A Triple Combination Antiviral Coronavirus Therapy (TriACT) RCT Comparing Nitazoxanide, Ribavirin and Hydroxychloroquine vs. Placebo

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RUTGERS
Robert Wood Johnson
Medical School

Department of Medicine
Division of General Internal Medicine

CONSENT TO TAKE PART IN A RESEARCH STUDY

Title of Study: A Triple Combination Antiviral Coronavirus Therapy (TriACT) RCT Comparing Nitazoxanide, Ribavirin and Hydroxychloroquine vs. Placebo
Principal Investigator: Jeffrey L Carson, MD

STUDY SUMMARY: This consent form is part of an informed consent process for a research study and it will provide information that will help you decide whether you want to take part in this study. It is your choice to take part or not.

The **purpose of the research** is to determine whether treating people like you who test positive for coronavirus infection (COVID-19) but who do not have symptoms, or who have mild symptoms, will reduce the amount of virus and the chances of getting sick. Currently there are no proven treatments for COVID-19. There is some evidence that medications currently used to treat other viruses might also work against COVID-19, especially if they are used in combination. If you take part in this study, you will be assigned to take the medicine combination being studied or to take pills called placebo that do not have any effect. You will be asked to answer questions about yourself and your health. You will self swab your nose and allow us to take blood samples, pregnancy test, and electrical tracings of your heart (ECG) using a hand held machine. You will have small patch placed on your upper chest that you will keep on for 10 days to monitor your heart beat. Your first visit will take about 35 minutes (15 minutes to complete a questionnaire and 20 minutes for the medical testing and to be given the study medicines that are assigned to you). You will be given supplies to take home including a small device that clips to your fingertip to check the oxygen level in your blood, kits to swab your nose, and a thermometer. You will take the study medications 2 times a day for the next 5 days. For the next 10 days you will take your temperature and your fingertip oxygen level and complete a 5 minute questionnaire. On days 3, 6 & 10 you will use one of the kits that we have provided to take a swab of your nose and ship the specimens to the research laboratory. You will come in for a 10 minute visit on day 14 to provide a blood sample and return the ECG monitoring patch. On day 28 you will complete the final 5 minute questionnaire and also come in for a final study visit to provide a blood sample and pregnancy test.

Possible harms or burdens of taking part in the study may be discomfort from giving the samples and having side effects from the study medications, such as an upset stomach, a skin rash or itching, or an irregular heart beat. The possible benefits of taking part may be that taking the study medicines decreases how sick you become from the infection.

An alternative to taking part in the research Your alternative to taking part in the research study is not to take part in it.

The information in this consent form will provide more details about the research study and what will be asked of you if you choose to take part in it. If you have any questions now or during the study, if you choose to take part, you should feel free to ask them and should expect to be given answers you completely understand. After your questions have been answered and you wish to take part in the

research study, you will be asked to sign this consent form. You are not giving up any of your legal rights by agreeing to take part in this research or by signing this consent form.

Who is conducting this study?

Jeffrey L Carson, MD is the Principal Investigator of this research study. A Principal Investigator has the overall responsibility for the conduct of the research. However, there are often other individuals who are part of the research team.

Jeffrey L Carson, MD may be reached at 125 Paterson Street, New Brunswick, New Jersey 08901; 732-235-7122

The Principal investigator or another member of the study team will also be asked to sign this informed consent. You will be given a copy of the signed consent form to keep.

Sponsor of the Study: Rutgers University

Why is this study being done?

The coronavirus disease-2019 (COVID-19) is spreading throughout the United States. There are no proven therapies to treat those who have become sick and what, if any treatment, should be provided is unknown. There is some evidence that a combination of three medications currently used to treat other viral infections could be effective in fighting this new virus. This combination includes one medication currently used to treat diarrhea (nitazoxanide, also known as Alinia), one medication currently used to treat severe lung infection and hepatitis (ribavirin, also known as Rebetol), and one medication currently used to treat rheumatoid arthritis, lupus, and malaria (Hydroxychloroquine sulfate, also known as Plaquenil).

