Informed Consent Template Document

Study Title: Randomized Master Protocol for Immune Modulators for Treating COVID-19

NCT Number: Pro00106301

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IRB Approved Template
MUST BE APPROVED
FOR SITES BEFORE USE
AS MODIFIED
Dec 31, 2020

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

TITLE: Randomized Master Protocol for Immune Modulators for Treating COVID-19

PROTOCOL NO.: ACTIV-1 IM
WIRB® Protocol #20202874

SPONSOR: Daniel K. Benjamin, MD, MPH, PhD

INVESTIGATOR: Name
Address
City, State Zip
Country

STUDY-RELATED PHONE NUMBER(S): Phone Number
Phone Number (24 hours)
[24 hour number is required]

Key Information

This form is for use in a research study that may involve participants who may or may not have the capacity to consent to take part in the study. When the participant cannot legally consent to take part, pronouns “you” and “your” should be read as referring to the participant rather than the person (legally authorized representative) who is signing and dating this form for the participant. In cases where the participant’s representative gives consent, the participant should be informed about the study to the extent possible given his/her understanding. During the course of the study, if the participant regains the capacity to consent, informed consent will be obtained from the participant and the participant offered the ability to leave the study if desired.

Summary

PURPOSE	This is a research study and your participation in this study is voluntary. The purpose of this study is to evaluate the ability of various experimental drugs to improve health outcomes for people hospitalized with COVID-19. We also want to see if these study drugs are safe to use, and if these study drugs can stop the disease process and prevent you getting sicker. This study is designed to quickly identify safe and effective drugs that may treat COVID-19.

STUDY DRUG	Remdesivir (Veklury) is an anti-viral drug that is approved by the U.S. Food and Drug Administration (FDA) for use in treating adults and children 12 years of age and older weighing greater than 40 kilograms who have COVID-19 that is severe enough to require hospitalization. Use of remdesivir in the US is considered part of usual care for patients like you. Use of remdesivir in this study is investigational because this study includes the additional administration of a second study drug known as an immune-modulator drug. All study participants, except those with poor renal (kidney) function, may receive remdesivir as part of their usual care. Your providers may also include other medications to fight COVID-19 as part of usual care. In addition to the usual care, you will receive one of three immune modulators referred to as “study drugs” or its matching placebo. The three study drugs target inflammation, they include infliximab (Remicade), abatacept (Orencia), and cenicriviroc (CVC). A placebo looks like a “real” drug, but it does not have any active drug. You will be randomly assigned to receive either usual care (which may include remdesivir), plus one of the three study drugs, or usual care (which may include remdesivir), plus a matching placebo for one of the three study drugs. Approximately 75% of participants, or 3 out of 4, will receive active immune-modulator study drug and 25% of participants, or 1 out or 4, will receive matching placebo. You will know which of the three immune modulator study drugs to which you are randomly assigned, but you will not know whether you receive the active drug or the matching placebo. This study will test whether adding one of the three immune-modulator study drugs listed above to standard of care treatment including remdesivir is safe and effective for the treatment of COVID-19. The study drug you receive will be either an active drug or a placebo.
NUMBER OF PARTICIPANTS	2160

LENGTH OF STUDY	Your participation in the study will last for about 60 days (2 months). You will be seen several times during the first 29 days and contacted again 60 days after you enroll in the trial. During those 60 days you will not be allowed to enter any other clinical trial that studies treatments of COVID-19, with the exception of the ACTIV-4 trial. If your treating physician considers it appropriate, you will receive remdesivir for up to 10 days total. Depending on which immune-modulator study drug you are assigned to at random, the study drug or placebo will be administered up to a maximum of 28 days.
REQUIRED ACTIVITIES	If you are in this study, the following study procedures are required: • you will receive study drugs, • you will provide blood samples, • after you are discharged from the hospital, you may be asked to return to the clinic a few times for in-person visits for blood draws and assess your health. If you cannot return to clinic in person, a member of the study staff will call you for a telephone interview.
RISKS	There are some risks that are specific to the study drugs that you might receive. • Side effects of remdesivir are rare. The most common are allergic reactions (which may result in increase or decrease in blood pressure, increase or decrease in heart rate, rash or difficulty breathing), and effects on liver activity. • Participants receiving infliximab (Remicade) have a higher risk of getting infections including pneumonia and other infections caused by viruses, bacteria, or fungi. • The most common side effects with abatacept (Orencia) include headache, upper respiratory tract (airway) infection, nasopharyngitis (pain and inflammation in the nose and throat), and nausea. • The most common side effects with cenicriviroc (CVC) are gastrointestinal problems, joint pain, rash, vomiting, fever, joint swelling, abnormal physical weakness or lack of energy, contact dermatitis and increases in levels of liver enzymes. We will tell you more details about the risks in the second part of this consent form.
BENEFITS	If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you will receive no benefit from being in this study. Information learned from this study will help others who have COVID-19.

OTHER CHOICES	Instead of being in this study, you have the option of receiving: • treatment with prescription drugs available to you through your health care provider • treatment with other investigational drugs if you qualify • no treatment

This document may contain words and information that you do not understand. Please ask your study doctor or study staff to explain anything that is not clear to you. Please take time to read all the information carefully and talk about it with friends and relatives if you wish.

What is the purpose of this study?

