INFORMED CONSENT FORM

REVIVE_TOGETHER

"A Multicenter, Adaptive, Randomized, Double-Blind, Placebo-Controlled, Prospective Study of Pharmacological Interventions in Participants with Clinical Features Consistent with Long COVID-19: The REVIVE-TOGETHER Protocol"

OFFICIAL STUDY TITLE : A Multicenter, Adaptive, Randomized, doublE-blinded, Placebo-controlled Study in Participants With Long COVID-19: The REVIVE Trial

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UNIQUE PROTOCOL ID - **TOGETHER_REVIVE**

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STATEMENT
This following document is an English translation of the original Portuguese informed consent form. It is provided for public posting and informational purposes in ClinicalTrials.gov. The original Portuguese version remains the source document maintained by the sponsor/ investigator in accordance with applicable local regulatory, ethics, and institutional requirements in Brazil.

CONFIDENTIALITY NOTE
No research participant names or directly identifying personal information are included in this document.

Study Title:	**A multicenter, adaptive, randomized, double-blind, placebo-controlled, prospective study of pharmacological interventions in participants with clinical symptoms consistent with Long COVID-19: The REVIVE-TOGETHER Protocol**
Protocol Number:	**REVIVE_TOGETHER**
Principal Investigator:	**Gilmar Reis**
Institution Name:	**CARDRESEARCH – Clinical and Research Cardiology.** **735 Otoni Street, *... intentionally cut*** **Belo Horizonte, MG, Brazil.** **ZIP Code: 30150-274**
24-hour contact number:	***Intentionally cut***
Participant Name:	
Participant Number:	

INTRODUCTION

You are being invited to participate in a clinical study because you are experiencing persistent symptoms that may be associated with COVID-19.

To help you make a decision, we will provide you with information about the study's purpose, procedures, risks, benefits, discomforts, and the precautions taken. Take as much time as you need to carefully read the following information and discuss it with others. Ask your doctor or the study team to explain any words or information that are not clear to you, to ensure that you understand the details of your participation before giving your consent.

If you agree to participate in the study, you must sign and date two copies of this consent form, initialing every page of each copy. One copy will be given to you and the other will remain with the researcher.

PURPOSE OF THIS RESEARCH STUDY

Your health problem has been identified as likely caused by a specific type of virus, which is causing this disease worldwide. This new virus originated in China, where it emerged in late December 2019 and caused a major epidemic in less than 90 days across the globe, including in our country. This severe flu was named COVID-19 and was declared a pandemic. Although the World Health Organization has declared the end of the COVID-19 pandemic, cases are still common in virtually every country.

The likelihood of a person dying from this disease has decreased significantly with the discovery of effective treatments and the use of vaccines. However, this risk is still higher than that of the "flu," caused by the influenza virus, which is the reason for annual vaccination of the population. A particular type of complication has been concerning health authorities worldwide. A significant number of people with COVID-19 develop symptoms of tiredness, fatigue, "poor memory," forgetfulness, depression, insomnia, and various other symptoms; it is currently estimated that up to 15% of all people with COVID-19 may experience these symptoms. It is common for these symptoms to interfere with daily tasks and the ability to work, and it is also common for these symptoms to persist for several months, or even years.

The cause is not yet fully understood, but it is definitely linked to significant changes in the body's inflammatory and immune responses, which, for reasons that remain unknown, fail to return to normal after COVID-19. This condition is called "LONG COVID," which, by

definition is the persistence of these symptoms for more than 12 weeks after the initial episode of COVID.

To date, there are no treatments for this condition. The objective of this study is to evaluate whether

medications considered promising for alleviating this condition play a role in reducing its severity. This study is assessing whether two medications—Fluvoxamine and Metformin—may be useful for the treatment of COVID-19.

Fluvoxamine and Metformin are existing medications that have been approved in our country for clinical use for several years. There is evidence, though still preliminary, that these medications may reduce the intensity of LONG COVID symptoms or even reverse this condition if used for a period long enough for the body to reverse the chronic inflammatory changes triggered by the COVID-19 episode. There is therefore a possibility that these medications may be useful in reducing or eliminating these chronic and persistent symptoms; however, this has not yet been scientifically studied in a research program involving a large number of people with LONG COVID, and the information currently available is considered insufficient for us to adopt these medications in the treatment of this complication. This study is specifically designed to evaluate whether these medications actually work in patients with this condition, reducing symptoms of fatigue and exhaustion or even eliminating these symptoms, thereby improving your quality of life.

