Informed Consent Model Form

Informed Consent Form for adult patients over 18 years of age diagnosed with chronic Chagas disease

Main Project Title: CUIDA Chagas Project-**C**ommunities **U**nited for **I**nnovation, **D**evelopment and **A**ttention for the Chagas disease.
In Charge for the Main Project: Andréa Silvestre de Sousa
Study Title: Double blind, phase III randomized, multicenter, safety and efficacy non-inferiority trial to evaluate two short benznidazole regimens for the treatment of adults in the chronic phase of Chagas disease in its indeterminate andmild cardiac forms in Bolivia and Colombia.
Name of the Institution: Evandro Chagas National Institute of Infectious Diseases – Oswaldo Cruz Foundation (INI/Fiocruz)
Name of the responsible researcher: Israel Molina Romero
Proposal name and version: Chagas Consortium, Clinical Trial Protocol. Version 4.0 Febuary 14th 2023

This Informed Consent Form has two parts:
Part I: Information sheet (to share information about the trial with you)
Part II: Certificate of consent (for signatures if you agree to participate)
You will receive a copy of the complete Informed Consent Form (ICF).

PART I: Information sheet

Introduction

I, _____ of the institution/health unit _____, together with a group of international and national researchers, we are doing trial on Chagas disease, a very common disease in your country and in the region where you live. We are going to study two different manners of using the same medication for Chagas disease and evaluate which one has the best results. This trial will help us understand the most appropriate treatment time for Chagas disease and these results will benefit other patients with this same disease. I will give you more information and invite you to take part in this trial.
Before making a decision, it is important that you read this document carefully. Take the time you need to be sure about you participation. Please ask me, the trial physician, the health care team, or anyone else you feel comfortable with about words or procedures that you do not clearly understand. You should not sign this document if you have any questions that have not been satisfactorily clarified. You should only participate in the trial if you wish. You may refuse to participate or withdraw from this trial at any time without any prejudice and without needing to provide an explanation. Please feel free to ask as many questions as necessary to decide whether you want to participate in this trial or not.

Context

This trial will be developed by Fiocruz (Oswaldo Cruz Foundation), an institution in Brazil that has been working for over 100 years with public health and trial into various infectious diseases, such as Chagas disease, seeking to understand how much people can be affected by them, how they can be prevented and treated. The trial is carried out in collaboration with important institutions in other countries, such as Instituto Nacional de Laboratorios de Salud - INLASA (Bolivia); and Instituto Nacional de Salud - INS (Colombia).

Purpose of the trial

You have been diagnosed with Chagas disease, which is an infectious disease caused by a parasite found in the feces of an insect called vinchuca or vinchuca in Argentina, Bolivia, Uruguay and Chile, barbeiro in Brazil, chipo in Venezuela and also known as kissing bug or barber bug in English. There are three main forms of transmission of the Chagas parasite to humans: in contact of the insect's feces with the person's blood or if mixed with consumed food or drink; through blood transfusions or organ transplantation; and from mother to child, during pregnancy or childbirth.

Chagas disease has two phases: an acute phase (when infection occurs) and a chronic phase. The latter can be divided into the following forms: indeterminate form (uncomplicated) or visceral form (when the infection affects the heart and/or the digestive tract, and when left untreated, can even lead to death in severe cases). You are in the chronic phase, but at the moment, no serious health conditions have been identified, and therefore, treatment for Chagas disease may have benefits for you. The earlier the treatment is done, the greater the benefit, and the disease may even be cured, which is more common when the person is treated in the acute phase. In the chronic phase you are in, the cure can be difficult to define, but we can avoid complications, which unfortunately can still happen later.

Currently, there are only two treatments available for Chagas disease - benznidazole and nifurtimox. Both are known to cause some complications associated with their use, especially in adult patients. Also, these treatments need to be done for a long time, 2-3 months. Studies seem to show that the majority of people who do not complete the treatment, abandon it because of these complications or because the medication use time is considered long.

To alleviate these problems, the trial we are inviting you to participate in is aimed at testing whether benznidazole when used for just two weeks has a similar effect to treatment given in the usual eight weeks (2 months) for people with early chronic forms of Chagas disease, with the standard dose of 300mg per day being maintained.

