Standard Operating Procedure:

Project Oversight and Quality Management

# Purpose

This standard operating procedure (SOP) describes the procedures for establishing appropriate project oversight and quality management strategies, based on the type of the clinical research and associated risk.

# Scope

This SOP is applicable to all clinical research sponsored by the University of Birmingham (UoB). Where clinical research is sponsored by another institution, this SOP should be followed as far as possible, and in line with the contractual agreement between the UoB and the other institution. This SOP also applies to clinical research approved by a UoB research ethics committee (REC), which is required to follow the UoB Principles of Good Clinical Practice (GCP) for Clinical Research (UoB-GCP-POL-001). This SOP may be used as a guidance document in all other cases.

# Implementation plan

This SOP will be implemented in line with this document’s effective date.

# Stakeholders

* Chief investigator (CI): the CI may delegate some activities to members of their research team, however evidence of CI involvement and approval is still required. It is highlighted within this SOP where activities are, and are not, appropriate for delegation to a team member. For clinical research approved by a UoB REC, the role of CI may be referred to as the UoB principal investigator (PI), or the supervisor for the postgraduate research student.
* Project oversight committees: including but not limited to, for example, project management groups, project steering committees, and data monitoring committees.
* Senior management providing oversight: including but not limited to, for example, operations managers, committees and clinical research compliance managers. This may be the CI in relation to a specific project’s compliance review where specified.
* Monitor.
* Clinical Research Compliance Team (CRCT).
* Research Ethics, Governance & Integrity Team (REGI).
* UKCRC-registered UoB Clinical Trials Unit (CTU). Note that where a CTU is involved, the CTU may take on responsibility for aspects of project management and oversight. The CTU may delegate these duties further to their trials team(s). All delegation of duties will be documented (e.g. using the Clinical Trials Task Delegation Log (UoB-SPO-QCD-001)).

# Background and rationale

For the purposes of this SOP the terms ‘clinical research’ or ‘project’ will cover: clinical trials of investigational medicinal products (CTIMPs), other interventional trials (e.g. surgical trials, device trials, non-CTIMP trials, and any other projects deemed to be ‘interventional’ by the sponsor), and clinical studies.

Institutions/sponsors are expected to have robust systems in place to ensure full control of a project. Each project will need a different level of control to ensure project-specific risks are managed appropriately. To identify the project-specific risks, the research team is expected to perform risk assessments on an ongoing basis from the project-design stage, continuing through to the end of the project.

The UoB’s quality management system (QMS) helps to ensure the quality of all aspects of a project. By following the UoB QMS, generic research risks can be managed appropriately (e.g. adverse event reporting). Project-specific risks can be managed by central monitoring, (also referred to as ‘in-house’ or ‘remote’ monitoring). They can also be managed by on-site monitoring; ‘on-site monitoring’ may be conducted remotely, or by using a mixed-model approach of remote and in-person visits. The purpose of monitoring clinical research is to verify that the:

* rights and wellbeing of participants are protected
* reported clinical research data are accurate, complete, and verifiable from source documents
* conduct of clinical research is in compliance with the current approved protocol/amendment(s), the principles of GCP, and the applicable regulatory requirement(s).

Where appropriate, project oversight committees can help to manage project-specific risks. This may include a:

* project management group (also referred to as trial management group), responsible for the day-to-day management of the clinical research
* project steering committee (also referred as trial steering committee), providing independent oversight of the clinical research
* data monitoring committee (DMC), providing an independent assessment of the safety, scientific validity and integrity of the clinical research.

The types of quality management strategies used, and the extent to which these are used, depends on the clinical-research design and project-specific risks. This SOP describes the process for identifying any project-related risks, and summarises the monitoring methods and management activities available to help mitigate risks.

