FREE AND INFORMED CONSENT TERMS – TCLE

You are being invited to participate, as a volunteer, in the research called “Phase 1 Study: Point-of-Care Pharmacogenomic Testing to Optimize Isoniazid Dosing in the Treatment of Latent Tuberculosis”. My name is Julio Croda and, with Jason Andrews, I am the researcher responsible for this research. After receiving clarifications and information about the research, you will have adequate time to think, consult family members or other people you trust, to decide whether you want to participate in the study. If you agree to participate, initial all pages and sign at the end of this document, which is printed in two copies, one of which is yours and the other, the person who is talking to you. I clarify that if you do not want to participate you will not be punished in any way. By agreeing to participate, questions about the research can be clarified by team members at any time.

We are doing this research to find out if it is possible to change the dose of one of the medicines used to treat latent tuberculosis, isoniazid, for each person.
In short, we have a substance in our body (called N-acetyltransferase-2 - NAT2) that eliminates isoniazid after it takes effect. Some people eliminate isoniazid more quickly, which we call “rapid acetylators” and, therefore, we would need a higher dose of this medicine. On the other hand, we have those people who eliminate isoniazid more slowly, the “slow acetylators”, who would need a lower dose of the medicine.

We will also look for other substances (called AADAC, SLCO1B1 and CYP2E1) responsible for eliminating another medicine used to treat tuberculosis called rifapentine from your body. This way, we will be able to identify factors that lead you to have reactions when using this medication.

In this study, we need to do two things.

First test a new test to find out if you eliminate isoniazid quickly or slowly, using blood from your fingertip and secretion from your mouth, because with this, we will be able to know how you eliminate isoniazid at the time of the consultation, without needing a laboratory .

Secondly, give only a different dose (higher or lower) of isoniazid in the second week of your follow-up, depending on the speed at which you eliminate the medicine, during your twelve-week treatment for latent tuberculosis.

Your participation in this research will be in three stages:

In the **first stage** you will answer a questionnaire, administered by one of our team members and you will be asked questions about your lifestyle habits (diet, use of cigarettes and other drugs); your current and past health status, including signs and symptoms of tuberculosis.
Then we will collect around 20mL (one tablespoon) of your blood, to do a complete blood count (blood test), measurement of allanate aminotransferase - ALT and aspartate amino transferase - AST (two substances produced by your liver, which allow us to evaluate how he is) and genetic research of determinants associated with drug metabolism (NAT2, AADAC, SLCO1B1 and CYP2E1), and RNA profiling to evaluate how your body metabolizes drugs and to identify risk factors for adverse events caused by these drugs . We will also collect secretion from your mouth, with a cotton swab, to store in the Infectious Diseases Laboratory of the Federal University of Mato Grosso do Sul, until the moment we test the new NAT2 acetylation profile exam.

I clarify that this storage is temporary and we will do so to use samples from all participants at once.

If during the interview you report signs and symptoms of tuberculosis (cough, night fever, weight loss, difficulty breathing), we will perform an X-ray examination of your chest, if possible. you haven't made one in the last 3 months. After that, we will need a sample of your phlegm (2 ml), to do this, we will give you a jar, you will take a deep breath and cough, pulling the phlegm from your chest and spitting into the jar, without touching your mouth to it. With this sample of

phlegm, we will do a test called Xpert MTB/RIF, to find out if you have tuberculosis.
Regardless of the results of your tests, you will be evaluated by a doctor and, if necessary, you will be referred for tuberculosis treatment, offered free of charge in Brazil, by the Unified Health System.

The time to perform this step is up to 30 minutes if it is not necessary to perform an x-ray.
If necessary, the time will be up to two hours.

