Standard Operating Procedure:

Compliance Review

# Purpose

This standard operating procedure (SOP) describes the processes for ensuring quality in clinical research projects. This includes the approval of vendors, and the implementation and management of compliance programmes, such as the audit programme.

# 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

Where the UoB takes on the sponsor’s responsibility for QA, the UoB will delegate the majority of these duties to the chief investigator (CI), clinical trials unit (CTU), and/or the Clinical Research Compliance Team (CRCT). All delegation of duties will be documented (e.g. via the CI declaration and the Clinical Trials Task Delegation Log (UoB-SPO-QCD-001)).

* CRCT
* Clinical Trials Oversight Committee (CTOC)
* Human Tissue Oversight Committee (HTOC)
* UKCRC-registered UoB CTU. Herein referred to as ‘UoB CTU’.
* Senior management providing oversight: including but not limited to, for example, operations manager, committees (e.g. CTOC/HTOC) and clinical research compliance manager. This may be the CI in relation to a specific research project’s compliance review where specified.
* Compliance reviewer: the competent person completing QA activities, e.g. auditor.
* Compliance reviewee: the person receiving the QA activities.
* CI: the CI may delegate some activities to members of their team; however, evidence of CI oversight and approval is still required. It is highlighted within this SOP where it is not appropriate to delegate activities 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 postgraduate research students.

# 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 and non-CTIMP trials, and any other projects deemed to be ‘interventional’ by the sponsor), and clinical studies.

There is a requirement to have mechanisms in place to provide assurance that the UoB’s clinical research activities are conducted in accordance with:

* applicable current regulations
* the UoB quality management system (QMS)
* international standards including GCP and Good Manufacturing Practice (GMP) for medicinal products
* the standards as set out for UKCRC-registered CTUs
* the Human Tissue Authority (HTA) research and applications licensing standards.

Quality assurance includes all the planned and systematic actions that are established for a project’s compliance. They ensure that the project, and any data generated and documented/recorded, are in compliance with GCP and the applicable regulatory requirements as detailed within the UoB QMS. This SOP focusses on compliance reviews and describes the overarching process for selecting their topics. It outlines the procedures for carrying out compliance reviews and reporting their findings. It also describes the requirements for reviewees to respond to reports, and implement corrective and preventative actions (CAPA) where applicable.

Projects may require services from a different institution or commercial entity external to the UoB, either in exchange for money or for free. These are commonly known as a ‘vendors’, ‘suppliers’ or ‘third-party service providers’, but they will all be referred to as ‘vendors’ within this SOP. It is essential that a robust appraisal of vendors is performed, as the responsibility for oversight of their conduct remains with the sponsor.

The [UoB Internal Audit Service](https://intranet.birmingham.ac.uk/finance/internal-audit/index.aspx) follows its own processes and is responsible for carrying out a programme of audits across all areas of the UoB. It focusses on the controls that departments have put in place to ensure adequate governance, risk management, quality assurance, and adherence to regulations, policies and procedures.

# Procedure

## Compliance review setup

1. Senior management or the CI (on a project-specific basis) will ensure that compliance reviews are conducted across the clinical research activity to provide assurance of its quality. A risk-based approach will be used to determine the type(s) of compliance review required, which may include:

* audits
* sponsor support visits (SSV)
* on-site monitoring visits (see the Project Oversight and Quality Management SOP (UoB-POS-SOP-001) for more information on both central and on-site monitoring)
* assessment of vendors
* study/trial master file (S/TMF) reviews
* quality checks.

1. Senior management will ensure compliance reviewers are appropriately-trained individuals, and where applicable that they are competent to perform audits, on-site monitoring visits and/or SSVs. Evidence of training and competency (where applicable) will be documented. See also the Training SOP (UoB-TRN-SOP-001).

* For details on the training and competency requirements for monitors, see the Project Oversight and Quality Management SOP (UoB-POS-SOP-001).
* Compliance reviewers performing audits are expected to be independent of the activities being reviewed. Where possible they are expected to report into independent lines of management (i.e. not to the CI) to ensure issues can be effectively and appropriately managed, and escalated where necessary.