The objective of this study is to determine whether these medications can reduce the intensity of persistent fatigue and exhaustion symptoms that arise after an episode of COVID-19 or even eliminate these symptoms.

WHERE THE STUDY WILL BE CONDUCTED AND NUMBER OF PARTICIPANTS
This study will be conducted at various healthcare facilities in Brazil and will involve approximately 1,500 participants with a clinical diagnosis or suspected case of LONG COVID.

WHO CAN PARTICIPATE
To participate, you must be at least 18 years old, have had a confirmed case of COVID-19, and be experiencing moderate fatigue that (1) began or (2) worsened with the COVID-19 episode and has persisted for more than 12 weeks, and (3) have had your last episode of COVID-19 within 24 months of this initial evaluation.
You will not be able to participate in the study if:

1. You have another diagnosis for your fatigue or there is another clear explanation for the worsening of your symptoms;
2. You are currently taking any of the medications being evaluated;
3. You have a known sensitivity or allergy to fluvoxamine or metformin;
4. You have a severe or uncontrolled psychiatric or neurological condition.

DURATION OF YOUR PARTICIPATION
If you agree to participate in this study, you will need to provide informed consent, which is the first step in this research.

1. We will explain the purpose of the study and the potential risks and benefits, and we will give you sufficient time to consider your participation, including discussing it with your family members and any other people you trust. If you agree to participate, you will be asked to sign this informed consent form at the end of this document.
2. The study staff will review your medical records and verify the medical history you have provided to obtain information relevant to this study. They will also ask you to answer a few questions to clarify parts of your medical history.
3. If eligible, you will be randomly assigned to one of the following treatment groups, which may or may not include medication:

    - Fluvoxamine for 60 days (see Table 1 below).
    - Metformin for 60 days (see Table 1 below)
    - Placebo pills for 60 days (placebo group).

    In this randomization, the chance of receiving the medications or being assigned to the control group is equal. **The control group (without medication) is necessary so that we can properly assess**

whether the medications are beneficial for your medical condition. A computer program for randomization (a random selection, like flipping a coin, for example) will conduct this random assignment among the options above. Neither you nor the research staff, including the doctors, will know which group you will be assigned to.

, beautiful 1 - Study Treatment Regimen

	Treatment schedule	
Clinic Visit	**Fluvoxamine**	**Metformin XR**
Randomization (D_0)	**100 mg/dose**	**500 mg**
D_1 to D_{60}	**100 mg every 12 hours**	**500 mg every 12 hours**
D_{61} to D_{90}	**100 mg every 12 hours**	**500 mg every 12 hours**

4. You will be instructed to take the medications for this study for 60 days. If you have been prescribed other medications by your doctor, you must not stop taking them. This is very important, as the medications for this study must be taken in conjunction with all treatments prescribed by your doctors.
5. The research team will contact you, either in person or by phone/social media. During each of these contacts, you will be asked about your health, your medications, and whether you have experienced any side effects from the study medications. Your medical records and/or electronic health records may also be reviewed for test results, hospitalizations, other serious events, and relevant clinical/laboratory evaluations, and you will be asked questions related to fatigue symptoms. By participating in this study, you hereby authorize the research team to access your medical data solely for purposes related to this study. After you finish taking the medication, we will continue to contact you to find out how you are feeling and whether your COVID-19 condition has worsened, as well as to determine if there have been any adverse reactions to the study medications. Our final contact will be 90 days after you begin taking the medications
6. You will continue to manage your health (including any medical conditions you may have) as directed by your healthcare team, including making adjustments if they deem it appropriate. Participating in this study will not change the way your health conditions are treated in any way, and this decision is yours and that of the doctors treating you.
7. If you attend any visits, you and your companion will be reimbursed for any expenses (e.g., transportation and meals) incurred as a result of your participation. If necessary and/or recommended by health authorities, you and your companion will be provided with masks and, if needed, other recommended protective equipment to prevent the risk of COVID-19 infection.
8. If there is any indication that a surgical procedure will be performed during the study, you must notify us as soon as you become aware of this need, as it will be necessary to stop taking the medications 48 hours before the procedure. The medications can be restarted after surgery, as soon as your doctor authorizes you to take them.

