Part 1 of 2: MASTER CONSENT

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. You are being invited to take part in a research study. This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study this consent form includes two parts. Part 1 of this consent form is the Master Consent and includes information that applies to all study sites. Part 2 of the consent form is the Study Site Information and includes information specific to the study site where you are being asked to enroll. Both parts together are the legal consent form and must be provided to you.

We are giving this document to you to tell you about this research study. Please read and ask any questions you have. You may choose to not be in this study. That will not change how we care for you or your rights. You can stop being in this study at any time. The word "you" in this form refers to the person who will be in the study. Your legal representative will be asked to read and sign this consent form to give permission for you to participate, if you are unable to do so yourself

What is the purpose of this study?

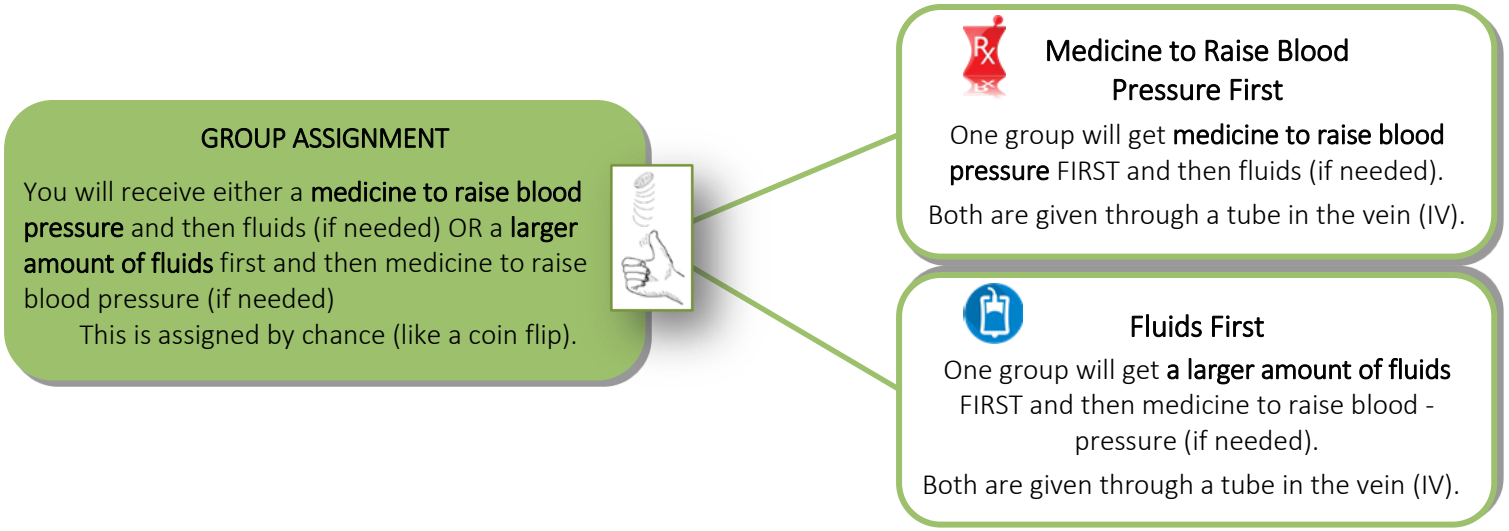
You are invited to take part in a research study of different ways to use "intravenous fluids" (fluids given through a small tube placed in your vein) and "vasopressors" (medicines used to raise blood pressure) to treat "sepsis," (a serious infection). This study is paid for by the National Institutes of Health. We are asking you to be in this study because: a) you have been diagnosed with low blood pressure due to an infection and b) your blood pressure has stayed low after your doctors gave you fluids. We do not know which approach is better in this situation: a) starting medicines to raise blood pressure first and then giving more fluids (if needed), or b) giving a larger amount of fluids first and then giving medicines to raise blood pressure if needed. Right now, the choice of approach is left to the doctors. Some doctors use medicines to raise blood pressure followed by extra fluids, and others use extra fluids followed by medicines to raise blood pressure. Some doctors use a combination of the two. This treatment part of the study will last for 24 hours, and then we will follow you until you go back to where you live. We want to find out whether one of these approaches compared to the other can improve a patient's chances of survival.