Trial activities

This trial will involve taking blood to assess the amount of parasites in your blood before starting the treatment. The test that will be performed is called PCR and tries to find pieces of the parasite that causes Chagas disease, which can be in your blood even in the chronic phase of the disease. Blood will also be collected at another 4 visits to assess the effect of treatment (6, 12, 18 and 24 months after completing treatment). Additional interventions and activities including physical examinations and filling questionnaires will be also required. See the chronogram of the scheduled visits.

12. Schedule of Activities

	Screening visit D-21	Baseline visit D0	Treat V S2 D14 (+/-2d)	Treat V S4 D28 (+/-2d)	EOT V S8 D56 (+/-7d)	Follow up Visits 1, 4, 6, 8, 12 and 18 months after EOT (+/-10 d)	End Visit 24 months after EOT (+/-15d)		Adverse Event Visit (not scheduled)
Informed Consent Form	X								
Demographic data	X								
Medical History	X								
Toxic habits	X								
Chagas disease interview	X			X					
Concomitant medication	X	X	X	X	X	X	X		X
Clinical interview	X	X	X	X	X	X	X		X
Physical exam	X		X	X	X	X	X		X
Pregnancy test[1]	X				X				
Hematology[2]	X		X		X				X
Biochemistry[3]	X		X		X				X
EKG	X					X	X		
Echocardiography[4]	X					X	X		
Serology	X						X		
PCR	X					X	X		
Adverse events[5]			X	X	X				X
Randomization[6]		X							
Treatment administration[7]		X	X	X					
WHOQOL BREF Questionnaire[8]		X					X		
EQ-5D-3L questionnaire[8]		X	X	X	X	X	X		
Cost-effectiveness Questionnaire		X	X	X	X	X	X		

Your treatment can be either the reduced 2-week schedule, 4-week schedule or the standard 8-week schedule, which will be chosen in the form of a draw.

Participants selection

We are inviting all adults over the age of 18 with a diagnosis of chronic Chagas disease, without serious illnesses caused by Chagas disease, to participate in the trial that will assess whether the reduced time treatment with benznidazole is as good as the usual 8-week treatment.

Voluntary participation, right to refuse or withdraw from the trial

Your decision to participate in the trial is completely voluntary, you can choose to participate or not. If you choose not to participate, you will continue to receive medical care provided at the health center at no cost or loss.

If you decide to participate, you may discontinue your participation or withdraw your permission to use and share your health information among the trial team at any time. However, before you decide to stop participating in this trial, we recommend that you talk to your trial physician. If you drop out of the trial, no new data about you will be collected after that, unless there has been a complication that may have been associated with the treatment. You could also ask to delete all the data related to your participation. If a complication does occur, it may be necessary to review your entire medical record and you will be informed about all this.

You may withdraw your permission to use your medical information and store your blood samples at any time.

If you choose to discontinue participation in this trial, your decision will not cause any harm or loss of benefits to which you may be entitled and will not affect your relationship with your physician or any of your rights as a patient at the health center.

Subject's initials _____ Investigator's initials _____

Witness initials_____

It is also possible that we may decide to withdraw you from the trial if we believe it is the best option for your health, with your prior knowledge (such as, for example, in the case of any changes in blood tests). In this case, you should receive, as soon as possible, one of the standard treatments for Chagas disease.

Study drug information: benznidazole

The drug we are testing in this trial is called benznidazole, which began to be used worldwide by Roche in 1971, and is currently marketed by the Laboratório Farmacêutico do Estado de Pernambuco S/A – LAFEPE, in Brazil; and by Laboratório ELEA-Phoenix, in Argentina.

Benznidazole works by killing the Chagas disease parasites. In this way, we hope to reduce the amount of parasites in your blood with the treatment; and in some cases even healing can occur. It is hoped that, with this treatment, it will no longer be possible to find the Chagas disease parasite in your blood. The most recent trials that evaluated a small number of people with Chagas disease showed that a shorter treatment time of 2 weeks may be as good as the 60 days that were needed in the older studies. We need to assess whether this is confirmed by a trial with a larger number of people, like the one we are doing now.