In the **second stage,** you will be placed in one of the study groups, which will be formed according to its NAT2 acetylation profile:

- Intermediate acetylator group (control group). Participants in this group will receive the standard dose of isoniazid (900mg) and rifapentine (900mg), once a week, for 12 weeks (about 3 months).
- Fast acetylator group (group 1). Participants in this group will receive 11 standard doses of isoniazid (900mg) and a single increased dose (25mg/kg, maximum 1,500mg) in the second week of treatment. The dose of rifapentine will be standard (900mg) during the 12 weeks. So, in the first week they will take the standard dose (900mg of isoniazid and 900mg of rifapentine), in the second they will take the increased dose of isoniazid and, in the remaining 10 weeks, they will take the standard dose of isoniazid again.

- 3) Slow acetylator group (group 2). Participants in this group will receive 11 standard doses of isoniazid (900mg) and a single smaller dose (5mg/kg, maximum 300mg). in the second week of treatment. The dose of rifapentine will be standard (900mg) during the 12 weeks. So, in the first week they will take the standard dose (900mg of isoniazid and 900mg of rifapentine), in the second they will take the reduced dose of isoniazid and, in the remaining 10 weeks, they will take the standard dose of isoniazid again.

With weekly doses of isoniazid and rifapentine, you will take a dose of 50mg of pyridoxine (vitamin B6), to reduce the risk of having inflammatory neuritis (which is an inflammation of the nerves mainly in the legs and arms), due to the use of isoniazid.

In the **third stage,** you will be accompanied by study doctors and nurses during entire treatment (12 weeks, approximately 3 months). This monitoring includes:

- **Medical and nursing consultations:** in the first 3 weeks you will be evaluated by a doctor or nurse, weekly, to find out if you have or have had any unexpected effects resulting from the treatment. At these visits, your weekly dose of medicine will also be administered. In the third week after medication
  , You will be given all the pills for the 12 weeks of
  treatment and, during weekly contacts, you will be reminded to take them.
- **Blood collections:** peripheral venous blood samples will be collected in weeks 2, 3 and 12.
  - o Weeks 2 and 3, up to 45ml total blood volume will be collected (2 spoons of soup), divided into the following times: 1, 2, 8 and 24 hours after taking the dose of medicine (a scalp will be placed to minimize venipunctures). With this blood sample we will measure isoniazid and rifapentine in your blood, measure 2 enzymes in your liver (AST and ALT) and analyze your total RNA profile.

  - o Week 12, 5ml (half a tablespoon) will be collected to measure 2 enzymes in your liver (AST and ALT).
- **Telephone calls and contacts via WhatsApp:** we will contact you weekly by phone call or WhatsApp message, to find out your general health status and check whether you took the corresponding dose of medication that week. If you are serving a prison sentence, we will visit you at the penal unit.

After we measure liver enzymes (the substances produced by your liver) with your blood in these collections from weeks 2 and 3, 5mL will be stored in our laboratory until the last participant finishes the study, when we will send it to the Dartois laboratory, at the Center for Discovery and Innovation, in Nutlley, New Jersey in the United States, where tests will be carried out that measure the amount of isoniazid and rifapentine in your blood, as these tests are not yet available in Brazil. This storage is necessary so that we can send all samples at once after completing the project. After the tests are carried out, your samples will be destroyed. At any time, you may withdraw your consent to the storage and use of the material stored in our laboratory (biorepository) by means of a written and signed statement. After withdrawing consent, your samples will be destroyed. Your samples will only be used as described in this

term and in the project submitted to the Ethics Committee for research involving human beings at the Federal University of Mato Grosso do Sul (CEP/UFMS).

In some cases, it will eventually be necessary to repeat the collection, as the exams may undergo changes during collection, transport or even during their execution, which lead to an indeterminate result. If this occurs, we will contact you to explain what happened and collect the new sample, if you agree.

