Standard Operating Procedure:

Investigator Site Management

# Purpose:

This standard operating procedure (SOP) describes the procedures involved in the set-up, initiation and closure of investigator sites. Note: for laboratories, please refer to UoB-CRL-SOP-001 Laboratory Set Up and Management.

# Scope:

This SOP is applicable to all University of Birmingham (UoB) sponsored clinical research where the sponsor takes on the sponsor’s responsibilities for investigator site management. 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. This SOP also applies to clinical research approved by UoB Research Ethics Committee (REC) that are required to follow UoB-GCP-POL-001 UoB Principles of Good Clinical Practice (GCP) for Clinical Research. This SOP may be used as a guidance document in all other cases.

# Implementation plan:

This SOP will be implemented directly after its implementation date for clinical research that is still in the set-up phase and where site set-up has not yet started. For clinical research in different stages of investigator site set-up or where all investigator sites have been set up and are not yet in the stage of being closed, the SOP will be implemented as far as possible directly after its implementation date and at least from ‘Procedures ongoing from site initiation to site closure’ onwards. For clinical research where investigator sites are being closed the SOP will be followed as far as possible, ensuring any regulatory requirements, and other REC requirements, are met.

# Stakeholders:

Note that where UoB takes on the sponsor’s responsibility for investigator site management, the UoB will delegate the majority of these duties to the chief investigator (CI) and/or to a clinical trials unit (CTU), who may delegate these duties further to their research team(s). All delegation of duties will be documented (e.g. using either the CI declaration and/or the UoB-CLN-CTM-002 Clinical Trial Task Delegation Log).

* CI: The CI is responsible for coordinating the investigators who take the lead at each site, which includes appropriate investigator site management. The CI may delegate specific tasks to members of their team, although evidence of CI involvement and approval is still expected and must not be delegated where ‘no delegation allowed’ is indicated. The SOP will state where delegation is possible. It is strongly recommended to have delegation of tasks documented, e.g. via job descriptions of clinical research team members, a delegation log and/or in CTUs via SOPs.
* Principal investigator (PI): The PI is responsible for the conduct of clinical research at their site. The PI may delegate specific tasks to members of their team at site. All delegated tasks must be documented.
* Research Governance Team (RGT).
* UKCRC-registered UoB CTUs.

# Background and rationale:

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

An investigator site is defined as a hospital, health centre, surgery or other establishment or facility at or from which clinical research is conducted. Please note that although the UoB may act as an investigator site for non-CTIMPs studies, it would not normally act as an investigator site for regulated clinical trials or surgery trials. While exceptions to this may occasionally be made, where an exception is made this will be documented in writing in a letter from the University’s Head of Research Governance and Integrity. This means that no participants in CTIMPs, regulated device trials or surgery trials may be recruited, receive treatment or other interventions on university premises without the express written permission of the Head of Research Governance and Integrity.

Central to the success of clinical research is the efficient management and monitoring of investigator sites. An appropriate level of site management and oversight enables investigator sites to effectively recruit, treat/test, and retain research participants. Furthermore, it ensures regulatory compliance, protocol adherence, the protection of participants’ rights, safety reporting, and overall management of screened and enrolled participants.

# Procedure:

## Investigator site selection and set-up

### Identification of potential investigator sites

1. The CI (or delegate) will identify potential investigator sites at the early stages of the clinical research set-up. Sites may be identified based on previous experience of using that site, or by contacting investigators who have previous experience in the research/therapeutic area. Recommendations may also be made by the CI, Project Steering Committee and members of the Project Management Group, or via professional groups or research networks.
* Consideration to the specific participant population served by the site might also be given.
* Additional investigator sites may be added at later stages (e.g. after recruitment has commenced).
1. If investigators/investigator sites indicate an interest in the research project, the CI (or delegate) will assess the site’s suitability to participate. It is also recommended that, if available, the research protocol or a summary of the research is sent to the site contact (and if appropriate to their R&D team). The assessment may include the use of a feasibility questionnaire as a tool. Where appropriate, factors to consider in the site’s suitability to participate include those listed below.
* Experience and qualifications of the PI and site research team.
* Availability of eligible participant population.
* Anticipated rate of participant recruitment.
* Conflicting studies at a site.
* Appropriate staff resource and facilities to support the project and comply with the protocol and GCP. This may include consideration of both non-clinical activities (e.g., case report form (CRF) completion, data queries and management of the Investigator Site File (ISF)), as well as participant-focused clinical care and medical cover.
* Availability of any specialised diagnostic or therapeutic equipment required by the research protocol.
* Adequate space and storage conditions.
* Accessible resources in support departments (for example; within the NHS).
* Proven track record of recruiting.
* [Excess Treatment Costs](https://www.nihr.ac.uk/researchers/collaborations-services-and-support-for-your-research/run-your-study/excess-treatment-costs.htm) can be met.