Some people who test positive for the coronavirus infection do not appear to be sick or have mild symptoms. We are trying to learn more about the infection in these people within the month after being diagnosed. We want to learn if taking the three medication combination might help those with coronavirus infection who have not developed serious illness.

This study is to see how much infection (measured in samples taken from nasal swabs) there is at the beginning of the study and how much that changes during the study. We also want to see who develops new symptoms (for example, a new fever or cough), or if there is any change in mild symptoms. The study will see whether there is any benefit to taking these medications.

Who may take part in this study and who may not?

You may take part in this study if you are 21 or older and have been tested for coronavirus (Sars-CoV-2) within the past 7 days and told that those results were positive and you do not have symptoms requiring hospitalization and you are not currently short of breath.

You cannot take part in this study if you have a known reaction to any of the study medications (Nitazoxanide, Ribavirin, and Hydroxychloroquine sulfate) or are currently taking these medications, have a heart rhythm problem that requires medication, take medicines that might lead to heart rhythm problem, or are known to have had serious disturbances to your heart rhythm, or if you have problems in your retina (back of your eye). You cannot participate if you are on kidney dialysis, if you have difficulty taking

medications by mouth, or if you are pregnant or nursing, or planning to become pregnant within the next 6 months.

If you are a female of childbearing potential both you and your partner must agree to the use of two highly effective forms of birth control for the 6 months after you enter the study. Acceptable methods of include abstinence, tubal ligation, combined oral, transdermal or intra-vaginal hormonal contraceptives, medroxyprogesterone injections (e.g., Depo-Provera), copper-banded intra-uterine devices, hormone impregnated intra-uterine systems. All methods of contraception should be used in combination with the use of a condom by your partner.

If you are a male you must use a condom during sexual intercourse with all sexual partners including a pregnant female partner during the study and for 4 weeks after discontinuing study treatment. If your partner is not using effective contraception and is of childbearing potential, you must use a condom during sexual intercourse during the; study and for 6 months after discontinuing study treatment.

Why have I been asked to take part in this study?

You have been notified that your test results show that you have coronavirus infection and you do not have symptoms or you have symptoms that do not require hospitalization and you are not short of breath. This study is being done to better understand how best to treat the infection in people like you.

How long will the study take and how many subjects will take part?

There will be about 70 participants in the study. From time of enrollment, each participant will be actively followed for one month. It will take one year to complete the study.

What will I be asked to do if I take part in this study?

If you take part in this study, you will complete questionnaires. You will have 3 study visits 1) an initial study visit when you are first enrolled, 2) a second visit on day 14, and 3) a final visit at day 28 when the study ends. You will have an ECG and fingertip oxygen level when you enter the study, provide a nose swab, and have a blood sample (about 3 teaspoons) of blood taken. You will have a small patch applied to your upper chest that you will keep on for 10 days to measure your heart rhythm. You will take the study medications that you are given for twice a day for 5 days. You will be given home collection kits to swab your nose on days 3, 6 and 10. These kits also contain packaging materials and postage paid labels for you ship your specimens to the study research laboratory on each of the collection days. You will also be given a thermometer and a fingertip oxygen measurement device (known as a pulse oximeter). For the first 10 days, you will also take your temperature and your fingertip oxygen level and complete questionnaires. You will return for a study visit on day 14 to provide a blood sample (about 3 teaspoons) and to return the ECG monitoring device. You will have a blood sample (about 3 teaspoons) taken and a pregnancy test at the day 28 (final) study visit.

After your eligibility has been confirmed and you sign this consent form, you will come to the study location at the 93 French St, New Brunswick, N.J. If your ECG shows that you are at risk for the study medication causing a disturbance to your heart rhythm, or if your fingertip oxygen level is less than 92%, you will not be included in the study; your participation will end, and we will suggest you contact your healthcare provider. If you are a female of childbearing age, you will be given a urine pregnancy test to confirm that you are not pregnant.

