Standard Operating Procedure:

Essential Documents Development and Maintenance

# Purpose

This standard operating procedure (SOP) describes the procedure for the development, review, implementation and filing of essential documents involved in clinical research conducted within the University of Birmingham (UoB).

# Scope

This SOP applies to clinical research where the UoB is the sponsor or takes on the sponsor’s responsibilities for essential documents’ development and maintenance. This SOP also applies to clinical research approved by a UoB Research Ethics Committee (REC) that is 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 effective date for all CTIMPs and any clinical research that is in set up. For existing clinical research that is already set up and in the recruitment phase (or further) at the time of implementation, this SOP will be implemented within three months of the effective date.

# Stakeholders

Note that where the UoB takes on the sponsor’s responsibility for essential documents’ development and maintenance, 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 team(s). All delegation of duties will be documented (e.g., using the CI declaration and/or the Clinical Trials Task Delegation Log; see *UoB-CLN-CTM-QCD-002 Clinical Trials Task Delegation Log*).

* CI: the CI may delegate some activities to members of their research team. 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 principal investigator (PI), or the supervisor for postgraduate research students.
* Principal investigator (PI)
* Laboratory academic lead (LAL)

# 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 trials (e.g. surgical trials, device trials and non-CTIMP trials, and any other projects deemed to be ‘interventional’ by the sponsor), clinical studies and clinical research approved by a UoB REC.

Essential documents individually and collectively permit evaluation of the conduct of clinical research and the quality of the data produced.

This SOP details the requirements for the development of the protocol, participant information sheet (PIS), informed consent form (ICF), case report form (CRF) and investigator brochure (IB). However, it can also be applied to the development of project specific documents. The list of essential documents detailed in section 8 of the [International Conference on Harmonisation (ICH) Guidelines for GCP E6(R2) (PDF – 693 KB)](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf) provides a useful guide for the minimum documents that are considered essential; however this is not recommended as a definitive checklist for the study/trial master file (S/TMF) and laboratory master file (LMF) content. For the LMF content, see also UoB-CRL-QCD-001 Setting up a Laboratory Master File. Examples of other documents that are essential for reconstruction of the project conduct but are not contained above include the qualified person (QP) certification, the regulatory green-light document for release and shipment of investigational medicinal product (IMP) and the database lock documentation.

# Process map



Procedure

Agree on local processes surrounding essential documents’ development

1. The CI (or delegate) will create the essential documents required.

Document and version control

1. The CI (or delegate) will consistently apply version control to all draft and final versions of essential documents to allow differentiation between draft and active versions. See recommendations below.

* A suggested version control system is for the first ever draft version to have version number 0.1. Any following drafts will have 0.2, 0.3 etc.; typically, the number changes following an update and at the time the updated draft is circulated for review.
* Where a review of a draft version has been conducted, the reviewer will add their initials to the existing version number e.g., v0.1 will become v0.1+SC. The version number of the reviewed document will not be changed.
* The first finalised version would therefore have the version number 1.0. Any draft updates following on from the first version will have version number 1.1, 1.2 etc. Any further finalised versions will have version number 2.0, 3.0 etc.
* Ensure the version number and date are added to the end of the file name and within the document, i.e. on the title page and in the header or footer of each page.
* Ensure all documents are dated, including notes to file.
* Ensure that version control is consistently applied to all essential documents created for the research project.
* Ensure where signatures are required (i.e. as prompted on the essential document) that these are either in ink and dated or using appropriate electronic signatures where the names and date of signatures are clearly specified and attributed to the signatures.
* Ensure previous versions in the S/TMF and LMF (if applicable) are marked as superseded and the PI at site is notified regarding any updates to the essential documents and they are instructed to mark any previous versions as superseded.

1. It is expected that the CI (or delegate) keeps and maintains a version control log of essential documents in the S/TMF; see UoB-CLN-ESD-QCD-006 Version Control Log and also for CTIMPs, see UoB-CLN-ESD-QCD-001 Essential Documents Checklist.

Translation of materials

1. The CI (or delegate) will ensure any materials to be translated are translated using a reputable translation service provider.

* For essential documents such as the protocol and PIS/ICF, a back translation is recommended.

1. The CI (or delegate) will document appropriately the process of translation.

Internal review

1. The CI (or delegate) will decide on an internal process of quality checking all draft versions of essential documents, including the selection of appropriate reviewers, ensuring compliance with any applicable UoB SOPs, and documentation of the process.
2. The CI (no delegation allowed) will approve the final version of the protocol, PIS/ICF and CRF and subsequent amendments to these documents. This approval will be documented.
3. The CI (or delegate) will ensure essential documents have been reviewed in accordance with this internal process.

Development of essential documents

The section that follows provides guidance for the development of the protocol, PIS, ICF, CRF and IB. However, this SOP can be applied to the development of other essential documents specific to the research project.

1. When developing essential documents, the CI (or delegate) is expected to refer to the [UoB Information Classification Standard](https://collaborate.bham.ac.uk/it/itas/Published/Standards/Information%20Classification%20Standard.pdf) (PDF – 944 KB).

Protocol

1. The CI (or delegate) will create the protocol that describes the background, rationale, objectives, design, methodology, statistical considerations and organisation of the research project.

* For CTIMPs, refer to *UoB-CLN-PRO-QCD-002 Protocol Template for CTIMPs*.
* For non-CTIMPs and clinical studies, refer to *UoB-CRT-NCTM-QCD-001 Non-CTIMP and Studies Protocol Template*.

