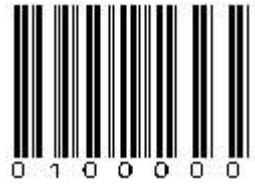

Medical Record Number: _____

Consent of an Adult to Be in a Research Study

In this form "you" means a person 18 years of age or older who is being asked to volunteer to participate in this study.

Participant's Name_____

Medical Record # _____

Principal Investigator:	Alexandra Kadl, MD University of Virginia Department of Medicine, Pulmonary and Critical Care PO Box 800738 1102 Pinn (formerly Jordan) Hall Charlottesville, Virginia, United States of America 22908 434-924-5210

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 signed copy of this form.

Why is this research being done?

The purpose of this study is to evaluate the effectiveness of an investigational drug called Midodrine, to help restore and stabilize blood pressure in patients with septic shock. Sepsis is a potentially life-threatening complication of an infection. Sepsis occurs when chemicals released into the bloodstream to fight the infection trigger inflammatory responses throughout the body. This inflammation can trigger a cascade of changes that can damage multiple organ systems, causing them to fail. If sepsis progresses to septic shock, blood pressure drops dramatically, which may lead to death.

When medicines are given through a vein (intravenously), over an extended period of time, patients can become more vulnerable to developing infections that may continually require administration of antibiotics. Researchers at UVa are also evaluating with this study, whether the addition of Midodrine to normal/standard of care for the treatment of low blood pressure,

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can help reduce the time that medicines are given through veins to increase blood pressure. Medicines used to keep blood pressure up are called vasopressors.

Potentially, if a medication is studied and found useful, for combating the symptoms noted above, then this might lower the time that central venous catheters have to stay in place, reduce the number of days a patient may have to stay in the intensive care unit (ICU), and perhaps reduce costs to patients.

Midodrine is approved by the U.S. Food and Drug Administration (FDA) for use in patients with a specific kind of low blood pressure called orthostatic hypotension. Midodrine, for this study, is being used to treat a different kind of blood pressure and is not approved by the FDA for use in this way.

You are being asked to be in this study, because you have septic shock and are receiving blood pressure supporting medications being given through your veins.

Up to 149 patients will be in this study at UVA.

How long will this study take?

Your participation in this study will take place while you are in the Medical Intensive Care Unit (MICU). If you agree to participate, the administration of the investigational drug or placebo (which does not contain any active medication) will include nine (9) doses over the course of 3 days.

What will happen if you are in the study?

SCREENING:

If you agree to participate, you will sign this consent form before any study related procedures take place. A member of the study team will review your medical records to make sure you are eligible and it is safe for you to participate.

In addition, if you are a female able to have children, you will have a urine pregnancy test, if this was not already done as part of standard medical care. This pregnancy test must be negative in order to continue study participation.

STANDARD MEDICAL CARE

You will continue to receive the standard medical care for septic shock (low blood pressure due to a bad infection) which includes IV antibiotics and IV medications given through your large veins to raise your blood pressure. As part of your medical care, nurses and medical staff will monitor

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your heart rate and blood pressure frequently. You will continue to receive standard medical care whether you are in the study or not.

Once the consent is signed and you are deemed eligible, you will receive 9 doses of the study drug or a "sugar pill" -type drug over the course of 3 days.

RANDOMIZATION and STUDY TREATMENT

You will be randomly assigned (like the flip of a coin) to 1 of 3 study groups. You have an equal chance of being assigned to either of the groups. Neither you nor your study doctor can choose which group you are assigned. This is a double blind study, which, means that neither you nor your study doctor will know which of the study groups you are assigned to. However, in the event of an emergency, the study doctor can find out.

GROUP 1: Standard medical care plus Midodrine 10mg three times a day for 3 days

GROUP 2: Standard medical care plus Midodrine 20mg three times a day for 3 days

GROUP 3: Standard medical care plus Placebo for 3 days

*For the remainder of this consent, we will refer to both Midodrine and Placebo as the "study drug"

STANDARD MEDICAL CARE for all groups

Group 1, Group 2 and Group 3 subjects will receive usual or standard medical care. Receiving midodrine or placebo will not change the usual medical care. How long you will be required to stay in the ICU, how long you stay in the hospital, how long you need IV medications to keep your blood pressure up, and how long you have a central venous catheter will be decided by your doctor based on your health and will not be determined by study participation. You will receive the same care you would normally receive even if you are not part of the study.