Complications associated with medication

Benznidazole is a well-known medication and the most common complications associated with its use include: skin allergy with redness, sores and itching (29–50%), nausea or vomiting (5–15%) and general symptoms such as loss of appetite, weakness, headache and sleep disorders (40%). Rarely, there may be sensitivity problems in the legs or arms with numbness and decrease in the production of "natural defenses". Treatment is stopped in 9–29% because of these complications, but they all usually return to normal and severe cases are very rare (less than 1% of cases). If you experience vomiting after taking the trial drug, you should consult your trial doctor, who will advise you if you should take the drug again. You should be aware of these complications and if any different complaints arise, you should tell your investigating physician right away. On the other hand, your medical researcher can interrupt your participation, if necessary, always with your knowledge.

Trial description

The aim of this trial is at evaluating whether the treatment with benznidazole in a shorter time, of 2 weeks or 4 weeks has the same effect and fewer complications when compared to the standard treatment of 60 days (8 weeks). The monitoring of the treatment will be carried out by the exam that assesses the amount of parasites in your blood (the PCR), which should decrease or disappear with the treatment. In order to assess this effect, we will draw blood before treatment and at 7 times over 24 months of follow-up after the end of treatment, with a total of seven (7) blood collections in this period.

Since we don't know whether a reduced benznidazole regimen is as good as the currently available long-term regimen, we need to compare the two. You will be distributed through a raffle, with equal chances of being in one of the 3 treatment groups. Whoever is chosen for the use of shortened medicine (2 weeks or 4 weeks) will continue taking pills for the same period of 8 weeks as the other group, but in the last 6 weeks the pills will not contain the substance that kills the parasite. These pills with no effect on the body are called placebo. The placebo is the same as the real pill in appearance, so we can't swap treatments among the other people in the trial. This strategy of using the placebo pill is used in all trial that compares different treatments, so that we don't influence the results by our will. Neither your trial doctor nor you will know which treatment group you will be drawn into:

• Group A (B300/2) – benznidazole (100 mg tablet), 300 mg - 2 weeks: Benznidazole 300 mg, divided into three daily doses, for 2 weeks, and placebo for the next 6 weeks.

• Group B (B300/4) - BZN (Abarax, tablet 100mg), BZN 300 mg,divided in three daily doses, for 4 weeks, and placebo for the next 4 weeks.
• Group C (B300 /8) – benznidazole (100mg tablet), Benznidazole 300mg, divided into three daily doses for 8 weeks.

Participants in Group A will only receive the real pills for 2 weeks, participants in Group B will only receive the real pills for 4 weeks while participants and in Group C will receive the pills with the medication for 8 weeks, because this is the current recommendation for treating Chagas disease. It is important that neither you nor us know which of the regimens is being used. This information will be in our files, but we will not examine these files until the trial is complete, unless there is a major complication that needs to be cleared up. Only at the end of the 2-year follow-up of all participants will we be able to know the result of the comparison and which was their group.

The health care team will take great care of you and other participants during the trial. If we're concerned about what the drug is doing, we'll look at the files to find out what drug you're getting and we'll make the changes. If there is something that concerns you or is bothering you with the trial, please speak to me or any of the members of the trial team at any time.

The trial will be conducted in 2 different countries, Colombia and Bolivia and will involve around 672 participants. Routine tests will be performed at your doctor's request, such as electrocardiogram, echocardiogram if any changes are found in the electrocardiogram, blood tests to assess the amount of Chagas disease parasites in the blood (PCR) and other blood tests to monitor during the treatment the functioning of the liver, kidney and blood cells. For the PCR test, your blood will be collected from your vein 5 times over the **26 months** of your participation in the trial. In blood collections, you may feel a little local discomfort due to the needle prick, but the exam will be performed by competent professionals, in a reserved environment, who will try to minimize such discomfort.

