Informed Consent Document

PROCLAIM – A Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Efficacy and Safety of Misoprostol in the Prevention of Recurrence of *Clostridium Difficile* Infection in Adults

NCT03617172

June 23, 2021

Part 1 of 2: MASTER CONSENT

Name of participant: _____Age:_____

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.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether you still want to be in this study.

What is the purpose of this study?
You are being asked to take part in this research study because you were recently diagnosed with and treated for an infection caused by the bacteria *Clostridium difficile (C. diff)*.

C. diff is an infection that causes diarrhea and colitis (swelling of the colon). It is one of the most common healthcare-associated infections. *C. diff* infection (CDI) ranges in severity from mild diarrhea to severe colitis (sometimes resulting in septic shock and/or death). After treatment, CDI has a high chance of recurring (coming back). CDI recurs in about 25% of patient initially treated with standard of care therapy. The rate of recurrence increases with age. Once a first recurrence has occurred, the risk for future recurrences exceeds 40% with highest rates being in older adults. There are patients for whom the cycle of recurrences does not stop.

The purpose of this research study is to learn about how safe and effective the drug misoprostol is in preventing the infection from coming back. Misoprostol (Cytotec) is FDA approved to decrease the chance of getting stomach ulcers related to taking NSAIDS (nonsteroidal anti-inflammatory drugs, including aspirin). Misoprostol is investigational in this trial, meaning not FDA approved for *C. diff*.

About 440 people across the country will take part in this research study.

What will happen and how long will you be in the study?
This study is a randomized, double-blind, placebo-controlled study which means that you will either receive capsules containing the study drug, misoprostol, or placebo (capsules that do not have any study drug) that look like the study drug. Randomized means that no one can choose who receives the study drug and who receives placebo, so it is up to chance (like flipping a

coin). Double-blind means that you, the study doctor and the study team will not know which capsule you receive.

If you agree to be in this study your involvement will last about 10 weeks. Below you will find information and what you can expect if you agree to take part in this study.

In-person Visit 1 (2-7 days after you start standard treatment) – This visit will last about 1.5 hours and could take place at the study site or at your home. Home visits will be conducted by a study team member in your home. If available, the stool sample that you provided to your doctor when you were diagnosed with *C. diff* may be saved for future testing. The following will occur at this visit:

- The study team will discuss the study with you and answer all your questions.
- The study team will discuss your medical history with you.
- The study team will confirm that you no longer have *C. diff* symptoms.
- If you are a woman who could become pregnant, a urine pregnancy test will be collected to make sure you are not pregnant. The study team will also discuss birth control options with you.
- A physical exam will be done by either a study physician or other health care professional approved by the study.
- You will have your blood drawn (about 4 teaspoons).
- A stool sample will be collected (if you are unable to provide a stool sample, you will be asked to provide a rectal swab).
- You will complete a symptom questionnaire and a quality-of-life questionnaire.
- You will be placed into either the study drug (misoprostol) or placebo group.
- You will receive the study drug to take along with an at home stool/rectal swab collection kit with instructions
- The study team will discuss the study diary with you and provide you with the diary to also take and return to us.

Start of Study Drug (Day 7 of your standard treatment, or approximately 7-10 days after a positive lab test) - You will begin taking the study drug on Day 7 of your standard treatment if you are on a short course of antibiotics, otherwise you will begin taking the study drug 7-10 days after receiving a positive CDI lab test. If you have already completed the in-person study visit 1, the study team will contact you to remind you to begin the study drug and to answer any questions that you have. The study drug should be taken with food. You will take 2 study drug capsules 2 times a day for 14 days. You will record information daily in your study diary about when you took the study drug and the appearance of your stool which is important for the study.

Follow Up Phone call 1 & 2 (3 days and 7 days after starting the study drug) – The study team will call you to ask how you are feeling and to complete the symptom questionnaire and

quality of life questionnaire with you. If you prefer, the quality-of-life questionnaire can be sent to you as an email link to the survey as well. During the call they will also ask if you have been taking the study drug, completing the study diary and will answer any questions that you have. The study team will also remind you to return your diary back after you have taken your last dose of study drug.

Follow-Up Phone calls 3 – 9 (starting after you have stopped taking the study drug) – The study team will contact you every week to ask how you are feeling and to complete the symptom questionnaire and quality of life questionnaire with you unless you have chosen to complete the quality-of-life questionnaire as an electronic survey.

