OXFORD TROPICAL RESEARCH ETHICS COMMITTEE (OxTREC)
Application Form for Minimal Risk Studies

The University of Oxford places a high value on the knowledge, expertise, and integrity of its members and their ability to conduct research to high standards of scholarship and ethics. The research ethics clearance procedures have been established to ensure that the University is meeting its obligations as a responsible institution. They start from the presumption that all members of the University will take their responsibilities and obligations seriously and will ensure that their research with human participants is conducted according to the established principles and good practice in their fields and in accordance, where appropriate, with legal requirements.

ONLY TYPEWRITTEN APPLICATIONS THAT ARE SENT BY EMAIL WILL BE ACCEPTED.

PLEASE ENSURE THAT YOUR FORM BEARS THE NECESSARY SIGNATURES.

This form is designed for **minimal risk medical or health-related research** that will be conducted **outside the European Union** (or research that is funded by US federal funding agencies). Please visit the OxTREC application process page to view the full set of criteria for minimal risk applications. Applicants planning research that carries more than minimal risk should complete the full OxTREC application form.

Before completing this application form, please consult the following guidance documents available on the Research Ethics web pages:

- OxTREC minimal risk criteria and approval process
- Glossary
- Frequently Asked Questions

Please complete the sections that follow.

SECTION A1: FILTER FOR STUDIES THAT ARE NOT APPROPRIATE FOR OxTREC REVIEW
1. Does your study involve human participants outside the EU? YES
2. Is your study funded by the US National Institutes of Health (NIH) or another federal funding agency? NO
If you have answered '**no**' to questions 1 **and** 2, your study **does not fit the criteria for ethical review by OxTREC**. It may instead require review by another University ethics committee. Please consult https://researchsupport.admin.ox.ac.uk/governance/ethics/apply for further details. If you have answered 'yes' to at least one of the questions above, please proceed to the next section.

SECTION A2: FILTER FOR STUDIES THAT DO NOT REQUIRE ETHICAL REVIEW
1. Is your study an audit or service review? Please refer to the OxTREC application process page for definitions of these terms. NO
2. Does your study involve data only (i.e. no biological samples/specimens), and are all the data about people to be used in the study previously collected anonymised data which no one involved in the study can trace back to the individuals who provided them (e.g. census data, administrative data, secondary analysis)? Please refer to the definition of personal data in the CUREC glossary and FAQ A.3 for further guidance. NO
If you have answered '**yes**' to either of these questions, you **do not need to submit** your study for ethical review. If you have answered 'no' to both these questions, please proceed to the next section.

SECTION A3: FILTER FOR STUDIES THAT REQUIRE FULL COMMITEE REVIEW
1. Does your study involve a drug or medical device? NO
2. Does your study involve an invasive procedure (class A in the CUREC glossary)? NO
3. Does your study involve venous blood sampling from children, or from adults who are unwell? NO
4. Does your study involve venous blood sampling from **healthy** adults to a volume **greater than 1ml/kg in 8 weeks**? NO
5. Does your research raise issues relevant to the **Counter-Terrorism and Security Act (the Prevent duty)**, which seeks to prevent people from being drawn into terrorism? Please see advice on this on our Best Practice Guidance web page. NO
If you have answered '**yes**' to any of these questions, then your study needs to be **submitted for full committee review**. Please stop work on this application form and refer to the OxTREC application process page for details of how to apply for full committee review. If you have answered 'no' to all of these questions, please proceed to the next section.

SECTION B: INVESTIGATOR AND STUDY DETAILS	
Principal investigator/student researcher name and title	Dr George Busby, Senior Research Associate in Translational Genomics
Full title of project	The Mobile Malaria Project
Short title of project (this should be in lay language and suitable for use on the PIS and consent form)	The Mobile Malaria Project
Study design (e.g. retrospective review)	Cross-sectional, opportunistic genome sequencing of *P.falciparum* parasites and African Anopheline mosquito.
Name and title of supervisor (for student research projects only)	N/A
Degree programme (for student research projects only)	N/A
Department or institute	Big Data Institute, Nuffield Department of Medicine
Address of PI/student researcher for correspondence	First Floor, Big Data Institute, Old Road Campus, Old Road, Oxford, OX37FZ
Email and telephone contact of PI/student researcher	george.busby@bdi.ox.ac.uk 07786 638236
Names and status of other investigators taking part in the project	Jason Hendry, DPhil Student (genomic medicine and statistics) Isaac Ghinai, Academic Clinical Fellow in public health

