OXFORD RESPIRATORY TRIALS UNIT

NUFFIELD DEPARTMENT of MEDICINE

UNIVERSITY OF OXFORD

Collaborating with ORTU

A Chief Investigator's Guide

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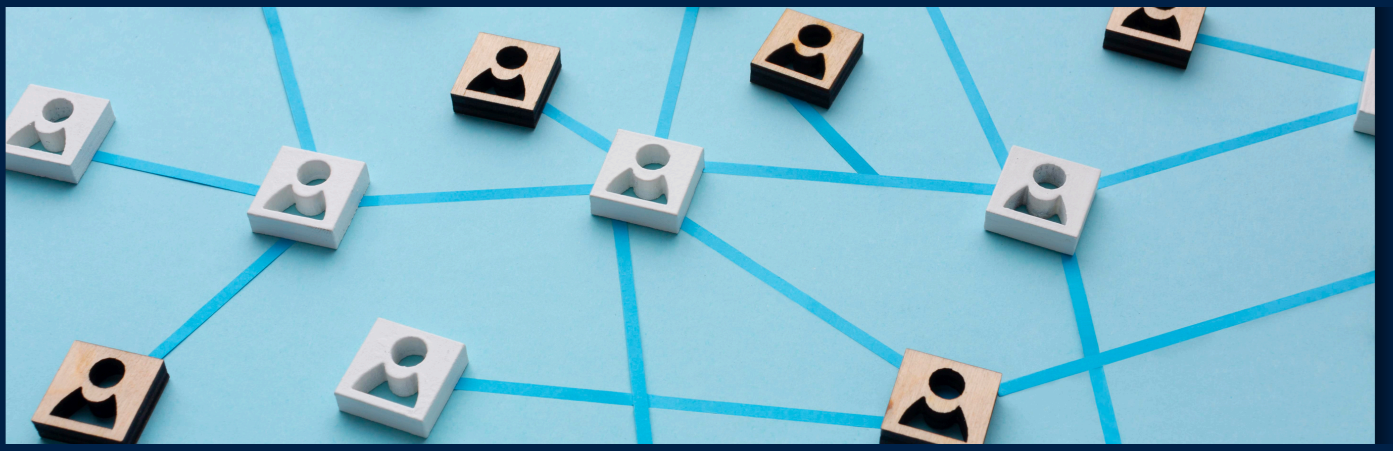

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Purpose

The purpose of this document is to aid discussion and agreement about the roles and responsibilities of the parties involved in the design and implementation of studies undertaken in collaboration with Oxford Respiratory Trials Unit (ORTU).

Studies can be complex, challenging, and expensive, so good communication between Clinical Trial Units (CTUs) and their collaborating investigators is crucial to successful implementation. It is essential that ORTU and the CI develop and maintain a strong relationship, to ensure study activities are performed in accordance with the CTU standard operating procedures (SOPs) and regulatory requirements. This includes a clear understanding of roles, responsibilities, and expectations early in the collaboration. More specifically, it aims to clarify the responsibilities of ORTU and Chief Investigators (CI). It is not intended to provide an exhaustive list of all tasks that will be undertaken during the course of design and implementation of a study, but does cover the key areas. This provides an overview of key responsibilities when ORTU is providing full study management and oversight. There are some responsibilities outlined below that may not be applicable to all studies, specific details may be established in a Division of Responsibilities agreement.

This document takes elements of the NIHR CTU Network Efficient Trial Conduct CI Agreement.

About Oxford Respiratory Trials Unit

We are delighted to be working with you. ORTU is a very friendly and collaborative Clinical Trials Unit.

As part of Experimental Medicine within the Nuffield Department of Medicine, Medical Sciences Division of the University of Oxford, we are a specialist centre for the management of respiratory research and one of a limited number of trials units in the UK that specialises in respiratory research.

Our portfolio is varied and includes Clinical Trials of Investigational Medicinal Products (CTIMPs), Non-CTIMP interventional studies, cohort and epidemiological studies. We cover numerous disease areas such as pleural diseases, COPD, asthma, respiratory sleep and breathing disorders. We can also manage and support non-respiratory studies.