If you continue in the study, the research staff will supervise your self nose swab and draw your blood. We will also place a small patch on your upper chest that is to stay in place for the next 10 days. This may require that we shave any hair that could be in the way. You will be able to shower and perform your usual activities while the patch is in place.

You will then be assigned by random rules of research (like a coin flip) to receive one of the treatment plans being studied. One treatment plan is the combination of the medicines (Nitazoxanide, Ribavirin, and Hydroxychloroquine sulfate) and the other plan is not to receive any real (active) medications. You will have an equal chance of being in each of the plans. Neither you nor the research team will know which plan you are in. The research staff will give you a 5 day supply of pills. The number of pills and the schedule for taking them is the same in each of the plans. If you are in the plan where you are not taking the real medication, the pill that you receive will look the same but it will not have any ingredients that will affect you (for example, it may be made of sugar or starch). This pill is called a placebo. All pills are always to be taken by mouth. The schedule for taking the pills is

	Number of Pills to Take 2 Times Each Day	
	First Day	Next 4 Days
Nitazoxanide (Real or Placebo)	2	2
Ribavirin (Real or Placebo)	3	2
Hydroxychloroquine sulfate (Real or Placebo)	2	1

The treatment plans are:

Plan 1: Nitazoxanide, Ribavirin, and Hydroxychloroquine sulfate
Plan 2: Placebo (not real) Nitazoxanide, Placebo (not real) Ribavirin, and Placebo (not real) Hydroxychloroquine sulfate

The initial questionnaire will capture information about your health history including what diseases and conditions you already have, the medications you are currently taking, and what symptoms you are currently experiencing. The follow-up questionnaires will ask you to confirm that you have taken the required number of study medications, your temperature and fingertip oxygen levels, and will ask about your current health and if you have any new symptoms to report. We will keep in touch with you by telephone or other secure communication to be sure that you are taking the study medication, collecting and shipping your specimens, review study procedures and to answer any questions that might arise.

Your participation will end at the day 28 study visit which will take place at 93 French St, New Brunswick, N.J.

Below is the schedule of the study activities for participants:

	Baseline	Days 1 to 5	Days 6 to 10	Days 3, 6 & 10	Day 14	Day 28
Initial Questionnaire	X					
Nose Swab	X			X		
ECG (electrocardiogram)	X	X	X			
Blood Specimen	X				X	X
Urine Pregnancy Test	X					X
Study Medication		X				
Temperature, Fingertip Oxygen Level	X	X	X			
Follow-up Questionnaire		X	X			X

All of the testing (nose self swab instruction, baseline ECG, blood specimen) at the site visits will be administered by trained research staff.

Routine blood analysis will be performed at the Robert Wood Johnson University Hospital laboratory. Antibody testing will be performed at Gennaro Lab, The International Center for Public Health research laboratory at the Rutgers University Newark campus. The nose swabs will be sent via FedEx to Altasciences in Everett, Washington will they will processed and stored until transfer to The Translational Genomics Research Institute (TGen) Phoenix, Arizona, the study research laboratory, where they will be analyzed for amount of virus.

Should you develop symptoms from coronavirus disease-2019 (COVID-19) that require medical treatment, we would like to request records related to that treatment. If you agree, we will have you sign a form that gives the study doctors permission to review all of your medical records related to the infection for the month that you are in the study, or until the infection clears. We would not review records unrelated to COVID-19 or records from before you entered the study or after you leave the study.

You will also provide your contact information and the names and contact information of 2 individuals who know you well to use if you have missed a study activity and we are not able to reach you.

What are the risks of harm or discomforts I might experience if I take part in this study?

Risks associated with Nitazoxanide

The common (1/100 to 1/10) side effects are:

- abdominal pain
- headache
- change in the color of urine
- nausea

Risks associated with Ribavirin

The common (1/100 to 1/10) side effects are:

- rash and itching
- hives or swelling
- feeling tired
- nausea
- appetite loss
- cough

The uncommon (1/1000 to 1/100) side effects are

- bloody diarrhea or stools (bowel movements)
- severe stomach or low back pain
- bruising
- other bleeding
- anemia (reduction in the number of red blood cells you have which can be dangerous, especially if you have heart or breathing problems (chest pain or shortness of breath))

The most serious side effect that has been reported is harm to unborn children. This drug may cause birth defects or death of an unborn child. You should not take this drug if are pregnant or planning to become pregnant within the next 6 months.