SARS-CoV-2 is a new virus that has caused a widespread outbreak of an illness called COVID-19. In some people, it causes mild to moderate symptoms, like a “cold.” In others, this virus can cause pneumonia (an inflammation of the lungs), which can be serious and life threatening.

The Food and Drug Administration (FDA) has approved the use of remdesivir to treat adults and children 12 years of age or older weighing greater than 40 kilograms who have COVID-19 that is severe enough to require hospitalization. Remdesivir acts to block the growth of the virus, SARS-CoV-2 which causes COVID-19. Some people still get sicker even though they receive remdesivir. We think this may be due to an overactive immune response to the virus.

The study is designed to rapidly evaluate new therapies to treat the overactive immune response that has been observed in some COVID-19 patients. We are studying three different study drugs called infliximab (Remicade), abatacept (Orencia), and cenicriviroc (CVC). All three drugs target inflammation (overactive immune response) and have been studied in animals and people; however, none are approved by the FDA to treat COVID-19 and are considered investigational in this study. Two of the drugs, infliximab and abatacept, are approved by the FDA to treat other inflammatory medical conditions such as arthritis, bowel disease and severe skin disease. Cenicriviroc (CVC) is not approved by the FDA as a treatment for anything.

This study will compare the effects and safety of remdesivir when used with and without each of the three study drugs. Remdesivir may be provided to all study participants except those with poor kidney function. Remdesivir may also be available to you outside of this study. Your doctor may also prescribe other medications to treat your COVID-19 infection. This study will also provide you with one of these three study drugs or its matching placebo. The combination of remdesivir (including other medications used to treat COVID-19) with the study drugs is investigational because it has not been studied before.

What does the study involve?

If you decide to join the study, you will be asked to sign and date this consent form. When you sign your name or put your mark on the consent form and date it, it means that you agree to be in the study. You can change your mind at any time and leave the study. If you decide not to join the study or to leave the study later, there will be no penalties, and you will not lose any benefits you are otherwise entitled to or regular health care services you already are getting.

Each study participant, with the exception of those with poor kidney function, may receive remdesivir. In addition to remdesivir, participants in this study will be put into one of four groups (assigned by chance, like pulling a name out of a hat or rolling dice). One group (about one out of four, or 25% of participants in the study) will be given a placebo (IV infusion or a pill with no drugs in it). The other three groups (about three out of four or 75% of participants in the study) will get one of three study drugs. The study team will use a computer to randomly decide which group you will be in. The study team will not tell you if you are receiving a study drug or placebo. Only the pharmacist who is preparing the medication will know if you are getting the study drug or placebo.

If you would like to be in this study, after you have read, signed, and dated this consent form, the following activities will occur over the course of the study.

Screening (Day -1 to Day 1)	The study team will:
	• Confirm you have a positive COVID-19 test result recorded
	• Ask about your medical history and the medications you are taking and confirm with your records
	• Collect information from your medical records including test results, treatments, and vaccines that you have received
	• Perform a physical exam
	• Record your vital signs (temperature, blood pressure, breathing rate, heart rate, oxygen levels)
	• Check if you are pregnant (if applicable)
	• Do blood tests to check your health, 10ml (about 2 teaspoons)
	• Ask you not to:
	  ○ get pregnant, impregnate your partner, or breastfeed through Day 60
	  ○ take part in another treatment study through Day 60 (with the exception of the ACTIV-4 study).

Day 1	Before you receive remdesivir and study drug/placebo, the study team will: • Check and record how you are feeling and any problems you may be having • Review and record your medical condition and the medications you are taking and update any changes • Record your vital signs (temperature, blood pressure, breathing rate, heart rate, oxygen levels) • Do blood tests to check your health and record results, 10ml (about 2 teaspoons) • Take extra blood samples for future research, 18ml (about 4 teaspoons), if you agreed to provide them [remove if your site will not be collecting this sample] • Take an extra blood sample for future genetic testing, 8ml (about 2 teaspoons), if you agreed to provide it [remove if your site will not be collecting this sample] • Depending on which study drug you will receive, you may require additional tests for other infections. If you test positive, you may need additional treatment. You will still receive the study drug regardless. • Place a small tube called an intravenous (IV) catheter into your vein to allow for medications to be given (if you do not already have one). You will then receive study drugs: • You may receive remdesivir which will be given by an infusion into a vein. • NOTE: Remdesivir will be given for a maximum of 10 days; this includes days you received remdesivir before you joined the trial. • You will also receive the study drug or matched placebo that has been randomly assigned to you. Depending on which study drug you have been assigned to, you may be given an intravenous infusion or pills by mouth. o If you are randomized to receive infliximab or abatacept or their matched placebo as study drug, you will receive a single dose. It will be given into a vein over 30-120 minutes and will not be given at the same time as the remdesivir dose. o If you are randomized to receive oral study drug cenicriviroc (CVC) or the corresponding placebo pills, you will take your first dose. It should be taken with food and will not be given at the same time as the