Collaborating with the CI, we provide full study management oversight, including protocol and participant facing document development and submissions to gain Sponsor and ethical/regulatory approvals. Our Data Management Team, oversee the development and management of IT systems to manage randomisation and data collection from concept to end of study recruitment, study closure and publication.

ORTU provide specialist governance, regulatory, and other methodological advice, and co-ordination. We have dedicated, Study and Data Management Teams and Quality Assurance oversight, as well as higher level oversight with the Head of Operations and the CTU Director.

ORTU is part of the Oxford Collaborative Clinical Trials Unit (OxCCTU), which is a registered trials unit with the UK Clinical Research Collaboration (UKCRC). The other groups within this collaborative unit are Oxford Vaccine Group (OVG), the Jenner Institute and Primary Care CTU (PCCTU). ORTU work closely with these and other groups within the University of Oxford to collaborate, particularly in the areas of statistical and health economics support.

ORTU provides physical storage and performs governance and oversight for a human tissue collection under a University of Oxford Research HTA (Human Tissue Act) licence (12217).

Over the course of our collaboration with a CI, ORTU will provide Quality Assurance oversight, based in our Quality Management System that supports all our studies.

Quality Assurance

ORTU has a comprehensive suite of SOPs and Risk Assessments that govern our studies. ORTU performs an audit programme and manages a process for incident / non-compliance reporting including root cause analysis and Corrective and Preventive Actions (CAPA).

ORTU will:

- develop and maintain a strong QA framework for all our studies including SOPs, audits and non-compliance reporting.
- update processes as required by changes to regulatory or best practice guidance.
- provide the required documents (e.g. SOPs, risk assessments) to staff for training.
- ensure ORTU staff are appropriately trained for their role.

The CI will:

- undertake training on the SOPs as required by ORTU
- provide evidence of training (e.g. GCP) to ORTU
- update training when any changes are made

Communication

It is important to recognise that regular and substantial communication will be needed between ORTU and the CI noting, urgent responses may be required from the CI. ORTU will work with the CI to agree mutually agreeable processes. Some decisions will need to be communicated by e-mail to ensure a documented trail.

ORTU will:

- provide a lead person (usually the trial manager) who will have the expertise and experience to contribute to the design and oversee the implementation of studies.
- identify a second member of the ORTU team who will provide support should the lead not be able to do so (e.g. in periods of extended absence).
- take responsibility for advising the CI throughout the study design and implementation, of regulatory and practical issues.

The CI will:

- be available to communicate with the Sponsor, the funder, the Research Ethics Committee (REC) and other review bodies during the application process and the whole duration of study implementation.
- agree regular times to be available to talk with the ORTU teams as often as weekly at times.
- be available to answer ad-hoc informal queries as and when they arise.
- where possible, nominate one or two members of the study team to be able to make decisions on their behalf in case of absence. Separate nominees may be required for different types of decisions e.g. regarding clinical/participant safety, study processes, negotiations with site investigators.

Key Responsibilities When Working With ORTU

Grant Development and Submission

Ideally, ORTU should be approached at the point at which it is decided that a grant application will be made. ORTU require a near final draft application and clear idea of division of responsibilities at least 4 weeks prior to the submission deadline to be able to provide an accurate estimate at stage 1.;

ORTU will:

- ensure the collaboration process is efficiently managed and allow sufficient time to support the CI in the development of the grant funding application.
- ·provide the CI with support to enable them to submit a complete and competitive grant application including but not limited to, advice on study design, sample size, statistical design, project planning, research costs and any relevant regulatory and governance issues.
- help to identify collaborators with appropriate methodological expertise e.g. statisticians, qualitative health economics evaluation, modelling and systematic reviewing.
- work with the statistician, collaborating sites and CI to explore the feasibility of the proposed effect sizes.
- work with local Research Delivery Network (RDN) and NHS partners to determine the research, service support and excess treatment costs associated with the project.
- provide advice and guidance in the costing model for the study.
- advise the CI on the cost levels and models likely to be acceptable to the funder.
- advise on human tissue governance, storage and control requirements.