### Investigator site set-up

1. The CI (or delegate) will confirm that all relevant local approvals are in place, as a minimum this will include those listed below.
* Site permissions e.g. NHS R&D management permission or confirmation of capacity and capability.
* Organisation information document (OID), UK model agreement for non-commercial research (mNCA) or ‘GP practice agreement’) as applicable.
* Where appropriate, bespoke sub-contracts and service level agreements (with external suppliers such as central laboratories and external statisticians).
* Where appropriate, substantive contracts, honorary contracts or letters of access for all investigator site staff engaged in activities in the NHS.
* For HRA-approved clinical research, favourable ethical opinion is required to add additional sites. This is via a substantial amendment for CTIMPs, or a non-substantial amendment for non-CTIMPs and studies. See UoB-SET-SOP-001 Project Setup for more information on amendments.
1. The CI (or delegate) will confirm suitability of the PI, with evidence retained in the ISF. As a minimum this will include evidence of appropriate GCP training (see also Clinical Trials Quality Manual) and a signed and dated CV containing proof of relevant education and experience (see also UoB-TRN-SOP-001 Training).
* For CTIMPs, the PI must be an authorised healthcare professional.
* Whilst this does not need to be a medically qualified doctor, there are a number of trial-related activities that are required to be performed by a medically qualified doctor (e.g. eligibility, decision to dose and safety reviews). Such activities must be formally delegated by the PI to a medically qualified doctor. See below for delegation of duties.
* Where delegation of duties at the site is required, the PI (no delegation allowed) will provide documented authorisation of appropriately trained and qualified individuals to undertake the specific research-related tasks. It is expected that, for NHS Trust sites, a site signature and delegation log is used, see UoB-CLN-ESD-QCD-003 Site Signature and Delegation Log as a template. Each new team member who joins the project after it has started is also expected to receive training in GCP (proportionate to their role) and the protocol, as well as be delegated appropriate responsibilities via the delegation of duties log (or alike), prior to undertaking these activities.
1. The CI (or delegate) will ensure each site has access to the latest approved versions of the project-specific documents e.g. protocol, participant information sheet (PIS)/informed consent form (ICF), case report form (CRF) and project-specific manual(s)/guidelines for inclusion in the ISF. See also UoB-CLN-ESD-QCD-001 Essential Document Checklist for ISF content guidance.
2. Where appropriate, the CI (or delegate) will prepare any investigator site training documents to be used as part of the site initiation process e.g. project-specific presentations and written guidelines.
3. The CI (or delegate) will arrange for supply of the research medication/device (where applicable) and document this. See also UoB-MED-SOP-001 Medicinal Product Management and *UoB-FNC-SOP-001 Food and Nutritional Components*.
* Consideration needs to be given to protecting blinding where necessary. See also *UoB-RND-SOP-001 Randomisation and Blinding*.
* For CTIMPs, the IMP must not be dispatched to any investigator site prior to certification by a QP, regulatory approval (as a minimum REC and CA authorisation), and an agreement between the IMP supplier and the sponsor. See UoB-MED-SOP-001 Medicinal Product Management for more information on the two-step green light process.