For CTIMPs, a joint project between the Medical Research Council (MRC), Department of Health (DH) and the Medicines and Healthcare Products Regulatory Agency (MHRA) published a paper in 2011 called “[Risk-adapted Approaches to the Management of CTIMPs (PDF - 4.5 MB)](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf%22%20%5Co%20%22Link%20to%20the%20MRC/DH.MHRA%20Joint%20statement%20on%20Risk-adapted%20Approaches%20to%20the%20Management%20of%20CTIMPs%20%28PDF%20%E2%80%93%204.5%20MB%29)”. This paper defines a simple risk categorisation for clinical trials based on the marketing status of the investigational medicinal product (IMP) and standard medical care. This simple risk categorisation for clinical trials highlights the risks associated with the IMP and can inform the trial procedures for monitoring.

Note: for clinical research approved by a UoB REC the protocol may be set out as part of the ‘Application for Ethical Review Form’ submission. When used in this document, the term ‘protocol’ refers to both a standalone protocol, and a protocol contained within an ‘Application for Ethical Review Form’.

# Process map



# Procedure

## Risk assessment

1. The CI (or delegate) will perform and document a project-specific risk assessment and, where appropriate, this will be performed in collaboration with the study/trial coordinator, statistician and programmer. This may be documented in the protocol or within a separate document e.g. within the health and safety risk assessment. For clinical trials, the Risk Assessment Report (UoB-POS-QCD-001) may be used as a tool to consider different aspects of the trial (the template may also be adapted for clinical studies). The risk assessment will include consideration of:
* the risks related to the project design and method, participant safety and reliability of the data/results
* how risks can be appropriately managed. For example, this may be via the design of the project as captured in the protocol, by training made available to the project/site teams, use of external service providers (e.g. randomisation), use of project oversight committees, use of central and on-site monitoring (see below).

Note: a health and safety risk assessment is required for all research (clinical and non-clinical) prior to the research commencing. Also, a biological risk assessment is required when working with human tissue. See [UoB Safety Services](https://bham.sharepoint.com/sites/SafetyServices/) for more information (UoB login required). Where appropriate, these assessments may be combined into a single document, with the project-specific risk assessment.

1. For gene therapy trials, trials that use genetically-modified agents (e.g. modified immune cells) or trials that use self-replicating nucleic acids, the CI (or delegate) will ensure a specific gene-modified-agent risk assessment is performed for each relevant site. It is expected that this will be conducted in consultation with the gene therapy safety committee at each site. Contact details for the committee should be obtained from the relevant R&D office(s).
2. For CTIMPs where an external, non-UoB laboratory, will be used, the CI (or delegate) will risk assess suitability of the external laboratory in accordance with the External Laboratory Set-up and Oversight SOP (UoB-CRL-SOP-006).
3. For CTIMPs, the CI (or delegate) will submit the risk assessment as part of the initial sponsorship submission, and the REGI will document the review of the risk assessment as part of their sponsor review. See also the Project Setup SOP (UoB-SET-SOP-001).

Note: for non-CTIMPs and studies, the REGI may request a copy of the risk assessment.

1. The CI (no delegation allowed) will review and approve the finalised version of the risk assessment.
2. The CI (or delegate) will perform an updated/new risk assessment by reviewing the project’s risk profile following any significant change(s) to the project, including:
* a substantial amendment to the protocol
* a change to the organisation of the project (e.g. governance, funding, personnel)
* a significant change to the summary of product characteristics/investigator’s brochure (if applicable)
* after a serious breach or significant event/near miss
* a change in the risk identified during an interim analysis by the DMC.
1. Where the risk profile has changed, the CI (or delegate) will ensure the updated/new risk assessment is documented, e.g. via a risk-assessment report. It is also recommended to document where the risk profile has not changed e.g. on the latest risk-assessment report.
2. The CI (no delegation allowed) will review and approve each updated/new version of the risk assessment.
3. The CI (or delegate) will file each updated/new version of the risk assessment in the study/trial master file (S/TMF).
4. For CTIMPs, the CI (or delegate) will forward each updated/new version of the risk assessment to the REGI for information.

Note: for clinical research approved by a UoB REC, if the health and safety risk assessment is used to document the project-specific risks, additional approval of each updated/new version of the risk assessment may be required (e.g. by the chair of the relevant health and safety committee or the relevant head of college). See UoB guidance on [Research Risk Assessment and Mitigation Plans (RAMPs)](https://bham.sharepoint.com/sites/SafetyServices/SitePages/ramps.aspx) (UoB login required).