Risks associated with Hydroxychloroquine sulfate

The common (1/100 to 1/10) side effects are:

- skin changes including a bleaching of hair
- changes in skin pigment
- nausea

The uncommon (1/1000 to 1/100) side effects are:

- vomiting
- diarrhea
- muscle weakness (lack of strength)
- low red blood cell counts (which make you feel tired or weak)
- low platelet counts (which may make you more likely to bruise or bleed)
- headaches
- dizziness
- irregular or slow heart rate
- fluttering in your chest

The rare (1/10000 to 1/1000) side effects are:

- eye problems (including abnormal color vision)
- shortness of breath

The study cardiologists will be reviewing the ECG recordings from your monitoring patch twice a day during the 10 days you are wearing it. If they detect a concern within the first 5 days when you are still taking the study medications, you will be instructed to stop taking the study medication. The cardiologist will monitor your ECG every 6 hours until the reading looks the same as when you entered the study. If there is a serious finding, you will be promptly contacted, and directed to seek medical treatment as appropriate

The use of the three study medications (nitazoxanide, ribavirin, and hydroxychloroquine) in combination has not been studied. While there is a possible benefit from using the combination, it is also possible there is an increased risk of side effects.

Risks associated with the questionnaire: We will ask questions pertaining to your health and medical conditions that you have. This information will be secured and used only for the purposed described in this consent.

Risks associated with blood draw: When blood is drawn, there may be a bruise, or bleeding, or infection, at the place where the blood is drawn. However, infection is rare.

Risks associated with nose swab: A nose swab test has few risks. You may also feel slightly uncomfortable, but you should not feel any pain. You may have a minor nosebleed afterwards.

Risks associated with ECG: The baseline ECG will be performed with a handle held device by having you place both thumbs on the top sensors, and touching the bottom sensor to the bare skin of your left leg (knee or ankle). There are no risks. The continuous ECG monitoring is performed using a 2-by-5-inch adhesive patch, worn much like a bandage, on the upper left side of the chest. It is water resistant and can be kept on around the clock while you sleep, exercise, or take a shower.

Reproductive Risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important to understand that you need to use birth control while on this study. You also must avoid getting pregnant for up to 6 months after receiving the last dosing of study drug. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. If you become pregnant or father a baby within 6 months after the last study drug dose, you must inform your study doctor immediately.

Are there any benefits to me if I choose to take part in this study?

If the study finds that one of the treatment plans reduces amount of virus or illness, then the participants assigned to that plan may benefit. However, we do not know if there will be any benefit to taking the study medications.

You will be allowed to keep the thermometer and the pulse oximeter.

There is much that is unknown about coronavirus infection. Your participation in this study will provide valuable information towards the development of treatments and strategies to combat the illness and its spread.

What are my alternatives if I do not want to take part in this study?

Your alternative is not to take part in this study and to discuss treatment with your personal physician..

How will I know if new information is learned that may affect whether I am willing to stay in the study?

During the study, you will be updated about any new information that may affect whether you are willing to continue taking part in the study. If new information is learned that may affect you after the study or your follow-up is completed, you will be contacted.

Will I receive the results of the research?

In general, we will not give you any individual results from the study. If we find something of urgent medical importance to you, we will inform you, although we expect that this will be a very rare occurrence.

At the end of the study, we will provide your antibody results from your blood test.

Will there be any cost to me to take Part in this study?

There is no cost to you for participating in this study. All study medications as well as the Zio Patch continuous ECG monitoring will be provided to you free of charge. Should you require medical attention for COVID-19, those costs will be paid by the insurance plan that you are covered by.

Will I be paid to take part in this study?

