Patient Information Sheet & Informed CONSENT Form – Adults/representatives

Study Title: Metformin as adjunctive therapy in overweight and obese patients with dengue: an open-label safety and tolerability trial

Short Title: Metformin in **D**engue with **O**besity (MeDO)

OxTREC reference number: OxTREC 36-19

Please read the following information carefully. Do not hesitate to discuss any questions you may have with the study staff or your doctor.

Introduction

We would like to invite you/your child to take part in a study looking at the safety and the tolerability of metformin in dengue treatment in overweight/obese patients. The clinical symptoms, immune responses and overall severity of dengue collected from you/your child and other patients in this trial (the treatment group) will be compared to those of obesity patients in whom the metformin therapy is not provided (non-treatment group), in order to better understanding whether metformin is safe and acceptable for dengue treatment in obesity people. You are being invited to take part in this study because your doctor suspects that you might have dengue. If you are considering consent on behalf of your child or relative, please read this form in their consideration.

Being a part of this study is entirely your choice. We are asking you to read (or have someone read to you) this form carefully so that you can fully understand this study and what it requires. If you agree (or give permission for your child) to take part in this research, you will be asked to sign (or add your fingerprint to) this form. Please ask us to explain anything you may not understand. You will be given a copy of this form to keep.

This study will include 60 overweight/obese participants with dengue and is conducted by the Hospital for Tropical Diseases (HTD) and the Oxford University Clinical Research Unit (OUCRU), Ho Chi Minh City, Vietnam. The study has been reviewed and approved by the ethical committees of HTD, Vietnam Ministry of Health and Oxford Tropical Research Ethics Committee (OxTREC).

What is the reason for doing the study?

Dengue is a disease caused by a virus that is transmitted between humans through the mosquitoes' bites. The disease symptoms can range from very mild illness, which is hardly noticeable, to more significant symptoms, including high fever, headache, nausea, rash and joint pain. In a small proportion of patients, dengue can cause severe complications such as bleeding, blood clotting problems, and leaky blood vessels that may threaten patients' life. There is a suggestion that over-weight/obese patients are more likely to have severe disease compared to non-obese patients. This may make the management of dengue in over-weight/obese patients more complicated than that of non-obese individuals.

In addition, currently there are no specific drugs or effective vaccines available for dengue. Metformin is a common drug that is widely used to treat diabetes; however recent studies have

shown they have additional benefits in infectious illnesses, such as tuberculosis, hepatitis C and dengue. Metformin is generally a safe medication in both adults and children, with very low risk of reduction in blood glucose level and other serious side effects. In addition, this drug also shows benefits on weight in people with obesity. In this study, we hope to learn whether metformin is safe and effective to treat over-weight/obese patients with dengue.

What will happen if I participate in the study?

Whether or not you/your child join the study, you/your child will receive the standard treatment for dengue according to the guidelines of the Viet Nam Ministry of Health.

If you/your child are in the study, you/your child will need to stay in hospital for at least 5 days (beginning today).

At enrolment:

- The study doctor will record all your/your child's symptoms. Two blood samples (about 3ml in total, equivalent to a half of teaspoonful) will be taken to confirm the clinical diagnosis and to perform the clinical tests relevant to dengue. We will also perform the pregnancy test in the urine samples of all female patients. These clinical symptoms and tests will help us decide whether your/your child's health status could meet all safety requirements for the treatment with metformin.
- If you/your child are eligible for the treatment, the first dose of metformin will be given orally with a light snack. Three additional blood samples (7.5ml in total, equivalent to one and a half of teaspoonful) will be taken before you take drugs for testing the blood cells and for measuring your body's responses to the virus infection.
- If you/your child are not eligible for starting treatment with metformin, all study procedures will be stopped and you/your child will receive the standard care for your illness.

