INFORMED CONSENT FORM

TITLE: A Randomized, Double Blind, Placebo-Controlled Trial To Investigate The Effects Of Vitamin C, Hydrocortisone, And Thiamine On The Outcome Of Patients With Sepsis.

NAME OF INSTITUTION: Community Medical Center

INSTITUTION ADDRESS: Community Medical Center
99 West Rt 37, Toms River, NJ 08755

NAME OF IRB: Community Medical Center IRB

IRB/EC APPROVAL DATE: June 12th, 2017

Introduction:

You are being invited to take part in a research study (also known as a clinical trial) of three drugs, ascorbic acid (Vitamin C), thiamine, and hydrocortisone. To allow you to make an informed decision as to whether or not you want to take part in this research study, this document describes the purpose of the study, your rights and obligations, the procedures needed by the study, and the possible benefits and risks of participating in the study. Please take time to read the following information carefully. Feel free to talk with your doctor, nurse, family, or friends before deciding. If you have any questions, you may ask your study doctor, Dr. Jose Iglesias, for more explanation.

Study Purpose:

This study has been created to compare the addition of intravenous (IV) vitamin C, thiamine, and hydrocortisone to the usual standard of care of sepsis and septic shock. Sepsis is a possibly life-threatening condition in which a patient may have organ dysfunction due to an infection. Septic shock is defined as low blood pressure and organ dysfunction that do not improve after administering IV fluids. Standard of care for sepsis and septic shock include early administration of IV antibiotics, IV fluids (sodium chloride), and vasopressors (medications used in the treatment of very low blood pressure) if need be to provide oxygen to vital organs.

A large amount of experimental data has shown that vitamin C and corticosteroids (hormones in your body that react in response to severe sickness) decrease the release of inflammatory substances which may lead to organ failure seen in sepsis. Vitamin C and corticosteroids also improve blood flow to vital organs and increase the body's ability to respond well to vasopressor medications used in septic shock. Low blood levels of both thiamine and vitamin C are common in sepsis. The study will be placebo

controlled, meaning one group will receive vitamin C, thiamine, and hydrocortisone, and the other will receive an inactive substance ("placebo"). The goal of the study is to compare the effects of receiving vitamin C, thiamine, and hydrocortisone (along with the standard sepsis care) versus placebo and standard sepsis care.

Who is sponsoring and conducting this research?

The research is not sponsored by any company and is being run independently by hospital practitioners.

Who has reviewed this research?

This study has been approved by the Institutional Review Board (IRB) of Community Medical Center, an organization that is responsible for protecting the rights and safety of participants who take part in research studies.

How many people will take part in the study?

Approximately 140 to 200 patients will take part in this study at this hospital.

What are my obligations if I take part in this study?

If you decide to take part in this study, you will be required to do the following:

- Inform study personnel about any symptoms you may have during or after administration of study medication
- Inform study personnel if you believe you might be pregnant
- Inform study personnel if you change your mind about participating in the study
- Inform your other doctors that you are taking part in this study
- Take the study treatment as instructed

How long will I be in the study?

You will be asked to receive an infusion of vitamin C, thiamine, and IV hydrocortisone or placebo immediately after you are enrolled in the study. Your total length of time in the study will be about 28 days, including screening, study drug dosing, and the follow-up period.

What will happen if I take part in this research study?

Screening assessments:

Before you begin the main part of the study, you will need to undergo the following tests or procedures to find out if you can be in the main part of the study. Some of these tests or procedures may be part of

your regular medical care and may be done even if you do not take part in the study. If you have had some of them recently, they may not need to be repeated.

- Discussion of this study and review and signing of this Informed Consent Form
- Recording of your demographic information, including your age, sex, and weight
- Review of your medical history
- Measurement of your vital signs
- Collection of blood for standard laboratory tests (including blood chemistry, blood cultures, and blood counts), and a pregnancy test if applicable
- Admitting diagnosis and possible site of infection

Study drug dosing:

You will be randomly assigned to one of the following drug dosing groups:

1. Treatment group

- Vitamin C 1.5g in Normal Saline 100mL every 6 hours for 4 days (or less if discharged from the ICU)
- Thiamine 200mg in Normal Saline 50mL every 12 hours for 4 days (or less if discharged from the ICU)
- Hydrocortisone 50mg/1mL every 6 hours for 4 days (or less if discharged from the ICU)