When the trial is completed for all participants, you will be able to know the group that was drawn and will receive the result of all tests that assess the presence of the parasite (PCR) that were performed during your treatment. If this PCR test is still positive at the end of your follow-up, you will be offered the usual standard treatment with benznidazole or with nifurtimox, as per your trial physician's prescription. This means that if the trial treatment doesn't work, you will have a chance to treat Chagas disease as recommended today. Treatment will be provided free of charge at no cost to you.

How will your participation in the trial be?
Initially you will take tests to see if you can participate in the trial. During this period, which lasts about 20 days, some evaluations will be scheduled. On the first visit (screening visit), you will be asked to take the following tests: blood tests, electrocardiogram and echocardiogram (if necessary).
If the results of this inclusion visit do not identify any important changes and you agree, the draw will be held to define which of the 2 trial groups you will be. You will receive the medications for the first 14 days and will take the first dose of treatment at this appointment (Day 1). Neither you nor the team will be able to choose your treatment group, which will be chosen by lot. Regardless of the group drawn, you will keep using the medication for 8 weeks, with a dose of one tablet three times a day.
At the second, fourth and eight weeks of treatment the trial team will ask about complaints and check the use of medications. Treatment will be provided at this time points.

After that, you will have follow-up appointments at 1, 4, 6, 8, 12, 18 and 24 months until you complete the 2 years of follow-up In these consultations, in addition to the medical visit, a blood test and an electrocardiogram will be performed. Your researcher physician, or someone appointed by him/her, will arrange all these dates with you to make it easier and more convenient for you to attend all appointments correctly.
In total, you will be asked to come to the trial center 12 times, for about 2 hours a day, in the 26 months of your participation.
In addition, at each visit, we will ask questions to obtain information about how the trial affects your quality of life, so that we can estimate the indirect costs of your participation (transport expenses, lost working days, among others).
Prior to the first visit, all details about all trial procedures will be explained to you and if you agree to participate, you must sign this Informed Consent Form, ensuring that you have received all necessary information and are willing to voluntarily participate in the trial.
You must also return to the health center at any time or call the trial physician immediately (including weekends and holidays) if you experience any health complaints or unexpected complications. If your researcher physician deems it necessary, additional blood tests and/or electrocardiograms will be repeated and/or consultation with other specialists may be requested at no cost to you.

What we ask to the participants:
If you agree to participate in this trial, you must:

- Attend 12 visits on scheduled dates. If it is impossible to attend, you should contact your researcher physician to arrange a new date that is right for you.
- Complete the trial treatment card and take it with the medication you were given at every visit during the treatment period.
- It is highly recommended to avoid any alcohol intake while participating in the trial; but during the treatment phase (while you are taking the medicine), any alcohol intake is prohibited because it can increase the risk of complications when the medicine is mixed with alcohol.
- Communicate with the trial physician if you have any questions, problems or concerns regarding your health and/or your treatment.
- You must not participate in another trial at the same time as this one, to avoid confusion between two trials.
- You must inform to your physician any take of new drugs and to avoid any concomitant intake of Herbal medicines, food supplements and energetic drinks
- It is recommended that you not be pregnant. Medications for Chagas disease can change the growing baby in the mother's womb. Your researcher physician will explain to you that there are several safe ways to prevent pregnancy, from avoiding sex to using a method of contraception that is considered effective. In the event that the participant does not use any contraceptive method, barrier contraceptives will be provided by the research team. The trial physician will explain that all women of childbearing age who have agreed to participate in the trial must use an appropriate and safe method to prevent pregnancy during the 8-week treatment period and up to 3 months after completion. All women with this possibility will have pregnancy tests performed before starting the trial treatment.
- By signing this consent form, you agree to avoid becoming pregnant and to use any contraceptive methods deemed effective as agreed with the trial physician.
- It is important for you to know that even if you are using any of the proper methods to prevent pregnancy, there is a risk (albeit a small one) that you will become pregnant. During the trial, if you

choose to use birth control pills or injections, your trial doctor will also ask you to use another contraceptive method, such as a condom, to increase the safety of avoiding pregnancy and possible risks to an unborn baby.