## Vendor assessment and management

1. The CI (or delegate) will identify and document the project functions being delegated to a vendor, prior to any clinical research activities commencing.
2. The CI (or delegate) will determine and document the method to be used in their assessment of a vendor’s suitability. The following criteria could be used to assess vendors that have been shortlisted to provide the product/service, in line with the project’s specification and timeline:

* review of marketing material to explain standards being used by the vendor
* assessment of CVs and previous experience of key staff members
* obtaining references to show the vendor is capable of delivering the product/service
* vendor can confirm their ability to meet the needs of the project, and to deliver within the specified time frame
* personal experience/knowledge of the vendor
* for medical devices, successful CE marking or UKCA marking (in effect as of 01-Jan-2021) is completed
* confirmation that GCP, GMP and/or Good Laboratory Practice (GLP) standards are adhered to, where applicable
* correct licences are in place e.g. manufacturer’s/importer’s authorisation for an investigational medicinal product (MIA (IMP)), where applicable
* review of the vendor’s policies, procedures and QMS
* conducting vendor audits and vendor site visits
* vendor’s company history and stability
* after-sales service, including any training relating to the product/service
* cost of the vendor’s product/service
* preferred-providers list held by the University, lead NHS trust, sponsor and/or funder.

1. The CI (or delegate) will assess the suitability of a vendor and document it in the S/TMF. The assessment will depend on the risk(s) associated with the specific tasks being delegated, and personal experience/knowledge of the vendor. The CI (or delegate) will work with their local [College Hub Team](https://intranet.birmingham.ac.uk/rssd/research-support/contracts.aspx), as per local processes, to arrange for the appropriate contract agreement to be put into place. Where appropriate, the [UoB Procurement Team](https://intranet.birmingham.ac.uk/finance/procurement/index.aspx) and [UoB Legal Services](https://www.birmingham.ac.uk/university/colleges/professional/executive/legal/index.aspx) will be consulted.
2. The CI (or delegate) will maintain documented oversight of vendors during the research project to ensure compliance with the terms of the contract, the research protocol, applicable regulations and standards. This may include the following activities:

* regular communications with the vendor e.g. teleconferences, meetings
* a formal communication plan can be developed to define the level and frequency of communication between parties
* documented regular updates/reports from the vendor
* being an authorised signatory on key research-specific documents e.g. data management/statistical analysis plans

The following must be performed by a compliance reviewer if used to maintain oversight of the vendor:

* periodic review, at a defined frequency, of the standard of work completed to date e.g. via audit
* review of specific activities, for example regulatory green-light checks or S/TMF review

1. The compliance reviewer will follow the relevant processes detailed in this document when carrying out vendor oversight/external compliance reviews.
2. The CI (or delegate) or compliance reviewer will ensure that the CRCT is notified prior to the commencement of any external compliance review. This includes any assessments of external laboratories as the CRCT is the UoB QA representative for GCP compliance in the laboratory (see point 21). See also the Laboratory Set-up and Management SOP (UoB-CRL-SOP-001).
3. The CI (or delegate) will develop an escalation plan for reporting significant non-compliance issues. This may be included within the risk assessment or monitoring plan, and is expected to be reflected in the contract between the sponsor and the vendor.

## Compliance review programme

1. The compliance reviewer in collaboration with senior management will develop an overarching compliance review programme for audits and/or SSVs. The programme will be informed by the use of risk-based strategies, the consideration of previous quality-check outcomes, audit and/or inspection outcomes, changes to legislation and working practices, and any other issues raised within the previous year.

* The compliance review programme may change focus based on the results of on-going activities such as inspection findings, as well as areas of concern identified through, for example, risk assessments and monitoring.

1. Where the compliance review programme is an audit programme, the compliance reviewer will include (but is not limited to) the topics listed below. The topics will be audited on a scheduled rolling basis against applicable regulations, international standards and relevant QMS(s).

* For clinical trials, it is expected that the audit-selection process will prioritise CTIMPs. The following topic areas will be audited for clinical trials by the CRCT/UoB CTUs:
* data management
* statistics
* pharmacovigilance
* investigational medicinal product (IMP) management (for CTIMPs)
* IT systems management
* training
* QMS development and management
* project oversight and quality management
* deviations and serious breach reporting.
* For HTA-licensed tissue banks, the following topic areas will be audited by the CRCT:
* consent
* governance and quality
* premises, equipment and facilities (PFE)
* traceability.
* For laboratories working to GCP in the laboratory standard, the following topic areas will be audited by the CRCT:
* laboratory set-up and management
* laboratory facilities
* sample management
* laboratory analysis
* reportable issues.
* For GMP areas, the following topic areas will be audited by the CRCT:
* pharmaceutical quality system (PQS)
* personnel
* PFE
* documentation
* production.
* quality control
* For HTA applications licensed areas, the following topic areas will be audited by the CRCT:
* governance and quality
* PFE
* disposal.

