University medical research conducted outside the UK and the EU: a guide to applying for ethical review

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1. Overview

The Oxford Tropical Research Ethics Committee (OxTREC) is the University ethics committee tasked with reviewing University medical and health-related research undertaken outside the UK and the EU (and any research funded by US federal agencies). This type of research, which may involve multiple partners across a number of different countries, can present different ethical challenges from those encountered when conducting research within the UK and the EU. This document considers some of the most commonly encountered challenges, and provides guidance on how to address them and mitigate related risks.

2. Applying for ethical review with OxTREC

2.1. Type of review required

All medical research studies that will take place outside the UK and the EU and involve University of Oxford investigators[1] should be submitted to OxTREC for ethical review.

OxTREC accepts two types of application for review: **minimal risk** and **full committee**. Broadly speaking, low risk, non-interventional studies will qualify for minimal risk review (and are reviewed on a rolling basis throughout the year), while higher-risk interventional studies and clinical trials must be reviewed at a meeting of the full committee, which convenes six times per year.

Different forms are required by OxTREC depending on the type of application, and all full committee applications must be accompanied by a protocol.

Further details on the OxTREC application process are available on the application process pages, including the conditions under which a waiver from ethical review may be considered.

2.2. Local ethical review

Ethical approval from OxTREC is always contingent upon local (in-country) ethical approval. Thus, in addition to applying to OxTREC for ethical review, it is necessary to apply to the relevant ethics

[1] Please refer to OxTREC application process | Research Support for further guidance on ethical review of studies led by non-Oxford investigators, but which involve Oxford investigators as collaborators.

committee in the country in which the research will take place. This may be the ethics committee of the local university, research institute or hospital in which the research will take place or to which collaborators are affiliated. In rare cases, there may be no in-country ethics committee to which to apply; in such cases you should contact the OxTREC secretariat for advice on how to proceed and approaches to obtaining local ethical review.

For multi-country studies, it is necessary to apply to the relevant ethics committee in each country in which the research will take place, in addition to OxTREC (unless in-country committees have agreed to waive this requirement, for instance by accepting and relying on review by an ethics committee in one of the countries involved, following prior discussion with the investigating team[2]). This can be a complex coordination task, but OxTREC does not dictate a specific order of ethical review. In other words, you may apply to OxTREC for ethical review first; to the in-country committees first; or to OxTREC and the in-country committees simultaneously.[3]

Once local ethical approval has been obtained, copies should be forwarded to OxTREC.

2.3. Overarching protocols

In general, before starting a study, it is important to ensure that the same versions of all documents have been submitted to and approved by both OxTREC and the in-country committee(s).

Note, however, that in some cases—for example, studies to be conducted in several countries—it may make sense to submit an overarching (or 'master') protocol to OxTREC for review, rather than submitting a separate protocol for each country. This would be appropriate where, for example, the protocols for the different countries are broadly the same with only minor local differences that do not affect the substance of the research and are easily accounted for within one master document.

Further advice can be obtained from the OxTREC secretariat.

Protocol templates can be found on the OxTREC web pages. Note that there is no requirement for investigators to use the OxTREC templates, provided that another GCP-compliant protocol is used. Other templates are available, for example the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) protocol guidelines for minimum protocol content.

2.4. Translated documents

All documents provided to OxTREC for review should be in English translation. There is no need to include the local language versions with the application.

[2] If this is the case, evidence of this agreement should be included in the application that is submitted to OxTREC.
[3] Note, however, that if revisions to a study are requested by an in-country ethics committee subsequent to approval having been obtained from OxTREC, those revisions must then be submitted to OxTREC for further review and approval.

2.5. Issues that commonly arise in review of OxTREC applications[4]

There are a number of areas in which OxTREC frequently provides feedback when reviewing applications. The following areas are particularly important, and therefore should be borne in mind and addressed carefully when submitting an application to OxTREC:

2.5.1. Genetic analysis

If a research study will involve genetic analysis of participants' samples (other than routine tests, e.g. for G6PD and Hb electrophoresis), then it is important that this is specified in the protocol and explained clearly and simply in the participant information sheet (PIS) for the study. It should also be made clear in the PIS that complete anonymisation of the genetic data is not possible.

In addition, the informed consent form (ICF) for the study must include a separate clause which enables participants to indicate their consent to genetic analysis. Please see the example PIS and ICF for OxTREC studies.

2.5.2. Export of samples

If a research study will involve participants' samples being transported overseas—for analysis that can't be performed in the country of origin, for example—then again, it is important that this is specified in the protocol and explained clearly and simply in the PIS for the study. The ICF should again include a separate clause which enables participants to indicate their consent to export of their samples. (Please refer to the example PIS and ICF for OxTREC studies.)