We will provide a ClinCard (which is a specially designed debit card for clinical research) at your initial study visit, which will be preloaded with money to pay for that day's parking. When you come in for the day 14 and 28 day visits, we will add money to that card to cover your parking costs on those days as well.

We will also add additional money to the card at the final (day 28) study visit. That amount (up to a maximum of $50) is based on completion of the study tasks: $25.00 for completion of all of the at home nose swabs and $25.00 for completing the day 14 & 28 visits (includes return of the ECG monitoring device).

Greenphire, the company which developed the ClinCard, will act as an agent of Rutgers University to manage the payment. You will be given a Greenphire ClinCard, which is a debit card that your study payments are loaded onto following completion of study visits. When a study visit is completed, the payment will be approved and loaded onto your card. The funds will be available within one hour of the completed visit, unless the study coordinator advises you that it may take a little longer. You may use the ClinCard as you choose. You will be issued one ClinCard for the duration of your study participation. If your card is lost or stolen, you can contact ClinCard support at (866) 952-3795. This phone number is also on the back of the card. If you do need a replacement card and you obtain it directly through the ClinCard customer support service, it will be mailed to your address. In that event, the balance from your lost card will be loaded onto your replacement card, minus a $7 replacement fee charged by the customer support service. Or, you may request a replacement card during your next visit with your study coordinator, who will provide you with a replacement card for a fee of $3.50, which will be subtracted from your ClinCard balance.

How will information about me be kept private or confidential?

All efforts will be made to keep your personal information in your research record confidential, but total confidentiality cannot be guaranteed. Rutgers will make every effort to keep the information collected from you private. In order to do so, we will assign all of your study materials (including your stored biological samples) a study number and remove all identifying information. All documents with your name on them will be kept in a locked file or encrypted (made impossible to read) on a computer. Only the study team will have access to this information. All staff associated with the project will be trained in procedures

for maintaining confidentiality. Results of the research may be presented at meetings or in publications, but your name and identity will never be disclosed. Sometimes, however, researchers need to share information that may identify you with people that work for the University, government regulators, or study sponsor

A description of this clinical trial will be available on 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 website at any time.

What will happen to my information or biospecimens collected for this research after the study is over?

Nose swabs and blood specimens collected will be used for the purposes of this research.

After information that could identify you has been removed, de-identified information and left over biospecimens collected for this research may be used by or distributed to investigators for other research without obtaining additional informed consent from you. Personal details that identify you, such as your name and date of birth, will not be shared in the future without your additional permission.

What will happen if I am injured during this study?

Participants in this study will be exposed to certain risks of personal injury in addition to those associated with standard forms of treatment, which include the risks of associated with Nitazoxanide, Ribavirin, and Hydroxychloroquine sulfate (the study medicines) that were described in the Risks section of this consent. In addition, it is possible that during the course of this study, new adverse effects of these medications that result in personal injury may be discovered. The University will make appropriate referrals for medical and/or dental treatment for subjects who sustain personal injuries or illnesses as a direct consequence of participation in the research. The subject's health insurance carrier or other third-party payer (or Charity Care if there is no insurance) will be billed for the cost of this treatment; provided that the University shall not submit to federally funded programs, e.g., Medicare, Medicaid or CHAMPUS, for reimbursement first if submission to such programs is prohibited by law. No financial compensation will be provided by the University and no other type of assistance is available from the University. However, by signing this form, you are not giving up any legal rights to seek further compensation.

What will happen if I do not wish to take part in the study or if I later decide not to stay in the study?

It is your choice whether to take part in the research. You may choose to take part, not to take part, or you may change your mind and withdraw from the study at any time.

If you do not want to enter the study or decide to stop taking part, your relationship with the study staff will not change, and you may do so without penalty and without loss of benefits to which you are otherwise entitled.