The CI will:

- work with ORTU to develop the grant application at all stages (stage 1 and stage 2) and allow sufficient time for collaborators to make a meaningful academic and practical contribution.
- develop a PPIE (Patient and Public Involvement and Engagement) plan. ORTU can lead on the development of this plan or collaborate with individuals who have been identified as being able to provide this input.
- discuss and reach agreements on internal and external co-applicants with ORTU, before inviting investigators to the team.
- take the lead on writing the grant application
- work with the statistician to provide input to the clinical aspects of the sample size calculation.
- answer costing queries relating to the participant pathway to ensure proper cost attribution.
- manage expectations of co-applicants on what can be included to ensure the proposal is not prohibitively complicated, ambitious or expensive.
- discuss with ORTU any planned substantial change in the study design/conduct prior to grant submission.
- provide a final copy of the grant submission to ORTU as soon after submission as possible.
- notify ORTU of the funding decision as soon as possible.

Document Development

Key Study Documents

In clinical research key documents include (but are not limited to):

- Protocol
- Participant Information Sheet (PIS)
- Informed Consent Form
- GP letter
- Participant questionniares

These require development in a timely manner with input from experts in areas such as statistics, risks, drug safety, trial management, monitoring, sponsorship requirements and quality review.

ORTU will:

- where appropriate, provide the CI with a template (e.g. protocol template) so that the CI can create an initial draft of the key documents.
- co-ordinate the multidisciplinary input from a team of experts in the required fields from both within and external to ORTU.
- manage key documents' review process.

The CI will:

- work on the initial drafts of the key documents by providing clinical input and expertise.
- ensure the processes are thoroughly thought out to avoid amendments in the study process once the relevant approvals have been received.
- support the review processes in order to finalise the key study documents.
- ensure the protocol has undergone scientific and statistical review.

Risk Assessment, Management and Monitoring Plan

Risk management includes all of the processes involved in identifying, assessing and judging risks, assigning ownership, taking actions to mitigate or anticipate them, monitoring and reviewing processes. It is therefore important to have a risk management culture that underpins and supports these activities.

ORTU and the CI are jointly responsible for developing and following the study risk assessment. The risk assessment requires a co-ordinated multidisciplinary approach across the study team.

ORTU will:

- generate a risk assessment using the ORTU template
- co-ordinate the input from a team of experts in the required fields from both within and exernal to ORTU.
- ensure the management and monitoring activities included in the risk assessment are undertaken during the study

The CI will:

- identify and evaluate potential risks.
- provide clinical input into the risk assessment including risks to participants, data intergrity, outcomes, regulatory compliance, and the overall success of the study.
- a final review and approve the risk assessment, management and monitoring plan.

Statistical Analysis Plans and Health Economics Analysis Plan

The Statistical Analysis Plan (SAP) is a technical document that describes in detail the planned statistical analysis of a study and should be reviewed in conjunction with the protocol. This plan ensures that the analyses to evaluate all planned study hypotheses and outcomes, are conducted in a scientifically valid manner and that all decisions are documented. It also provides detail on how the results will be presented and reported. If required, health economics analysis will be undertaken according to the protocol and / or the Health Economics Analysis Plan (HEAP).

ORTU will:

- engage with an appropriate statistician / health economist (if required) to draft the Statistical Analysis Plan / Health Economics Analysis Plan (according to the statisticians / health economists SOPs).

The CI will:

- review and agree the plan for the statistical analysis and health economics including clinical input where required.
- support the review process in order to finalise the Statistical Analysis Plan / Health Economics Analysis plan.

IT Systems

Case Reporting Form (CRF) and Database Design

Case Reporting Forms (CRFs) are key documents which allow investigators to collect appropriate clinical research data, in either paper or electronic form, as set out in the protocol, to evaluate the study outcomes measures. A study cannot begin until finalised CRFs / electronic CRFs and the database are in place.

Robust design, review and approval of CRFs help to ensure that data are collected and managed in an efficient manner, compliant with applicable regulations.

ORTU will:

- provide guidance on preparation of the data specifications document to the CI
- manage the CRF drafting process in parallel with the protocol drafting.
- create a final version of the CRF using ORTU approved templates/processes.
- ensure the completion of a Data Management Plan in line with ORTU SOPs.
- facilitate statistical review of CRFs.
- co-ordinate creation of a validated study database.
- manage access to the study database and overall control of the system
- co-ordinate creation of all IT support systems ensuring they are appropriately validated.