Note, further, that where a study will import human tissue samples into England, arrangements must be made before the samples are transferred to store them under the governance of a Human Tissue Authority (HTA) licence. It is a legal requirement that any tissue or fluid made up of or containing human cells to be used for the purpose of research is stored on premises licensed by the HTA unless covered by an exemption, and OxTREC approval is not a recognised exemption. Further information may be found in Best Practice Guidance 15: Ethics review of research with human tissue and on the University's human tissue governance web pages

2.5.3. Future use of samples

Researchers may wish to retain samples collected in one research study for use in future research studies and, generally speaking, this is considered appropriate and ethically justified, since it reduces the burden on participants and maximises the benefit of the original sampling.

However, for any study in which the researcher wishes to retain the samples collected for use in future research, the following needs to be made clear in the participant information for the current study:

- retention and future use is not mandatory (i.e. individuals may participate in the current study, but decline consent to the storage and future use of their samples);
- stored samples will only be used in a future study following review and approval of that specific future study by an ethics committee.

[4] Please also refer to section 5 (Participant information) of this document for more general guidance on provision of participant information.

In addition, the ICF for the current study should include a separate clause which enables participants to indicate their consent to storage of their samples for future research use. Please refer to the OxTREC example ICF, and note that, if the stored samples may be subject to future *genetic* analysis, this should be separately specified on the ICF.

2.5.4. Data collection and storage

Any research study will involve collecting and storing personal[5] and other research data. It is essential that all data collected are stored safely and securely and that participant confidentiality is maintained. Particular care needs to be taken with sensitive personal data (also known as 'special category data[6]') and, since OxTREC studies involve medical and health-related research, the data collected are likely to fall into this category.

The PIS should set out clearly and simply which data are being collected and why; where, how and in what form (fully identifiable, pseudonymised, anonymised) the data will be stored; how confidentiality will be maintained; whether the data will be shared with other parties outside the research team; and how long the data will be stored for. The PIS must also include the standard OxTREC data protection statement (see the example PIS). These measures will ensure that the study complies with the General Data Protection Regulation and the Data Protection Act (2018), which apply to research conducted overseas by University of Oxford researchers.

If the data will be transferred out of the country of origin, this should be stated clearly in the PIS, and the ICF should also include a separate clause which enables participants to indicate their consent to transfer of their data. (See the example PIS and ICF.)

Further guidance and advice may be found in Best Practice Guidance 09: Data collection, protection and management (the University's Data Protection and Research guidance) and on the University's Research Data website.

2.5.5. Inclusion and exclusion criteria

When designing a study, it is important to bear in mind that the participants as a whole should, as far as possible, include representation from all of the population groups affected by the disease/condition in question, in order to gain maximum benefit from the research. This means that, unless there is a sound ethical or scientific reason for excluding a particular population group, efforts should be made to include as wide a spectrum of participants as possible.[7]

[5] Data that relate to a living individual who can be identified (a) from those data, or (b) from those data and other information that is in the possession of, or is likely to come into the possession of, the data controller (e.g. through the use of a code devised by, or accessible to, the researchers). Examples include, but are not limited to, name, email address, audio/video recordings, identification number, IP address, location data, genetic data and biometric data.

[6] Data relating to race, ethnic origin, sexual orientation, political opinions, religious beliefs, physical/mental health, trade union membership, genetics, sexual life, biometrics (where used for ID purposes), or criminal activities.

[7] Examples of valid reasons for excluding particular groups might include the following: exclusion of minors from the study of a disease that only affects adults (sound scientific reason); exclusion of pregnant women from a study where the intervention is known to carry a risk for foetuses (sound ethical reason).

2.5.6. Incidental findings

It is important to consider how any incidental findings8 that arise during the course of the research will be handled: will they be fed back to participants or not, and what is the rationale for that decision? This is likely to vary from study to study and will be dependent on a variety of factors, including the nature of the findings, the potential harm or benefit that may be associated with feeding the findings back to participants, and the availability of healthcare in the local study context. When formulating a policy on incidental findings, researchers may find it helpful to refer to the Wellcome Trust's and the MRC's Framework on the Feedback of Health-related Findings in Research. Once a policy has been formulated, this should be set out clearly in the protocol and the PIS for the study.

2.5.7. Statistical design

Statistical design is an integral part of any research study and OxTREC will review this carefully. It is expected that the protocol will include detailed information about the statistical methods used in the study. OxTREC therefore strongly recommends that investigators seek specialist statistical advice when designing their protocols.

2.5.8. Community engagement

Community (or stakeholder) engagement is an important aspect in all research, but especially so in global health research, which often involves vulnerable populations and so may run the risk of unequal relationships developing between the research team and the local study population.

Investigators should therefore clearly demonstrate that their research is undertaken in collaboration with the local community, and that community members and local stakeholders play a meaningful part in the design and delivery of that research, and in related knowledge exchange and impact activities.

