Standard Operating Procedure:

Sponsor Oversight of Clinical Research

# Purpose

This standard operating procedure (SOP) describes the procedures for granting initial sponsor approval for and retaining sponsor oversight of clinical research at the University of Birmingham (UoB).

# Scope

This SOP is applicable to all clinical research sponsored by the UoB. Where clinical research is sponsored by another institution, this procedure should be followed as far as possible, and in line with the contractual agreement between the UoB and the other institution. It also applies to clinical research that does not require a sponsor, but where the UoB is responsible for institutional oversight. This includes clinical research approved by a UoB Research Ethics Committee (REC) that is required to follow the UoB Principles of Good Clinical Practice (GCP) for Clinical Research (UoB-GCP-POL-001).

# Implementation plan

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

# Stakeholders

* Clinical Trials Oversight Committee (CTOC)
* Human Tissue Oversight Committee (HTOC)
* Research Governance & Ethics Team (RG&ET)
* Clinical Research Compliance Team (CRCT)
* UKCRC-registered UoB Clinical Trials Units (UoB CTU)
* Chief Investigator (CI); the CI may delegate some activities to members of their research team, however evidence of the CI’s involvement and approval is still required and may not be delegated where ‘no delegation allowed’ is indicated. This SOP will state where delegation is possible. For clinical research approved by a UoB REC, the role of CI may be referred to as the principal investigator, or the supervisor for postgraduate research students.

# Background and rationale

The [UK Policy Framework for Health and Social Care Research (v3.3 07-Nov-2017)](https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/) requires that all health and social care research that falls under the responsibility of either the Health Research Authority (HRA) or the devolved administrations’ health departments has a formal sponsor. This framework sets out guidance on the expectations of sponsors for all clinical research in the UK.

The sponsorship responsibilities for clinical trials of investigational medicinal products (CTIMPs) are specifically described in the [Medicines for Human Use (Clinical Trials) Regulations 2004 (UK SI 2004 No. 1031)](https://www.legislation.gov.uk/uksi/2004/1031/contents/made) and subsequent amendments. Specific descriptions of the role of the sponsor are detailed in the regulations and are stated below.

* ‘A person who is the sponsor of a clinical trial in accordance with this regulation may delegate any or all of his functions under these Regulations to any person but any such arrangement shall not affect the responsibility of the sponsor’ (Regulation 3 (12) of SI 2004/1031).
* The ‘sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of GCP are satisfied or adhered to’ (Regulation 28 (2) of SI 2004/1031).

For clinical trials that fall outside of the scope of the UK Policy Framework for Health and Social Care Research and where a UoB REC has provided approval, there is no formal requirement for a sponsor. However, the University is still required to maintain institutional oversight of these trials. Therefore, the same oversight process, as detailed in this SOP, will be applied. In addition, where any other clinical research is designated by a UoB REC as having to work to the UoB Principles of GCP for Clinical Research (UoB-GCP-POL-001), it will follow the same process for sponsor oversight as captured in this SOP. For ease, the SOP will refer to sponsor oversight only from this point onwards, which can be read as ‘sponsor oversight’ or ‘institutional oversight’.

For the purposes of this SOP the terms ‘clinical research’ or ‘project’ will cover 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.

## Sponsor oversight at the University of Birmingham

At the UoB the design and management of a project is delegated to the CI through the UoB’s clinical research quality management system (QMS) and/or the CI declaration issued by the RG&ET and signed by the CI at the time of sponsorship approval. Where the CI is external to the UoB, an external CI agreement will be arranged by the Research Contracts Teams. The project may also be managed through a UoB’s CTU; where this is the case, the project-related tasks may be further delegated by the CI to the CTU and captured in a clinical trials task delegation log (see the Clinical Trial Task Delegation Log (UoB-SPO-QCD-001) for a template). The remaining functions, including maintaining oversight, are shared between the RG&ET, the CRCT, and the oversight committees (CTOC and HTOC). These functions are detailed in the *Procedure* section below or the relevant policy/SOP in the UoB’s clinical research QMS. See the Clinical Research Quality Manual (UoB-CQM-POL-001) for further details on the UoB’s research governance framework.