- Tell your researcher physician immediately if you become pregnant during treatment, as treatment will have to be stopped.
- "The data collected will be kept for at least twenty-five (25) years after the completion or discontinuation of the study, following the guidelines in force in the two participating countries".

How long will my participation in the trial last?
Your participation in the trial will take about 26 months.

Will I receive any compensation for participating in the trial?
You will not receive any compensation for your participation in the trial. However, all expenses related to the trial will be reimbursed, such as transportation expenses and lost workdays to attend the trial site visits, which has been estimated in 25 dollars per visit.
You are guaranteed the necessary medical care and assistance for the treatment of any complication that may be related to your participation in this trial. All exams necessary to carry out the trial and the treatment under evaluation will be given to you free of charge. You should contact your trial physician in case of any trial-related problems. In the event of an injury or illness during this trial, all costs related to the treatment of that injury or illness will be paid if it is indicated that these complications are related to the trial medication and/or procedures necessary for its performance. For other events that occur during the trial, you will be properly instructed by the doctor with the possibility of being referred to a specialist as needed. Sponsor will not pay for the treatment of any pre-existing illnesses or for the treatment of illnesses that arise after the trial and that are not related to your participation in this trial.

And what will be the benefits?
Simply because you participate in a trial, you will be monitored more frequently and with more details than usual, carried out by experienced people. The immediate direct medical benefit will be to receive treatment for Chagas disease. In addition, you can have the satisfaction of participating in a trial that can contribute to the advancement of knowledge in the treatment of Chagas disease, especially if it is demonstrated that the effects of the medication will be maintained with a shorter time of use, with greater safety, improving the lives of other future people affected by the same disease. After participating in this trial, your health condition may improve or remain the same. You can receive information about your health from the team, receiving all tests performed (blood, heart and physical exams). As part of the trial, we will assess whether the parasite causing Chagas disease is found or not in your blood at the end of the trial. As you are in the chronic phase of Chagas disease, which can last for many years, waiting until the end of the trial to find out whether or not you have undergone the complete 2-month treatment does not represent a risk of worsening for you. If indicated, you will receive the entire treatment again at the end of the trial, without harming the evolution of your disease.
In addition, you are entitled to free and immediate assistance and compensation in the event of loss related to the trial, as well as reimbursement of any expenses that were incurred for a reason directly associated with the trial.

What risks can I have by participating in the trial?

You may experience slight discomfort when a blood sample is collected. It is possible (although not likely) that you will have a purple or reddish spot at the needle entry site after the collection is performed. Your trial doctor and staff will do their best to minimize any possible discomfort or harm to you. The total volume of blood collected during the entire trial (26 months) is about 75 mL for all assessments (about 5 tablespoons in total). The amount of blood drawn does not cause anemia or problems related to the body's defense mechanisms. In order to avoid the risk of embarrassment, contact with the trial team, as well as blood collection, will take place in a private room. Only the trial team will have access to the information provided during their participation in the study. Your personal data did not appear in any document, thus protecting your identity at all times.
Possible risks related to your participation in this trial will be covered by an insurance policy.

Confidentiality
Your identity, medical records and your participation in this trial will be kept secret, that is, your name will not appear in the results, except in the health facility documentation, such as medical records and files restricted to your health care use. At the end of the trial, we will write a report on the trial results and publish the results so that others can know about this trial. This report will not include any personal information about the trial participants, for example, your name, where you live or any references that might identify you. All blood samples will be stored in a secure place. Your blood samples will be identified by a tag with a code that identifies you, without your name. This label keeps your participation secret and secure. Future evaluations with blood samples can be done to help better understand Chagas disease. In this case, new ethical approvals will be required, and new consents will be required from participants, including you.
If you decide to withdraw before the end of the trial, all information collected about you up to that point will be used in this trial. You may also be contacted by your trial doctor to inquire about any new complications.
By agreeing to participate in this trial, you grant permission for the medical staff, clinical monitors or auditors and regulatory authorities and the Ethics Committee to have access to this information to ensure that the trial is being conducted correctly.