Both OxTREC application forms include specific questions on community/stakeholder engagement, and these should be considered carefully and answered in full by investigators.

3. Empirical studies involving qualitative research methods

Empirical studies involving qualitative research methods present different challenges from those presented by clinical research studies. Studies involving qualitative methods may be standalone, or may form part of a larger clinical research study or trial. Thus, in the latter case, it is particularly important that ethical issues arising from the qualitative (part of the) study are considered *in addition to* those arising from the clinical (part of the) study.

For *all* qualitative research (whether standalone or part of a larger clinical study), the following areas should be addressed in the protocol and the application form:

[8] Also known as 'health-related findings', these are previously undiagnosed medical conditions that are discovered unintentionally during the course of a research study.

Experience of qualitative research

It should be clear which members of the study team will be conducting the qualitative research, and what experience of qualitative research they have.

Clarity and reasoning around methods used

The ethics application should specify:

- which methods (e.g. survey, semi-structured interview, focus group discussion) will be used and why these have been chosen;
- how many participants will be recruited and why that figure has been chosen;
- who the participants will be and why those particular groups have been chosen (e.g. age, gender);
- how particular participants will be selected for inclusion;
- which questions/topics will be covered (NB: the survey outline/interview guide/focus group discussion guide should always be included in the application).

Inviting participation

It should be clearly set out (a) how participants will be approached to invite their participation, and (b) how consent will be sought for participation. As with any research study, a PIS and an ICF should always be included for the qualitative (part of the) study. Please refer to the University's detailed guidance on informed consent, including templates suitable for qualitative studies. (Also see section 5 below.)

Ensuring fairness in benefits and burdens of participation

With qualitative studies, where research procedures may be less clear cut than in clinical studies, it is important to consider carefully what participation will involve in practice and what the likely costs of that participation will be. For example: where and when will data collection take place; how long will the activity last; and is compensation appropriate for those costs? (Also see section 6 below.)

It is also important to consider whether participation will have a significant impact on other responsibilities that participants may have. For example, scheduling an appropriate time and place will be particularly important when conducting interviews/focus group discussions with healthcare professionals.

Ensuring rigour in data collection and analysis

For data collection: it should be clear how the data will be documented (e.g. audio recording), where and how long the data will be stored, and how confidentiality of the data will be maintained (also see section 2.5.4 above).

For data analysis: it should be clear how the data will be analysed, what methods will be used and why, and how rigour will be ensured.

4. University sponsorship

The University of Oxford is able to provide sponsorship (and, importantly, insurance) for OxTREC-approved studies that have been designed by a University employee, where that employee is acting as the chief investigator for the study, and where the University has overall responsibility for the conduct and management of the study.

If you wish the University to sponsor a clinical trial or clinical research study that will be reviewed by OxTREC, you should make contact with the Research Services Risk and Insurance Team *as early as possible*, preferably at the time of the funding application. This will enable the Risk and Insurance Team to determine whether insurance cover can be arranged and, if so, any potential cost.

When applying for OxTREC review, you should list the University as sponsor on the OxTREC application form. The application will then be vetted by the Research Services Risk and Insurance Team in addition to undergoing detailed ethical review and, if appropriate, sponsorship will be confirmed at the same time as ethical approval.

5. Participant information

For any research study, participant-facing information such as the participant information sheet (PIS) and the informed consent form (ICF) should be written as clearly and simply as possible. However, this is especially important when generating such documents for studies to be conducted in countries outside the UK and the EU, where experience of formal education may be more diverse and/or potential participants may have less exposure to medical/scientific techniques and terminology.

In particular, the PIS and ICF should:

- include a short, non-technical title which can easily be understood by a lay person;
- be written in simple language and short sentences;
- avoid the use of technical terms or, of if such terms are unavoidable, include very short, simple explanations of what those terms mean;
- concentrate on the *research procedures* (there is no need to provide details about routine care);
- be as short in length as possible.

The example PIS and ICF for OxTREC studies include the kind of information and consent points that should be incorporated into all PISs and ICFs. Note, however, that in-country ethics committees may have their own templates, and some may mandate use of those templates. For this reason, OxTREC does not stipulate that a specific template or format should be used.

5.1. Obtaining informed consent

It is important that potential participants in any research study understand exactly what participation will involve for them and so are able to give fully informed consent to their participation in the study.

In situations where researchers are concerned that potential participants may have difficulty in reading PISs or signing ICFs, the following method is recommended for obtaining and recording informed consent:

In the presence of an impartial witness:

- the PIS is read out to, and discussed with, the potential participant by a member of the study team;
- the potential participant is given sufficient time to reflect on that information;
- all of the potential participant's questions are answered satisfactorily;
- if the potential participant wishes to proceed, they record their consent by thumb printing (or otherwise marking) the ICF;
- the witness then signs and dates the ICF to confirm the veracity of the process.