During hospitalisation:

- Standard care for dengue that you/your child will receive:
  - You/your child will be reviewed every day by a study doctor until the temperature settles and you/your child have recovered fully.
  - Each day, a small blood sample will be taken before the time you take the drug to check that the illness is not affecting the blood cells, in particular the platelets, which are special cells that help the blood to clot if you/your child cut yourself/themselves.
  - Every other day, your/your child's blood will also be checked to assess liver and other important organ systems that are sometimes affected by dengue.
  - An ultrasound scan of liver and internal organs will be done to check if there are any signs of leaky blood vessels.
- Study-specific procedure:

- At the same time of blood taking for the hospital routine tests, the research samples (1.5 – 5 ml, a teaspoon/day depending on study day) will be collected to monitor the safety and to learn about how the drug works.
- Metformin will be given orally (one up to three tablets every day, based on weight) for up to day 5 of study. The duration of treatment will depend on the clinical evolutions, and lab test results collected from you/your child.

After day 5 of study:

- If your/your child's general status fits to discharge criteria, the daily assessments, metformin use and blood tests will stop. However, around three to four weeks after you/your child had fever, we would like to see you/your child for another visit, to check that all is well. At this time, we would like to take two final blood samples (~ one and half teaspoon in total) to confirm the diagnosis and to better understand how severe the infection has been.
- If you/your child have to stay in the hospital for more than 5 days, you/your child will still be taken care of until discharge by the study doctors. However, no further assessment, metformin use or blood tests will be performed for the research purpose from this point.

What will happen to the samples taken?

Samples will be used to give results that help the doctor decide how to care for you/your child as well as answer the study questions. The tests that help us to better understand the responses of the body to the virus infection and how the drug works will be done in collaboration with the researchers in the UK and Singapore. However, we will send the samples that are labeled with the study code only. Your/your child's name and any identifiable information will not be shared.

If there is any blood remaining after the above tests have been done, it may be stored for future researches on infectious diseases to provide doctors more knowledge on how dengue affects patients' organ systems and what doctors should do to manage the disease more effectively.

In addition, a blood sample will be stored for the genetic study to understand why some people get sick from this disease, while others do not. This will involve studying the DNA from your/your child's cells.

Both the genetic study and the future research could be done outside Vietnam. You can choose if you agree to these by marking the last page of this form.

What are the possible risks or side effects?

If you choose (or give permission for your child) to participate in this study, you/your child will be reviewed every day for clinical assessments and blood tests. Although having blood samples taken can be uncomfortable for a short time and may leave a bruise, this amount of blood is quite safe to be taken from a patient from 10 years of age or older and will not cause any ill

effects. Ultrasound scans will be done, but these scans are not painful and can be helpful to the doctor in making decisions about your/your child's care.

The most common side effects of metfromin are digestive problems such as diarrhea and vomiting. However, there are very few risks to taking the short course of metformin that we are using in this study. Metformin may cause reduction in your/your child's blood glucose level and another severe condition called lactic acidosis, which results from a buildup of lactic acid. These effects are very rare but are potentially serious, however we will watch you/your child very carefully and check blood tests regularly, including daily glucose and lactate levels, so that we can stop the tablets if there is any problem. If you/your child have any problems which may get worse by using metformin, or if you are pregnant or breastfeeding we cannot give you metformin drugs. The study doctor will go through this with you.

Genetic blood tests which look at your DNA are not part of routine care. Some people may consider it an invasion of privacy to have studies done on their DNA. Results will be made available to other researchers but you/your child will not be identified and no one will know whose genetic information it is. If you do not agree for these genetic tests to be conducted, you/your child may still take part in the study.

In the unlikely event that you are harmed as a result of participating in this research study, the sponsor will be responsible for the reasonable cost of your care.

What are the possible benefits and compensation of the study?

You/your child may benefit from being closely monitored by experienced doctors and nurses during the course of treatment. Tests required by the study are helpful in following up and treating your/your child's illness.

You will not have to pay for any extra costs if you/your child participate in the study. Your hospital costs for treatment and tests will be covered by the study from enrolment until discharge, and for any study related procedures or visits.

When you/your child return to the hospital for study scheduled follow-up visits, we will reimburse you a travel fee according to patient's domicile (as per OUCRU financial policy).

Do I have to participate?

Your participation is completely voluntary. If you do not want to be in the study or if at any time during the study you decide to stop participating, the doctors will respect your decision. In both cases you/your child will receive standard medical treatment. You do not need to give any reason for withdrawal.

You may also choose withdraw your/ your child's information and blood samples if you want but this withdrawal is only valid before analyzing stage.