1. For the CRCT SSV programme, for projects managed outside of a UKCRC-registered CTU, the compliance reviewer will include the topics listed below. Projects will be reviewed against applicable regulations, international standards and relevant QMS(s).

* Principles of GCP.
* Handling and storage of human tissue.

1. Where there has been a previous compliance review programme, the compliance reviewer will include a summary of the outcome of the previous programme.
2. Senior management will review and approve the compliance review programme.

### For CRCT/UoB CTU compliance reviews programmes

1. The CRCT will submit an annual audit programme for approval to the CTOC and HTOC. The audit programme will be written in accordance with this SOP and the CRCT’s internal work instructions.

* Where changes are required (except to the timing of an audit), these will only be made following agreement from the chairs of the CTOC and HTOC.

1. The UoB’s CTUs will submit their internally approved audit programme(s) to the CTOC for notification; it is expected that the audit programme will be updated annually.

## Develop a plan

1. The compliance reviewer will document a plan that outlines a description of the activities and arrangements, including:

* defined aims and objectives, and rationale
* scope, i.e. the extent and boundaries of a compliance review. This generally includes a description of the physical and virtual locations, functions, organisational units, activities and processes, as well as the time period covered
* For external audits of the UoB, senior management, or for a specific project the CI (or delegate), will ensure that contracts are in place before any audit. The scope of the audit will also be clearly defined and have a focussed CAPA in responses required.
* criteria and any documented reference information e.g. SOPs, protocols, standards and regulatory requirements
* For external audits of the UoB, it is expected that the framework to be audited against will be specified by the auditor.
* resources required, including locations subject to review
* methodology, including what checks are needed, where and when they will be carried out, and the reporting process
* timelines.

1. The compliance reviewer will ensure that the plan is reviewed and approved by an independent person who is trained in reviewing, and competent in, the compliance-review process.
2. The compliance reviewer will prepare for the compliance review, by:

* developing any tools required
* informing the compliance reviewee of the review and confirming with them the scope, inputs, timing and resources required
* requesting relevant documentation from the compliance reviewee which may include (but is not limited to) topic-specific QMS documents, protocols, essential documents
* ensuring that the compliance reviewee is given a timeframe in which to return the requested documentation/information
* reviewing the relevant documentation received from the compliance reviewee
* clarifying who should receive the compliance review report, in addition to the compliance reviewee.

## Perform a compliance review

1. The compliance reviewer will carry out the following activities during a compliance review:

* carry out checks against the plan, and review key processes, through document review and interviews
* when performing a compliance review at a site, complete a site visit log (see the Site Visit Log (UoB-CPR-QCD-002) for a template) or equivalent (e.g. monitoring visit report)
* escalate significant issues to senior management within required timeframes, following applicable standards and regulations, and where appropriate, those outlined in the topic-specific QMS (see also the Deviations and Serious Breach Reporting SOP (UoB-DSB-SOP-001))
* where significant issues are identified and need further exploration, deviate from the plan
* if required, meet with the compliance reviewee to discuss findings.

1. For audits of external laboratories conducting analyses on trial samples for a CTIMP, the compliance reviewer will consult with, and carry out the compliance review in conjunction with, the CRCT.
2. The compliance reviewer will ensure that the compliance reviewee is informed of the timeframes for the generation of the report, and the response report.

Note: where the S/TMF is not readily available or accessible, or the S/TMF is incomplete to such an extent that it cannot form the basis of a compliance review and therefore impedes or obstructs the compliance reviewer from performing their duties in verifying compliance with the applicable regulations, this should be graded as a critical finding.

## Write a report

1. The compliance reviewer will write a report within stipulated timelines.

* For audits and SSVs conducted by the CRCT, a report will be provided within 30 working days of the closing meeting.
* For audits, any audit findings will be graded according to a predefined classification grid (see the Finding Classification Grid (UoB-CPR-QCD-001).

