

_____
Printed Name of Patient

_____Date/Time:_____
Patient Signature:

_____
Printed Name of Legally Authorized Representative/ Proxy Decision Maker

_____Date/Time:_____
LAR/Proxy Signature:

Note: Proxy decision makers cannot consent for future research because there is no treatment decision involved in this portion of the study.

Consent form explained by:_____Date/Time:_____

Signature: _____

Witness Name: _____

_____Date/Time:_____
Witness of Signature ☐ Witness of consent process ☐

Check (if applicable):

Use of Short-form ☐ Non-English speaking ☐ Non-reading ☐

Investigator: _____Date/Time: _____
Investigator must sign within 30 days

☐This section applies if the patient is in police custody or incarcerated after study enrollment and before 28 days.

You have a choice about being in this study. Being in this study will not change your release date, your parole status, or your living conditions.

The federal government requires us to keep your information private. But if you give us information about child abuse, we will have to report that. If you give us information about someone hurting someone else, we will have to report that. If a court orders us to hand over your study records, we will have to hand them over to the court.

☐Option #1: I choose to continue my participation in this research study and authorize the continued release of my medical records as stated in this consent.

☐Option #2: I choose to withdraw from this study and do not agree to any further data collection.

_____

Printed Name

_____Date/Time:_____

Signature:

Consented by:_____Date/Time:_____