WHAT WILL HAPPEN WHEN YOU COMPLETE THE STUDY

Once the study is completed, you will continue your medical care in the same way you did before participating in this study. If there is clear evidence that these medications benefit your condition, your doctors may request a supply of the study medication for a minimum period as specified in the study protocol, which will be provided to you at no cost.

The results of this clinical study will be made available to you as soon as they are released.

POSSIBLE RISKS OR SIDE EFFECTS IF YOU PARTICIPATE IN THIS STUDY

Study Medication:

Fluvoxamine is a medication used to treat depression. It is contraindicated if you have severe mental health issues, or if you have an uncontrolled neurological/mental condition considered severe. Common side effects of the medication include mood swings and emotional lability, dizziness, abdominal pain, nausea, diarrhea, and vomiting. Uncommon/rare side effects may occur, such as hives, angioedema, and psychosis. These and various other side effects are known and do not prevent the use of the medication, which is available at pharmacies for use with a prescription. The research team will advise you on how to proceed if you experience these effects.

Metformin is a medication used to treat diabetes and is considered the drug of choice for initiating diabetes treatment. It lowers blood sugar. Common side effects include nausea, abdominal discomfort, diarrhea, and changes in taste. Rare side effects may include allergies/hives, kidney changes, and increased blood acid levels, usually if there are severe infections or if you're using iodine-containing contrast agents. You cannot participate in this study if you are undergoing hemodialysis or peritoneal dialysis. Similarly, if you are undergoing kidney treatment, we must first have the most recent results of your kidney tests to determine whether you are eligible to participate in this study. Likewise, if you have a severe infection, need surgery, or will be using an iodine-containing contrast agent within the next 15 days, you will not be able to participate in this study. These and several other rare side effects are known and do not prevent the use of the medication, which is available at pharmacies by prescription; your doctor will advise you on how to proceed if these effects occur.

Study Procedures

An evaluation via an outpatient visit will be conducted with you if you agree to participate in this study. The average duration is 45–60 minutes. There will be no invasive procedures, blood draws, or collection of other material for laboratory testing. You will be asked about existing medical conditions and medications you are currently taking. If the doctors deem it necessary, an electrocardiogram (ECG) may be performed during the screening visit to check for any abnormalities that would prevent your participation. This test is performed by holding two points on a small pad (about the size of a small chocolate bar) or by wearing a wristband. You may experience some discomfort from holding the pad for a short time or wearing the wristband. There is no risk of electric shock. We will also measure your blood oxygen levels using a small device placed on your finger; this is a non-invasive procedure. You may feel slight pressure from the device on your finger, but there is no risk of electric shock. Both procedures take up to 90 seconds. An in-person visit may be scheduled, but the study is designed to be conducted via telemedicine visits.

We will administer questionnaires to assess the severity of your fatigue and how it may be affecting your daily life. We will also conduct a questionnaire to gauge your overall well-being. Both consist of 5 to 8 simple questions, with each questionnaire taking no more than 3 minutes to complete. If you are a woman of childbearing age, we will need to collect a urine sample for a urine pregnancy test. None of the collected materials will be stored for later analysis: All materials will be discarded immediately after the tests are completed (see below for more details), in your presence.

Pregnancy

Although there are no contraindications for the use of the medications proposed in this study, we have chosen to avoid using them in pregnant women. Therefore, women who are pregnant or planning to become pregnant within the next 90 days cannot participate in the study. If you have not had a hysterectomy and are of childbearing age (between 18 and 55 years old and have had at least one menstrual period in the last 12 months), we will perform a urine pregnancy test. You will provide a urine sample so that we can conduct the test. The collected urine will be used solely for this test and will be immediately discarded after the test is performed in your presence. If the test is negative and you agree to use effective methods of contraception, you may participate in this study. In this case, the doctor will decide with you on the temporary method of contraception to be used, and you will receive it at no cost.

If you are postmenopausal, have had a hysterectomy, or have not had a menstrual period for at least 12 months, you may participate in this study without needing to take the urine pregnancy test.

