Part 1 of 2: MASTER CONSENT

Name of participant: _____ Age: _____

***You are being invited to take part in a research study. This form will tell you about this study. Please read this form carefully and ask any questions you may have. This study is a multi-site study, meaning it will take place at several different places. 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 participate. Both parts together are the legal consent form and must be provided to you.***

**Key Information:**
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

## Key information about this study:

You are being asked to take part in this study because you have a severe infection (sepsis). In this study we are trying to understand whether acetaminophen (Tylenol) helps patients recover from sepsis compared to patients treated with a placebo (sugar water). Sepsis causes damage to red blood cells which can release a protein into the blood called hemoglobin. Hemoglobin can cause injury to the blood vessels and organs of patients with sepsis. In laboratory studies and in small studies of patients with sepsis, acetaminophen can stop some of the effects of hemoglobin. This may then limit injury to blood vessels and organs, and help people recover from sepsis.

Acetaminophen has been used many times in humans with good safety. Possible risks of acetaminophen include liver injury or lower blood pressure. You will be carefully monitored for these if you choose to participate.

If you agree to be in this study you could receive Tylenol or a placebo through an IV for up to 5 days while you are in the ICU. We will collect information from your medical record while you are in the hospital. Acetaminophen is not given to all sepsis patients outside of research, and if you do not join, your doctor will choose all therapies.

You may choose not to be in this study. If you choose not to be in the study, you will receive the medical treatment that you are receiving now and anything else that your doctors think might be helpful. You can stop being in this study at any time.

If we learn something while doing this study that could change the risks or benefits of you being in it, we will tell you so that you can decide if you want to stay in or join this study.

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.

**Detailed Information:**
The rest of this document includes detailed information about this study (in addition to the information listed above).

## What is the purpose of this study?

We are studying if acetaminophen helps people with sepsis. The study is paid for by the National Institutes of Health.

Sepsis can lower your blood pressure and worsen the function of your internal organs, including the lungs and kidneys. These effects of sepsis can be reversible (can be fixed). We are studying whether acetaminophen improves your blood pressure and/or the function of your lungs and kidneys.

If you agree to join the study, you will be assigned by chance (like a coin toss) to one of two groups.. One group gets acetaminophen intravenously (through a small tube in a vein) for 5 days. The other group gets a placebo (simple sugar water that does not contain acetaminophen) for 5 days. All groups will receive standard treatment for sepsis, including antibiotics, as directed by your treating physicians.

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

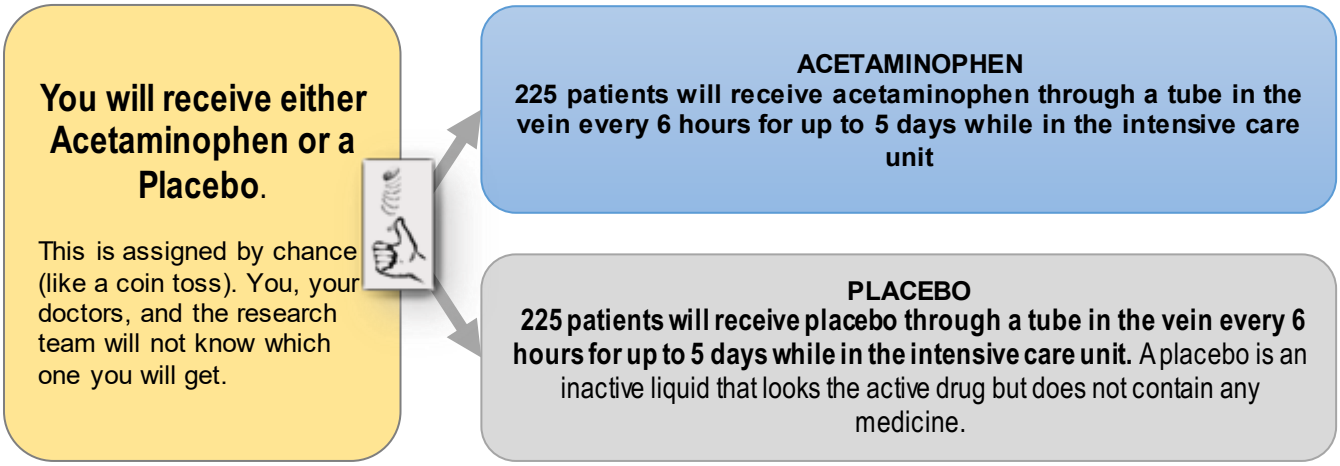
☑ **Overview:** We seek 450 people with sepsis to join this study in about 50 hospitals. Your hospital is one of these hospitals and expects to enroll 15 or more people. If you choose to participate in this study, you will be in the study for three months (90 days).

☑ **Review of your medical information:** First, we reviewed your medical information to ensure you are eligible to join the research study.

☑ **Pregnancy Check:** If you agree to join this study and are a woman who can have children, we will do a pregnancy test before you join the study, if your doctor has not already checked this as part of your normal care. If you are pregnant, you may not join the study.