All the information we collect from you, both from the interview and from the exams carried out, will be stored in a confidential database. Your name will be associated with a code, which only the main researcher knows, to ensure that your participation is anonymous. The results of this study may be presented at scientific or professional meetings, or published in scientific journals. However, your identity will not be disclosed.
The genetic sequence information from your NAT2 acetylation profile will be made available in a public database called GenBank®. This procedure is one of the duties of the institutions that are being financed by the *National Institute of Health* and participating in the project, both in Brazil and in the United States. This database will be accessible via the Internet. Only NAT2 acetylation profile sequence information will be placed in this database, available to anyone on the Internet. No identifying information used about you, such as your name, address, telephone number or medical information will be placed in this public database.

You will not receive direct benefits for your participation in this research, as you are eligible for tuberculosis preventive therapy regardless of participating in the study. You will receive the results of your *NAT2* and liver enzyme tests, but this has no proven benefit at this time. We believe that the benefits of the knowledge gained from this study to improve tuberculosis treatment outweigh the associated risks. If you are diagnosed with tuberculosis through our research, we will notify the responsible health sector in the municipality (Tuberculosis Program) and you will receive, free of charge, appropriate treatment and follow-up.

Your participation may pose risks to your health. Questions asked during the interview may cause some psychological damage due to the possibility of you having negative memories. If you do not feel comfortable answering, you are free to refuse at any time. Blood collection may cause minor bleeding and/or pain at the site where the blood was drawn and swelling under the skin containing blood (bruise). Collecting a swab (a cotton swab) can cause discomfort, temporary shortness of breath and coughing. To reduce these potential problems, blood and swab collections will be carried out by nurses trained in these procedures. Our team will be on hand to help you with whatever you need and reduce the risks we mentioned.
We will monitor your health condition and guarantee full, free assistance for as long as necessary for direct/indirect and immediate/delayed damages resulting from your participation in this research.

The use of these medications (isoniazid and rifapentine) is associated with a risk of reactions that we do not want. Rifapentine can cause your urine (mostly) or sweat to become

orange or reddish color and can stain contact lenses. In studies in which rifapentine was combined with isoniazid and other drugs to treat tuberculosis and administered once or twice weekly, rates of adverse reactions were similar with rifampicin and rifapentine, with increased liver enzyme activity in about 5% of patients. patients. Other adverse reactions that occurred in 1-5% of patients included the following: hemoptysis (bloody phlegm), dizziness, hypertension, headache, gastrointestinal disturbances, rash (itchy skin), cytopenias (change in blood count), hematuria (blood in the urine), pyuria and proteinuria (presence of defense cells and protein in the urine). The total incidence of all adverse effects of isoniazid is approximately 5%, many of which do not require a person to stop taking the medication. Peripheral neurotoxicity (inflammation of nerves in the arms and legs) is dose-dependent and is uncommon (<0.2%) at conventional doses. The risk of peripheral neuritis (also another type of nerve inflammation) increases for people who are malnourished or predisposed to neuritis due to other diseases. Administration of pyridoxine (vitamin B6) with these medications is recommended. Other nervous system reactions are rare at normal doses and include seizures, encephalopathy (brain disease), optic neuritis (inflammation of the eye), memory impairment, and psychosis (a type of mental illness). Gastrointestinal adverse effects include nausea, vomiting and stomach pain. Asymptomatic elevation of liver enzymes is common and occurs in 10-20% of people receiving isoniazid. However, serious liver problems are uncommon, but are more likely in older people (up to 2.3% incidence of hepatitis in people over 50) and can be fatal. These will be risks that would be encountered during the normal course of preventative therapy as clinically indicated, with the exception of rapid acetylators who will receive an increased single dose (25 mg/kg up to a maximum of 1500 mg, rather than 15 mg/kg up to a maximum 900 mg). To reduce these risks, you will be examined by study doctors, have a complete blood count and liver function tests, and clinical evaluation before starting medications. You will be evaluated weekly for the first month and then monthly: if necessary or if you wish, you will be evaluated by the study doctor.