What will happen and how long will you be in the study?

We will ask up to 2,320 people with sepsis (a serious infection) to join this study in about 50 hospitals. Your hospital is one of these hospitals and could enroll as many as 50 or more people.

Before entering the study:

- If you are a woman who can have children, we will do a pregnancy test before you join the study. If you are pregnant, you may not join the study.
- You have received an amount of fluids through a tube placed in your vein. After getting these fluids you will be put into one of the two study groups (see below). You will be in that group for 24 hours. After 24-hours, your doctor will decide how the medicine to raise blood pressure and fluids will be given (if they are still needed). All other treatments, medicines (such as antibiotics), and procedures commonly used for this condition are allowed in this study based on the judgment of your doctors.



During the study:

- ☑ **We will talk with your doctors.** The research team will inform your doctors about you being in this study. You will receive all other medications (e.g. antibiotics) and treatments that your doctors decide you need. The study team and your doctors and nurses will work together to give you intravenous fluids and medicines to raise your blood pressure based on the treatment protocol that you are assigned to and based on your needs.
- ☑ **We will talk with you** or your designated representative to obtain information about your health and functioning.
- ☑ **We will review your medical record.** While you are in the hospital, we will look at your medical records or check on you to see how you are doing. We will collect information like your blood pressure, medical history, and test results. We may ask questions to you or your doctors if something is not clear. If you go to another health care facility, we may contact you or the health care facility to find out how you are doing.

- ☑ **We will contact you by telephone at 6 months** to see how you are doing and feeling. Each call will be less than 30 minutes. Contact information will be collected for you and up to 2 family members and/or friends. We may also call you at other points in the future to see how you are doing.
- ☑ **We will confidentially and securely** collect your social security number and personal information so we can stay in contact with you and know if you are alive by checking national registries.
- ☑ **We would like to understand how this treatment affects your subsequent medical care**. To do that, we need to obtain information about your health care use, costs and diagnoses. In order to do this, we will review records from your hospitalization, and in some cases, from your insurance providers.
- ☑ **We will collect some of your blood.** We will collect up to 3 tablespoons of blood at the start of the study. We will also collect up to 3 tablespoons of blood after 1 day, and then again after 3 days in the study. Some of the blood samples will be stored for future studies of serious illness and other conditions. Samples will be identified by a study number and not your name. Some of these samples may be released to other researchers, but they will have no way to identify you. Only your hospital study team and the Coordinating Center at Massachusetts General Hospital will know your coded study number. These numbers will be kept private.
- ☑ **We will check to see when you go home.** An important part of this study is to find out when after your illness that you leave the hospital. We will check on you at least weekly until you are discharged from the hospital to see how you are doing and feeling.

Side effects and risks that you can expect if you take part in this study:

- Risk of Getting Extra Fluids: Patients in the Fluids First group may get extra fluids through a tube in a vein. It's possible that this could cause stress on your heart related to extra fluid, breathing difficulties, or increased swelling in your arms and legs.
- Risk of Getting Medicine to Raise Blood Pressure: Patients in the Medicine to Raise Blood Pressure First group may receive earlier or more medicine to raise blood pressure. It's possible that this could cause not enough oxygen to the heart, heart rhythm problems, not enough oxygen to the intestines, or not enough oxygen to arms, legs, toes, or fingers. The chances of these problems may be higher if the medicines are used early or before a larger amount of fluids are given.
- Risk of Putting in a Larger Tube in a Larger Vein: Some hospitals may require use of a larger tube (a "central line") placed in a large vein (in the neck, chest, or groin) for giving medicine to raise blood pressure. Whether you do (or do not) participate in the study - you may receive such a tube if your hospital or doctors feel that it should be placed. We do not know if you being in the study will result in an increase, decrease, or similar rate of having a larger tube placed in your vein. There is a

chance that patients in the Medicine to Raise Blood Pressure First group will have this larger tube placed more often than patients in the Fluids Before Medicine study group, or than patients who do not participate in the study at all. Things that might happen to your body as part of placing such a tube in a large vein include infection, a punctured lung, or a tear in the vein. There is also a small chance of the tube going into an artery instead of a vein by accident.

