Pilot phase 2 trial to optimise pharmacometric assessments in Chagas disease
(CHARM PLATFORM: CHAgas disease PharMacometrics)

Short title:
CHARM PLATFORM

PARTICIPANT INFORMATION SHEET

1. Why is this research being conducted?

Chagas disease is caused by a parasite named *Trypanosoma Cruzi* and vector transmited by an insect known as "kissing bug". The lack of a comprehensive understanding of this disease has slowed the discovery of new treatments. It is generally agreed that new, safe, effective, and reasonably priced drugs to treat Chagas disease are needed.
It is currently very difficult to define whether a new drug is effective to treat Chagas. A significant drop on the antibodies level and absence of detectable parasites in the blood are considered currently by regulatory authorities, such as the US FDA, as the most important determinants of treatment response. Unfortunately, as this significant drop in antibodies can take too long to happen, is not quick enough to select drugs when these have recently been developed. We designed this study to analyse the parasite changing aspects and how these relate to treatment drugs because we think that this information might help selecting new treatments in more precisely. You will go through different stages during this study and each stage evaluates different aspects of the parasite behaviour and treatment response.

The purpose of this study is to evaluate *Trypanosoma Cruzi* dynamics in patients with chronic chagas disease and its response to different treatments. We expect to enrol 75 subjects in this study.

After completing the study, you will receive definitive treatment as per national guidelines.

2. Why have I been invited to take part?

You have been invited because you have Chagas disease and live in the Belo Horizonte metropolitan area. The study staff will explain the study to you and answer any questions you may have. If you are interested in joining the study, you will be asked to follow study specific procedures and sign the informed consent form. You will go through study visits as below.

3. What will happen to me if I take part in the research?

During your consultation with your doctor, you have been invited will be invited to attend today at Fiocruz - Research Center Renê Rachou, where we will explain the study and do a ECG and a blood sample extraction to measure how many parasites you have in the blood. If you are female at childbearing potential, we would like to perform pregnancy test. You will be invited to sign the informed consent for all the procedures.

However, after these initial determinations, if the amount of parasites circulating in blood are enough to be studied, we will let you know. If you are happy to take part in the trial we will give you the next appointment date, otherwise, you can retract your participation at that stage.

If you are happy to take part in the research, you will be either followed up by a study nurse at your domicile or seen at the outpatients clinic. The visits will be bi-weekly during the first month and there will be blood extractions at each visit to determine how the parasites circulate, prior to receiving treatment. At

the end of this month you will be randomly assigned (like the toss of a coin) to receive a dose of treatment either: Benznidazole or Nifurtimox or Posaconazole and we will extract blood 4 times that day. The following 6 days, you will be seen daily and we will take only one blood sample per day. Finally, we will extract bloods every other day the following week and once a week until the 12th week.

If you agree, we would like to collect blood samples for some certain time points to measure drug level of treatment.

During the study participation, the study nurse will remind you not to take herbal medicines, food supplements and energy drinks for a period of 4 months after initiation of treatment.

Each visit should take approximately 20 minutes. And the total time required to participate in the study is approximately 4 months.

After finalising your participation in the trial, you will receive a full course of treatment as per national guidelines.

4. Are there any potential risks in taking part?

You may experience mild discomfort when a blood sample is taken. It is possible (although not likely) that you will have a bruise during this process. Your research doctor and staff will do their best to minimize any possible discomfort or harm to you. The total volume of blood collected during the trial is about 460 ml.
All drugs used in the study (Benznidazole, nifurtimox and posaconazole), are well-known drugs and their most common reactions include: hypersensitivity, mainly in the form of a rash (29–50%), digestive intolerance (5–15%) and symptoms general conditions such as anorexia, asthenia, headache and sleep disorders (40%). Bone marrow neuropathy and depression are considered rare. Treatment is interrupted in 9–29% of cases, although these reactions are reversible and severity only occurs in less than 1% of cases. In cases of vomiting after taking the study medication, you should consult your research doctor, who will advise you if you should take the medication again. Anyway, because you take a much lower than normal dosage, you would not be expected to have any adverse reactions. In any case, you are encouraged to tell your medical researcher anything that might bother you during the study. On the other hand, your medical researcher can interrupt your participation in the study if he deems it necessary.

5. Are there any benefits in taking part?

There will be no direct or personal benefit to you from taking part in this research. However, there is the chance of contributing to science. You may have the satisfaction of contributing to clinical research that can contribute to the advancement of therapy, improving the lives of other future patients affected by the same disease. Moreover, for the simple fact that you are taking part in a clinical trial, you will be monitored more frequently and in greater detail than usual.

6. Do I have to take part?

No. Your participation in this study is entirely voluntary. You can ask questions about the research before deciding whether or not to take part. If you do agree to take part, you may withdraw yourself from the study, without giving a reason and without negative consequences, by advising us of this decision. If you don't take part in this study, there won't be any effects on your medical treatment both now and in the future, including the relationship with the study doctor. You will be examined for diagnosis and treatment of your disease as normal standard care.

The study doctor and the study sponsor have rights to withdraw you from this study if it's considered that it is in your best interest.

Additional information concerning changes of this research study you are participated in which may directly or indirectly impact you, the study doctor will notify to you immediately and openly.

7. Expenses and payments

It should not cost you any money to join the study. You will be provided with the reasonable compensation for the cost of transportation and any lost work wages during the study participation.

If you withdraw or are withdrawn from the study before the study ends, then you will be compensated for the time you were actually in the study.

In case, you are experiencing any side effects or harms which are directly caused by the study, we will treat you according to the standard treatment free of charge.

8. What happens to the data/sample provided?

All of the information obtained during the study will be kept strictly confidential. There may be report of information in academic publications, but it will not include any information identifying you that you have participated in this study. Identifiable data will be removed whenever possible and any data transfer will be done securely under the Brazilian data protection law.

If you consent, some of your collected blood will be stored in a DNA bank and will be used in the future to help identify factors determining disease outcomes. Any additional testing apart from what indicated in this study will be tested only after permission by the IRB/IEC.

The research team will have access to the research data. In addition, the monitor(s), the auditor(s), members of the Ethics Committee, and regulatory authorities may be able to access your medical and study records for monitoring and/or audit of the research. However, any information is still confidential and your name will not be identified in the publications of this research outcome.

Research data (including consent forms) will be stored for at least 5 years after publication or public release of the work of the research or the period stablished by Brazilian laws whichever is longer.

We would like your permission to use anonymised data in future studies, and to share data with other researchers (e.g. in online databases). All personal information that could identify you will be removed or changed before information is shared with other researchers or results are made public.

Please bear in mind that the data collected until the point of withdrawal will still be analysed unless you request us not to do so.

9. Will the research be published?

The research may be published in academic publications.

10. Who is funding the research?

This protocol is funded by The Wellcome Trust.

11. Who has reviewed this study?

This study has been reviewed by, and received ethics clearance through, Oxford Tropical Research Ethics Committee and local Ethics committee.

12. Who do I contact if I have a concern about the study or I wish to complain?

If you have any inquiries relating to the study now or in the future, or when experiencing injury/illness from the study, you can contact : *Study team contact information.*

Or if you haven't been treated as specified in this information sheet or you wish to know the participant's rights, contact the Ethics Committee : *Ethics committee contact information.*

13. Data Protection

The University of Oxford is responsible for ensuring the safe and proper use of any personal information you provide, solely for research purposes