☑ **Laboratory Tests:** We will check your liver function levels in your blood before you join the study, if your doctor has not already checked this as part of your normal care. If you already have very high liver tests you will not be allowed to join the study.

**If you are eligible to be in the study, and you agree to participate:**




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

**Acetaminophen: At high doses, acetaminophen can injure the liver,** especially in patients who already have liver problems. For your safety, we will monitor your liver tests and will stop the study medicine if your liver tests suggest that your liver function is worsening. Stopping acetaminophen usually results in liver tests returning to normal without permanent damage.

Less commonly, a**cetaminophen can lower blood pressure**. We will watch your blood pressure after each dose of the study medicine. If your blood pressure goes down too much, your doctors may treat the low blood pressure as part of regular clinical care.

An allergic reaction is possible but rare; most are mild, with very few allergic reactions being life threatening. If you develop an allergic reaction to acetaminophen, your doctors will treat it.

**Drawing Blood:** 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 with a needle. You may experience minor discomfort, bruising or soreness from the needle. Drawing blood through a needle very rarely causes infection. Blood draws will be done by a trained professional.

**Health Information Privacy:** To ensure your privacy, your health information will be handled securely by the participating hospitals, the Clinical Data Center at Massachusetts General Hospital and the National Institutes of Health.

**Risks that are not known:**

We do not know if your blood pressure will be higher or lower or if the function of your lungs and kidneys will be better or worse if you choose to be in this study. We also do not know whether your risk of dying will be higher or lower if you choose to be in this study. If you are in the group that receives acetaminophen, there may be unknown side effects. If you are in the group that receives placebo, you will not get the possible benefit of acetaminophen that this study is testing. If we learn something new that affects the risks or benefits of being in

this study, we will change the study plan as needed. We will also make sure you are told about this new information while you are in the study.

Also, because acetaminophen is being used in this trial, fever cannot be treated with this medication. If you develop a fever, other medicines and cooling methods will be used if your doctors feel your fever should be treated, which may be different from standard practice.

### Good effects that might result from this study

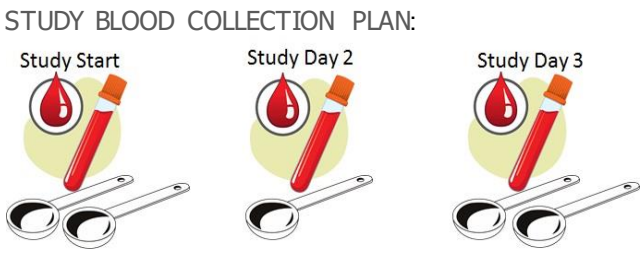
Early evidence suggests that acetaminophen may improve recovery from sepsis, although we are not sure of this. We cannot know whether acetaminophen will make your recovery better, worse, or the same. Your participation in this study helps us learn more about treating patients like you with sepsis and may help other patients in the future. The tests we do on your blood will not help you directly.

### During the study:

☑ **We will talk with your doctors.** The research team will tell your doctors about the study, and your doctors will decide on all of your additional treatments based on your needs.

☑ **We will review your medical record.** 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 collect some of your blood.** We will collect up to 2 tablespoons of blood at the start of the study. We will also collect up to 1 tablespoon of blood after 2 days, and then up to 2 tablespoons of blood 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 not have your name on them, and instead use a coded study number to protect your privacy. We will not include your name or other identifying information with the samples ever. Only your hospital study team and the research study Coordinating Center at Massachusetts General Hospital will know your coded study number. These numbers will be kept private.




☑ **We will collect some of your urine.** We will collect some of your urine (pee) three times during the study: at the start of the study, and on days 2 and 3. These samples will be labeled with a coded study number and kept private; the same as the blood samples.

☑ **We will monitor your liver function tests.** We will measure levels of two liver function tests at the start of the study, and then after 2, 3, 4, 5, and 7 days in the study. We do not anticipate that this will require an extra blood draw because this testing can usually be done in the clinical laboratory at your hospital on blood samples that your regular doctors are already sending. Rarely, this may require an extra blood draw. We are doing this because acetaminophen can affect the function of your liver.

☑ **We will check to see how you are doing in one month and in three months.** An important part of this study is to find out how you are doing after you leave the hospital. To make sure we can reach you, we will record your information, such as contact phone numbers and social security number. This information will be kept private.

- If you are still in the hospital, we will check on you in person or by telephone.
- If you are out of the hospital, we will contact you using the contact information you provide.
- If we cannot reach you, we will check hospital and national health records using the information you provide.

**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 you need whether or not you join the study or if you withdraw at any time. Acetaminophen is not given to all sepsis patients outside of research, and if you do not join, your doctor will choose all therapies.

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

The study doctor may take you out of this study if his/her judgment suggests that is better for you. 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 or a member of the study team. 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.

**Clinical Trials Registry**

A description of this clinical trial is available on www.clinicaltrials.gov, which will not include information that can identify you. Eventually, the Web site will include a summary of the study results but no personal information. You can search this Web site at any time.

**Privacy:**

Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

**Study Results:**

We will share the study results with you by letter within 3 months of the publication of the manuscripts reporting the results of the trial.