	remdesivir dose. NOTE: You will continue to take the pills twice daily for 28 days. After you receive remdesivir and study drug/placebo: • A blood sample will be drawn to check levels of study drug in your body, 4ml (about 1 teaspoon)
Daily while in hospital through Day 14	Every day while you are in hospital the study team will: • Check on and record your medical condition, changes in medications, and problems you may be having • Measure and record your vital signs (temperature, blood pressure, breathing rate, heart rate, oxygen levels) On Day 3 (+/- 1 day) you will have: • blood tests to check your health, 10ml (about 2 teaspoons) • blood samples for future research, 18ml (about 4 teaspoons), if you agreed to provide them [remove if your site will not be collecting this sample] On Day 5 (+/- 1 day) you will have: • blood tests to check your health, 10ml (about 2 teaspoons) On Day 8 (+/- 1 day) or on the day of discharge from hospital: • blood tests to check your health, 10ml (about 2 teaspoons) • blood samples for future research, 18ml (about 4 teaspoons), if you agreed to provide them [remove if your site will not be collecting this sample] • blood samples to check the levels of drug in your body, 4ml (about 1 teaspoon) On Day 11 (+/- 1 day) or on the day of discharge from hospital: • blood tests to check your health, 10ml (about 2 teaspoons) While you remain in hospital: • You may continue to receive remdesivir every day through the vein for up to a total of 10 days. • If you were assigned to receive cenicriviroc (CVC) or the corresponding placebo pills study pills, you will continue to take these twice daily with food for 28 days.

	If you are discharged from the hospital before Day 10, remdesivir will be discontinued. If you are readmitted to the hospital prior to Day 14 of the study: • you may be given the remainder of the remdesivir course (up to 10 days in total) • If you were receiving cenicriviroc (CVC) or the corresponding placebo study pills, you will continue to take pills twice a day (28 days in total) If you are discharged from the hospital prior to Day 8, the study team will schedule in-person visits (preferably) for Day 8 and Day 11, or over the phone visits (telehealth) if in-person visits are not possible. At these visits, the study team will (where possible): • Check on and record your medical condition, changes in medications, and problems you may be having • Measure and record your vital signs (temperature, blood pressure, breathing rate, heart rate, oxygen levels) • Take blood samples as specified for Day 8 and Day 11 above.
Day 15 +/- 2 follow-up visit	If you are hospitalized, this visit will take place on Day 15 (+/- 1 day) in the hospital. If you are already at home, the study team will schedule an in-person visit (preferably) or an over the phone visit if an in-person visit is not possible. At this visit, the study team will (where possible): • Check on and record your medical condition, changes in medications, and problems you may be having • Measure and record your vital signs (temperature, blood pressure, breathing rate, heart rate, oxygen levels) • Do blood tests to check your health and record results, 10ml (about 2 teaspoons) • Take blood samples for future research, 18ml (about 4 teaspoons) [remove if your site will not be collecting this sample]
Day 22 +/- 3 follow-up visit	If you are hospitalized, this visit will take place in the hospital. If you are at home, the study team will carry out the visit over the phone. The study team will: • Check on and record your medical condition, changes in medications, and problems you may be having

Day 29 + 3 follow up visit	If you are hospitalized, this visit will take place in the hospital. If you are at home, the study team will schedule an in-person visit. At this visit, the study team will (where possible): • Check on and record your medical condition, changes in medications, and problems you may be having • Measure and record your vital signs (temperature, blood pressure, breathing rate, heart rate, oxygen levels) • Do blood tests to check your health and record results, 10ml (about 2 teaspoons) • Take blood samples for future research, 18ml (about 4 teaspoons), if you agreed to provide them [remove if your site will not be collecting this sample] • Take blood sample to check the levels of drug in your body, 4ml (about 1 teaspoon)
Day 60 +/- 5	If you are hospitalized, this visit will take place in the hospital. If you are at home, the study team will carry out the visit over the phone. The study team will: • Check on and record your medical condition, changes in medications, and problems you may be having • Check on and record whether you have been re-admitted to the hospital

Will I receive the results of any tests?

Blood will be regularly collected from you to check your general health; these results may be shared with you if appropriate, and they will also be entered into the study database. Other blood samples are intended to check the levels of drug in your blood; these samples will be stored for testing at a later date and the results will not be shared with you.

- You may also be offered the option to provide five or six additional blood samples at different time points. These samples will be used for future exploratory research, and the results will not be shared with you. These tests will be described in greater detail at the end of this document, where you will be asked if you would like to provide these samples. You will still be allowed to participate in the study even if you decide not to provide these additional samples.

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them. As with all studies, if we find out important information that may affect your care, you will be provided with those results.

What side effects could remdesivir cause?

Remdesivir is currently approved in the United States for the treatment of hospitalized patients with COVID-19 and is considered to be part of standard of care.

The most common side effects include (greater than 5%):

- Nausea
- Changes in how your liver works, increase in your liver enzymes (shown in blood tests)

Rare side effects include:
Infusion-related reactions. Symptoms associated with infusion-related reactions may include increase or decrease in blood pressure, increase or decrease in heart rate, fever, difficulty breathing, rash, or chills. A slow infusion rate will be used as that may prevent these symptoms. Inform the study team immediately if you have any of these reactions.

Remdesivir contains a compound that is eliminated by the kidneys, for this reason, participants with poor kidney function will not receive remdesivir. We will monitor your kidney function; if you have abnormal test results, we may suspend or stop giving you remdesivir. We will share these results with you.

Remdesivir may also affect how your liver works. We will monitor how your liver is working, and if you have any abnormal test results we may stop giving you remdesivir. We will share these results with you.