- Risk of receiving medicines to raise blood pressure through a tube in a vein in your arm: Your doctors may decide to use a tube in your arm instead of a larger tube in your neck, chest, or groin vein to give the medicines to raise blood pressure. Giving these medicines this way is permitted in this study and will vary based on local hospital policy or the preference of your doctors. This may happen in either group but may be more likely in the Medicine to Raise Blood Pressure First group. The risk of getting these medicines through a tube in an arm vein is leaking of the medication into the tissues in your arm. This can cause tissue damage and pain.
- Risk of Death We do not know whether your risk of dying from your serious infection will be changed by choosing to be in this study.
- Blood draws: There are no major risks associated with drawing blood. We will usually take blood from tubes that are already in your vein or artery. If you do not have a tube in a vein or artery, then we will get the blood from a normal blood draw. You may experience minor discomfort, bruising or soreness from the needle. Sampling from a needle very rarely causes infection. Blood draws will be done by a trained professional.
- Confidentiality: Participation in research may cause you to lose some privacy. Your health information will be handled as securely as possible.

Risks that are not known

We do not know whether your risk of dying will be higher or lower if you choose to be in this study. Although both fluids through a tube in a vein and vasopressors are commonly used in the care of this condition, there is always the chance of unknown side effects of either treatment group. If we learn something new that affects the risks or benefits of being in this study, we could change the study plan. If that happens, we will make sure you are told about this new information while you are in the trial

Good effects that might result from this study

We do not know whether giving medicines to raise blood pressure first before additional fluids, or a larger amount of fluids before medicines to raise blood pressure will make your recovery better, worse, or the same. Your participation in this study will help us learn more about treating patients like you and may help other patients in the future.

Other treatments you could get if you decide not to be in this study

Taking part in this study is voluntary. You will receive the care your doctors feel is best, whether or not you join the study.

Payments for your time spent taking part in this study or expenses

You will receive a small gift card as a token of appreciation for completing the follow-up calls after you are discharged from the hospital.

Reasons why the study doctor may take you out of this study

The study team/doctor may take you out of this study if it is in your best interest. This decision may be based on new information about your condition or the study risks and benefits.

What will happen if you decide to stop being in this study?

You can stop being in this study at any time. If you decide to stop, tell your study doctor. Deciding to not be part of the study is completely up to you. This will not affect the care you receive.
If you stop being in the study, we will store your blood samples unless you request they be destroyed. We will continue to collect information from your medical record unless you ask us not to. We will give you any new information that may affect your decision to stay in the study.

Clinical Trials Registry

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

Confidentiality

The Coordinating Center at Massachusetts General Hospital (MGH) or other hospitals involved in this study may share your study information, without anyone knowing it is related to you specifically, with others or use it for other research projects not listed in this form. It is possible that other researchers may contact you in the future regarding potential participation in other studies and/or to see how you are doing. Other hospitals involved in this study, MGH, and their staff will comply with any and all laws regarding the privacy of such information. Your personal information will not be shared. There are no plans to pay you for the use or transfer of this de-identified information.

We have obtained a Certificate of Confidentiality from the National Institutes of Health (NIH). This keeps us from being forced to release study information as part of a court, legislative, administrative or other proceeding.
There are times when the Certificate cannot be used. For example, we cannot refuse to give information to government agencies that oversee or fund research, such as the NIH, Department of Health and Human Services (DHHS) or Food and Drug Administration (FDA).

The Certificate also does not stop us from giving information to government agencies, law enforcement personnel or others if we suspect you or someone else is in danger. The Certificate does not keep you from giving out information about yourself and your treatment in this study. We can release some study information, such as lab test results, if you wish us to do so and you give permission in writing. If you would like to read the Certificate or you have any questions, please ask the study doctor or study staff.

Part 2 of 2: STUDY SITE INFORMATION

Site Name:	**<< insert name of organization>>**
Site Principal Investigator:	**<< insert name & credentials of responsible PI >>**
Site Principal Investigator Contact:	**<<insert 10-digit phone for PI>>**

This part of the consent form includes information about the site that is asking you to participate in this study and is specific to participation at your site only. Before making your decision, both the site-specific information and the general study information should be reviewed with you. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Costs to you if you take part in this study:

<<Brief description of costs to participants. Only include if different than costs as described in the main consent document. >>

If you agree to take part in this research study, you and/or your insurance will not have to pay for the tests and treatments that are being done only for research. This includes the research blood tests, and time for the research staff to collect information.

