UTH NRO
University Teaching Hospital
Neurology Research Office

Informed Consent Form (ICF) for the parents/guardians of children between the ages of 2 and 11 years presenting to UTH Children's Hospital with the combination of malaria and new-onset central nervous system (CNS) impairment, and who are interested in participating in the Malaria Fever Control Study.

Principal Investigator:	Gretchen L. Birbeck, MD MPH DTMH
Organization:	UTH Neurology Research Office (UTH-NRO)
Sponsor:	National Institute of Neurologic Disorders and Stroke (NINDS), USA
Proposal:	Aggressive Antipyretics in CNS Malaria: a Randomized-Controlled Trial Assessing Antipyretic Efficacy and Parasite Clearance
Consent Form Version:	v4.5 (13 Dec 2018)

This Informed Consent Form (ICF) has two parts:
- Information Sheet (to share information about the study with you)
- Certificate of Consent (for signatures if you agree that your child may participate)

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction
Your child has malaria and needs admission to the hospital for care. We are seeking your permission for your child to participate in a clinical trial of antipyretics (Panadol and Brufen) for fever reduction.

Purpose
Panadol and Brufen are medications commonly used for treating fevers in children, but usually children with malaria only receive Panadol and they are only given a medication for fever reduction if their fever reaches 38.5ºC or higher. In previous research we found that children with higher fevers during their acute malarial illness had a greater risk of developing neurologic problems after they recovered from the infection and we know that in other conditions affecting the nervous system, therapies that prevent the patient from becoming febrile result in better neurologic outcomes.

Type of Research Intervention

This is a randomized, double-blinded, placebo-controlled study comparing 'usual care' for fever in children with CNS malaria to a more aggressive approach that may minimize both fevers and the complications associated with fever.

Participant selection
Your child has malaria and needs admission to the hospital for care.

- ***Questions to assess understanding:*** *Do you know why your child has been identified as a potential research participant? Do you know what the study is about?*

Voluntary Participation
Your child's participation in this research study is entirely voluntary. If you do not wish for your child to participate in this clinical trial, your child will continue to be cared for here. No care will be withheld.

- ***Questions to assess understanding:*** *If you decide that you do not want your child to take part in this research study, do you know what your options for him/her are? Do you know that you do not have to accept that your child takes part in this research study? Do you have any questions?*

Information on the Trial Drugs: Panadol and Brufen
1) This study is a phase III (3) clinical trial. "Phase III" means that we are assessing the study drugs for their efficacy (ideal conditions), effectiveness (real world conditions) and safety, and are doing so in what are recommended doses for each drug.
2) The two drugs to be used, Panadol and Brufen, will be used in approved doses for an approved purpose (fever). Because this is a double-blind study, the clinical staff and you should and will not know which study participant is in each group (usual care vs. aggressive antipyretics). Thus, the drugs required re-packaging, so the drugs were purchased in the USA and then re-packaged by a special compounding pharmacy also in the USA. The re-packaged drug labels include the individual participant's study ID numbers but do not tell what is inside the bottle (i.e., the real drug or instead a placebo), only the study statistician knows this blinding information.
3) Both study drugs (Panadol and Brufen) have been used for many decades throughout the world and have been shown to be very safe when used in recommended doses for approved reasons.
4) Known side-effects/toxicity of the two study drugs: this is described below in the "Side Effects, Risks and Discomforts" section. All other medicines that will and may be used to treat your child, such as to treat your child's malaria infection and for seizures, are those approved for use by the Zambia Medicines Regulatory Authority (ZaMRA).

Procedures and Protocol

A. Unfamiliar Procedures
In this study, we are going to randomly assign children to one of two groups, either the 'usual care' group, or the 'aggressive antipyretic therapy' group. In the 'usual care' group, children will get treatment with Panadol if they get a temperature of 38.5ºC or higher, *and* will also be cooled with a fan if the temperature remains high on Panadol alone. In the 'aggressive antipyretic therapy' group, children will get Panadol and Brufen immediately and then every 6 hours for 72 hours even if they do not have a temperature above 38.5ºC. If their fever remains high they will also be cooled with a fan. We do not know if giving Panadol and