BENEFITS
The potential benefits to you may include the possibility that these medications could help with LONG COVID, thereby reducing the severity of your symptoms or even making them disappear. We cannot guarantee this personal benefit from your participation in this study, as these medications are still being tested and we do not know if the findings from small studies or experimental trials will be confirmed. You may not experience any personal benefit from participating in this study; however, the information we obtain from this study may contribute significantly to the treatment of others with these same symptoms.

ALTERNATIVE PROCEDURES OR TREATMENTS
Your participation in this study is voluntary; in other words, you do not have to participate in this study to treat your health condition. The study doctor will discuss other treatments or medications with you to relieve the symptoms you are experiencing. To date, there are no specific treatments for LONG COVID, and none of the medications currently used to treat these symptoms have scientific proof that they work for this condition. You may refuse to participate in the study or withdraw from the study at any time without facing any penalties.

PARTICIPATION AND WITHDRAWAL FROM THE STUDY
Your participation in this study is entirely voluntary. Your decision not to participate will not result in any penalty or loss of benefits to which you are entitled. You may discontinue your participation in this study at any time without penalty or loss of benefits to which you are entitled. If you wish to withdraw your consent, please inform the study doctor immediately so that he or she can ensure you stop taking the study medication safely.

If you or the study doctor decides to stop the study medication, you will be asked to continue participating in medical visits in person or by phone until the end of the study. If you withdraw your consent, the information collected about you as part of the study between the date you signed the current form and the date you withdrew your consent will be retained and used anonymously, unless you specifically request that your information be removed from the database. This is important to protect the quality of the research results. However, no new information about you will be collected or used.

If you wish to withdraw permanently, we will ask you to see us one last time for a final evaluation, to check on your health, for your own safety. We may also ask for your permission for the study doctor to contact you later to collect minimal additional data about your health condition. You will be monitored throughout the study, provided you allow the research center staff to contact you in person or by phone. These contacts will only take place if you agree and provide your contact information.

The investigator, the CEP/CONEP (research ethics committee), or the team coordinating this research may terminate your participation in the study at any time and for any reason; however, the study will only be terminated after the CEP/CONEP system reviews and approves the reasons for termination. However, in urgent cases, to ensure the safety of participants, the researcher may terminate the study prior to this review, and the CEP/CONEP system will be informed at the earliest opportunity.

If the study is terminated, you will be notified, and the study physician will take all necessary steps to ensure your treatment is continued by the attending medical team (your primary care team), with the aim of maintaining the continuity of your treatment without any detriment to you.

They may also do this if you do not follow the study instructions. Your participation in the study may be discontinued if the sponsor determines that you or the investigator have not followed the study instructions, or if the sponsor or regulatory agencies decide to stop the study.

If you have other medical problems or side effects, the investigator will decide whether you can continue in the study, but you will be monitored until these problems are resolved and/or controlled.

RESPONSIBILITIES

All forms of medical diagnosis and treatment—whether routine or experimental—involve some risk of injury or illness. Side effects are possible in any research study, despite the use of high standards of care, and may occur through no fault of your own or that of the study doctor. Unpredictable harms may occur that may require medical attention.

If you experience any complications, they are most likely unrelated to the medications being tested. The study team—which may be the same team from the healthcare network where you first sought care for your COVID-19 symptoms—will help you obtain appropriate medical treatment, regardless of whether or not it is related to the medications being tested.

In the event of harm resulting from your participation in this study, you will have the right to seek compensation and will receive immediate and comprehensive medical care at no cost to you, for as long as necessary.

LEGAL RIGHTS
The statement above ("In Case of Research-Related Injury") does not waive your legal rights or relieve the associated institution's investigator of legal liability for negligence.

COST AND PAYMENT FOR PARTICIPATION
Your participation in this study will not incur any additional costs for you. You will receive the study medication free of charge.
Participants will not be compensated for participating in this study.