However, you and/or your insurance company are still responsible for paying for the rest of the care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

Payment in case you are injured because of this research study:

<<Please add any locally-required language for research-related injury. Only include if this is applicable>>

If it is determined by your hospital and the researcher that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided at your hospital to treat the injury. There are no plans for your hospital or the National Institutes of Health to pay for the costs of any additional care, or to give you money for the injury.

Who to call for any questions or in case you are injured:

*<<Please add any locally-required contact information outlining who participants should call in the event of any research-related injuries**. In addition, the following paragraph MUST REMAIN in this section when Vanderbilt University Medical Center IRB is the IRB of Record.** Only include if this is applicable>>*

If you should have any questions about this study or if you feel you have been hurt by being a part of this study, please feel free to contact (INSERT NAME OF RESEARCHER) at (INSERT RESEARCHER'S PHONE NUMBER) or (INSERT IF EMERGENCY CONTACT IS DIFFERENT FROM THE INVESTIGATOR). If you cannot reach the research staff, please page the study doctor at (INSERT INVESTIGATOR'S PAGER NUMBER).

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Medical Center Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Additional information about your local site:

<<Please insert any additional required language for your site, as applicable for this study. Examples may include, but are not limited to:

- *Local language regarding state law requirements for reporting of communicable diseases.*
- *Locally required language for any specific research procedures, e.g. commercialization of cell lines.*
- *Local conflict of interest disclosures.*
- *Additional site-specific confidentiality language>>*

- **Authorization to Use/Disclose Protected Health Information**

<<Please add any locally-required HIPAA Language. If your site requires separate HIPAA pages, delete this section and include your pages following this form. Only include if this is applicable>>

All efforts will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by _____. This includes data gathered for research studies that can be traced back to you. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, you are agreeing ("authorization") to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. [PI] and [HIS/HER] study team may share the results of your study and/or non-study linked information such as laboratory tests and x-rays, as well as parts of your medical record, to

the groups named below. These groups may include people from the Federal Government Office for Human Research Protections, the Vanderbilt University, _____ Institutional Review Boards, the Universities of Michigan and Washington (who will be doing the follow-up calls to you), and the Coordinating Center at Massachusetts General Hospital (MGH). Federal privacy rules may not apply to these groups. They may have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

Your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. [PI] in writing and let [HIM/HER] know that you withdraw your consent. [HIS/HER] mailing address is [ADDRESS]. At that time, we will stop collecting data about you. The data we stored before you withdrew your consent may still be used for reporting and research quality.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits.
You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally.
All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Participant

Participant's Name (Print):_____

Signature (If able to consent): _____ Date: _____/_____/_____

Surrogate

Legal Representative's Name (Print):_____

Relationship to Participant: _____

Signature:_____ Date: _____/_____/_____

Witness

(If Required) **Witness's Name** (Print):_____

Signature _____ Date: _____/_____/_____

Witness to: ☐ Discussion ☐ Signature

Study Representative Statement

I have explained the purpose of the research, the study procedures, the possible risks and discomforts, the possible benefits, and have answered all questions to the best of my ability.

Study Representative's Name (Print):_____

Signature:_____ **Date:** _____/_____/_____

Time Consent Obtained _____:_____ AM / PM

You will receive a copy of this form after it has been signed and dated.

CONSENT FOR GENETIC TESTING ON STORED SPECIMENS

The purpose of this study is to store samples of your blood. The purpose is to look for the genetic factors (such as DNA or RNA) that may cause or relate to severe illness or other diseases.

Description of the Procedures: An extra 1 teaspoon of blood will be drawn and stored for genetic testing purposes. The blood will be taken with other laboratory test samples so you will not get an extra needle stick. Your blood sample will be processed and may be tested and shared for research genetic testing. The sample will be sent to a repository at the NIH (National Institutes of Health). The NIH repository stores and distributes blood samples and associated data from people with many conditions. The purpose of sending your blood samples to the repository is to make samples available for future research by investigators not involved in this study. Researchers who use samples from the NIH repository must request and receive approval to do so from scientific reviewers at the NIH and from research oversight boards at their institutions.