The CI will:

- provide completed CRF specification documents as per ORTU SOPs
- provide input, review and approve the CRFs prior to the study opening, ensuring that all data will be captured as detailed in the protocol to answer the study endpoints.
- be responsible for approving data requests and authorising unlocking of the database after the final lock has taken place, where appropriate.

Randomisation System

A randomisation system may be required to randomise participants to different arms of the study.A randomisation system must be fit for purpose, adequately validated to ensure it is reliable for the study.

ORTU will:

- organise development of an appropriate randomisation system
- undertake user acceptance testing on a test system
- ensure the system is approrpiately validated, working with the statistician where appropriate.
- work with the CI to ensure the randomisaion system functions as required.
- provide access to the live system to approrpaitely trained and delegated site staff.
- maintain and manage the system and access throughout the life time of the study.

The CI will:

- review the randomisation system and provide feedback to ORTU.
- approve the randomisation system for use.

Study Management

ORTU will take the lead in study management and liaison with all co-applicants to deliver the study within time and budget.

ORTU will:

- liaise with potential sites, identifying and initiating participating sites and maintaining good communication with each site.
- set up the study and obtain relevant permissions (ethics approval, MHRA approval etc.).
- co-ordinate and manage essential study documents (e.g. delegation logs, training logs)
- oversee recruitment data (e.g. screening logs, consent forms) and participant data collected into the database from participating clinical sites.
- undertake monitoring and management acticvites as documented in the Risk Assessment.
- provide support to ensure the scientific integrity of the study throughout implementation.
- provide support to ensure the study is undertaken in accordance with regulatory standards.
- work with the study statistician who will conduct interim and final analyses.
- contribute to or prepare reports during the study (e.g. for funding bodies, REC, MHRA).
- oversee sample collection, inventory and storage.

The CI will:

- oversee or liaise with ORTU staff on all tasks to ensure mutual understanding and agreement of all study processes; to add clinical knowledge/perspective; and to be available to make final decisions throughout the study.
- provide clinical oversight and maintenance of the participant safety and clinical integrity of the study.

Amendments / Modifications

Amendments / Modifications are changes made to a study after it has received regulatory approval.

ORTU will:

- carry out an initial assessment of whether the amendment / modification is substantial or non-substantial and whether it impacts on any IT systems (e.g. randomisation system or changes to CRFs).
- make proposed changes to documents as required and ensure appropriate review
- ·submit the amendments to the funder and Sponsor who will confirm/or not whether the amendment is substantial or non-substantial.
- submit amendments to the relevant authorities i.e. REC
- make changes within systems if required and disseminate approved amendment documents to recruiting sites.

The CI will:

- be aware of the time required to undertake amendments and whether the changes are within the scope of the agreed budget.
- ensure no amendments are implemented prior to the required approvals being confirmed
- provide review and approve the required amendments

Study Governance

Each study will need appropriate oversight committees, including trial management, accruing data, recruitment and safety. The Trial Steering Committee (TSC) is the executive committee for the study and can make key decisions regarding study performance (such as deciding to close early).

ORTU will:

- in conjunction with the funder, advise on which oversight committees are required for a specific study
- organise and administer Trial Management Group (TMG), Data Safety Monitoring Committee (DSMC), and TSC meetings.
- in conjunction with the statistician, prepare study progress, data management, clinical safety and statistical reports for the oversight committees.

The CI will:

- identify and appoach potential members for TSC and DSMC
- attend all TMGs, TSCs and open DSMCs

Safety / Pharmacovigilance

Safety reporting / pharmacovigilance in clinical studies involves documenting, assessing and reporting adverse events, serious adverse events and those events that are reportable to the ethics committee or the regulator (e.g. MHRA) which are suspected unexpected serious adverse reactions (SUSARs) or unexpected serious adverse reactions (USARs). This is designed to ensure participant safety, identify potential intervention related issues and contribute to the overall understanding of the intervention's safety profile.