## Monitoring

1. The CI (or delegate) will define the need for, and approach to, monitoring in the protocol. The approach to monitoring will be proportionate to the type and risk of the clinical research, as determined by the risk assessment. The specific details regarding the type of monitoring to be used may be documented in the protocol, or in a separate document that is typically referred to as a monitoring plan. The term ‘monitoring plan’ will be used in this SOP to refer to both approaches.

Note: where the risk assessment determines that no monitoring is required, this must be documented in the protocol.

### Monitoring plan (where required)

1. The CI (or delegate) will develop a monitoring plan detailing any planned central monitoring and/or on-site monitoring required for that specific project (see also ‘central monitoring’ and ‘on-site monitoring’ sections below). The CI (or delegate) will ensure that the monitoring plan:
* focuses on risks identified in the risk assessment
* is in line with any contracts/agreements with co-sponsors and/or third parties, where applicable.
1. For CTIMPs managed outside of a UoB CTU, the CRCT will provide input into the development of the monitoring plan (where requested).
2. For CTIMPs managed outside of a UoB CTU, the CI (or delegate) will submit the monitoring plan to the REGI for review, and will ensure the finalised monitoring plan is in place prior to commencing participant recruitment. The REGI will either confirm their agreement or liaise with the CI (or delegate) for any further changes required.
3. The CI (no delegation allowed) will review and approve the finalised monitoring plan.
4. For CTIMPs managed by a CTU, the CI (or delegate) will forward the finalised monitoring plan to the REGI for information, and will ensure the finalised monitoring plan is in place prior to commencing participant recruitment.
5. The CI (or delegate) will review and update the monitoring plan, where required. This may be following changes to the risk assessment, or when other events/circumstances require changes being made to the monitoring plan. It is also recommended to document (e.g. on the latest monitoring plan) where a review has taken place but no updates have been required.
6. The CI (no delegation allowed) will review and approve each subsequent updated version of the monitoring plan.
7. The CI (or delegate) will file each updated version of the monitoring plan in the S/TMF.
8. For CTIMPs, the CI (or delegate) will forward each new updated version of the monitoring plan to the REGI for information.

### Central monitoring

1. Central monitoring consists of checks carried out off-site (e.g. within the coordinating centre/CTU/research team’s offices). The CI (or delegate) will decide the level of central monitoring required for the project and will document it in the monitoring plan. Examples of these types of checks include the review of:
* case report form (CRF) completion and return rate
* compliance with the protocol’s treatment and assessment schedule
* serious adverse event (SAE) report form completion
* SAE reporting rates
* notifications of protocol deviations
* validity of data
* quality of data entered
* statistical monitoring to identify outliers and data patterns
* reportable issues from a laboratory.
1. The CI (or delegate) will prepare, carry out and follow-up central monitoring. See also the Compliance Review SOP (UoB-CRP-SOP-001).
2. The CI (or delegate) will ensure any findings identified during central monitoring are followed up through to resolution, and where applicable ensure any issues are escalated appropriately.
* Where a serious breach is identified, the CI (or delegate) will ensure the reporting requirements are met as detailed in the Deviations and Serious Breach Reporting SOP (UoB-DSB-SOP-001).