## Investigator site initiation

1. All participating investigator sites will undergo a process of site initiation before commencing recruitment. The CI (or delegate) will determine what type of site initiation is required (e.g. site visit and/or teleconference, questionnaires or clinical research launch meeting), and will decide on the level of involvement required from site staff. As a minimum there will be evidence of appropriate PI involvement in the site initiation. The sub-section below (points 9 to18) details the checks to be undertaken as part of the site initiation.
* Consideration should be taken of the complexity of the project and the previous research experience of the investigator site.
* Representatives from any supporting departments (e.g., pharmacy, radiology, laboratories) should also be included where appropriate.

### During site initiation:

1. The CI (or delegate) will ensure that the PI and their research team are fully aware of their individual roles and responsibilities and the need to arrange adequate cover during absences, provide 24-hour emergency contact arrangements (if appropriate) and of their obligation for continuing oversight of the research project. This also includes keeping the CI (or delegate) appraised of any issues relating to the project.
2. The CI (or delegate) will discuss how the PI will maintain clear, documented evidence of their oversight and involvement in the project. PI oversight may be demonstrated through:
* documented evidence of eligibility assessments
* signatory of consent forms, as appropriate.
* involvement in participant research visits, as appropriate
* sign-off of completed serious adverse event (SAE) forms.
* Regular, minuted meetings with the research team, as appropriate
* email correspondence
* attendance at monitoring visits, if required
* documented review of incoming clinical data (e.g laboratory results, imaging)
* review of completed CRFs, as appropriate.
1. The CI (or delegate) will review the ISF and discuss maintenance of the ISF. See also UoB-CLN-ESD-QCD-001 Essential Documents Checklist. It is expected that the review will include:
* a check of staffs’ CVs and GCP training
* use of appropriate document version control. See also UoB-ESD-SOP-001 Essential Documents Development and Maintenance.
1. Where appropriate, the CI (or delegate) will review the local procedures for participant selection, informed consent, screening, randomisation and monitoring procedures specific to the research, unless stated in the protocol.
2. The CI (or delegate) will discuss with the investigator site their understanding of the protocol, aims of the research, participant eligibility, participant visit schedule and timelines/recruitment targets, including:
* highlighting (where appropriate) any data items that may not normally be captured in the source data
* discussion of responsibilities for CRF completion, storage and security, including the use of self-evident corrections when appropriate
* discussion of the site’s responsibility for archiving clinical research-related documentation
* discussion of the responsibilities of any other departments’ involvement (e.g. pathology, radiology and pharmacy).
1. If applicable, the CI (or delegate) will review all investigational medicinal product (IMP) related procedures including, but not limited to, receipt, labelling, storage, dispensing, accountability, return and destruction. Where appropriate, the CI (or delegate) will also check the following:
* storage conditions and temperature logs for the IMP
* staffs’ understanding of the procedure in place for the emergency unblinding.
1. If applicable, the CI (or delegate) will discuss how laboratory facilities and arrangements for the dispatch of samples are to be organised. See also UoB-CRL-SOP-002 Laboratory Facilities and UoB-CRL-SOP-003 Sample Management for further information. Where appropriate, it is recommended that the checks listed below are performed.
* Where samples are to be stored in freezers and/or fridges, storage temperatures are maintained according to project-specific requirements and the storage temperature monitored.
* Freezer and/or fridge logs are kept and will be archived for the appropriate time period.
* If site laboratory equipment is to be used for the assessment of clinical research primary endpoints, a discussion regarding accreditation/calibration/maintenance programmes and evidence of laboratory accreditation (if required).
* Local procedures are clearly documented.
1. If applicable, the CI (or delegate) will ensure the investigator brochure (IB) or summary of product characteristics (SmPC) for the IMP/device is filed in the ISF and that the investigator site is aware of these documents with respect to safety-reporting procedures.
2. Where appropriate, the CI (or delegate) will discuss the requirements for safety reporting and the procedures surrounding urgent safety measures and reporting protocol deviations; including serious breach reporting requirements, see UoB-DSB-SOP-001 Deviations and Serious Breach Reporting for further information. This will include the requirements listed below.
* Ensuring that investigator site staff are fully trained in the project-specific adverse event (AE)/serious adverse event (SAE) reporting procedures and pregnancy reporting procedures (if appropriate).
* Discussion of how SAEs should be identified and reported in a timely manner.
* Discussion of timeframes for expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA) and the REC and the process for this, see UoB-AES-SOP-001 Adverse Event Reporting for further information.
* The CI (or delegate) will answer all queries raised by investigator sites or arrange feedback on all queries after consulting others if required.
1. The CI (or delegate) will document evidence of the site-initiation activities undertaken as described in the points above, for example via a written report. Evidence will include details of when, how, by whom and who of the site staff were present. A copy of the report will be sent to the site for their information and filing in the ISF, and the original will be filed in the study/trial master file (S/TMF).
* It is recommended that the report includes a description of any local procedures and any specific questions and answers.
* A site initiation checklist to document this and provide a reference point for site initiation. See also UoB-SMA-QCD-002 Site Initiation Checklist *(under development)* for a template.