QUESTIONS AND CONCERNS
If at any time you experience any discomfort or have any questions, please contact the study physician, **Dr. Gilmar Reis**, or a member of his team at the address provided on the first page of this form or at any time by phone **at (31) 98831-5300.**

The Institutional Review Board (IRB) is a body whose purpose is to protect the well-being of research participants. It is responsible for evaluating and monitoring the ethical aspects of all research involving human subjects, with the aim of ensuring the dignity, rights, safety, and well-being of research participants. If you have any doubts or questions about your rights as a participant in this study, or if you are dissatisfied with the way the study is being conducted, you may contact the **Research Ethics Committee of the São Francisco de Assis Hospital Foundation at the following address: ..."*intentionally cut"***

You may also contact the *National Research Ethics Commission*, which also approved the conduct of this study in the country. Their contact information is as follows:

CONEP – National Research Ethics Commission Phone: "intentionally cut"
Address: PO700 Building – Block 701 - Lot D, 3rd floor - North Wing, ZIP Code: 70.719-040 – Asa Norte – Brasília/DF

CONFIDENTIALITY AND DISCLOSURE OF PERSONAL INFORMATION
Records identifying you at this center will be kept confidential and, to the extent permitted by applicable laws, will not be disclosed or made publicly available, except as described in this consent form. Data (information) derived from this study will be used for research purposes. The investigator and the study team will collect only the information necessary for this study. For the purpose of statistical analysis of the research, your data will be included in a database without any personal identifiers. The research center adheres to the General Data Protection Law, under which only individuals authorized by the investigator may access your data at any time, while confidentiality is guaranteed by the investigator in accordance with applicable legislation.

ANVISA and other regulatory agencies, the investigator and members of their research team, representatives of the sponsor, and the CEP/CONEP—which oversees the ethical conduct of this study in Brazil—will be granted direct access to your medical records and other records related to this study for analysis to verify that

the study information is accurate to the extent permitted by applicable laws and/or regulations.

Representatives from Brazilian regulatory agencies may have access to the study data. The investigator, members of the clinical and research teams, and representatives from the institutions with which your facility is affiliated may have access to participants' medical records, in accordance with institutional policies and confidentiality requirements. These records may include some or all of your medical records, including, but not limited to, hospital records and reports; X-ray films and reports; surgical reports; laboratory reports; treatment and test results; immunizations; allergy reports; prescriptions; consultations; clinical notes; notes regarding information obtained; and any other necessary records.

Any information leaving the research center will be de-identified (i.e., identifying information will be removed from the documents). Your name, address, or other information that could directly identify you will not be used. The records received by these organizations may contain your participant code, initials, gender, and date of birth.

In addition, the study results will be communicated to you, the sponsor, the Ministry of Health, and other Brazilian regulatory agencies, if applicable. In the event of any presentation or publication regarding this study, your identity will remain confidential. Your information and results will be archived by the investigator and sponsors in accordance with applicable laws and/or regulations in Brazil. By signing and dating this informed consent form, you agree to such inspection and disclosure.

With your permission, the investigator will notify your doctor about the study so that, if you need to see him or her for any reason, he or she will be aware that you are taking the study medication.

CONSENT FOR THE COVID_REVIVE STUDY

- **You must read the information form above or ask someone you trust to read it aloud to you and understand that the study involves research. You must also understand the purpose of the study, as well as the potential benefits and risks of participating in the study.**

- **You should ask any questions you deem necessary for your understanding and have all your questions and concerns adequately answered before signing this document.**

- **You must understand that your participation is voluntary and that you may withdraw from this study at any time, without needing to provide a reason, and without affecting your future treatment. Likewise, if you choose not to participate in this study in the first place, that decision will not affect your proposed medical treatment.**

- **You must allow auditors from the national regulatory authority, the sponsor, or CEP/CONEP direct access to your original medical records to verify procedures and/or clinical trial information to the extent permitted by applicable laws and regulations, if necessary.**

By signing this Consent Form, I am not waiving any legal rights. I, or someone I trust, has read to me all the information presented in this document, and I have had the opportunity to ask any questions I may have about my participation in this study. I understand that participating in this study is a voluntary decision, and I have freely chosen to participate. My signature or fingerprint below indicates that the study and the procedures related to it have been explained to me, and that I understand and agree to participate.

Participant's Name: _____

Signature: _____ Date: _____

LEGALLY AUTHORIZED REPRESENTATIVE/INDEPENDENT WITNESS

I have read the preceding information in its entirety. I had the opportunity to ask questions, and all my questions were answered to my satisfaction. I understand that I will receive a signed copy of this form.

Name of Representative/Witness: _____

Signature: _____ Date: _____

RESEARCHER

I hereby declare that this document complies with items IV.3 and IV.4 of CNS Resolution 466/2012.

Researcher's Name: _____

Signature: _____ Date: _____