Sharing the Results
The information obtained from this trial may help others with Chagas disease in the future, and your participation in the trial will allow for safer or more tolerable benznidazole regimens to be evaluated.
When the trial is complete for all participants, you will receive information about the treatment you received and the evaluation of tests that identify the parasite in your blood. If you still test positive for Chagas disease, you will be offered standard treatment as per your country's protocols, with benznidazole or nifurtimox.
You are assured that your identity will be kept secret and that no information will be given to anyone other than the trial team. When publishing the results of this trial, your name will not be mentioned, always having your privacy guaranteed.
You are guaranteed to receive clarification on any queries related to the trial and will be able to access your data anywhere in the trial.
You should know that your participation in this trial is voluntary and that you can choose not to participate or change your decision and withdraw your consent at any time during the trial, without affecting your relationship with your doctor or the health service or causing any harm to your treatment.

Collected material storage
We will store the blood samples in case the tests have to be repeated in the event of a problem in the laboratory. If another trial needs to use your stored blood, it will be submitted for approval by the Trial Ethics

Committee (CEP) and you will be asked if you agree with this new evaluation of your blood, and you must sign an authorization document again.

This proposal was reviewed and approved by the Trial Ethics Committee (CEP) of the National Institute of Infectious Diseases Evandro Chagas – Fiocruz, which is a committee whose function is to ensure that trial participants are protected from possible harm. If you would like to know more, please contact the Trial Ethics Committee of the Evandro Chagas National Institute of Infectious Diseases, Directors Building – 1st floor. Av. Brasil, 4365, Manguinhos. ZIP CODE: 21040-360 - Rio de Janeiro – RJ. Telephone Numbers: (21) 3865-9585 and 38659107 - Fax 3865-9567. If you wish, refer to the National Trial Ethics Commission (Conep): Phone: (61) 3315-5878 / (61) 3315-5879. E-Mail: conep@saude.gov.br.
This trial was also reviewed by the World Health Organization (WHO) Ethics Review Committee, which is supporting this study.
You can ask me more questions about any part of the trial if you wish. Do you have any questions?

You have the following authorization options:
( ) I agree to participate in this trial, but I DO NOT AUTHORIZE the storage of my biological material (my blood), which must be discarded at the end of the trial.
( ) I agree to participate in this trial and I AUTHORIZE the storage of my biological material (my blood), my consent being required for each new trial, which must be approved by the responsible CEP.

Disposal of stored material will be authorized in the following situations: at any time you wish your material to no longer continue in the search. In the event of death or incapacitating condition, the rights to the stored material must be given to: _____.

Any questions during the implementation of the project can be answered by Israel Molina Romero, responsible general researcher, on the telephone (31) 995057130 or by _____, responsible for the study in your country, on the telephone number _____.
You can also contact the Trial Ethics Committee of the Evandro Chagas National Institute of Infectology using the contacts described above.

Part II: Consent

I have read the information above or it has been read to me. I had the opportunity to ask questions about it and all the questions I asked were answered to my satisfaction. I confirm my voluntary consent to participate in this trial and understand that I have the right to withdraw from the study at any time without this decision in any way affecting my medical care. I received a signed copy of this Informed Consent Form, which all pages must be initialed by me and the responsible researcher.

Participant's name: _____

Signature of the participant: _____

Date: ____ / ____ / _____
Day Month Year

If illiterate:
I witnessed the consent form being read accurately to the potential participant and the individual was given an opportunity to ask questions. I confirm that the individual has freely given consent.

Participant Fingerprint

Witness Name: _____

Signature of the witness: _____

Date: ____/_____/_____
Day Month Year

Participant's fingerprinting

Statement by the researcher / person who obtained consent

I have accurately read the information sheet to the potential participant and, as best I can, have made sure that the participant understands everything that will be done.

I confirm that the participant had the opportunity to ask questions about the study, and that all questions asked by the participant were answered correctly and as best as possible. I confirm that the individual was not coerced into giving consent and that consent was given freely and voluntarily.
A copy of this informed consent form was provided to the participant.

Printed name of the researcher / person who obtained consent:

_____

Signature of the researcher / person who obtained consent:

_____

Date: ____/_____/_____
Day Month Year