## Investigator site activation

1. The CI (or delegate) will confirm the following is in place prior to the investigator site being activated and recruitment commencing.
* Completion of site initiation.
* Site permissions e.g., NHS R&D management permissions.
* Favourable ethical opinion.
* Evidence of suitability of PI, e.g., CV and GCP training.
* Where applicable, Health Regulatory Authority (HRA) approval.
* Where applicable, any additional essential approvals e.g., Administration of Radioactive Substances Advisory Committee (ARSAC).
* For CTIMPs, a signed Clinical Trial Authorisation (CTA) from the MHRA and NHS R&D management approval of the regulatory green light checklist.
1. For clinical trials, prior to the first site being opened, the CI (or delegate) will send an email to researchgovernance@contacts.bham.ac.uk stating the date the first site will open. It is expected that the RG number for the trial is stated in the subject of the email.
2. When an investigator site is ready to be activated, the CI (or delegate) will notify site staff in writing (by email or letter) that they can enter participants into the research project. This will include:
* a specific activation date
* instructions to the investigator site to file the notification in the ISF.
1. For clinical trials, the CI (or delegate) will ensure that the investigator site has acknowledged receipt of the site’s activation notice. Additionally, the CI (or delegate) will file a copy of this acknowledgment in the TMF.
* Note if initial notification is via email, it is recommended to follow up with a formal letter to the PI, pharmacist (where applicable) and main contact person at the investigator site and local R&D office.
1. The CI (or delegate) will notify any relevant third parties/collaborators (as required) of the site activation. This may include laboratories performing samples analysis or suppliers (e.g. pharmaceutical company) of trial medication.
2. Where applicable, the CI (or delegate) will ensure that all relevant clinical research management systems (e.g. project management databases) are updated to reflect the investigator site has been activated.

## Procedures ongoing from investigator site initiation to site closure

1. The CI (or delegate) will monitor the quality management at each investigator site according to the research risk assessment and, if applicable, the monitoring plan (determined and documented prior to start of the project). See UoB-POS-SOP-001 Project Oversight and Quality Management for further information.
2. The CI (or delegate) will ensure the site signature and delegation log (or equivalent document) is updated during the course of the research project to reflect any changes in staff and duties delegated. Where required, the CI (or delegate) will update the coordinating centre of any changes made to this document. See UoB-CLN-ESD-QCD-003-Site Signature and Delegation Log for a template.
3. The CI (or delegate) will maintain all essential documents in the S/TMF and ensure relevant copies are sent to the investigator site for inclusion in the ISF. See UoB-ESD-SOP-001 Essential Document Development and Maintenance for further information.
4. The CI (or delegate) will ensure that there are processes in place for the investigator site to be informed of any substantial and non-substantial amendments to the essential documents (including the protocol).
5. As per the risk assessment (and monitoring plan where appropriate), the CI (or delegate) will ensure ongoing monitoring and review of the project as per the examples below. See also UoB-POS-SOP-001 Project Oversight and Quality Management.
* Monitoring of recruitment targets.
* Ensuring AE monitoring is undertaken, with required timelines met and in accordance with UoB-AES-SOP-001 Adverse Event Reporting.
* Review of clinical research supplies (including IMP management for CTIMPs). See also UoB-MED-SOP-001 Medicinal Product Management and UoB-FNC-SOP-001 Food and Nutritional Components for further information.
1. The CI (or delegate) will provide ongoing training to investigator sites e.g. on CRF completion and self-evident corrections. See also UoB-TRN-SOP-001 Training.