# Procedure

## Clinical research portfolio oversight

1. The RG&ET will maintain an electronic database (at time of writing ReDA) that records all clinical research requiring sponsor oversight, including its status.
2. The RG&ET will report to the CTOC on changes to the portfolio of projects managed outside a UoB’s CTU at each CTOC meeting. The reports will include new applications and amendments received since the last CTOC meeting, the turnaround times for the RG&ET to complete their review of these applications, any outstanding annual reports, and the actions taken by the RG&ET.
3. The RG&ET will provide a list of new projects using human tissue that have received sponsorship authorisation since the last HTOC meeting.
4. The UoB’s CTUs will maintain oversight of their clinical research portfolio, ensuring any reporting timelines are met. Each of the UoB’s CTUs will provide an update to the CTOC at the CTOC meetings, identifying any major issues that have been raised within their CTU since the last CTOC meeting (see also ‘issue management’ section below).
5. The CTOC will review the reports provided during the CTOC meetings by the RG&ET and UoB’s CTUs. They will act where major risks have been identified to the UoB’s sponsored or co-sponsored clinical research, participants and/or the organisation. This may include liaising with CIs or delegates and up-escalating to heads of colleges or RGEIC.

## Clinical research oversight

### Sponsor review conducted by the RG&ET

1. Upon receipt of a new sponsorship application, the RG&ET will:

* assign a sponsor number (‘RG number”)
* log the project onto the sponsor’s database (at time of writing, ReDA)
* review the application within 10 working days of receiving the full application, with reference to the Sponsor Review Tool (UoB-CRG-QCD-001).
* Where the project does not meet all the criteria for the UoB to take on sponsorship, the RG&ET will forward the project to the chair of the CTOC for advice.
* Where further changes are required, the RG&ET will review any subsequent updates within 10 working days and either provide feedback to the researcher or approve the project.

1. Where requested, the chair of the CTOC will review a project that does not meet all criteria for the UoB to take on sponsorship and will provide advice. If required, the chair of CTOC will discuss the project in more detail with members of the CTOC and liaise with the CI.
2. Where the project meets the criteria for the UoB to sponsor the project and no further changes are required in the project documentation, the RG&ET will carry out the actions listed below.

* Approve the initial application, or required changes to the initial application, in the Integrated Research Application System (IRAS), and notify the CI in writing of their approval following the review. For CTIMPs, the RG&ET will instruct the CI (or delegate) to contact the CRCT if the trial involves any laboratory analysis (including the use of external UoB laboratories).
* Select 10% of the new UoB CTU-managed CTIMPs (per annum) and perform a further detailed review of the project-specific risk assessment and related monitoring plan for these CTIMPs. This may be performed in collaboration with the CRCT.
* Review the confirmation from the CI that any conditions set out within the REC’s or, if applicable, the competent authority’s (CA) approval letter have been met.

1. Throughout the duration of the project, the RG&ET will monitor the submission of annual reports to the REC and, if applicable, to the CA, as described in the Project Set-up SOP (UoB-SET-SOP-001) and Adverse Event Reporting SOP (UoB-AES-SOP-001).

* Reports include:
* for CTIMPs, the development safety update report (DSUR) to be sent to the CA and the REC, and the annual progress report (APR) to be sent to the REC
* for non-CTIMPs and studies, the APR to be sent to the REC.
* The RG&ET will liaise with the CI (or delegate) where the deadline (i.e. the due date extended with the grace period) has not been met. See also point 2 above.
* Upon receipt of the annual reports, the RG&ET will review the reports received, update the research governance database, and file the annual report in the relevant project folder.