SECTION C. DESCRIPTION OF STUDY

Brief (no more than 500 words) description of the study, its purpose, and the use to which the results/data will be put

Purpose

The Mobile Malaria Project is a scientific expedition to Africa supported by the 2018 Royal Geographical Society Land Rover Bursary. We have two main aims:

Aim 1. Communication of the current status of malaria in Africa

We will document and communicate the past success and future challenges of malaria control in southern Africa. The team will drive from Namibia to Kenya, via Zambia and Tanzania, from regions of low to high malaria prevalence. We will visit researchers and organisations working on malaria across Africa.

Aim 2. Mobile genetic sequencing of malaria parasites and mosquitoes.

Working with local collaborators at 3 field sites, we will trial mobile genetic sequencing technology in remote field locations, as a proof of principle that DNA sequencing can be performed in a low resource field setting.

Study description

Aim 1 will be achieved through documenting interviews conducted both before and during the field work, through articles and images on our expedition website.

Aim 2 will be achieved by working with research groups in country. We have identified collaborators in Zambia and Kenya and will work with these groups to obtain IRB approval and the relevant permits to work in country.

In Zambia, we will sequence parasite DNA which has been collected as part of our collaborators' projects**.**

- Parasite DNA will be extracted from dried capillary blood spots taken from a convenience sample of people presenting to hospital or a healthcare facility with clinical malaria. A capillary blood sample is a routine part of the diagnostic process (for making a blood film to be examined under a microscope, or for a rapid diagnostic test). At the time the fingerprick is taken for diagnosis, four blood spots will be blotted onto filter paper for DNA analysis. Dried blood spots will be passed to us delinked from any patient identifiable data.
- Parasite DNA is extracted from dried blood spots, amplified and sequenced using a MinION (provided by Oxford Nanopore Technology, ONT) in a mobile sequencing laboratory in our expedition vehicle.
- Data will be analysed using a MinIT (ONT). We will amplify the parasite DNA before sequencing and any human DNA carried over in the sequencer will be bioinformatically removed prior to analysis.
- Two protocols will be trialled (a) we will attempt to sequence the whole genome of the parasite samples, and (b) we will amplify and sequence specific antimalarial resistance genes (*K13, CRT*, *DHPS*, *DHFR*).
- We will take neither blood spots nor extracted DNA out of country: all extraction and analyses will happen whilst in country.

In Kenya, we will sequence DNA from wild-caught mosquitoes.

- Working with entomological collaborators, we we collect mosquitoes opportunistically.
- DNA will be extracted and sequenced as above.
- Two protocols will be trialled (a) we will attempt to sequence the whole genome of the mosquito samples, and (b) we will amplify and sequence specific insecticide resistance genes (*KDR*).

Use of results

The scientific component of our project (Aim 2) will have two outputs:

1. **Generating data with mobile genetic sequencers.** The project will be a proof of principle that genetic sequencing of malaria parasites and mosquitoes can be performed in a low cost, low resource field environment.
2. **Capacity building.** Our in country collaborators will have the opportunity to trial the technology and generate sufficient data to form the basis of a future grant application or scientific peer-reviewed publication.

Primary objective of study (this is the key question that your research aims to answer)

Is it possible to extract and sequence DNA from malaria parasites and mosquitoes in the field using only equipment and personnel that can fit into a single vehicle?

Primary endpoint/outcome measure

Successful extraction of DNA and generation of sequence read data using only the mobile laboratory.

Secondary objectives of study (these are the other questions that your research aims to answer)

Using only the mobile laboratory,:

1. Can we generate a full genome sequence of a *Plasmodium* parasite?
2. Can we identify presence/absence of known antimalarial drug resistance mutations?
3. Can we generate a full genome sequence of an Anopheline mosquito?
4. Can we identify presence/absence of known insecticide resistance mutations?