### On-site monitoring

1. The CI (or delegate) will decide the level of on-site monitoring required for the project and document it in the monitoring plan. These types of checks include:
* reviewing informed consent form (ICF) completion and the documentation of the informed consent process (including re-consent, where appropriate)
* reviewing participants’ eligibility
* checking that participants’ eligibility has been confirmed at site by a suitably qualified healthcare professional prior to the participant being entered into the clinical research (for CTIMPs, this will be an authorised health professional)
* performing source data verification (SDV) and reviewing CRF completion
* checking for evidence that laboratory reports and other project-specific test reports (e.g. MRI, CT scan and full blood count) intended for clinical assessment have been assessed by a suitably qualified healthcare professional, in a timely fashion
* confirming the project is being conducted at site according to current approved documents (e.g. current protocol)
* confirming the site is reporting safety data to the sponsor as expected
* ensuring any non-compliance with the protocol, GCP or regulations is reported to the sponsor
* reviewing essential documents in the investigator site file, including safety updates from the sponsor
* ensuring site staff members listed on the site signature and delegation log are appropriately qualified, in terms of experience and training relevant to any delegated tasks
* checking for evidence of the principal investigator’s oversight of the clinical research
* where appropriate, visiting the pharmacy and checking IMP receipt, storage, labelling, accountability and destruction
* where appropriate, checking that randomisation was performed as per the protocol
* for blinded trials, checking that site staff do not have access to unblinded data.
1. For CTIMPs, it is expected that a degree of on-site monitoring will occur. The level of on-site monitoring will depend on the trial’s risk profile, and it may be carried out in combination with some central monitoring activity. In exceptional circumstances, sole use of central monitoring may be considered appropriate. In these instances, the CI (or delegate) will document their justification for the absence of on-site monitoring activity.
2. Senior management will ensure the monitor(s) are competent and appropriately trained individuals. Evidence of their competency and training will be documented. See also the Training SOP (UoB-TRN-SOP-001) and Compliance Review SOP (UoB-CRP-SOP-001). The monitor’s qualification(s)/training will include:
* relevant scientific and/or clinical knowledge needed to monitor the project adequately
* familiarity with the protocol, investigational products, ICFs and any other written information to be provided to the participant, the applicable QMS, and relevant standards and regulatory requirements.
1. The monitor will prepare, carry out and follow up on on-site monitoring as per the designated written procedures (e.g. the sponsor’s SOPs) and/or any project-specific procedures for monitoring.
2. The monitor will produce a documented report after each visit, which will include the following:
* date, site name/reference, name of the monitor, and name of the investigator or other individual(s) contacted
* summary of what was reviewed including, where applicable, sufficient detail to verify and document monitoring-plan compliance
* highlighting any significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance.
1. The monitor will ensure any findings identified during an on-site monitoring visit are followed up through to resolution, and where applicable ensure any issues are escalated appropriately.
* Where a serious breach is identified, the CI (or delegate) will ensure the reporting requirements are met as detailed in the Deviations and Serious Breach Reporting SOP (UoB-DSB-SOP-001).

Note: for CTIMPs managed outside a UoB CTU, the CRCT may perform on-site monitoring as part of the trial-specific monitoring plan (where required). It is expected this is suitably costed as part of the grant application process. See also the Clinical Research Quality Manual (UoB-CQM-POL-001).

1. Where on-site monitoring is performed by the CRCT, the CRCT will carry out the visits in accordance with the CRCT’s internal working instructions and the Compliance Review SOP (UoB-CPR-SOP-001). The CRCT will complete monitor visit reports within 30 working days of the actual visit and submit the completed reports/summary (as appropriate) to the Clinical Trial Oversight Committee (CTOC) for discussion at the next appropriate meeting.

### Review of monitoring visit reports

1. For UoB-sponsored clinical research that is managed by a UoB CTU, the UoB CTU will provide a list of all on-site monitoring visits, conducted over the previous 6-month period, to the CRCT for sponsor review. As a minimum, it is expected that the list will contain the following:
* project name/acronym
* project type (e.g. CTIMP or non-CTIMP)
* date of the visit
* name of the site
* name of the monitor(s).
1. The CRCT will review the extent and quality of on-site monitoring conducted by a UoB CTU against the corresponding project-specific monitoring plans. This will be done through review of at least two (where applicable) on-site monitoring visit reports per CTU. It is expected that the CRCT will carry out these reviews on a rolling-basis, rotating between the CTUs every 3 months.
2. The CRCT will report the outcome of any UoB CTU review of their monitoring visit reports to the CTOC.