Your usual medical care involves continuous or frequent monitoring of blood pressure and heart rate, antibiotics and treatment with medications for increase your blood pressure given through a central venous catheter.

Note: If you cannot swallow the study drug in a pill form, it will be crushed and put into your feeding tube.

For all groups: You will be monitored and continue to be treated as part of your standard clinical care until you have recovered from your illness and are discharged from the hospital.

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For the purpose of this study, we will collect information from your medical record. Information about you will be recorded using a code instead of your name to protect your privacy. Some examples of the kind of information we want to collect about you for the study are: how you are doing with your treatments, what kinds of treatments you have while in the hospital, any side-effects you have to any of your treatment including the study drug, how many days you stay in ICU, and how many days you have to have a central venous catheter in place.

END OF STUDY:

Your participation in the study ends when you leave the hospital. Once you leave the hospital we will not collect any additional information about you for the study.

What are your and your legal guardian's responsibilities in the study?

You and your legal guardian have certain responsibilities to help ensure your safety.

These responsibilities are listed below:

- Your and/or your legal guardian must bring you to each study visit.
- You and/or your legal guardian must be completely truthful about your health history.
- Follow all instructions given.
- You or your legal guardian should tell the study doctor or study staff about any changes in your health or the way you feel.
- Ensure that the study drug is taken as instructed.
- Ensure that the study drug is taken only by you, the person for whom it has been prescribed.
- Answer all of the study-related questions completely.

What are the risks of being in this study?

Risks and side effects related to the Midodrine

Common, BUT NOT SERIOUS

- itching and/or rash which may involve your entire body in up to 15 out of 100 patients
- numbness and tingling in your hands or feet in up to 1 in every 5 patients
- problems with urination including pain or inability to urinate in up to 13 out of 100 patients

Rare but serious

- higher than normal blood pressure, requiring treatment outside of the study and stopping of the study drug. The frequency of this effect is unknown, although

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higher than normal blood pressure occurred in up to 7-8 patients out of 100 receiving this medication for another reason. Because this study is looking to raise blood pressure, it is believed that higher than normal blood pressure requiring additional treatment will be exceedingly rare.

- slow heart rate requiring treatment outside of the study and stopping of the study drug Midodrine. The frequency of this effect is unknown, although lower than normal heart rate not causing symptoms occurred in up to 15 out of 100 patients receiving this medication in a recent study. It is believed that lower than normal heart rate requiring additional treatment will be exceedingly rare.
- You may accidentally aspirate, or have the study drug or placebo "go down the wrong pipe" while it is being administered. Such an event may be insignificant but may sometimes result in severe inflammation of your lungs. This undesired event is not unique to the study drug but can occur with any swallowed drug, food or drink.
- Loss of confidentiality. Because under this study some of your personal health information will be stored, there exists a risk that this information may be unintentionally disclosed to persons outside of the study. This study's investigators are taking precautions to prevent such disclosure from occurring, which include storage of data in a secured location.

<u>All of the potential side effects of the study medication, should they occur, are expected to be temporary and reversible with discontinuation of the drug under study.</u>

<u>Pregnancy and Contraception</u>

There have been no studies about the use of Midodrine in pregnant women. We do not know if using Midodrine is safe or unsafe for a developing baby. As a precaution, you will not be allowed to participate if you are pregnant. Because midodrine is removed from the body fairly quickly, it is not expected to affect women who become pregnant after completion of the study.

Being in this study might hurt your unborn baby, so you will not be able to join or stay in the study if you are pregnant. If you have questions about birth control, please ask the study leader. If you are pregnant now, or get pregnant during the study, please tell us right away.

<u>Other unexpected risks:</u>

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

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Could you be helped by being in this study?

You may or may not benefit from being in this study. Possible benefits if you are placed in Group 1 or 2 include:

- Shorter stay in the ICU
- Shorter need for intravenous vasopressors
- Shorter need for central venous catheters.