2. Placebo group

- Normal saline 100mL every 6 hours for 4 days (or less if discharged from the ICU)
- Normal saline 50mL every 12 hours for 4 days (or less if discharged from the ICU)
- Normal saline 1mL IV every 6 hours for 4 days (or less if discharged from the ICU)

If you are placed into the placebo group, you will not receive the test drugs (vitamin c, thiamine, and hydrocortisone). If you are placed into the treatment group, you will not receive the placebo. When you are "randomized" into the study, this means that you are put into a group by chance (like tossing a coin). Neither you nor your study doctor may choose the group you will be in. You will have an equal chance of being placed in either group. Neither you nor your study doctor will know which treatment group you receive. If your safety is at risk, your study doctor can find out which treatment group you are receiving. An IV line (needle in your vein) will be started for the administration of the study drug or placebo. The study drug or placebo will be administered to you intravenously.

Assessments during the study:

If the screening assessments show that you can be in the main part of the study, and you choose to take part, you will undergo the following tests and procedures at the following visit time points. Most of these tests and procedures are part of your regular medical care, but they may be done more often for this study.

- Admission order to ICU from attending physician for sepsis or septic shock

- Blood tests will be taken for the following:
    - Vitamin C level
    - Thiamine level
    - Procalcitonin
- Routine laboratory data for 4 days including:
    - Serum creatinine
    - White cell count (WBC)
    - Platelet count
    - Total bilirubin
    - PaO2/FiO2 ratio
    - Procalcitonin (repeated only on day 4)
    - Lactate level
- Review of blood culture results
- Assess for acute kidney injury through review of blood chemistry test
- Use of vasopressor medication will be recorded
- Assessments
    - Acute Physiology and Chronic Health Evaluation (APACHE) II and APACHE IV scores will be recorded upon admission, which are scores used in the ICU to predict patient outcomes
    - Daily Sepsis-related Organ Failure Assessment (SOFA) score will be recorded for the first 4 days to describe organ dysfunction or failure
    - Daily urine output (for the first 4 days)
    - Fluid balance after 24 and 72 hours
- Length of stay
    - ICU
    - Hospital
    - Discharge location
- 28-day follow-up via phone call from study doctor or study staff will review if you have had any health issues during your time in the study

Can I stop being in the study?

Yes. You can decide to stop participating at any time. Tell the study doctor if you are thinking about stopping or decide to stop. The study doctor will tell you how to stop safely.

The study doctor may stop you from taking part in this study at any time, even if you want to continue, for reasons that include but are not limited to the following:

- Your safety would be at risk if you continued in this study.
- You failed to adequately follow instructions or procedures.
- You need a treatment that is not allowed by the study.
- The study has been cancelled.

In any case, you will still continue to receive appropriate medical care for your disease.

What are the possible side effects or risks of being in the study?

You may have side effects from the drugs or procedures used in this study. Side effects can vary from mild to very serious, and they may vary from person to person. Everyone taking part in the study will be watched carefully for any side effects. However, the study doctor does not know all of the side effects that could occur.

Side effects known to be associated with Vitamin C:

Vitamin C has known to be tolerated well in doses much higher than those used in the treatment group of this study. One risk associated with intravenous vitamin C at high doses is the development of oxalate crystals which may form in the kidney and can affect its function at doses >40g per day (Buehner 2016). Patients who have a hypersensitivity to vitamin C will be excluded from the study.

Side effects known to be associated with Thiamine:

The safety of 400mg per day of thiamine is well studied and universally accepted. Side effects of intravenous thiamine may include flushing, nausea, sweating, itching, or weakness. Patients who have a hypersensitivity to thiamine will be excluded from the study.

Side effects known to be associated with Hydrocortisone:

Patients may experience sleep problems, mood changes, bruising or discoloration, increased sweating, headache, dizziness, nausea, stomach pain, heartburn, bloating, convulsions, and/or increased blood sugar. Patients who have a hypersensitivity to hydrocortisone will be excluded from the study.