Secondary endpoints/outcome measures

1. Alignment of sequence reads from a single parasite sample run on the MinION sequencing machine to generate a full genome sequence. Estimate of the per base error rate of less than 5%.
2. Amplification of three known antimalarial resistance genes (*CRT, DHFS, DHPR*) in 10 parasite samples and an assessment on the proportion of known resistance mutations across the samples.
3. Alignment of sequence reads from a single mosquito sample run on the MinION sequencing machine to generate a full genome sequence. Estimate of the per base error rate of less than 5%.
4. Amplification of one known insecticide resistance gene (*KDR*) in 100 mosquito samples and an assessment on the proportion of known resistance mutations across the sample.

Please list **all** procedures, e.g. blood and other **samples taken**, **tests performed**, **questionnaires**, **interviews**, etc. Include a description of the procedure, when it occurs, how long it takes, and who administers it.

Procedure	**When**	**Average time taken**	**Administered by whom**
Consent taken for genetic analysis of blood spot	At presentation to a health facility	5-10 minutes	Local collaborators (see below)
Capillary blood sample on filter paper	At presentation to a health facility	2 minutes	Local collaborators (see below)
Capture of wild mosquitoes using light traps	Around field stations at dusk	1-5 hours	Mobile Malaria Project team and local collaborators
Parasite DNA extraction from dried blood spot	Within three days of sample collection	2 hours	Mobile Malaria Project team and local collaborators
Mosquito DNA extraction from caught mosquito	Within three days of sample collection	2 hours	Mobile Malaria Project team and local collaborators
Sequencing	Within a week of sample collection	48 hours	Mobile Malaria Project team and local collaborators
Analysis	Initial data analysis within a month of sample collection	4 weeks	Mobile Malaria Project team and local collaborators

For blood samples: give the total volume of blood to be taken and over what time period

Around 2 microlitres (µL) per dried blood spot, therefore a total of 8µL taken per participant, once at initial diagnosis (i.e. one off).

List all sites where project will be conducted	**Kenya**

	- Dr Eric Ochumu, KEMRI/CDC Research and Public health collaboration. Box 1578. Kisumu. Nyanza. 40100. Kenya. Mosquitoes to be collected in multiple field sites around Kisumu, Lake Victoria. **Zambia** - Dr Dan Bridges, PATH-MACEPA Mikwala House Stand 11059, off Brentwood Lane, Longacres Lusaka, Zambia. Exact field sites TBC.
Anticipated duration of project	23 months (5 months preparation, 2 months fieldwork, 6 months data analysis and 10 months write up) Field work (provisional date): 15/02/2019 - 15/04/2019
Anticipated start date	01 / 11 / 2018
Anticipated end date	30 / 09 / 2020
Study sponsor (please refer to the definition in the CUREC glossary)	University of Oxford
Study funder	Royal Geographical Society with Institute of British Geographers

SECTION D. SCREENING PROCESS

1. Give an overall description of the study participants (e.g. healthy volunteers aged…)

Patients over 12 months old presenting to healthcare facilities at partner sites with clinical malaria.

2. What are the inclusion criteria of the study?

Participants must:

- Be over 12 months old
- Present to healthcare facilities run by in-country collaborators
- Have malaria confirmed by rapid diagnostic test or microscopy
- Have a blood spot taken anyway as part of the patient's routine clinical care/diagnostic process
- Have given valid consent for analysis of their samples for surveillance purposes.

3. What are the exclusion criteria of the study?

- Under 12 months old
- Unable to consent (e.g. due to language, drowsiness etc)

4. How will the potential participants be identified, approached, screened and recruited?

Participants will be identified, approached, screened and recruited by Zambian clinicians opportunistically when they present to health centres with symptoms.

5. How many participants will be recruited? Give the total sample size and justify the sample size.

Between 10-30 participants per country (30-90 in total). This has not been derived from a formal sample size calculation, but we believe these numbers will give us sufficient volume to demonstrate proof of concept and these sample sizes should be achievable to recruit.