Brufen immediately and together will result in less fevers. This study is designed to determine if there is a reduction in fevers in the children who receive aggressive antipyretic therapy vs. routine care. All the children who have a fever will receive active medication to reduce that fever. Some will receive the active medication before a fever reaches 38.5, if their temperature goes over 38.5 they will be given inactive medication (placebo). This is the aggressive medication group. The second group, usual care, will receive inactive pills (placebo) initially, and active medication if their temperature goes above 38.5. We will not know which group your child is in. It is important to remember that all children who have a fever will receive treatment for their fever. If you agree to allow your child to participate in this research study, your child will be assigned by chance (like flipping a coin) to receive aggressive antipyretics vs. 'routine care'. Neither you nor your child's doctor will know which group he or she is assigned to.

B. Description of the Process

The medications are both liquids to be given by mouth every 6 hours for the next 3 days. If your child is unable to swallow the medication, we will place a tube in your child's nose going into the stomach and the medication will be delivered through that tube until your child wakes up. Once your child is awake and able to take the medication, we will remove this tube. All children in this study will have a small sticker placed in their axilla and attached to a machine to measure their temperature for 3 days. All children in this study will have blood taken every 6 hours by finger pricks to check the parasite count and glucose and kidney function. The total volume of blood taken over the full course of the study will be less than 2 mls. If your child is confused or sleepy from the malaria and cannot be easily awakened, we will also place some metal discs on the head attached with glue to record your child's brain activity. This is to measure continuous electroencephalogram (EEG) activity, or the electrical activity in the brain. The EEG will allow us to know if your child is having any seizures that we cannot see by just looking at the child. Seizures can happen in the brain and not be apparent by just looking.

Duration

Your child's participation in the study would last for 72 hours (3 days). After that, if your child requires continued hospitalization, s/he will receive all standard care as available at UTH. If there is need to monitor and/or manage study-related adverse events, a 30-day follow-up visit may be scheduled according to each study site's clinical care protocol and at the discretion of the study clinician discharging the patient.

- ***Questions to assess understanding:*** *Can you tell me if you remember how long your child would need to be in the study? How often would we be giving the study drugs to your child? How often would we need to complete finger pricks to check for malaria parasites and for the other study tests? After your child completed the in-hospital study period and was discharged, would we need to see your child again? Do you have any other questions? Do you want me to go through the procedures again?*

Side Effects, Risks and Discomforts

What are the specific risks to your child if he/she participates in this research project? Research staff will be reviewing your child's medical records and recording information important for the study in a research file. To limit the risk to your privacy, when we record data in the research file, a study ID and not your child's name will be recorded. If your child is in this study and they are unable to swallow, then they will have a nasogastric tube (NGT) placed so that the study medications can be given to them. If your child is not in the study, no

NGT will be placed today. This tube may cause nasal or throat irritation or bleeding. This is usually a minor problem but in a small number of cases this could result in the medication going into the child's lungs and would require removal of the tube and further treatment, like suction. As part of the research, when your child is pricked for malaria parasite counts, we will take an extra small tube of blood (*hold up capillary tube*). Malaria can cause problems with bleeding, poor liver function and poor kidney function. It is possible that the medications given in this clinical trial could worsen the problems caused by malaria. The Brufen could cause your child to have problems with bleeding. We will monitor for this closely and if we see any signs of problems with bleeding, we will stop the study medications. The glue and metal discs for the EEG are not harmful although the glue has a strong smell and some people get mild skin irritation where the glue and electrodes are placed. The Panadol and Brufen are generally safe medications but stomach irritation and stomach pain can result from taking these medications. These medications might also worsen problems the malaria causes to your child's liver and kidneys. We will monitor for signs that the medications are causing problems and stop treatment if needed. If your child experiences any adverse effects from the drug, we will provide care and treatment plus any other assistance as may be deemed necessary.

- ***Questions to assess understanding:*** *Do you understand that, while the research study is ongoing, no one would know to which group (either the 'usual care' group or the 'aggressive antipyretic therapy' group) your child is assigned? Do you understand that your child may have some unwanted side effects from the medicines? Do you understand that these side effects can happen whether or not your child is in the research study? Do you have any questions?*

Benefits

What are the possible benefits to your child if he/she participates in this research project? The EEGs may alert us to seizures we cannot detect otherwise and will allow us to treat these seizures, which might otherwise go without treatment possibly resulting in brain injury. If your child is randomized to aggressive antipyretics, your child may be more comfortable during this admission since in addition to fever reduction, these medications also treat pain (e.g. the headache usually associated with malaria).