1. Upon receipt of an amendment, the RG&ET will carry out the actions listed below.

* Review the substantiality assessment as conducted by the CI and refer to the Sponsor Review Tool (UoB-CRG-QCD-001) as required. If the RG&ET is in agreement, this will be evidenced for substantial amendments by the RG&ET approving the submission to REC and CA as applicable. The RG&ET will contact the CI (or delegate) where the RG&ET is not in agreement with the substantiality assessment.
* Review the application within 10 working days of receiving the application (or by return if amendment is due to an urgent safety measure).
* Where further changes are required, the RG&ET will review any subsequent updates within 10 working days (or by return if amendment is due to an urgent safety measure) and either provide feedback to the researcher or approve the project.
* Where no further changes are required, the RG&ET will approve the application in IRAS.
* Review the confirmation from the CI that any conditions set out within the REC’s or, if applicable, the CA’s approval letter have been met.
* File the final versions of the essential documents submitted to the REC and, if applicable, the CA in the RG&ET electronic folder, together with a copy of the IRAS form, approval letters and any further relevant correspondence.

1. When informed of a trial’s closure, either through an annual report, a trial closure report or otherwise, the RG&ET will monitor that relevant documentation is submitted to the REC and, if applicable, the CA in a timely fashion, and that the trial summary report is submitted within a year following submission to the REC and, if applicable, the CA. The RG&ET will liaise with the CI (or delegate) where timelines are not met, and report to the CTOC where delays have been observed, and the actions taken by the RG&ET. See also the Project Closure SOP (UoB-CLO-SOP-001).

### Sponsor review conducted by the UoB’s CTUs

The UoB’s CTUs have been delegated sponsor review activities as described in a memorandum of understanding kept at the RG&ET; see ‘Memorandum of Understanding: Delegation of Sponsor Review Activity to CTUs’, available from the RG&ET*.*

### Compliance review

1. The UoB’s CTUs will maintain their internal audit programme(s) and submit all audit reports and response reports to the CRCT, in accordance with the Compliance Review SOP (UoB-CPR-SOP-001). In addition, the UoB’s CTUs will submit their internally approved audit programme(s) to the CTOC for notification; it is expected that the audit programme is updated annually.
2. The CRCT will submit an annual audit programme for approval to the CTOC and HTOC. The audit programme will be written in accordance with the CRCT’s internal work instructions and the Compliance Review SOP (UoB-CRP-SOP-001).

* The CRCT will execute the audit programme. Where changes are required (except to the timing of an audit), these will be made only following agreement from the chairs of the CTOC and HTOC.
* Upon completion of an audit, the CRCT will submit the full report (to include responses from auditees) to the relevant oversight committee(s) (as per the relevant audit plan) for discussion.

1. The CRCT will select projects managed outside of a UKCRC-registered CTU for a sponsor support visit using a risk-based approach. The CRCT will conduct the sponsor support visit, produce a report within 30 working days of the closing meeting, and submit the completed report to the relevant oversight committee(s) for discussion, in accordance with the CRCT’s internal work instructions and the Compliance Review SOP (UoB-CRP-SOP-001).
2. 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 liaising with CIs or delegates and up-escalating to heads of colleges or the RGEIC.

### Issue management

Note: serious breaches will be handled in accordance with the Deviations and Serious Breach Reporting SOP (UoB-DSB-SOP-001).

1. The UoB’s CTUs will maintain a clear process for internal escalation of issues relating to clinical research, their local QMS, resourcing, operations or otherwise. Where issues are considered to significantly impact the CTU and thereby the UoB, the director of the CTU or deputy will report these to the CTOC.
2. Where CTOC/HTOC members, RG&ET staff or CRCT staff are made aware of a complaint in relation to the way the UoB supports and oversees clinical research, the staff member will escalate the complaint to the chair of the CTOC, who will investigate further with the complainant and define a plan of action to resolve the issue highlighted. This may include liaising with CIs or delegates and up-escalating to heads of colleges or the RGEIC. Where the complaint relates to the chair of the CTOC, the staff member will instead escalate the complaint to the Pro-Vice-Chancellor for Research & Knowledge Transfer.
3. Should a serious issue occur that affects the risk profile of the UoB or may harm the reputation of the UoB, it is expected that the resources within the RG&ET and/or CRCT are temporarily redirected to address the issue. This should occur, once:

* the review of the issue, subsequent decision and instruction has been given directly by the relevant oversight committee (CTOC/HTOC)
* the CRCT has obtained agreement from the MDS and LES deputy directors of operations (Research and Knowledge Transfer); and/or the RG&ET has received agreement from the head of Research Support Services in Finance
* the remit of the support has been clarified and agreed via a memorandum of understanding or equivalent.