You are not expected to receive any benefit from being in this study if you are assigned to receive the placebo (Group 3).

The information researchers get from this study may help others in the future.

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

You do not have to be in this study to be treated for your illness or condition. You can get the usual treatment for septic shock even if you choose not to be in this study. The usual treatment for sepsis would include:

- Medicines to keep blood pressure up (Intravenous vasopressors)
- Antibiotic therapy
- Usual medical treatment at UVa provided by ICU staff

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.

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 health insurance:

Up to 9 doses of midodrine (10 or 20 mg) or placebo three times daily.

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

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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.

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 you can normally get at the University of Virginia.

Even if you do not change your mind, the study leader can take you out of the study. Some of the reasons for doing so may include

a) Your study physician is concerned about your health
b) Your condition gets worse
c) The side effects of the study treatment are too dangerous for you
d) New information shows the study treatment will not work or is not safe for you
e) The study is closed for safety, administrative or other reasons

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 personal information be shared?

The UVa researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you 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 you:

- Personal information such as name, address and date of birth
- Social Security number ONLY IF you are being paid to be in this study

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

Who will see your 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
- Insurance companies or other organizations that may need the information in order to pay your medical bills or other costs of your 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 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.

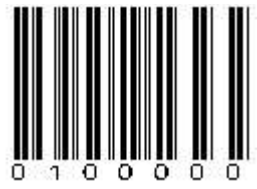
Some of the people outside of UVa who will see your information may not have to follow the same privacy laws that we follow. They may release your information to others, and it may no longer be protected by those laws.

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

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

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 you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation.



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

Please contact the researchers listed below 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 regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principle Investigator: Alexandra Kadl, MD
University of Virginia, Department of Medicine, Pulmonary and Critical Care
PO Box 800738, 1102 Pinn (formerly Jordan) Hall
Charlottesville, Virginia, United States of America 22908 Telephone: 434-924-5210

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.

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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 join the study. You will receive a copy of this signed document.

Consent From Adult

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

Person Obtaining Consent

By signing below you confirm that you have fully explained this study to the potential subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

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

Surrogate Consent

In the event the adult participant is unable to give informed consent for participation in this study:

_____/_____	_____
PERSON GIVING CONSENT FOR PARTICIPANT (Signature/ Printed)	DATE

RELATIONSHIP TO PARTICIPANT: _____

Person Obtaining Consent of the Surrogate

Medical Record Number: _____

By signing below you confirm that you have fully explained this study to the potential subject's surrogate, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

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

Consent From Impartial Witness

If this consent form is read to the subject's surrogate because the subject's surrogate 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's surrogate may place an X on the "Person giving consent for participant" signature line above.

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

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

Attending Physician Approval

I am the doctor that provides medical care for this subject. I believe that his/her health might be helped by being in this study. I approve his/her participation in this research study.

_____	_____	_____
ATTENDING PHYSICIAN (SIGNATURE)	ATTENDING PHYSICIAN (PRINT NAME)	DATE

Note: If the researcher is also the attending physician for the patient, they may also sign here as the attending physician.

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Person Obtaining Assent of the Adult Subject

The subject is unable to give assent due to the following reason:

_____

By signing below you confirm that the study has been explained to the adult subject, all questions have been answered and the adult subject has not demonstrated resistance or dissent by word or gesture to enroll in the study. You also confirm that if the subject demonstrates resistance or dissent at any point in the study that they will not be subjected to any additional study interventions.

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

Consent of the Participant to Continue to Be in the Study

Your legal representative gave his/her permission for you to be in this research study. This is because you were not able to make your own decision due to your illness. Your condition is now better. You are being asked to decide whether to continue to be in this study. The decision is up to you. Before you sign this form, please ask questions about any part of this study that is not clear to you. When you sign below, you are saying you understand the information we gave you about the study and in this form.

If you sign this form it means that you agree to continue being in the study.

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

Person Obtaining Consent of the Subject

By signing below you confirm that you have fully explained this study to the subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

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

Medical Record Number: _____

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):

☐ Subject
☐ Subject's surrogate

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

Notification of My Health Care Provider

☐ Your health care provider will be notified of your participation in this study.

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Leaving the Study Early

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

Consent From Adult

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

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