After the study dose (which will be administered in the second week of treatment), you will be seen within 24 hours, contacted within 72 hours, and seen after 7 days, with liver function tests performed within 24 hours and 7 days. The doctor may decide to stop treatment based on risk assessment.

If you are diagnosed with tuberculosis during the study, there is a risk that your identity will be discovered and this disease can generate prejudice, due to the lack of knowledge that people have regarding it. It is difficult for us to control this, as you will return home with treatment medication and, therefore, your family, friends and others may discover that you have tuberculosis. Furthermore, we are obliged, by determination of the Ministry of Health, to report cases of tuberculosis to the municipality's epidemiological surveillance services. To reduce this problem, we will deliver your exam results directly to you, in a private room. Tuberculosis notifications will be delivered by hand to the epidemiological surveillance service of the Municipal Health Department of Campo Grande/MS, in a sealed envelope. There is also a risk that the NAT2 genotyping data, which will be shared with the NIH, will be individualized. To reduce this risk, your data will be stored on encrypted, password-protected devices and we will make completely de-identified data available on NCBI in accordance with NIH Genomic Data Sharing requirements.

Your participation in the study is voluntary. Participating in the study will not change your relationship with the researchers or institutions involved. You can choose not to take part in the study or you can withdraw at any time. You will not be prohibited from participating in further studies. You may be asked to leave the study if you do not follow the procedures or meet the requirements we require. You are guaranteed compensation and reimbursement resulting from the research by Resolution No. 466 of 2012 of the National Health Council. O

The main researcher is responsible for future compensation and reimbursements that may occur as a result of this research.

If you are currently detained in a prison, please be aware that the decision to participate in this study is completely yours and is not mandatory. Your decision to participate or not will in no way affect your treatment in prison or your sentence. You can choose not to participate in the study at any time or decide to stop it if you wish, without any penalty.

All expenses or necessary medical care arising from the research will be the responsibility of the responsible researcher/sponsor, that is, you will not pay for procedures and/or exams and will not receive any additional financial compensation (payment) associated with your participation. If during the application of the questionnaire and/or collection of the material, you present a problem or we detect that you need specialized assistance, we will provide you with assistance with the doctor who is part of the project team, and, if necessary, assistance at HUMAP/UFMS or in the health sector of the prison unit where you are serving your sentence

If you are not satisfied with the way this study is being conducted, or if you have any concerns, complaints or general questions about the research or your rights as a participant, please contact the UFMS Ethics Committee (CEP) to speak to someone independent of the research team, on the phone (67) 3345 7187, or at Avenida Costa e Silva s/n, Bairro Universitário, CEP: 79070-900 – Campo Grande/MS, from Monday to Friday, from 08:00 to 17:00. You can also contact the National Research Ethics Commission (CONEP) of the National Health Council (CNS), via telephone (61) 3315-5878 or at SRTV 701, Via W 5 Norte, lot D – Building PO 700, 3rd floor – Asa Norte, CEP: 70719-040 – Brasília/ DF 8am to 6pm. The Ethics Committee and the National Research Ethics Commission are groups of people from various areas of science who are not part of the research team.

Its objective is to defend the interests of research participants in their integrity and dignity.

If you have any questions regarding the project, you can contact the responsible researcher, Júlio Croda, by telephone (67) 98122-9959, including by collect call. You can also send an electronic message to the email julio.croda@fiocruz.br or in person at the Federal University of Mato Grosso do Sul, Unit II, block 9 (FAMED old building), room 111, at Avenida Costa e Silva s/n, Bairro Universitário, CEP: 79070-
900 – Campo Grande/MS, Monday to Friday, from 8:00 am to 5:00 pm. If you are serving a prison sentence, just talk to a member of the project team during your daylight hours.

I declare that I understand the objectives, risks and benefits of my participation in the research and I agree to participate.

_____, _____ in _____ in _____.
City day month year

_____ _____
Signature of the Principal Investigator Participant Signature