6. Describe groups and numbers per group (if appropriate).

N/A

7. Has statistical advice been sought in calculating the sample size? Please specify and give details of statistical methods.

No – please see question 5.

8. Please give details of the consent process, including details of who will take consent and how it will be done. Please submit copies of the consent form and any information provided to participants (e.g. written information sheets, videos, interactive material) with this application.

Informed, oral consent to take a capillary blood sample will be sought by in-country partners in accordance with the usual clinical guidelines in country.

This consent is for clinical diagnosis. Additional, oral consent is routinely sought for dried blood spots that are taken (from the same capillary blood sample) for **genetic** analysis for surveillance purposes conducted by the National Malaria Control Programme. We will be analysing discarded/excess dried blood spots after they have served their primary surveillance purpose. Oral consent follows a discussion with the clinician about the risks and benefits of taking these samples. No written or recorded information material is used in these discussions beyond that which the clinician deems necessary to achieve informed consent. Consent is documented in the medical notes, but not on specific consent forms.

For this study of parasite genetics, no specific consent will be sought as blood samples will be anonymised and not linkable to humans and no human DNA will be analysed. i.e. the samples will be anonymised discard samples

9. Will there be advertisement for recruitment of participants, e.g. posters, flyers, emails? If so, please provide copies.

No. Blood samples will be taken from patients opportunistically presenting at health facilities. There will be no active recruitment.

10. Describe the arrangements for withdrawal of participants from the study.
Participants should have the right to withdraw from the study at any time. State whether withdrawal will result in exclusion of that participant's data/samples from the analysis. State whether withdrawn participants will be replaced.

As this analysis is conducted only on anonymised blood samples, there will be no possibility for participants to withdraw from the study as no samples will be linkable to humans. However, participants have the opportunity to decline to give samples for surveillance when the blood spot is taken.

SECTION E. ETHICAL ISSUES

1. What are the potential adverse effects, pain, distress, inconvenience, risks or hazards for participants from your research?

Participants will not experience any additional adverse events by taking part in this study (beyond routine diagnostic procedures).

Taking a capillary blood sample causes transient mild pain, equivalent to being pricked on the fingerpad with a sharp object. Participants will be given a plaster/cotton bud to prevent bleeding. There is a very small chance that it may get infected, however, the clinicians taking capillary blood samples will use a sterile lancet and clean the finger with an alcohol-based steret before taking blood to reduce this chance. This is a very common procedure and complications are very rare. Participants will be safety-netted to ensure they know any warning signs to look out for and advised where they may seek care if they notice any signs of infection. However, this capillary blood sample is a routine part of the diagnostic process, so participants will not experience any additional adverse effects for participating in our research.

2. Are there any potential benefits to the participants?

This study will not change the immediate experience of participants – i.e. the samples are collected alongside routine diagnostic processes and the analysis of these samples will not change their clinical management. (Although we aim to

determine the drug resistance status of parasites, our work is experimental and not linked to individual patients, so this will not alter current treatment protocols).

Indirect benefits to participants include an improved understanding of malaria transmission in the region, identifying the source of importations and ascertaining the population prevalence of drug resistance - as well as building capacity with in-country scientists - which will all inform malaria control policies and hopefully prevent future infections in subsequent years.

3. Are there any risks or benefits to the wider community?

We do not envisage any risks to the wider community.

The improved understanding of malaria epidemiology in these areas (e.g. prevalence of drug resistance, likely source of importations, enhanced capacity of local scientists etc.) will hopefully benefit the wider community in the medium term. In the long term, proof of concept that genome sequencing in the field is a practical and effective tool may revolutionise malaria diagnostics and epidemiology.

4. What are the main ethical issues? How do you propose to address them?
Please do not answer 'none'. OxTREC needs to see evidence that you have identified potential ethical issues with respect to your research and have taken steps to address them. These issues might relate to: data protection; participant confidentiality; researcher safety, etc.

Consent – as outlined above, the consent process (executed by our local partners) includes consent for analysis of samples for surveillance purposes.