What side effects could the study drugs cause?

The possible side effects are different depending on which study drug you receive. The potential side effects of each are detailed below.

Infliximab (Remicade)

Most patients in the clinical studies where these side effects were observed received multiple doses of infliximab for chronic conditions. If you are randomized to receive infliximab while in this study you will receive one dose.

Most common side effects (greater than 10%):

- Headache
- Abdominal pain
- Nausea
- Infections (including viral, bacterial and fungal)
- Reaction to the infusion
- Pain

Less common side effects (1% to 10%):

- Flushing, increased sweating
- High blood pressure, low blood pressure
- Tiredness, problems sleeping
- Indigestion, diarrhea, constipation
- Low white cell count, low red cell count, or both
- Changes in how your liver works, increase in your liver enzymes (shown in blood tests)
- Difficult or painful breathing, chest pain
- Nettle-type rash (hives), itchy rash
- Balance problems or feeling dizzy
- Fever, chills
- Bruising
- Swollen lymph nodes
- Eye problems, including red eyes and infections
- Pain in the joints or muscles
- Psoriasis, skin problems such as eczema, hair loss and dry skin

Infliximab can cause serious side effects including:

- Serious infections: Subjects receiving infliximab have a higher risk of getting infections including pneumonia and other infections caused by viruses, bacteria, or fungi. There have been uncommon (greater than 1/1,000 to less than 1/100) reported cases of serious infections leading to death associated with infliximab.
    - Tuberculosis: Tuberculosis (TB), including reactivation in patients who were unaware that they had dormant TB, has been reported uncommonly (greater than or equal to 1/1,000 to less than 1/100) in patients treated with infliximab after multiple doses. Patients with TB have frequently presented with widespread or atypical disease. You will be tested for TB at the beginning of the study. As the results can take several days, we will not wait for the result before giving you the study drug. If your TB tests are positive, you may need additional treatments.
    - Hepatitis B: Rarely (greater than 1/10,000 to less than 1/1,000), treatment with TNF-blocking agents such as infliximab may result in a reactivation of the hepatitis B virus in people who have been known to carry this virus. Patients with untreated hepatitis B have experienced worsening liver function and liver failure. You will be tested for hepatitis B at the beginning of the study. As the results can take several days, we will not wait for the result before giving you the study drug. If your Hepatitis B tests are positive, you may need additional treatments.
    - State law requires positive test results for certain communicable diseases, including HIV, hepatitis, sexually transmitted infections, and tuberculosis, to be reported to a local health agency. This study involves some of these tests. The study doctor can discuss this with you.

- Congestive Heart Failure (CHF): Uncommonly, patients with CHF had worsening of their disease and some died.
- Allergic reactions: Allergic reactions can happen after receiving infliximab, including, uncommonly, a serious condition known as anaphylaxis. Tell your physician if you have ever received infliximab in the past, as this could increase the risk of an allergic response. Uncommon cases of reactions up to 2 weeks after treatment have occurred in patients treated with infliximab in the past. Also, if you receive infliximab in this study, you will need to tell your healthcare care provider in case infliximab is ever considered for you again in the future.
- Cancer: Certain kinds of cancer have been reported in subjects receiving multiple doses of infliximab. The risk is felt to be very low with a single infusion.
- Central nervous system: Rarely, patients, who have a disease of their nervous system, have reported that this disease got worse. Seizures and multiple sclerosis are examples of nervous system diseases.

Abatacept (Orencia)
Most patients in the clinical studies where these side effects were observed received multiple doses of abatacept for chronic conditions, if you are randomized to receive abatacept while in this study you will receive one dose.

Most common side effects with abatacept (greater than 10%):
- Headache
- Upper respiratory tract (airway) infection
- Nasopharyngitis (pain and inflammation in the nose and throat)
- Nausea

Less common side effects (1% to 10%):
- Diarrhea
- Dizziness
- Cough
- Back pain
- Bronchitis
- Urinary tract infection
- High blood pressure
- Inflammation of the sinuses
- Stomach upset
- Flu
- Fatigue

Other common symptoms that could be related to abatacept treatment:
Some subjects in clinical studies with abatacept have had cold sores (oral herpes), some have had mouth ulcers, and some have had stomach pain.

Abatacept can cause serious side effects including:

- Serious infections: Subjects receiving abatacept have a higher risk of getting infections including pneumonia and other infections caused by viruses, bacteria, or fungi. There have been reported cases of serious infections leading to death associated with abatacept.
- Allergic reactions: Allergic reactions can happen after receiving abatacept.
- Cancer: Certain kinds of cancer have been reported in subjects receiving abatacept. While it is not known if abatacept increases your chance of getting certain kinds of cancer, to date, no increased risk of developing cancer has been identified in human studies with abatacept.
- Patients with COPD experienced a higher frequency of COPD-related adverse reactions (COPD exacerbation, cough, dyspnea, pneumonia, rhonchi).