1. The compliance reviewer will ensure that the report is reviewed and approved by an independent person who is trained in reviewing, and competent in, the compliance-review process.
2. The compliance reviewer will retain and file the report and ensure that it is sent to the compliance reviewee within the set timeframe. The compliance reviewer will also ensure that copies are forwarded to the pre-agreed relevant parties.
3. The compliance reviewee will respond to the report with a CAPA plan within stipulated timelines.

* For audits conducted by the CRCT, it is expected that a response is provided within 20 working days (or earlier if required), and within 10-working days for further audit clarifications (where applicable).

1. The compliance reviewer (and senior management where necessary) will review the responses. Where required, the compliance reviewer/senior management will request further clarifications. Where the responses address the findings appropriately, the compliance review will be progressed to closure.

## Close of a compliance review

1. The compliance reviewer will close the compliance review by completing the actions (where applicable) that are listed below.

* For audits:
* an audit certificate will be generated and forwarded to the compliance reviewee for filing
* critical and major findings will be logged and followed up with the reviewee until resolution
* all internal audit response reports (including those conducted by the UoB CTUs) will be submitted to the CRCT for information, within 3 working days of finalising the audit response report. Where required, the CRCT may request a copy of the audit report.
* all reports from external audits of the UoB will be submitted to the CRCT for information, within 3 working days of receiving/accepting the audit report. Where local approval of a report is required by a department/team (such as approval from a quality management group or equivalent), the report will be submitted to the CRCT within 3 working days of that local approval being obtained.
* any response report to an external audit will be submitted to the CRCT within 3 working days of it being finalised.
* For audits performed by the CRCT, the CRCT will submit the response report to the relevant oversight committee(s) (as per the relevant audit plan) for discussion.
* Relevant information will be forwarded to key stakeholders. It is expected that this information is used to inform discussion and decision-making regarding requirements for organisational CAPA, as per their local procedures.
* File all relevant documentation.

1. The compliance reviewer will ensure that any outstanding issues are reported to senior management for continuous review through to resolution.
2. For audits, the CRCT will log critical and major findings, from all sources, on their issues-management tracker.
3. For SSVs conducted by the CRCT:

* the compliance reviewer will hold a follow-up meeting with the reviewee to monitor progress with addressing the compliance issues identified
* the CRCT will provide CTOC and/or HTOC with a summary of the SSVs that have been completed, since the last committee meeting.

1. The UoB CTU will provide a summary of all compliance reviews conducted/received and any significant findings noted in a 6-monthly report to the CTOC.

## Sponsor oversight

1. The CTOC and/or HTOC will review information provided to them relating to compliance-review activities during the scheduled meetings. The CTOC/HTOC will take further action where major risks to the UoB’s sponsored or co-sponsored project, participants and/or the organisation have been identified. This may include consulting with CIs or delegates and up-escalating to heads of colleges or the Research Governance, Ethics and Integrity Committee (RGEIC).

# List of expected outputs

* Evidence of staff training and competency (for audits, monitoring visits and SSVs) in compliance reviews.
* Evidence of a compliance-review programme (where appropriate). For the CRCT/UoB CTUs, evidence of this being submitted to, and reviewed by (if required), the relevant oversight committee(s).
* Evidence of the CRCT being notified of any external compliance reviews, including any vendor assessments of external laboratories.
* A documented compliance-review plan.
* Where a compliance review has occurred at site, evidence via a site visit log or equivalent.
* Evidence that a compliance review has been carried out.
* Evidence of responses to any findings identified during the compliance review.
* Audit certificate (where appropriate).
* Escalation of findings (where appropriate).
* Evidence of internal audit response reports, and external audit reports & response reports submitted to the CRCT.
* Evidence of the CRCT’s summaries of compliance reviews sent to the CTOC/HTOC.
* Evidence of the CRCT’s issues-management tracker.
* Evidence of the CTU’s 6-monthy summary reports on all compliance reviews conducted/received sent to the CTOC.

### Where a vendor is used:

* Evidence of research functions being delegated to a vendor.
* Evidence of a documented assessment of the suitability of a vendor.
* Evidence of an appropriate contract between the UoB and a vendor.
* Evidence of documented oversight of vendors during the research project.