#### External audits and inspections

The UoB is subject to external audits (e.g. by pharmaceutical companies acting as the sponsor for a clinical trial) and regulatory inspections (e.g. inspections from the Medicines and Healthcare products Regulatory Agency (MHRA) and the Human Tissue Authority (HTA)). The audits and inspections can be of the UoB in their role as the sponsor, or of a department within the UoB e.g. a UoB’s CTU or laboratory facility.

1. For external audits, or inspections of the UoB as the sponsor, the head of Research Governance and Integrity (or delegate) will act as the main contact with the external auditor/inspector. Where the scope of the audit/inspection is laboratory related (e.g. a MHRA GCP in the laboratory inspection), the clinical research compliance manager (laboratory) will act as the main contact. The main contact will:

* upon receipt of the notification, inform the CTOC and/or HTOC (as applicable) of the scheduled audit/inspection
* organise the audit/inspection in liaison with the auditor/inspector and key UoB’s stakeholders, to include collating a dossier if required and handling the logistics of the audit/inspection
* upon receipt of the audit/inspection report, forward to the CTOC and/or HTOC (as applicable) for notification
* collate a response report, and ensure feedback is received from experts as required
* organise for the CTOC and/or HTOC (as applicable) to review a near final version of the response report
* arrange for sign-off and submission of the response report
* create a corrective and preventative action (CAPA) plan, and provide updates on the resolution of the CAPA during CTOC and/or HTOC meetings (as applicable).

1. For external audits or inspections of a UoB’s CTU, the UoB’s CTU will act as the main contact with the external auditor/inspector. The CTU will manage internally, the preparation for and the follow-up to, the audit/inspection.
2. In addition, for inspections the UoB’s CTU will:

* upon receipt of the notification, inform the CTOC of a scheduled inspection
* upon receipt of the inspection report, forward it to the CTOC for notification
* collate a response report
* organise for the chair of CTOC, head of Research Governance and Integrity, clinical research compliance manager and a further clinical academic member of the CTOC to review the near final version of the inspection response report, allowing for two working days for the review. The chair of the CTOC will take responsibility for sign-off on behalf of the CTOC.
* create a CAPA plan and provide updates on the resolution of the CAPA during CTOC meetings.

1. Where required, the CRCT and/or RG&ET will provide support to any UoB staff in preparing for the audit or inspection and preparing responses to findings.
2. The CTOC and HTOC will review information provided to them relating to inspection reports, audit reports and response reports during the relevant 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 liaising with CIs or delegates and up-escalating to heads of colleges or the RGEIC.
3. The CTOC/HTOC will identify the areas highlighted during audit/inspection that may require further training. The UoB’s CTUs will review these against their own circumstances and identify the areas that would need to be trained on locally. The UoB CTUs will organise the necessary training and invite the CRCT and/or RG&ET to the training (where appropriate).
4. The CTOC/HTOC will monitor the completion of the CAPA plans at the relevant meetings until completion.