Beginning on the date that you withdraw your approval, no new personal health information will be used for research. However, the study doctor/investigator may continue to use the health information that was provided before you withdrew your approval. To withdrawal your approval you must do this in writing to Jeffrey L Carson, M.D. Rutgers, Robert Wood Johnson Medical School, 125 Paterson Street, New Brunswick, New Jersey 08901

If you decide to withdraw from the study for any reason, you may be asked to return for at least one additional visit for safety reasons.

Who can I contact if I have questions?
If you have questions about taking part in this study or if you feel you may have suffered a research-related injury, you can contact the Principal Investigator: : Jeffrey L Carson, M.D. Rutgers, Robert Wood Johnson Medical School, 125 Paterson Street, New Brunswick, New Jersey 08901, Telephone: 732-235-7122 email: jeffrey.carson@rutgers.edu

If you have questions about your rights as a research subject, you can contact the Rutgers IRB Director at: New Brunswick/Piscataway HealthSci IRB 335 George St., Liberty Plaza Ste. 3100, New Brunswick, NJ 08901, (732)235-9806 email us at humansubjects@ored.rutgers.edu or write us at 65 Bergen St., Suite 507, Newark, NJ 07107.

PERMISSION (AUTHORIZATION) TO USE OR SHARE HEALTH INFORMATION THAT IDENTIFIES YOU FOR A RESEARCH STUDY

The next few paragraphs tell you about how investigators want to use and share identifiable health information from your medical record in this research. Your information will only be used as described here or as allowed or required by law. If you sign this consent form, you agree to let the investigators use your identifiable health information in the research and share it with others as described below. Ask questions if there is something you do not understand.

What Is The Purpose Of The Research And How Will My Information Be Used?
You are being invited to take part in this research study which is described at the beginning of this form. The purpose of collecting and using your health information for this study is to help investigators answer the questions that are being asked in the research.

What Information About Me Will Be Used?

If you require medical treatment for COVID-19 during the month that you are in this study, we will request the medical records related to that treatment.

Who May Use, Share or Receive My Information?

The research team may use or share your information collected or created for this study with the following people and institutions:

- Rutgers University Investigators Involved In The Study
- The Rutgers University Institutional Review Board and Compliance Boards
- The Office for Human Research Protections in the U.S. Dept. of Health and Human Services
- The Food and Drug Administration
- The study Data Safety Monitoring Board (a group who meets to make sure the study is conducted safely and fairly)
- SynaVir, the company providing the funds to cover the costs of conducting this research

Those persons or organizations that receive your 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 the laws governing them.

Will I Be Able To Review My Research Record While The Research Is Ongoing?
No. We are not able to share information in the research records with you until the study is over. To ask for this information, please contact the Principal Investigator, the person in charge of this research study.

Do I Have To Give My Permission?
No. You do not have to permit use of your information. But, if you do not give permission, you cannot take part in this study. (Saying no does not stop you from getting medical care or other benefits you are eligible for outside of this study.)

If I Say Yes Now, Can I Change My Mind And Take Away My Permission Later?
Yes. You may change your mind and not allow the continued use of your information (and to stop taking part in the study) at any time. If you take away permission, your information will no longer be used or shared in the study, but we will not be able to take back information that has already been used or shared with others. If you say yes now but change your mind later for use of your information in the research, you must write to the researcher and tell him or her of your decision: Jeffrey L Carson, M.D. Rutgers, Robert Wood Johnson Medical School, 125 Paterson Street, New Brunswick, New Jersey 08901, Telephone: 732-235-7122

How Long Will My Permission Last?

There is no set date when your permission will end. Your health information may be studied for many years.

AGREEMENT TO PARTICIPATE

Subject Consent:

I have read this entire consent form, or it has been read to me, and I believe that I understand what has been discussed. All of my questions about this form and this study have been answered. I agree to take part in this study.

Subject Name (Print):_____

Subject Signature:_____ Date:_____

Optional:

I prefer not to have my medical records accessed. Initials: _____

Signature of Investigator/Individual Obtaining Consent:

To the best of my ability, I have explained and discussed all the important details about the study including all of the information contained in this consent form.

Investigator/Person Obtaining Consent (Print):_____

Signature:_____ Date: _____