# Related documents

* UoB-CPR-QCD-001 Finding Classification Grid
* UoB-CPR-QCD-002 Site Visit Log
* UoB-CRL-SOP-001 Laboratory Set-up and Management
* UoB-DSB-SOP-001 Deviation and Serious Breach Reporting
* UoB-GCP-POL-001 UoB Principles of GCP for Clinical Research
* UoB-POS-SOP-001 Project Oversight and Quality Management
* 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:

* British Standards Institution, BS EN ISO 19011:2018 - Guidelines for auditing management systems. Can be accessed via: [https://bsol.bsigroup.com](https://bsol.bsigroup.com/) (requires UoB login).
* Human Tissue Act 2004: <http://www.legislation.gov.uk/ukpga/2004/30/contents>
* ICH Guidelines for GCP E6(R2): <https://www.ich.org/page/efficacy-guidelines>
* MHRA (2022) *Rules and Guidance for Pharmaceutical Manufacturers and Distributors*. Eleventh edition. UK: Pharmaceutical Press.
* The Medicines for Human Use (Clinical Trials) Regulations 2004 (and subsequent amendments): <https://www.legislation.gov.uk/uksi>
* UoB Research Contracts: <https://intranet.birmingham.ac.uk/rssd/research-support/contracts.aspx>
* UoB Internal Audit Service: <https://intranet.birmingham.ac.uk/finance/internal-audit/index.aspx>
* UoB Legal Services: <https://www.birmingham.ac.uk/university/colleges/professional/executive/legal/index.aspx>
* UoB Procurement Team: <https://intranet.birmingham.ac.uk/finance/procurement/index.aspx>
* UK Policy Framework for Health and Social Care Research: <https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/>

# Abbreviations and definitions

| Term | Description |
| --- | --- |
| Audit | A systematic and independent examination of both project-specific activities and their related documentation. An audit is used to determine whether the activities that have been evaluated were carried out in accordance with the project’s protocol, the sponsor's SOPs, GCP, GCP in the Laboratory, HTA research licensing standards, GMP and any other applicable regulatory requirement(s). An audit will also assess whether the clinical research data were appropriately recorded, analysed and accurately reported. |
| CI | Chief investigator. |
| Compliance reviewee | The individual/team or organisation in receipt of the compliance review. |
| Compliance reviewer | An appropriately trained individual, and where applicable competent to perform audits, monitoring visits and/or SSVs, whose qualifications should be documented. They conduct the compliance review. |
| Corrective and preventive action (CAPA) plan | A plan produced by the compliance reviewee detailing the actions to be taken following a compliance review, to correct any issues found and to prevent those issues from reoccurring. |
| CRCT | Clinical Research Compliance Team. |
| CTIMP | Clinical trial of an investigational medicinal product. |
| CTU | Clinical trials unit. |
| GCP | Good Clinical Practice. |
| GLP | Good Laboratory Practice. |
| GMP | Good Manufacturing Practice. |
| HTA | Human Tissue Authority. |
| PFE | Premise, facilities and equipment. |
| PI | Principal investigator. |
| PQS | Pharmaceutical quality system. |
| MIA (IMP) | Manufacturer’s/Importer’s authorisation for an investigational medicinal product |
| QMS | Quality management system. |
| Quality assurance (QA) | All the planned and systematic actions that are established for a project’s compliance. They ensure that the project is conducted in compliance with GxP and the applicable regulatory requirements. They also ensure that any data generated, documented/recorded, and reported is also compliant with relevant regulatory requirements/legislation. |
| Quality control (QC) | The operational techniques and activities undertaken within the quality assurance system, to verify that the requirements for quality of the project-related activities have been fulfilled. |
| REC | Research ethics committee. |
| SOP | Standard operating procedure. |
| Sponsor support visit (SSV) | A visit to the investigators and their teams by the CRCT where the UoB is the sponsor or provides institutional oversight for the clinical research. The SSV involves discussions with the research team and a review of the project, including key processes and documents such as participant consent and enrolment, collection and processing of data and tissue sample management, as applicable. The SSV allows best practice to be shared between research teams, as well as providing feedback in areas of work that need further attention to ensure full adherence to applicable regulations and standards. |
| S/TMF | Study/trial master file. |
| UoB | University of Birmingham. |
| Vendor | Various types of external providers to whom a sponsor may delegate their functions e.g. contract research organisations, laboratories, consultants, freelancers/ contractors etc. They exclude research collaborators and clinical research sites. |

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