## Investigator site and project closure

1. The CI (or delegate) will implement the project and/or investigator site closure procedures in accordance with UoB-CLO-SOP-001 Project Closure. This will occur when:
* the end (as defined in the protocol) has been reached
* an early termination of the project has occurred (e.g. due to poor recruitment rates, safety concerns)
* an investigator site closure is required (e.g. due to poor recruitment rates, insufficient resources at site). If an approved site is closed prematurely, the REC should be notified.

### Investigator site closure

Investigator site closure is the process of ensuring all project-related activities at a participating site are reconciled and/or complete. Each investigator site participating in a project should be formally closed after the project has come to an end. Investigator site closure may be conducted by a visit or by written communication.

1. The CI (or delegate) will ensure the ISF is complete. This includes ensuring (where appropriate):
* all data queries are resolved where feasible
* all SAEs are resolved
* all issues flagged up during previous quality checks (e.g. monitoring) are resolved or documented.
1. The CI (or delegate) will ensure all financial matters are resolved and confirm all investigator site payments are complete as agreed and documented in clinical research-related contracts/agreements/approvals.
2. For CTIMPs, the CI (or delegate) will verify final drug accountability is complete and destruction/return of unused clinical research medication is documented. See also UoB-MED-SOP-001 Medicinal Product Management.
3. The CI (or delegate) will reconcile any code-break envelopes maintained at investigator site (if applicable).
4. The CI (or delegate) will ensure Investigator(s) are aware of and have implemented relevant ongoing requirements such as site archiving, subsequent audit/inspection procedures and any ongoing reporting requirements.
5. If applicable, the CI (or delegate) will notify laboratory and/or other departments involved in sample collection and shipment of the investigator site closure and check that all samples and documentation have been received according to the protocol.
6. The CI (or delegate) will inform Investigator(s) about the study/trial publication requirements, as documented in the protocol and/or contracts/agreements.
7. The CI (or delegate) will report which investigator site closure activities were undertaken, when, how and by whom and who of the site staff was present. A copy of the report will be sent to the site for their information and filing in the ISF, and the original will be filed in the S/TMF.
* It is recommended that the report includes a description of any local procedures and any specific questions and answers.
1. Where required, the CI (or delegate) will update the S/TMF with documents retrieved from the investigator site.
2. The CI (or delegate) will confirm closure of the investigator site in writing to the site once all activities related to close-out are complete. Confirmation of the closure will be filed in the ISF and S/TMF.

# List of expected outputs:

* Evidence of the suitability of the PI, e.g., CV.
* Documented evidence of appropriate delegation of PI duties, with evidence of appropriate site staff training/experience to perform their delegate tasks.
* Evidence of PI attendance during site initiation activities.
* Documented evidence that site initiation activities were undertaken when, how and by whom and which site staff were present.
* Documented evidence that all relevant approvals and permissions are in place prior to recruitment starting.
* Written evidence notifying site staff that participants can be entered into the research project and for clinical trials, evidence of site acknowledgement.
* Evidence of monitoring of participant recruitment and recruitment targets being met.
* ISF contains latest versions of project-specific documents.
* Evidence of ongoing PI oversight of the research project.
* Processes in place for the investigator site to be informed of any substantial and non-substantial amendments to the protocol.
* Documented evidence that investigator-site-closure activities were undertaken when, how and by whom and which site staff were present.
* Written confirmation of investigator site closure to the site once all activities related to close-out are complete.