Reimbursements

There are no anticipated costs to be incurred by individual as a direct result from participating in this study. If you agree for your child to be in this study, we will provide you and your child with transportation home or funds for transportation home.

- ***Questions to assess understanding:*** *Can you tell me if you have understood correctly the benefits that your child will have if you allow him/her to take part in the study? Do you know if the study will pay for your and your child's travel costs and your time lost, and do you know how much you will be reimbursed? Do you have any other questions?*

Confidentiality

The information about your child from this study will be kept here at Queen Elizabeth Central Hospital (QECH) or University Teaching Hospital (UTH) in locked study offices. This information will be used by researchers on this study. In addition, this information will be made available to the Independent Study Monitors, the Research Ethics Committees at this hospital and the University of Rochester, Michigan State University, the Malawi Pharmacy Medicines

& Poisons Board, the Zambia Medicines Regulatory Authority and the US National Institute of Health. Your privacy will be protected to the maximum extent allowable by law. By signing this consent form you are agreeing that these entities can have access to your child's records. For all other purposes, your child will be assigned a study identifier and information sent outside of QECH will include this identifier, not your child's name. The study records will be kept for a minimum of three years following the completion of the study.

- ***Questions to assess understanding:*** *Did you understand the procedures that we will be using to make sure that any information that we as researchers collect about you and/or your child will remain confidential? Do you have any questions about them?*

Sharing of the results

While your child is participating in this study, we will provide you immediately with any new findings about this study or the antipyretic medications. A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Right to Refuse or Withdraw

If you agree to your child's participation now, but later decide you do not wish for your child to be part of our study, you may withdraw the child from participation at any time. On the side of investigators, there are no foreseen circumstances under which the principal investigator may terminate a subject's participation in the study.

Alternatives to participating

If you do not wish for your child to participate in this clinical trial, your child will continue to be cared for here. No care will be withheld. Your child's fevers will be treated with the 'usual care' detailed above. This will include treatment with Panadol, additional treatment with Brufen if Panadol does not lower the fever, and the usual amount of EEGs, temperature monitoring, an additional small tube of blood when your child is getting a finger prick for parasites, and an NG tube if your child cannot swallow the medicines.

Who to Contact

If you have any questions about your child's participation as a subject in human research or need to contact someone about a research-related injury, you may contact the investigators in charge. Or, you may contact the Chair for the Research Ethics Committee:

Dr. Gretchen Birbeck 0978-086957 Dr. Manoj Mathews 0977-625727 Dr. Musaku Mwenechanya 0966-766052 UTH Neurology Research Office Private Bag RW-1X Ridgeway UTH Lusaka, Zambia	UNZA Biomedical Research Ethics Committee Ridgeway Campus PO Box 50110 Lusaka, Zambia Tele 01-256067 Email: unzarec@unza.zm

PART II: Certificate of Consent

Parent/Guardian Certificate of Consent

I have been invited to have my child participate in research of treatment of fever for malaria in children also suffering from related brain dysfunction. I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily for my child to participate as a participant in this study.

Print Name of Participant _____

Print Name of Parent or Guardian _____

Signature of Parent or Guardian _____

Date _____
Day/month/year

If Parent/Guardian is Illiterate

A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb print as well.

I have witnessed the accurate reading of the consent form to the parent/guardian of the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print Name of Witness_____ AND Thumbprint of parent

Signature of Witness _____

Date _____
Day/month/year

Statement by the Researcher/Person Taking Consent

I have accurately read out the information sheet to the parent/guardian of the potential participant, and to the best of my ability made sure that the person understands that the following will be done:

1. Randomization
2. In-hospital for 3 days study
3. Everyone gets standard/usual treatment, but some children will also receive additional treatment for their fevers

I confirm that the parent/guardian was given an opportunity to ask questions about the study, and all the questions asked by the parent/guardian have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/Person Taking the Consent _____

Signature of Researcher/Person Taking the Consent _____

Date _____
Day/month/year

Screening number: **sZ __ __ __**

Study Identification (ID) number: **Z __ __ __**