Inadvertent sequencing of human DNA – the sequencing method used will selectively amplify parasite DNA only, therefore we expect relatively little human DNA to be sequenced. Our bioinformatics pipeline will automatically align all sequenced DNA with an appropriate human reference genome. Any DNA that aligns (i.e. appears to be human) will be automatically sorted (without human oversight or interaction) into a designated folder which will then be immediately deleted. Thus, no human DNA will be visible to the research team to be included in the analysis phase, only parasite DNA will remain.

Data protection – we will receive anonymised dried blood spots with no participant identifying information.

In-country approval – we will be collaborating with in-country partners who, as outlined above, will be identifying, consenting and recruiting participants for their ongoing, existing work. This study merely supplements their existing analysis – we are partnering with in-country research teams who already have approval from the relevant local bodies to perform genetic analysis on parasite samples.

5. Will participants receive reimbursement of expenses or any payment or gifts? If yes, how much?

NO

SECTION F: MANAGEMENT AND HANDLING OF PERSONAL AND OTHER RESEARCH DATA

Your management and handling of personal data and special category data of human participants, either directly or via a third party, will need to comply with the requirements of the General Data Protection Regulation (GDPR) and the new Data Protection Act, as set out in the University's Guidance on Data Protection and Research. In answering the questions below, please also consider the points raised in the Data Protection Checklist.
For advice on research data management and security, please consult with the University's Research Data Team (researchdata@ox.ac.uk) and/or your local IT department and the University's web pages on research data management.

1. Will your research involve the collection of **records of consent** (e.g. written forms, audio-recorded, or other recorded consent)?	NO

If 'Yes', these will be classed as fully identifiable personal data (directly linked to an individual).	
2a. Will your research involve the collection of **other personal data**?	NO
2b. **If 'Yes'**, specify in what form(s) this will this be stored:	
Fully identifiable (directly linked to an individual)	N/A
Pseudonymised (potentially identifiable as data may be attributed to an individual if linkage information can be accessed elsewhere by researchers)	N/A
Fully anonymised (i.e. cannot be linked to an individual)	N/A
3a. Will any of the personal data that you collect classify as **special category** data?	NO
3b**. If 'Yes'**, specify in what form(s) will this be stored:	
Fully identifiable (directly linked to an individual)	N/A
Pseudonymised (potentially identifiable as data may be attributed to an individual if linkage information can be accessed elsewhere by researchers)	N/A
Fully anonymised (i.e. cannot be linked to an individual)	N/A
4. How will any personally identifiable data be collected, transferred and backed up? Please describe the arrangements for any physical transfer of personal data (including paper records and data captured electronically via portable media) from where it is collected to local storage.	
N/A	
5. Where, and for how long, will participants' personally identifiable data be stored during and after the study? (Please outline the procedures for ensuring confidentiality, e.g. security arrangements, anonymisation or pseudonymisation of such data. Please distinguish between records of consent and other forms of personally identifiable data stored.)	
N/A	
6. If storing pseudonymised data, please confirm that identifiers will be held separately from the research data and linked through a unique study number. Specify how and at what point the pseudonymisation will occur, how the linkage information will be stored and state whether or not (and when) the linkage will be destroyed.	
N/A	
7. Who will have access to the personally identifiable data? If personally identifiable data is to be shared with another organisation, how will it be transferred/disclosed securely?	
N/A	
8. When and how will personally identifiable data be destroyed? (NB: Personally identifiable data should be destroyed when no longer required.)	
N/A	
9. How, where and for how long will other research data be stored after the study has finished? For more information about University and research funder retention policies, please see the University's web pages on research data management.	

The approximate date and site of collection of the sequenced *P.falciparum* genomes will be added into MalariaGEN's global database of *P.falciparum* genomes and retained indefinitely. These are totally anonymised and unlinked to any human data.

10. What are the arrangements for storage and disposal of the biomedical samples (if applicable)?

No biomedical samples will be stored. All biomedical samples (dried blood spots) will be disposed of with clinical waste in country.