Cenicriviroc (CVC)
Most common side effects with cenicriviroc (CVC):

- Diarrhea
- Nausea
- Joint pain
- Rash
- Vomiting
- Flatulence and Abdominal distention (gas)
- Fever
- Joint swelling
- Abnormal physical weakness or lack of energy
- Dermatitis contact - skin rash or irritation caused by touching something
- Increases in levels of liver enzymes

Risks that are not known:
You may experience unknown risks and problems related with the use of any of the study drugs, including allergic reaction to the medicine or a bad effect because the study drug is taken at the same time as another medication. Whenever someone takes any new medications, there is a risk that an allergic reaction may occur. Such reactions can be serious or fatal. If you suffer from allergies to medications, food products, or environmental elements, please tell the study doctor.

What are the other risks or discomforts of the study?

Loss of confidentiality
In any research, there is a possible risk of loss of confidentiality of the personal information you have provided. Every effort will be made to keep your information confidential; however, this cannot be guaranteed. See ‘how will my privacy be protected’ for more details about how your privacy will be protected.

Risks of Placing a Catheter
If you do not already have one, a small tube called an IV catheter may be placed in your vein to allow for the medications to be given. You may feel momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Risks of Blood Draw
Having blood drawn may cause some discomfort, bleeding, bruising, and/or swelling where the needle enters the body, and in rare cases it may result in fainting. There is a small risk of infection.

Risk of infusion reaction
Intravenous infusion reactions may affect any organ system in the body. Most are mild in severity, although severe and even fatal reactions occur. The most common signs and symptoms of infusion reactions are:

- Fever and/or shaking chills
- Flushing and/or itching
- Alterations in heart rate and blood pressure
- Difficulty breathing or chest discomfort
- Back or abdominal pain
- Nausea, vomiting, and/or diarrhea
- Various types of skin rashes

For Women, Risks Related to Pregnancy:
If you are a woman, you cannot be enrolled in this study if you are:

- Pregnant
- Planning to become pregnant during the study
- Nursing a child

If you are pregnant or nursing a child during the study, there may be risks to you, the embryo, fetus, or nursing child.

If you can become pregnant, you must use an acceptable non-hormonal method of birth control, from screening until Day 60 of the study.

Highly effective methods of non-hormonal contraception (less than 1% failure rate) include, but are not limited to:

- implanted contraceptives
- intrauterine device (IUD)
- abstinence

Effective methods of contraception include, but are not limited to:

- diaphragms with spermicide

Please speak to the study doctor or staff about acceptable methods of birth control. You should not participate in this study if you can become pregnant and cannot use one of these birth control methods. Some methods of birth control do not work as well when you are taking certain drugs (cenicriviroc). Be aware that women can still become pregnant even if using an acceptable birth control method.

If you become pregnant while you are in this study, you should report this immediately to the study team and you will not receive any further study drugs. With your permission, the study doctor or study staff will ask about your health, collect information from you through the outcome of your pregnancy, and collect scheduled blood samples. The study team may share this information with the study sponsor, the pharmaceutical collaborator(s), the data and safety monitoring board (DSMB), and with the Institutional Review Board (IRB), a group of people who review research studies to protect the rights and welfare of research participants.

For Men, Risks Related to Pregnancy:
If you are male, and your female partner is capable of becoming pregnant, your partner must use an acceptable non-hormonal method of birth control, from screening until Day 60 of the study.

Highly effective methods of non-hormonal contraception (less than 1% failure rate) include, but are not limited to:

- implanted contraceptives
- intrauterine device (IUD)
- abstinence

Effective methods of contraception include, but are not limited to:

- diaphragms with spermicide

Please speak to the study doctor or staff about acceptable methods of birth control. You should not participate in this study if your partner can become pregnant and you cannot use one of these birth control methods. Some methods of birth control do not work as well when you are taking certain drugs (cenicriviroc). Be aware that women can still become pregnant even if using an acceptable birth control method.

If your partner becomes pregnant while you are participating in the CVC study, you should report this immediately to the study team.

Are there benefits to being in the study?

You may not benefit from being in this study. If the study drugs work and you received them in this study, you may benefit by getting better sooner and/or getting less severe disease.

Your participation in this study is important to learn more about the study drugs and if they are safe and work in hospitalized patients with COVID-19. The work done in this study may also help in the development of treatments for COVID-19.

What will happen to my samples and personal information?

The study team will store samples that are collected to test the level of study drug in your blood and those that will be used for future research until we are able to test all samples. Your stored samples and data will be marked with a code and not with your name.

Your study information will be placed in a secure electronic system. It will not include your name. This information cannot be traced back to you.

Your samples will not be sold. As part of this study, the study team will collect extra blood samples to store and use for secondary research. Secondary research may help us to understand how remdesivir and the other study drugs work, to study other infections or diseases, and/or to develop other treatments. This secondary research on your samples will be done without obtaining additional permission from you. These samples may be shared outside of the study team conducting the trial: with laboratories, investigators, and the pharmaceutical collaborators whose drugs are being tested in the study.

You will not be paid for any products that result from this research. The only risk of allowing us to store your samples would be an accidental release of your identity.

The data center for this study may share your data and specimens with other people who study COVID-19. The center will remove any information that could possibly be used to identify you before sharing. This is called “anonymizing the data.” We will not ask you for additional consent for this sharing. The center will only share data and specimens for research projects that are approved by the group that is conducting this study.

Can I change my mind about my samples being stored or my data being used?