## Project oversight committees

1. The CI (or delegate) will determine the need for, and type of, project oversight committees that are required depending on the type, size, complexity and duration of the project and associated risks. The oversight arrangements will be defined in the protocol, with further details in the project-specific monitoring plan (if applicable).
* This may include, but is not limited to, a project management group, project steering committee and/or data monitoring committee (see sub-sections below for more information).
1. Where a project oversight committee is required, the CI (or delegate) will document the committee’s membership, any terms of reference (or charter) and meeting minutes in the S/TMF.
2. Where terms of reference (or charters) are required, the CI (or delegate) will ensure these include, as a minimum:
* the responsibilities and scope of the committee
* frequency, format and documentation of meetings
* arrangements for handling urgent/emergency situations (if applicable).

### Project management groups

1. Where appropriate, the CI (or delegate) will set up a project management group prior to commencing the project. The membership may include the CI, study/trial coordinator, statistician and data manager.
2. The project management group will ensure the clinical research is designed, conducted and reported in accordance with applicable internal and external regulations and standards (including relevant SOPs). See also the UoB Principles of GCP for Clinical Research (UoB-GCP-POL-001).
3. The project management group will monitor the conduct and progress of the clinical research, ensure that the protocol is adhered to, and take appropriate action to safeguard both the participants and the quality of the clinical research.

### Project steering committees

1. Where appropriate, the CI (or delegate) will setup a project steering committee prior to commencing the project. It is expected that all members of the committee are independent of the investigators, including the committee chairperson. This may include members of the public, patients, their carers and sponsor representatives.
* Project steering committees are usually appointed for randomised trials. They make recommendations to the sponsor regarding the conduct of the trial, and they ensure regulatory compliance.
1. The project steering committee will provide advice to the investigators on all aspects of the clinical research (e.g. recruitment, competing trials, CRF return, deviations etc.).

### Data monitoring committees

1. Where appropriate, the CI (or delegate) will setup a DMC prior to the enrolment of participants, and will take into consideration the composition of the DMC, qualifications needed by DMC members and the independence of DMC members.
* Potential DMC members will have scientific expertise relevant to the indication being studied, practical experience with conducting clinical research and a good understanding of the problems and limitations of clinical research.
* Potential DMC members may also include qualified clinicians to assess the clinical aspects of safety and/or efficacy monitoring.
* For clinical trials, also refer to the [European Medicines Agency (EMA) Guidelines on DMCs (PDF - 75 KB)](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-data-monitoring-committees_en.pdf) and consider using the DAMOCLES study group template for the DMC charter (see references).
1. The DMC will have (can request) access to unblinded data (if applicable) and will review accruing data at intervals to monitor the progress of the clinical research, the safety data, and the critical endpoints.
2. The DMC will make recommendations (typically to the project steering committee or research team) on whether to continue, modify, or stop the clinical research, and assess whether there are any safety issues that should be brought to the participants’ attention.

# List of expected outputs

* Evidence of a project-specific risk assessment (and monitoring plan, where appropriate) with evidence of CI approval.
* For CTIMPs, evidence that the risk assessment has been submitted to the REGI as part of the initial sponsorship submission.
* For CTIMPs managed outside of a CTU, evidence that the monitoring plan has been submitted to, and approved by, the REGI with the finalised version in place prior to commencing participant recruitment.
* For CTIMPs managed by a CTU, evidence that the monitoring plan has been forwarded to REGI for information with the finalised version in place prior to commencing participant recruitment.
* Where significant changes to the project occur, evidence that the project-specific risk assessment and monitoring plan (if applicable) have been reviewed and updated with evidence of CI approval.
* For CTIMPs, evidence that each new updated version of the risk assessment and monitoring plan (if applicable) has been forwarded to REGI for information.
* Evidence of appropriate central monitoring, and/or on-site monitoring, being conducted.
* Evidence that all findings identified through central monitoring, and/or on-site monitoring, have been followed up through to resolution.
* Where required, evidence of the CRCT setting up, performing, and reporting on on-site monitoring of CTIMPs managed outside a UoB CTU.
* Evidence of the CRCT reviewing UoB CTUs’ on-site monitoring visit reports and reporting their review outcomes to CTOC.
* Evidence of project oversight committees’ membership, terms of reference (or charter) and meeting minutes, where applicable.