The research doctors can withdraw you/your child from the study if they think your/your child's health is placed at risk due to study participation. The sponsor or the ethics committees can also stop the study if they consider it necessary.

If you agree to be in the study, you will be responsible for following the study schedule of tests and taking your drugs.

Will anyone know that I am participating in this study?

In this study we will collect medical information about you/your child. However, we assure that all information about you/your child will be kept confidential – the information will only be identified by a code number and we will not use your/your child's name or let anyone identify you/your child. This information will be kept in a safe place where only project staff can access it. Your/your child's medical records will be reviewed in strict confidence by those who are working on this study and may also be reviewed by the ethics committees and health authorities reviewing the study.

Results from this work will be published in due course in articles and medical journals, and/or may be placed on the internet, but no one will know whose information it is and you/your child will not be identifiable.

How will study results be disseminated?

Results of this study will be published in international peer reviewed journals. Your/your's child name will not be used in any of publications about this study.

Has the study been reviewed by an ethics committee?

The study has been reviewed and approved by the Ethics Committee of HTD, Vietnam Ministry of Health and the OxTREC.

What if I have more questions?

- You are encouraged to ask any questions related to this study during the time of participation. If you have any questions about this program, its procedures, risks and benefits, or alternatives please call Dr. Dong Thi Hoai Tam at 0918 141 641.
- If you have any questions about your rights as a subject in this study, and want to speak to someone outside of the program you may contact the OUCRU Clinical Research Unit at +84 3924 1983.

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.

Thank you for your time and your consideration to participate in this study.

INFORMED CONSENT FORM

To be signed by all participants or the parent/guardian/representative

Study Title: Metformin as adjunctive therapy in overweight and obese patients with dengue: an open-label safety and tolerability trial

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SCREENING ID: [__|__]-[__][__][__]

- I have read the information given to me and freely agree (give permission for my child) to be in this study. I also have had a chance to discuss it with the study staff.
- I have been told about the risks and benefits. I got answers that I could understand to all my questions.
- I know who to contact if I need more information. I understand that confidentiality will be preserved.
- I understand that I (my child) can withdraw from the study at any time and it will not affect my (my child's) future care.
- I agree that all information collected on me (my child) can be made available to others in the future (open access) provided no one can identify me (my child) from the details provided.

Please check the boxes below:

- ☐ YES or ☐ NO I AGREE (for my child) to take part in this study
- ☐ YES or ☐ NO I AGREE that the samples taken can be used for genetic testing and that these tests may be done outside of Viet Nam.
- ☐ YES or ☐ NO I AGREE that my/my child's clinical information and any residual samples can be used for other research studies, including genetic testing, and that these studies may be done outside of Viet Nam if approved by an ethics committee.
- If I decide to stop the study:

  ☐ YES or ☐ NO I AGREE that the information and blood samples collected up to the point when I (my child) stop, may continue to be used.

Participant:

By signing my name here, I confirm what is written above and that I have a copy of this form to keep until my part in the study ends.

x_____	x_____	___/____/_____
Participant Signature/Finger print	Name	Date of Signature

OR – If someone else gives consent on behalf of the participant (eg: parent or guardian for someone under the age of 18 years or relatives/legal representative of adult patient who is unable to give consent):

Participant's name: x _____	
x_____ Signature of Person Giving Consent	x_____ Name of person giving consent:
Relationship to Participant: x_____	Date of Signature: ___/____/____

See associated <u>informed ASSENT form</u> for person 10 – <18 years of age ☐

Investigator/Designee:

I, the undersigned, have fully explained the relevant information of this study to the person named above and will provide her/him with a copy of this signed and dated informed consent form.

x_____ Investigator/Designee's Signature	x_____ Investigator/Designee's Name	____/____/_____ Date of Signature

Witness: *(If the person giving consent cannot read the form her/himself, a witness who is independent of the study must be present and sign here)*

I was present throughout the entire informed consent process with the participant. This form was read accurately to the volunteer, all questions from the volunteer were answered and the volunteer has agreed to take part in the research.

x_____ Witness's Signature	x_____ Witness's Name	_____/_____/_____ Date of Signature