# Related documents:

* Clinical Trials Quality Manual
* UoB-AES-SOP-001 Adverse Event Reporting
* UoB-CLN-CTM-QCD-002 Clinical Trials Task Delegation Log
* UoB-CLN-ESD-QCD-001 Essential Documents Checklist
* UoB-CLN-ESD-QCD-003 Site Signature and Delegation Log
* UoB-CLN-ESD-SOP-001 Essential Documents Development and Maintenance
* UoB-CLO-SOP-001 Project Closure
* UoB-CRL-SOP-001 Laboratory Set Up and Management
* UoB-CRL-SOP-002 Laboratory Facilities
* UoB-CRL-SOP-003 Sample Management
* UoB-DSB-SOP-001 Deviations and Serious Breach Reporting
* UoB-FNC-SOP-001 Food and Nutritional Components
* UoB-GCP-POL-001 UoB Principles of GCP for Clinical Research
* UoB-MED-SOP-001 Medicinal Product Management
* UoB-POS-SOP-001 Project Oversight & Quality Management
* UoB-RND-SOP-001 Randomisation and Blinding
* UoB-SET-SOP-001 Project Setup
* UoB-SMA-QCD-002 Site Initiation Checklist *(under development)*
* UoB-TRN-SOP-001 Training

Note the UoB QMS documents can be found on the CRCT website. Internal work instructions can be obtained from the CRCT (crct@contacts.bham.ac.uk) and/or from the RGT.

# References and frameworks:

* Medicines and Healthcare products Regulatory Agency (MHRA). *Good Clinical Practice Guide*, London: The Stationery Office, 2012
* National Institute for Health Research (NIHR) Excess Treatment Costs: <https://www.nihr.ac.uk/researchers/collaborations-services-and-support-for-your-research/run-your-study/excess-treatment-costs.htm>

# Abbreviations and definitions:

| Term | Description |
| --- | --- |
| AE | Adverse event  |
| ARSAC | Administration of Radioactive Substances Advisory Committee |
| Authorised health professional | An authorised health professional is defined as a doctor, dentist, nurse or pharmacist. |
| CI | Chief investigator |
| Closed project | Research project where any project closure procedures have been completed and where all outstanding action points have been completed.  |
| Closed site | Site where any site closure procedures have been completed and where all outstanding action points have been completed.  |
| Coordinating centre | A term commonly used to refer to the team responsible for the overall management of the clinical research and their physical location. A coordinating centre may be based in a clinical trials unit and may also be referred to as a trials office. There may be many coordinating centres involved in a project, e.g. for international projects the international and national coordinating centre, and for clinical research managed regionally the central and local coordinating centre.  |
| CRF | Case report form |
| CTA | Clinical trial authorisation |
| CTIMP | Clinical trial of an investigational medicinal product |
| CTU | Clinical trials unit  |
| CV | Curriculum vitae |
| GCP | Good Clinical Practice |
| HRA | Health Regulatory Authority |
| IB | Investigator brochure |
| ICF | Informed consent form  |
| IMP | Investigational medicinal product |
| ISF | Investigator site file. See ’Site file’. |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| mNCA | UK model agreement for non-commercial research |
| NIHR | National Institute of Health Care |
| OID | Organisation information document |
| PIS | Participant information sheet  |
| PI | Principal investigator |
| REC | Research ethics committee |
| RGT | Research Governance Team |
| SAE | Serious adverse event |
| Site | A hospital, health centre, surgery or other establishment or facility in the UK at or from which the research, or any part of the research is being conducted on participants. Please note that although the UoB may act as an investigator site for non-CTIMPs and studies, it would not normally act as an investigator site for regulated clinical trials or surgery trials (i.e. CTIMPs or of medical devices). While exceptions to this may occasionally be made, where an exception is made this will be documented in writing in a letter from the University’s Head of Research Governance and Integrity. This means that no participants in CTIMPs, regulated device trials or surgery trials may be recruited, receive treatment or other interventions on the university’s premises without the express written permission of the Head of Research Governance and Integrity. |
| Site file | The site file contains all essential documents held by principal investigator(s) conducting a trial which individually and collectively permit the evaluation of the conduct of a trial and the quality of the data produced. Also known as the investigator site file (ISF). |
| S/TMF | The study/trial master file consists of essential documents kept at the sponsor’s (or delegate’s) site, which enables both the conduct of a clinical study/trial and the quality of the data produced to be evaluated. The filing system can be in the form of a single file or a number of files as deemed most appropriate. |
| SmPC | Summary of product characteristics  |
| 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).