In-person Visit 2 (Day 62 of study) – This visit will last about 1.5 hours and could take place at the study site or as a home visit conducted by a study team member in your home. The following will occur at this visit:

- The study team will discuss how you are feeling.
- You will have your blood drawn (about 4 teaspoons)
- A stool sample will be collected (if you are unable to provide a stool sample, you will be asked to provide a rectal swab).
- You will complete a symptom questionnaire and a quality-of-life questionnaire.

***C. diff* Recurrence Visit (if applicable) –** If you have any diarrhea (loose/water stool) or if your doctor has confirmed that the *C. diff* infection has come back during the study, you will be asked to come in for a study visit or have a home visit and provide a stool sample or swab. If multiple recurrences occur, the study team may ask you to come back for each recurrence. The following will occur at this visit:

- The study team will discuss how you are feeling.
- You will have your blood drawn (about 4 teaspoons)
- A stool sample will be collected (if you are unable to provide a stool sample, you will be asked to provide a rectal swab).
- You will complete a symptom questionnaire and a quality-of-life questionnaire.

If you are unable to complete an in-person visit, please contact the study team so that the stool sample/rectal swab, which will be in your take home kit, can be picked up at your home.

Side effects and risks that you can expect if you take part in this study:
Side effects associated with the use of misoprostol:
Common side effects:

- Diarrhea (loose or watery stool)
- Stomach pain

Misoprostol capsules taken as an FDA-approved treatment for other conditions, have been known to cause diarrhea, stomach pain, and/or nausea in some people, when given at higher doses than the dose being given in this study. In most cases these problems developed during the first few weeks of therapy and stopped after about a week. In this study, you will be only be taking the study medication for 14 days. However, you can minimize possible diarrhea by making sure you take Misoprostol capsules with food and avoiding magnesium containing antacids. Because these side effects are usually mild to moderate and usually go away in a matter of days, most patients can continue to take Misoprostol capsules. **If you have long-lasting difficulty (more than 8 days), or if you have severe diarrhea, cramping and/or nausea, call your doctor or study team immediately**. If symptoms continue the study doctor may reduce the dose to 1 capsule twice a day after speaking with the study team.

Misoprostol Pregnancy Risks
You cannot be in this study if you are pregnant or breastfeeding. If you are pregnant or become pregnant during the study, the study drug may cause harm to your unborn child. The study drug, misoprostol, can cause birth defects, pregnancy loss, and premature birth.

If you are a female, you must not get pregnant while in this study or for one month after the study is over. The only certain way to not get pregnant is to not have sex. It is important to follow the approved birth control options below for pregnancy prevention if you are a woman of childbearing potential (able to get pregnant):

- Condoms with spermicide
- Condoms with diaphragm
- Diaphragm with spermicide
- Intrauterine device (IUD) with a documented failure rate of less than 1% per year
- Oral, injectable, or implanted hormonal contraceptives used in combination with an additional double barrier method such as condom or diaphragm with spermicide.

If you become pregnant during the study, stop taking the study drug immediately and call your study doctor right away.

Other Possible Risks Associated with Taking Part in this Study

Blood draw: The risks of having your blood drawn include discomfort from the needle stick, bruising, bleeding, and rarely, infection.

Stool swab collection: You may experience some discomfort with this collection, there is also a risk of getting stool on your skin or clothing during collection.

Risks that are not known:

Because this treatment is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time.

Good effects that might result from this study:

a) The benefits to science and humankind that might result from this study: The results of this research may guide the future treatment of *C. diff* infection and science may gain further the understanding of why this infection sometimes comes back after treatment.
b) The benefits you might get from being in this study: There is a chance that by taking part in this study you may be less likely to experience a recurrence of *C. diff* infection if you are randomized to the study drug. If you are randomized to the placebo group then it is unlikely you will experience any benefits.

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

You do not have to take part in this study to receive treatment. There are other options that may prevent *C. diff* from coming back. You can discuss these other options with your study doctor.

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

You will be taken out of this study if the study doctor determines that it is no longer in your best interest to be in the study. If you are taken out of the study, you will be told the reason.

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

If you decide to stop being part of the study, you should tell your study doctor. Deciding not to be part of the study will not change your regular medical care in any way.

Clinical Trials Registry:

A description of this clinical trial will be available on 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 search this Web site at any time.

Confidentiality:

All efforts, within reason, will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. The study results will be kept in your research record for at least six years after the study is over or as long as we need the information for the study. All the information on paper will be locked in a secure location. Any information kept on a computer will be through REDCap (an electronic data management system), which has many safeguards. Only members of the study team will be able to see any of the information that would identify you. Any research data entered into your medical record will be kept as long as it is needed.

This study receives support from the National Institutes of Health (NIH). Therefore, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.