SECTION G: MANAGEMENT OF THE RESEARCH

1. Give details of the local ethics committee(s) to which you have applied.

In country ethical approval application is currently underway but requires us to first have approval from OxTREC. The PI intends to travel to Kenya and Zambia in January 2019 to ensure that these are in place before the trip.

Zambia
In Zambia, we will be collecting dried blood spots to analyse parasite DNA. The dried blood spots are collected from humans.

We will apply for approval from the National Health Research Ethics Board of the National Health Research Authority (NHRA). The appropriate NHRA meeting (covering the period of our data collection) is 26-30th November 2018. Before considering an application from foreign applicants, they require approval from their home institution. We have initiated contact with the Ministry of Health and National Malaria Elimination Programme; and PATH, who are currently approved by the Ministry of Health to provide PCR analysis on anonymised samples for surveillance for the National Malaria Elimination Programme.

Kenya
In Kenya, we will be collecting mosquitos to analyse mosquito DNA - i.e. there are no human subjects.
We will be collaborating with the Kenyan Medical Research Institute (KEMRI) and will submit to their internal IRB for approval for mosquito collection and sequencing. All locally-approved studies are automatically sent on to the National Ethics Committee at National Council for Science, Technology and Innovation (NACOSTI) for final approval.

2. If the sponsor is other than the University of Oxford, have they agreed to provide **indemnity** for the study? If not, please specify the alternative arrangements.

N/A

3. Please indicate what training in research ethics those working on this study have received, e.g. GCP training; training in ethics/human subject protection. (Online training is available at http://researchsupport.admin.ox.ac.uk/support/training/ethics.)

'Good Research Practice' from MRC and Research Ethics Online, from the Global Health Training Centre at the Global Health Network (ongoing, Isaac Ghinai).

4. How do you intend to report and disseminate the results of the study?

Interim results from that particular site, available within a week of sample collection, will be shared with local collaborators as soon as possible. Confirmed results, aggregated across all sites, will be available within a year of sample collection and shared with all study sites.

The final results will also be written up into a peer-reviewed open access manuscript and distributed throughout the scientific community through presentations at various conferences and scientific meetings.

We also hope to engage school students and the public through events such as science fairs with hands-on demonstrations of the sequencing capabilities of a portable laboratory, and our results will demonstrate a crucial real-world example of the utility of these technologies.

5. If this study is funded by the US National Institutes of Health (NIH) or another US federal funding agency, please complete the form for NIH funded studies available on the OxTREC application process page and submit it with your application.

N/A

6. Is there any additional information that you consider relevant for the purposes of ethical review?

NO

SECTION H: SIGNATURES

1. Principal investigator/student researcher signature (**for all projects**)

I declare that the answers above accurately describe my research as presently designed and that I will submit an amendment should the design of my research change in any way.

Signed by principal investigator:…….

Date:……08/10/2018……

Print name (block capitals)……GEORGE BUSBY……

2. Supervisor signature (**for student research projects only**)

I confirm that the above particulars are correct.

N/A

3. Departmental endorsement signature (**for all projects**)

I have read the research project application named above. On the basis of the information available to me, I:
(i) consider the principal investigator to be aware of her/his ethical responsibilities in regard to this research;

(ii) consider that any ethical issues raised have been satisfactorily resolved and that it is appropriate for the research to proceed (noting the principal investigator's obligation to report should the design of the research change in any way);

(iii) am satisfied that the proposed project has been/will be subject to appropriate peer review and is likely to contribute something useful to existing knowledge and/or to the education and training of the researcher(s) and that it is in the public interest.

Signed by Head of Department or nominee (example nominees for student research include the Director of Graduate Studies/Director of Undergraduate Studies):

Signature: 

Date: 15th October, 2018

Print name (block capitals) PROFESSOR GILEAN MCVEAN

Position held (block capitals) DIRECTOR, BIG DATA INSTITUTE

Please send your signed application form by email to oxtrec@admin.ox.ac.uk.

NB: for minimal risk studies only, it is no longer necessary to include a protocol with your application.

Please include other supporting documents, if appropriate (e.g. participant information sheet, consent form, questionnaire, interview guide, recruitment material, evidence of approval from local ethics committee, peer review and response).