# Related documents

* UoB-CQM-POL-001 Clinical Research Quality Manual
* UoB-CRL-SOP-006 External Laboratory Set-up and Oversight
* UoB-CRP-SOP-001 Compliance Review
* UoB-DSB-SOP-001 Deviations and Serious Breach Reporting
* UoB-GCP-POL-001 UoB Principles of GCP for Clinical Research
* UoB-POS-QCD-001 Risk Assessment Report
* UoB-SET-SOP-001 Project Setup
* UoB-SPO-QCD-001 Clinical Trials Task Delegation Log
* UoB-TRN-SOP-001 Training

Access to the full UoB QMS for clinical research is available via the [CRCT website](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/index.aspx).

# References and frameworks

* DAMOCLES Study Group: A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet* 2005; 365: 711-722.
* EMA Guideline on DMCs: <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-data-monitoring-committees_en.pdf>.
* ICH Guidelines for GCP E6(R2): <https://www.ich.org/page/efficacy-guidelines>
* MRC/DH/MHRA Joint Project on Risk-adapted Approaches to the Management of CTIMPs: <https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf>
* UoB Guidance on RAMPs (UoB login required): <https://bham.sharepoint.com/sites/SafetyServices/SitePages/ramps.aspx>
* UoB Safety Services (UoB login required): <https://bham.sharepoint.com/sites/SafetyServices/>

# Abbreviations and definitions

| Term | Description |
| --- | --- |
| Authorised health professional | An authorised health professional is defined as a doctor, dentist, nurse or pharmacist.  |
| CI | Chief investigator. |
| CRCT | Clinical Research Compliance Team. |
| CRF | Case report form. |
| CTIMP | Clinical trial of an investigational medicinal product. |
| CTOC | Clinical Trials Oversight Committee. |
| CTU | Clinical trials unit. |
| Data monitoring committee (DMC) | An independent group of experts appointed by the sponsor, who provide independent assessment of the safety, scientific validity and integrity of the clinical research.  |
| DH | Department of Health. |
| EMA | European Medicines Agency. |
| GCP | Good Clinical Practice. |
| Healthcare professional | A healthcare professional is defined as an authorised health professional, or a qualified and registered (or alike) [Allied Health Profession](https://www.england.nhs.uk/ahp/role/) such as a physiotherapist, dietitian or radiographer. |
| ICF | Informed consent form. |
| ICH GCP | International Council on Harmonisation: Guidelines for Good Clinical Practice (ICH GCP). This is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve human participants. |
| IMP | Investigational medicinal product. |
| MHRA | Medicines and Healthcare products Regulatory Agency. |
| Monitoring | The act of overseeing the progress of a clinical research project to ensure that it is conducted, recorded and reported in accordance with the protocol, written procedures, Good Clinical Practice and the applicable regulatory requirements.  |
| MRC | Medical Research Council. |
| PI | Principal investigator. |
| Project management group | The group normally includes those individuals responsible for the day-to-day management of the clinical research project, such as the chief investigator, study/trial coordinator, statistician and monitor. The role of the group is to monitor all aspects of the conduct and progress of the project, ensure that the protocol is adhered to, and to take appropriate action to safeguard both the participants and the quality of the clinical research itself. For clinical trials, also known as a trial management group (TMG).  |
| Project steering committee | The role of the committee is to provide the overall supervision of the clinical research project. Ideally, it should include members who are independent of the investigators, their employing organisations and sponsors. The committee should monitor the project’s progress and conduct, and advise on scientific credibility. For clinical trials, also known as a trial steering committee (TSC). |
| QMS | Quality management system. |
| RAMP | Research risk assessment and mitigation plans. |
| REC | Research ethics committee. |
| REGI | Research Ethics, Governance & Integrity Team. |
| SAE | Serious adverse event. |
| SOP | Standard operating procedure. |
| Source data verification (SDV) | The process of checking the accuracy and completeness of case report form (CRF) entries against the source data contained in source documents. |
| S/TMF | Study/trial master file. |
| UoB | University of Birmingham |

See also the [Glossary of Terms](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/Glossary-of-Terms.aspx).