ORTU will:

- liaise with CI regarding safety reporting requirement including, timeframes, excluded events, and appropriate Reference Safety Information (RSI).
- send reports of all reported SAE's to the medical reviewers for medical oversight.
- communicate information regarding potential Suspected Unexpected Serious Adverse Reactions (SUSARS)/safety events to the CI.
- report SUSARs and USARs to the relevant oversight bodies and Sponsor.
- prepare required safety reports to oversight bodies, funders and regulators.

The CI will:

- work with ORTU to develop the safety reporting requirement including, timeframes, excluded events, coding systems and identify the appropriate Reference Safety Information (RSI).
- ensure the risks and side effects listed in the participant information sheet are consistent with the RSI and / or known safety profile.
- answer any safety related queries.
- review safety alerts.
- keep up to date with the literature to ensure the team are aware of the relevant clinical developments and safety information.

The CI will: *Continued*

- give a clinical opinion on any changes to the study risk-benefit assessment and the clinical management of participants following the update of RSI and completion of DSUR for IMPS and advise of any changes required to the Participant Information Sheet (PIS), management of the study and protocol.
- complete RSI review on receipt of update.

Change Management

ORTU work to the principles of Good Clinical Practice, which does not allow changes to key documents, databases or processes integral to the running of a study, without prior review and authorisation. ORTU manages a process of documented change management to ensure adequate level of oversight, risk assessment and approval of any requested changes. It's important to emphasise that changes can be hugely time consuming and have major practical repercussions to the running of a study. Where changes are required:

ORTU will:

- advise of sensible timing for the requested change process to be performed (noting there is no gauratee the change will be approved).
- discuss with key experts (e.g. statistician, data manager, QA Manager) regarding implicatons of changes
- ensure appropriate review, risk assessment and approval of any changes

The CI will:

- endevour to keep changes to a minimum
- understand that changes cannot be made quickly
- understand that requested changes may need to be actioned in order of priority and other planned work across all the studies that ORTU is managing
- Consider and be able to cover any additional costs that could be incurred
- thoroughly consider the implications of changes in order to reduce the need for further changes at a later time and support the change process ORTU will manage.

End of Study

The writing, approving and distribution of the end of study reports are a study team responsibility and although ORTU will facilitate the activity, this activity needs input from all parties.

ORTU will:

- prepare and submit end of study notification to applicable bodies.
- Working with the CI, upload a summary of results to the required platforms
- co-ordinate the writing of the end of study report(s) for submission to applicable bodies liaising with all collaborators and investigators as appropriate.

The CI will:

- author any sections of the end of study report as agreed with the ORTU,
- edit, review, approve and sign off end of study reports.
- ensure that the study team, at minimum the ORTU Trial Manager and statistician, are aware of drafts and the final submission in a timely manner prior to submission.
- for any human samples collected during the study, ensure any remaining samples are destroyed or have appropriate plans for long term storage in place.

Publication (Final Study Manuscript Plus Other Articles)

ORTU reserve the right to have the ORTU Director and up to 5 other authors (as decided by the ORTU Director) on all publications arising from ORTU managed studies.

ORTU will:

- as early as possible in the study, agree a publication plan in collaboration with the CI.
- assist in the manuscript preparation in association with the CI
- help to identify the target journal (s) for publication if required.
- ensure appropriate and relevant tables and figures are provided
- ensure a final statistical report and statistical input into the manuscript in line with the Statistical Analysis Plan (SAP).
- it should be noted that at the time of paper writing the study funding may have ended and study management, administrative staff and statisticians (who are all grant funded) may no longer be available.

The CI will:

- ensure the ORTU Director and up to 5 other authors (as decided by the ORTU Director) are included on the publication.
- deliver the primary publication of the study in collaboration with the ORTU and collaborating investigators.
- initiate and lead on the preparation of the final study manuscript process.
- identify target journal(s) for publication.
- review and approve the final statistical report (according to statisticians procedreus).
- identify who will be involved in the writing up of the final study manuscript.
- produce the final study manuscript (ready for submission).
- ensure that the study team, at minimum the ORTU Trial Manager and TrialStatistician, are aware of drafts and final submission in a timely manner prior to submission.

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OXFORD RESPIRATORY TRIALS UNIT
University of Oxford, Churchill Hospital
Oxford, OX3 7LE, United Kingdom
www.expmedndm.ox.ac.uk/ortu