Confidentiality of Your Blood Samples: We will freeze your samples and store them for years for future studies. We will protect your privacy and give all samples coded study numbers. Only your hospital study team will know your coded study number identity, which will be kept secure. The stored blood samples will not contain your name or identifying information.

How Long Will The Samples Be Stored: The samples will be stored for an unknown period time (usually years). The samples may be thrown away at any time when they are no longer needed. The results of tests run on your samples will not be recorded in your records and neither you nor your doctor will be told of the results. No one else, including relatives, doctors, or insurance companies can get the stored samples or results. Your samples will be used only for research and will not be sold or used directly to produce commercial products.

Risks: One possible risk might be the release of your name which could link you to the stored samples and/or the results of the tests run on your samples. This may cause problems with insurance or getting a job. You are currently protected from genetic discrimination by employers or insurance companies through the Genetic Information Nondiscrimination Act (GINA 2008). To protect you from this risk we will keep the link between the samples and your personal ID as secure as possible. This link will only be kept by the local study team. The NIH repository and future researchers will not have access to any of your personal information so they will not know who you are or be able to contact you.

Benefits: You will not receive any direct benefit from your samples. Information obtained from the tests may provide useful information, to help other patients, about the causes, risks, and prevention of severe illness and other diseases.

Voluntary Participation/Right to Withdraw Your Permission for Genetic Testing: Your decision to join this study is completely up to you (voluntary). Your decision will not change the quality of the care you receive. You are still eligible to join the study described in the other consent form even if you do not want your blood samples stored for genetic testing. At any time, you may ask to have your sample destroyed. You should contact Dr. *[PI]* in writing to have your sample destroyed and no longer used for research. We will not be able to destroy research data that has already been gathered using your sample. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

Costs or compensation of study: There will be no costs to you or compensation

Participant

Consent: Please *INITIAL* next to ***yes*** or ***no*** and **sign** your name, indicating you have freely given your answers and consent:

⇒ My blood sample may be stored for future genetic research in severe illness Yes_____ / No_____

⇒ My blood sample may be stored for future genetic research involved with other medical conditions (for example: obesity, diabetes, cancer, heart disease, Alzheimer's disease etc.) Yes_____ / No_____

_____ ___/___/_____
Signature (Subject OR Surrogate/Legally Authorized Representative) Date

_____ _____ ___/___/_____
Signature of Person Obtaining Consent Printed Name and Title Of Person Date

CONSENT FOR CONTINUED RESEARCH PARTICIPATION

You have been taking part in the research study: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (**CLOVERS**). Consent for your participation was obtained from your legal representative because you were unable to provide consent at that time. We are now asking for you to consent to continue being in the study. Your continued participation is entirely voluntary. If you decide not to continue in this study, it will not affect your relationship with your doctor or with _____ and will not result in any penalty or loss of benefits to which you are otherwise entitled.

STATEMENT OF VOLUNTARY CONSENT

I have read this form and the attached consent or have had them read to me. I have been told what to expect if I take part in this study, including risks and possible benefits. I have had a chance to ask questions and have had them answered to my satisfaction. I have been told that the people listed in this form will answer any questions that I have in the future. By signing below, I am volunteering to continue to be in this research study.

Participant's Name (Print): _____

Signature: _____ Date: ___/___/____

- My blood sample may be stored for future genetic research in severe illness _____YES/ _____NO
- My blood sample may be stored for future genetic research involved with other medical conditions (for example, obesity, diabetes, cancer, heart disease, Alzheimer's disease). _____YES/ _____NO

Witness

(If Required) Witness's Name (Print): _____

Signature: _____ Date: ___/___/____

Witness to: _____Discussion _____Signature

STUDY REPRESENTATIVE STATEMENT

I have explained the purpose of the research, the study procedures, the possible risks and discomforts, the possible benefits, and have answered all questions to the best of my ability.

Study Representative's Name (Print): _____

Signature: _____

Date: ___/___/____ **Time** Consent Obtained: ___:___ AM / PM_____

You will receive a copy of this form after it has been signed and dated