5.2. Participation of minors

For research studies involving minors, it is generally considered very important to involve the minor in the decision about whether or not to take part in the study. Researchers should therefore always consider producing (a) a simplified, age-appropriate PIS for minors; and (b) a simple assent form, which can be used by the minor to assent to participation in the research. (Note that these documents will be *in addition to* a PIS for parents/guardians and a parental/guardian consent form, since formal parental/guardian consent must be obtained in order for a minor to take part in a research study.)

It should be noted, however, that the concept of a minor in research ethics does not necessarily coincide fully with the legal definition of a minor. For example, some countries have the category of 'emancipated minor', which includes young people under the legal age of majority who are able to consent to participate in research on their own. The relevant in-country ethics committee will be best-placed to provide guidance in this area.

6. Compensation

With any research study, it is important that participants are compensated appropriately for their participation. Specifically, levels of compensation should be low enough that they do not constitute an undue inducement to participation, but sufficient that they cover any direct and indirect losses[9], expenses, or inconvenience incurred by participants.

When setting levels of compensation for a study, it is critical to take careful account of the local contexts in which the research will take place, including family circumstances, transport

[9] For example: loss of earnings would constitute a direct loss; needing to cover childcare at home whilst a mother visits a healthcare facility with one of her children would constitute an indirect loss.

challenges, and government recommendations on daily wages for equivalent groups. It may also be desirable to draw on community advisory boards or groups to inform approaches to compensation.

As a general guideline, reimbursement for travel expenses, lost earnings and any indirect losses should be provided. Importantly, if the study involves hospitalisation, medication, tests or procedures additional to standard care, the study (and not the participant) must bear the cost.

Additional guidance on compensation may be found in Best Practice Guide 05: Payments and incentives in research.

7. Researcher safety

Many ethics applications reviewed by OxTREC are for research conducted by the University's Major Overseas Programmes and the research will therefore be carried out in established hospitals and clinics in conjunction with locally-based colleagues. There will be little risk to a researcher's safety in this situation. However, for researchers who are working alone in unfamiliar environments, personal safety may be more of an issue. Detailed guidance and advice on staying safe may be found in Best Practice Guidance 01: Researcher safety.

8. Clinical trial registration

For any clinical trial reviewed by OxTREC, the trial should be registered on a clinical trial registration site and the clinical trial registration number supplied to OxTREC. Registration is mandatory and the trial will not be granted ethical approval in the absence of a registration number.

The World Health Organisation provides guidance on what constitutes a clinical trial.

Trials should be registered on ClinicalTrials.gov, the ISRCTN registry, or another register listed on the WHO International Clinical Trials Registry Platform. The grant reference number, funder, sponsor name, summary of trial, and data sharing plan should all be included on the initial registration documentation. The registry entry should then be reviewed regularly and updated with the summary results from the trial, the final enrolment numbers, and the date that the primary study was completed. In cases where a clinical trial has been terminated, the registry entry should be updated to include enrolment numbers up to the termination date and the termination date.

9. Publication of results and data sharing

In line with funder conditions, it is expected that investigators will maximise opportunities to make their research findings freely available, including null and negative results:

- summary results from clinical trials should be posted to the registry on which the trial is registered;
- research findings should be published in a peer-reviewed journal;
- any peer-reviewed publications should be made freely available online (open access);
- data underlying research publications should be made accessible to other researchers, either openly or via a managed access approach.

10. Funder considerations

Funders may attach certain conditions to the terms of their grants. Investigators should familiarise themselves with any such conditions and ensure that they adhere to them.

Guidance related to the US National Institutes of Health (NIH) and the Wellcome Trust (two of the most common funders for OxTREC-reviewed studies) can be found below:

NIH

For any study that is funded by the US National Institutes of Health (NIH), applicants should complete the NIH-funded studies form in addition to the relevant OxTREC application form. The NIH-funded studies form includes questions related to data and safety monitoring, ethnicity/race of participants, inclusion of participants across the lifespan, and genomic data sharing. It is a condition of the NIH grant funding that these questions are answered, hence completion of the form is compulsory.

Investigators should note that, for all NIH-funded clinical trials, the NIH require that an IRB-approved (i.e. ethics committee-approved) version of the informed consent form for the trial be posted on a public federal website. This must be done after enrolment ends and within 60 days of the last study visit. Further details can be found on the NIH's website.

Wellcome Trust

Investigators who are conducting clinical trials funded by the Wellcome Trust should refer to its Clinical Trial Policy. This policy forms part of Wellcome's grant conditions, and sets out the requirements for grantholders before, during and after clinical trials, including requirements regarding sponsorship and insurance, trial registration, governance, monitoring, and publication of results. The Clinical Trial Policy should be read in conjunction with Wellcome's Research Involving Human Participants Policy.