You may change your mind and withdraw consent for the storage and use of your coded samples or information at any time. You will need to contact the study doctor using the contact information listed on page 1 of this form. We will do our best to follow your wishes but cannot promise that we will always be able to destroy your samples or data. For example, if your samples were already used, we would not be able to destroy them.

What do I need to do for follow-up on this study?

If you develop any new side effects or feel sicker at any time during your participation in the study, it is important that you quickly tell the study team at the hospital or call the study contact number provided to you. If you have been discharged from the hospital, we may ask you to return to the clinic for a medical exam.

Will it cost me anything to be in this study?

It will not cost you anything to be in this study.

Who is paying for the study?

This trial is supported with US federal funding from the Biomedical Advanced Research and Development Authority (BARDA), Department of Health and Human Services. The National Center for Advancing Translational Sciences (NCATS) within the National Institutes of Health (NIH) provides oversight of the trial. Technical Resources International implements the study.

Will I be paid if I join this study?

You will be paid up to a total of $[Amount] if you complete this study. You will be paid for the visits you complete according to the following schedule:

- $[Amount] for Visits [Number].
- $[Amount] for Visits [Number].
- $[Amount] for Visits [Number].

If you do not complete the study, for any reason, you will be paid for each study visit you do complete.

You will be paid [select: "after each visit," "annually," "bi-weekly," etc.]

If you have any questions regarding your compensation for participation, please contact the study staff.
[OR]
You will not receive any monetary compensation for your participation in this study.

Who is watching over this study?

A Data and Safety Monitoring Board (DSMB) will be looking at the study information very closely. The DSMB is made up of doctors and other people who are not directly involved in the study and who have a good understanding of severe coronavirus infections like COVID-19 and research studies. The DSMB may recommend changing

the study or stopping the study earlier than planned if they think it is not safe to continue, or if one of the study drugs proves to be effective in treating COVID-19. The local institutional review board, health authorities, and the U.S. Food and Drug Administration will have the authority to stop the study at any time.

How will my privacy be protected?

We will keep your study information private. All files with information that could identify you will be kept in locked cabinets behind a locked door or on secure password protected computers.

People responsible for making sure that the research is done properly may look at your study records. This includes people who are conducting the study and their designees, including staff from this hospital. External groups including the National Institutes of Health (NIH) and their designees and the U.S. Food and Drug Administration (FDA), and international regulatory entities as part of their duties. Your records may also be viewed by the Institutional Review Board (IRB), responsible for approving the study, staff with Technical Resources International and their authorized representatives. In addition, pharmaceutical collaborators that make the drugs, and their designees, may view your records. The pharmaceutical collaborators are Gilead Sciences, Inc. (remdesivir), Bristol-Myers Squibb (abatacept), Janssen Biotech (infliximab), and AbbVie (cenicriviroc). All of these people will also keep your identity private.

Results from this study, but not your identity, may be shared with local medical providers, makers of the study drugs, or government health organizations to help them better understand COVID-19. When results of an NIH research study are reported in medical journals or at scientific meetings, the participants who take part in the study are not named or identified.

To help us protect your privacy, this study is covered by a Certificate of Confidentiality (Certificate) from the NIH. Study staff cannot provide to any person not connected with the research your name, or any materials that contain identifiable, sensitive information about you, unless permitted by a legal exception, such as U.S. state laws that require reporting of some contagious diseases. The most important protection provided by the Certificate is that the study staff cannot be forced to provide any of your identifiable, sensitive information, in any U.S. Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, such as if there is a court subpoena, without your permission. The study team will use the Certificate to resist any demands for information that would identify you.

Your information protected by the Certificate may still be disclosed or used when the information:

1. Is disclosed to people connected with the research, for example, information may be used for program evaluation internally by the NIH; or

2. Is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal US Food and Drug Administration (FDA);
3. Is necessary for your medical treatment and you have consented to this disclosure;
4. Is for other research;
5. Is disclosed with your consent (for example, an insurer or medical care provider gets your written consent for us to disclose the research information).

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing and dating below you consent to those disclosures.

Will the study require any of my other health care providers to share my health information with the researchers of this study?

As a part of this study, the researchers may ask to see your health care records from your other health care providers. You will be asked to give us a list of other health care providers that you use.

To do this research, we will need to collect, use, and share your private health information. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record. You may be asked to sign and date a separate document to authorize the collection, use, and disclosure of your personal health information.

The permission you give us to access your medical record will last until the end of the study. Your permission for the researchers to use your research information will not expire unless you revoke it.

What other things should I know about this research study?

ClinicalTrials.gov
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.

Conflict of Interest
The policy of the NIH is to evaluate investigators at least yearly for any conflicts of interest. Research participants may review the system for assessing conflicts of interest by checking the web site link: http://ethics.od.nih.gov/forms/Protocol-Review-Guide.pdf. Copies of the standards may also be requested by research participants. No NIH investigator involved in this study receives payments or other benefits from any

company whose drug, product or device is being tested. This study has investigators that are NIH employees and some that are not. All non-NIH investigators are required to follow the principles of the Protocol Review Guide but are not required to report their financial holdings to the NIH.

Whom to Contact About This Study?

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

For any questions about the study or a research-related injury, or if you have complaints, concerns or suggestions about the research, contact [Name] at [Number] during regular business hours and at [Number] after hours or on a weekend or holiday.

An Institutional Review Board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or questions, concerns or complaints regarding this research study, contact the IRB at 800-562-4789 or Help@wirb.com.