# List of expected outputs

* Evidence of the RG&ET maintaining the electronic database (at time of writing ReDA).
* Evidence of the RG&ET’s reports to the CTOC on changes to the clinical research portfolio.
* Evidence of the UoB’s CTUs’ update reports to the CTOC.
* Evidence of the chair of the CTOC reviewing and providing advice on trials that do not meet all the criteria for the UoB to take on sponsorship.
* Evidence of the RG&ET informing the CI of their initial sponsorship approval.
* Evidence of the RG&ET performing a further detailed review of project-specific risk assessment and related monitoring plans.
* Evidence of the RG&ET’s review to confirm that the conditions set by the REC or the CA have been met.
* Evidence of the UoB’s CTUs and CRCT submitting their audit programmes and audit reports to the relevant oversight committee(s) and relevant oversight committee(s)reviewing the content.
* Evidence of the CTOC/HTOC reviewing reports from the RG&ET, UoB’s CTUs and any information provided to the CTOC/HTOC (as applicable).
* Evidence of a clear process for the escalation of internal issues at the UoB’s CTUs.
* Evidence of the redirecting of resources within the RG&ET and CRCT to address issues, to include appropriate agreement.
* Evidence of the RG&ET/CRCT’s role and the UoB’s CTUs’ role as the main contact for external audits or inspections, their communications with the CTOC/HTOC to ensure the CTOC/HTOC is fully appraised, and their role in leading the development of a response report and drafting a CAPA plan.
* Evidence of the UoB’s CTUs organising training resulting from audits/inspections, to include inviting the CRCT and/or RG&ET (where appropriate)
* Evidence of the CTOC/HTOC reviewing CAPA plans through to a resolution.

# Related documents

* UoB-AES-SOP-001 Adverse Event Reporting
* UoB-CLO-SOP-001 Project Closure
* UoB-CPR-SOP-001 Compliance Review
* UoB-CQM-POL-001 Clinical Research Quality Manual
* UoB-CRG-QCD-001 Sponsor Review Tool
* UoB-DSB-SOP-001 Deviation and Serious Breach Reporting
* UoB-GCP-POL-001 UoB Principles of Good Clinical Practice (GCP) for Clinical Research
* UoB-SET-SOP-001 Project Set-up
* UoB-SPO-QCD-001 Clinical Trial Task Delegation Log

Note the UoB QMS documents can be found on the [CRCT website](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/index.aspx). Internal work instructions can be obtained from the CRCT ([crct@contacts.bham.ac.uk](mailto:crct@contacts.bham.ac.uk)) and/or from the RGT ([researchgovernance@contacts.bham.ac.uk](mailto:researchgovernance@contacts.bham.ac.uk)).

# References and frameworks

* ICH: Guidelines for GCP E6(R2): <https://www.ich.org/page/efficacy-guidelines>
* MHRA. (2012). *Good Clinical Practice Guideline* (1 ed.). UK: TSO Information and publishing solutions.
* The Medicines for Human Use (Clinical Trials) Regulations 2004 (UK SI 2004 No. 1031): <https://www.legislation.gov.uk/uksi/2004/1031/contents/made>
* UK Policy Framework for Health and Social Care Research (v3.3 07-Nov-2017): <https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/>

# Abbreviations and definitions

| Term | Description |
| --- | --- |
| APR | Annual progress report |
| Audit | A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analysed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s). |
| Inspection | The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization’s (CRO’s) facilities, or at other establishments deemed appropriate by the regulatory authority(ies). |
| CA | Competent authority |
| CAPA plan | Corrective and preventative action plan |
| CI | Chief investigator |
| CRCT | Clinical Research Compliance Team |
| CTIMP | Clinical trials of investigational medicinal products |
| CTOC | Clinical Trials Oversight Committee |
| DSUR | Development safety update report |
| GCP | Good Clinical Practice |
| HRA | Health Research Authority |
| HTA | Human Tissue Authority |
| HTOC | Human Tissue Oversight Committee |
| IRAS | Integrated Research Application System |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| QMS | Quality management system |
| REC | Research ethics committee |
| RG&ET | Research Governance & Ethics Team |
| RGEIC | Research Governance, Ethics and Integrity Committee. A committee at the University of Birmingham, made up of senior management, that provides oversight of the UoB’s research activities. It establishes and implements research-related policies within the university, with referral to the University Executive Board where necessary. |
| Sponsor number | The unique identifier that the Research Governance Team will assign to any project put forward for the UoB’s sponsorship. May also be known as the RG number. |
| SOP | Standard operating procedure |
| 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).