Possible risks and discomfort associated with drawing blood:

During this study, small amounts of blood (approximately 2 to 3 tablespoons) will be drawn and used for tests that allow your study doctors to see how you are doing. Drawing blood may cause pain where the needle is inserted. There is a small risk of bruising or infection at the place where the needle is inserted. Some people experience dizziness, upset stomach, or fainting when their blood is drawn.

Possible risks with Placebo:

Some people in the study will get placebo instead of treatment medications. Placebo is a substance that looks like a drug but has no drug in it. Ask the study doctor or study staff if you have questions about placebo.

Possible risks with study drug infusion:

Treatment medications will be administered intravenously (IV). While IV's are used fairly frequently, they do run some risks, such as risk for infection or infiltration. Infiltration occurs when fluid infused escapes the vein and begins to swell the tissue around it. Since this can look dramatic quickly, it usually

noticed and treated. Should you see swelling start to occur at or around the IV site, please bring this to the attention of a nurse or a study doctor right away.

Other risks of study drug infusion include:

- Irritation of the vein. Your skin near the vein could become warm, swell, hurt, or get red.
- Damage to your vein.
- Damage to your skin or tissue around the injection site.
- Too much or too little of the study drug may be given to you.
- Increase or decrease in electrolyte levels (the amount of certain salts and other chemicals in your blood), causing health problems.
- A blood clot or an air bubble could form, which could block a blood vessel in another part of your body.

Some of these problems could be very serious.

Are there benefits to taking part in the study?

There is no guarantee that you will receive any benefits from this study. Taking part in this study may or may not cause your health to improve. Information from this study may help doctors learn more about vitamin C, thiamine, and hydrocortisone use in sepsis and septic shock. This information may benefit other patients with sepsis and septic shock in the future.

Will I be told about new information?

During the study, you will be told in a timely manner about new information or changes in the study that may affect your health or your willingness to continue in this study. When informed of this new information, if you agree to continue in the study, you, or your legally authorized representative will be asked to sign an updated consent form.

What other choices do I have if I do not take part in this study?

Your other choices may include the following:

- Getting treatment or care for sepsis / septic shock without being in a study
- Taking part in another study
- Refusing treatment or care

Talk to your doctor about your choices, including the risks and benefits of each choice, before you decide if you will take part in this study.

Will I be paid if I take part in this study?

You will not be paid for taking part in this study. You and your family will not receive any financial benefits or compensation from or have rights in any developments, inventions, or other discoveries that might come from this study.

Will it cost anything to be in this study?

You or your health plan will need to pay for medicines and clinic, hospital, and doctors' services that are part of your regular medical care. Some health plans will not pay these costs for people taking part in research studies. Your study doctor can check with your health plan to find out what they will pay for. After your participation in the study ends, you and your health plan will need to pay for medicines and clinic, hospital, and doctors' services that are part of your regular medical care.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Dr. Jose Iglesias, if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him at (609) 978-9940.

You will get medical treatment if you are injured as a result of taking part in this study. Your study doctor will explain the treatment options to you and tell you where you can get treatment. Neither Community Medical Center nor the study doctor will pay for this medical treatment, and you will not receive any other kind of payment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose to either take part or not take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

If you agree to participate in the study, your study doctor will inform your regular doctor about your participation in the study.

Will my health information be kept private?

Patient information:

As part of this research study, your study doctor, study staff, and Community Medical Center will collect and record data about you. These data will include medical and personal information about you, such as information about your general health, how you have responded to the study drug, any side effects you may have experienced, and the results of any tests performed during the study. The information collected about you will be held by Community Medical Center. If information from this study is

published in medical journals or presented at scientific meetings, you will not be identified by name, picture, or any other personally identifying information.

Your medical and personal information will be kept as confidential as possible within the limits of the law. Your medical and personal information may be given out if required by law.

To help ensure that your health information is kept confidential you will be assigned a unique participant identification number. Your forms, records, and samples associated with this study will be labeled with this identification number; they will not be labeled with your name, picture, or any other personally identifying information.