What should I do if I am injured or ill as a result of being in this study?

Immediate necessary medical care is available at [Institution] in the event that you are injured because of your participation in this study. However, there is no commitment by [Institution], your physicians, Duke University (Duke Clinical Research Institute), or the regulatory sponsor to provide monetary compensation or free medical care to you in the event of a study-related injury. There is no program for compensation through the NIH or through Duke University. The cost for this treatment will be charged to you or your insurance company.

A new public health declaration, called the Public Readiness and Emergency Preparedness Declaration (PREP), was issued by the Department of Health and Human Services on March 10, 2020.

This declaration may limit the legal rights of a subject participating in a COVID-19 clinical study that uses a drug, device or vaccine designed to treat, diagnose, cure or prevent COVID-19. This includes remdesivir (Veklury) and the study drugs abatacept (Orencia), infliximab (Remicade), and cenicriviroc (CVC). Subjects using abatacept (Orencia), infliximab (Remicade), or cenicriviroc (CVC) in this study may have limits on their right to sue the manufacturers, the study sponsor, healthcare providers and others for significant injuries and adverse reactions.

Under some circumstances, compensation may still be available under the PREP Declaration for certain patients who sustain injuries. To find out more, go to https://www.hrsa.gov/cicp/about/index.html or call 1-855-266-2427.

Permission To Store And Use My Blood Sample For Future/Secondary Research Including Genetic Testing

Your body, like all living things, is made up of cells. Cells contain deoxyribonucleic acid, also known as “DNA”. DNA is like a string of information put together in a certain order. Parts of the string make up “genes”. Genes contain instructions on how to make your body work and fight disease. Differences or changes in DNA explain some of the physical differences among people. These differences partly explain why some people get diseases like cancer or diabetes while others do not. Genetic testing looks at the differences in people’s DNA. This testing also looks at how differences affect health and the body’s response to disease and treatment.

If you agree to allow genetic testing of your cells, a sample of your blood will be collected on Day 1. This blood may in the future be used to study whether there are genetic differences in how sick people get when they are infected with SARS-CoV-2 or how they respond to study drugs. This genetic testing might include whole genome sequencing (WGS). “Sequencing” is looking at the order of a person’s genes to see how this order is different from the order of most people.

A U.S. federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans and most employers to discriminate against you based on your genetic information.

This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that the sponsor will get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that the sponsor will get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans and all employers with 15 or more people must follow this law.

Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance or long-term care insurance.

In addition to this genetic testing, the study team would like to collect additional blood samples for future research throughout the study (Days 1, 3, 8, 15, and 29). These blood samples will be collected for secondary research related to COVID-19. Secondary research is research that is not part of this study, and the research is not planned yet. This extra research will occur in the future and it will help us understand how the study drugs work and to develop new treatments and lab tests. Some of these tests will be done after you are done with the study, and other tests are not yet approved by the FDA and are still considered "research" tests. These tests will **not** involve genetic testing, and may include:

- the level of inflammation markers and clotting factors in your blood
- if your body developed antibodies to SARS-CoV-2

If you do not want to allow your samples to be stored for this future research, you may indicate this below.

You do not have to agree to participate in this future research including genetic testing. Even if you do not agree, you can still participate in the rest of the study.

Please put your initials below to indicate your choice regarding **genetic testing**:

_____ (initials) I understand, and I agree to the genetic testing of my samples.

OR

_____ (initials) I understand, but I do not agree to the genetic testing of my samples.

Also, please put your initials below to indicate your choice regarding future research that will **not** involve genetic testing:

_____ (initials) I understand, and I agree to the use of my blood samples for other future research that will not involve genetic testing.

OR

_____ (initials) I understand, but I do not agree to the use of my blood samples for other future research that will not involve genetic testing.

Consent for Future Contact

The study team may be interested in finding out about long-term health outcomes after COVID-19 infection. At some point in the future, after you complete your participation in this study, the study team may wish to contact you to assess your health and possibly ask your consent for future studies. By providing your initials below, you are only giving study staff permission to contact you.

Please put your initials below to indicate your choice:

_____ (initials) I understand, and I agree to be contacted in the future by study staff.

OR

_____ (initials) I understand, but I do not agree to be contacted in the future by study staff.

Statement of Consent to Participate in the Study

Study staff have described this research study to me. I have read this consent form. I have been encouraged to ask questions and all of my questions have been answered by the study staff to my satisfaction. I voluntarily consent to participate in this research study with the understanding that I may withdraw at any time. My consent includes allowing storage of samples and/or use of my study information and samples for an indefinite period of time. By signing and dating this consent form, I have not given up any of my legal rights. I will get a copy of the signed and dated consent form for my records.

Information below can only be completed by the participant. If you agree to be in this study, please sign and date below.

_____ Date: _____/_____/_____
Signature of participant mm dd yyyy

_____
Printed name of participant

Adult Assent Instructions:
All subjects unable to consent are required to assent, unless the investigator determines that the capability of the subject is so limited that the subject cannot reasonably be consulted. A Legally Authorized Representative (LAR) must consent for an adult participant who is unable to consent for themselves.

If assent is obtained, have the person obtaining assent document assent on the consent form.

Statement of Adult Assent

- By signing below I confirm that I understand the information within this form and was given enough time to consider the decision to participate in this research study.
- The purpose of this research study, procedures to be followed, risks, and benefits have been explained to me.
- I have been encouraged to ask questions, and my questions have been answered to my satisfaction.
- I have been told whom to contact if I have questions, to talk about problems, concerns, or suggestions related to this study.
- I agree to give my assent to participate in this research study, and for the use of associated protected health information, with the understanding that participation in this research is voluntary.
- I have been told that I may stop participating in this study at any time without any penalty or loss of access to treatment or other benefits to which I am otherwise entitled.

I have been told that my legally authorized representative (LAR) will be given a signed and dated copy of this form.

_____ Date: _____/_____/_____
Signature of participant, as able mm dd yyyy

_____
Printed name of participant

- ❑ I have explained the study to the extent compatible with the subject's capability, and the subject has agreed to be in the study.

OR

- ❑ The subject is not able to assent because the capability of the subject is so limited that the subject cannot reasonably be consulted.

_____ Date: _____/_____/_____
Signature of investigator/designee mm dd yyyy

_____
Printed name of investigator/designee

For adults not capable of giving consent

_____ Date: _____/_____/_____
Signature of Legally Authorized Representative (LAR) mm dd yyyy

_____
Printed name of LAR

_____
Relationship of LAR to Participant

Witness to Consent Interview
On the date given next to my signature, I witnessed the consent interview for the research study named above in this document. I attest that the information in this consent form was explained to the participant, and the participant indicated that his/her questions and concerns were adequately addressed.

_____ Date: _____/_____/_____
Signature of witness mm dd yyyy

_____
Printed name of witness

****For Sites in California****

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?

The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits.

Who may use and give out information about you?

The study doctor and the study staff. [They may also share the research information with [enter SMO company name], an agent for the study doctor. delete if the site does not have an SMO]

Who might get this information?

The sponsor of this research. "Sponsor" means any persons or companies that are:

- working for or with the sponsor, or
- owned by the sponsor.

Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries,
- The institution where the research is being done,
- Governmental agencies to whom certain diseases (reportable diseases) must be reported, and
- Institutional Review Board (IRB)

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to make sure that the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
This permission will be good until December 31, 2070.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

Authorization:

I have been given the information about the use and disclosure of my health information for this research study. My questions have been answered.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

AUTHORIZATION SIGNATURE:

_____ _____

Signature of Subject **Date**

_____ _____

Signature of Legally Authorized Representative (LAR) **Date**

_____

Printed name of LAR

_____

Relationship of LAR to Participant

IRB Approved Template
MUST BE APPROVED
FOR SITES BEFORE USE
AS MODIFIED
Dec 31, 2020

RESEARCH PARTICIPANT CONSENT ADDENDUM

TITLE: Randomized Master Protocol for Immune Modulators for Treating COVID-19

PROTOCOL NO.: ACTIV-1 IM
WIRB® Protocol #20202874

SPONSOR: Daniel K. Benjamin, MD, MPH, PhD

INVESTIGATOR: Name
Address
City, State Zip
Country

STUDY-RELATED PHONE NUMBER(S): Phone Number
Phone Number (24 hours)
[24 hour number is required]

What treatments are currently available for this study?

The ACTIV-1 IM study involves multiple different types of potential treatments. You will be asked to review information for each study treatment to learn more about its risks and benefits. The current list of possible study treatments is below in Table 1, and more detailed information about these treatments is included in this consent form. The study team has marked (put an X or check mark) next to the treatments that are available for you to possibly receive.

Table 1: Available Treatments

Study Treatment	**Study Staff will 'X' or check all available Treatments**
Remdesivir and Infliximab (Remicade)	
Remdesivir and Abatacept (Orencia)	
Remdesivir and Cenicriviroc (CVC)	

Please sign below to indicate you understand the available treatment options in the study:

_____ Date: _____/_____/_____
Signature of participant mm dd yyyy

_____
Printed name of participant

IRB Approved Template
MUST BE APPROVED
FOR SITES BEFORE USE
AS MODIFIED
Dec 31, 2020

Assent Instructions:

- All subjects unable to consent are required to assent, unless the investigator determines that the capability of the subject is so limited that the subject cannot reasonably be consulted.
- If assent is obtained, have the person obtaining assent document assent on the consent form.

_____ Date: _____/_____/_____
Signature of participant mm dd yyyy

_____
Printed name of participant

- ❑ I have explained the study to the extent compatible with the subject's capability, and the subject has agreed to be in the study.

OR

- ❑ The subject is not able to assent because the capability of the subject is so limited that the subject cannot reasonably be consulted.

_____ Date: _____/_____/_____
Signature of investigator/designee mm dd yyyy

_____
Printed name of investigator/designee

For adults not capable of giving consent

_____ Date: _____/_____/_____
Signature of Legally Authorized Representative (LAR) mm dd yyyy

_____
Printed name of LAR

_____
Relationship of LAR to Participant

Witness to Consent Interview

On the date given next to my signature, I witnessed the consent interview for the research study named above in this document. I attest that the information in this consent form was explained to the participant, and the participant indicated that his/her questions and concerns were adequately addressed.

_____ Date: _____/_____/_____
Signature of witness mm dd yyyy

_____
Printed name of witness