The following people and groups of people may look at and/or copy your medical information to make sure that the study is being done properly, to check the quality of the data, and/or for research purposes:

- Community Medical Center monitors and representatives
- Community Medical Center's collaborators and licensees (people and companies who partner with Community Medical Center)
- The Institutional Review Board or Ethics Committee responsible for protecting the rights and safety of the participants who take part in research studies
- Regulatory health authorities (government agencies involved in keeping research safe for people)
- Qualified researches
    - Your medical and personal information may be shared with qualified researchers who are not participating in this study, for research purposes and to advance medical care and science. In such cases, additional steps will be taken to protect your information from being linked to you. Before receiving your medical and personal information, the researchers have to agree that they will use it for research purposes only and that they will not make any attempts to trace your information back to you.

If you agree, your family doctor may be told that you are taking part in this study.

Study results:

A clinical study report containing the results of this trial will be made available to anyone who requests a copy. Before this report is provided, additional steps will be taken to protect your information from being linked to you.

How will my health information be used and disclosed?

If you sign this consent form, you give permission to Community Medical Center to use or disclose (share) your health information that identifies you only for the purposes of this research study and for

research directly related to sepsis / septic shock or its symptoms, the use of intravenous vitamin C, thiamine and hydrocortisone therapy and/or the development of tests that help with detection or understanding of your disease. You do not have to sign this consent form, but if you do not, you may not take part in this research study.

The health information for which you are giving permission to be used and shared includes all health information about you that has been and will be created or received by Community Medical Center and that is in your medical record kept by Community Medical Center.

This health information about you may be used by and/or disclosed to study monitor, representatives, collaborators, and licensees, the Institutional Review board or Ethics Committee, and representatives of the FDA or other national and local health authorities. Your health information and data may be analyzed in any country worldwide. Those persons who receive your health information may not be required by federal privacy laws to protect it and may share your information with others without your permission, if permitted by laws that apply to them.

You have the right to see and get a copy of your medical records kept by Community Medical Center that are related to the study. However, by signing this consent form, you agree that you generally will not be able to review or receive some of your records related to the study until after the entire study has been completed, to protect the scientific integrity of the study.

Your authorization (permission) to use and disclose (share) your health information does not have an expiration date, but that use and sharing will only be for the purposes described in this consent form.

You are free at any time to limit Community Medical Center's use and sharing of your health information, without penalty or other consequence. However, you may not be allowed to take part or continue to take part in this research study if at any time you choose to limit Community Medical Center's use and sharing of your health information that is necessary for the completion of this research study.

You may change your mind and revoke (take back) this authorization at any time. If you revoke this authorization, no new health information will be collected about you. However, Community Medical Center will still be able to use and disclose any health information about you that has already been collected during this research study. To revoke this authorization, you must contact Dr. Jose Iglesias (see contact information in next section).

Federal law requires Community Medical Center to inform the Centers for Medicare & Medicaid Services (CMS, the agency responsible for administration of the Medicare program) when Community Medical Center is going to reimburse for patient injury expenses for treatment of an injury to Medicare

beneficiary. To comply with a Medicare reporting obligation, Community Medical Center's representative may need to collect and share with CMS certain personal information about you, such as your name, date of birth, sex, social security number, and Medicare ID number (if you have one).

Who can answer my questions about the study?

You can talk to your study doctor if you have any questions or concerns about this study, if you would like to withdraw your consent to take part in this study, or if you think you have been injured as a result of taking part in the study. Contact your study doctor, Dr. Jose Iglesias, at (609) 978-9940.

For questions about your rights while taking part in this study or if at any time during this study you feel that you have not been informed enough about your privacy rights about your health information, or you feel that the privacy of your health information has not been protected, you may contact the Risk Management Department at Community Medical Center, 99 Route 37 West, Toms river, New Jersey, 08755 or by calling 732-557-8032.

Signature

I understand that I will be given a copy of all pages of this form after it has been signed and dated. I have read it, or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this research study as described above and authorize Community Medical Center and Dr. Jose Iglesias to use and disclose (share) my health information as described in this Informed Consent Form.

Participant name (print)

If applicable – Name of participant's legally authorized representative (print) – Relationship to patient

Participant signature or signature of participant's legally authorized representative Date

I, the undersigned, have fully explained this informed consent to the participant named above and/or the participant's legally authorized representative.

Name of person conducting informed consent discussion (print)

Signature of person conducting informed consent discussion Date

Witness name[a] (print)

Witness signature[a] Date

[a] If the Principal Investigator or Institutional Review Board or Ethics Committee deems a witness signature is necessary.