Participant information sheet and informed consent form

1. The CI (or delegate) will develop the PIS and ICF in adherence with the specifications of the protocol and the instructions provided in *UoB-PEI-SOP-001 Participant Engagement and Informed Consent*.

* Refer to *UoB-CRG-QCD-001 Sponsor Review Tool* for guidance regarding the minimal essential detail required in the PIS and ICF in order for the university to proceed with sponsorship.
* If the arrangements for the clinical research involve the movement of participant identifiable information (e.g. a copy of the ICF from an NHS Trust site to a UoB research office), the PIS or privacy notice will clearly state what participant identifiable data will be moved, where it will be stored and what will happen with the data at the end of the research project. It is recommended that the ICF is designed to capture agreement of the participants to this process.
* If the research project includes optional elements, these will be detailed in the PIS and labelled as ‘optional’ on the ICF.
* For further information, see also UoB-CLN-ESD-QCD-004 Informed Consent procedure for site staff and the university’s privacy notice on [How the University uses your data](https://www.birmingham.ac.uk/privacy/index.aspx).

1. Where human tissue is to be collected, the CI (or delegate) will ensure the PIS and ICF include the following information:

* The PIS details how the tissue will be collected and shipped, where it will be stored, how it will be processed and if it will be destroyed. The ICF will be designed to capture the explicit consent of the participant to the sample pathway described in the PIS.
* Where tissue is expected to be used in future ethically approved clinical research or moved to a Human Tissue Authority (HTA) licensed research tissue bank, this is to be clearly stated in the PIS and explicit consent obtained in the ICF.
* If genomic analysis is to be performed on the sample, if the sample is to be used in animal research, or if the research involves commercial partners, this will be stipulated in the PIS and the ICF designed to capture the explicit consent of the participant to these processes.
* See also [HTA Code of Practice A - Guiding Principles and the Fundamental Principle of Consent (PDF – 1.1 MB)](https://content.hta.gov.uk/sites/default/files/2020-11/Code%20A.pdf).

Case report form – including quality of life questionnaires

1. The CI (or delegate) will create the CRF in accordance with UoB-CRT-CRF-SOP-001 Case Report Form Development.

Investigator brochure

1. For CTIMPs, the CI (or delegate) will create the IB, where applicable. The process for creating the IB will include:

* Referring to [Section 7 of the ICH Guidelines for GCP E6(R2) (PDF – 693 KB)](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf), which lists the minimum information on what should be included in an IB and provides suggestions for its layout, including information that is expected to be included on the title page and a recommended table of contents.
* Ensuring reference safety information (RSI) is identified/created and clearly visible on the IB.

Note that for certain CTIMPs an approved summary of product characteristics (SmPC) may be used to document the RSI, instead of the IB. Also, access to an approved SmPC and/or IB may be required for non-CTIMPs or studies where non-investigational medicinal products (NIMPs) are used.

Project-specific documentation

1. The CI (or delegate) will ensure other research project-specific essential documentation is created as required, including but not limited to those listed below.

* For sites, a site signature and delegation log. See UoB-CLN-ESD-QCD-003 Site Signature and Delegation Log for a template.
* For clinical research management, a study delegation log, which is expected to include the following information about members of the clinical research team; name, role, date started and date finished.
* The organisational information document that replaces the HRA Statement of Activities used in England and Wales for non-commercial clinical research and the site-specific information form, used in Northern Ireland and Scotland.
* Schedule of events required for HRA approval.

Correspondence and advertising

1. The CI (or delegate) will ensure any correspondence to participants relating to the clinical research or research project promotional materials form part of the essential documents. Letters that are sent out to participants and promotional material aimed at participants are subject to the same guidance regarding development, review and approval.
2. For clinical research taking place in the UK, the CI (or delegate) will ensure all correspondence is printed or photocopied onto the headed paper of the local institution.

External review, approval, and implementation of essential documents

Note: points 19 – 25 (inclusive) are not applicable to clinical research with favourable opinion from a UoB REC.

1. Where the UoB takes on the sponsor’s role for review and approval of essential documents, the CI (or delegate) will undertake the tasks listed below.

* Send the protocol and any other documents intended to be submitted to the REC and HRA, and any regulatory body to the RGT for their review. See also UoB-SET-SOP-001 Project Setup (currently under development).
* Following their approval, proceed with submissions to the REC and HRA to obtain a favourable ethical opinion.

1. For external sponsors, the CI (or delegate) will follow their local processes for obtaining sponsorship and, following their approval, will proceed with submissions to the REC and HRA.
2. The CI (or delegate) will submit to the MHRA any relevant documentation accordingly to obtain clinical trial authorisation (CTA).

* For CTIMPs, the competent authority(s) for each country in which the research is being conducted is required to authorise the trial. In the UK, the competent authority is the Medicines and Healthcare products Regulatory Agency (MHRA).

1. Submissions of documents to the REC and HRA (and MHRA for CTIMPs) are made via the Integrated Research Application System (IRAS). The CI (or delegate) will complete and submit the required documents and forms listed on IRAS.

* Ensure the correct forms are completed and submitted to avoid delays in the processing of the application.

1. For CTIMPs, the CI (or delegate) will submit any new applications via the [combined review process](https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/), formerly known as Combined Ways of Working (CWoW), see also UoB-SET-SOP-001 Project Setup (currently under development).

Approval documentation

1. Upon receipt of correspondence from the REC and HRA (and MHRA for CTIMPs), the CI (or delegate) will review the letters to ensure they refer to the correct research project and documentation sent for approval and that any further requests or provisos are appropriately dealt with.
2. The CI (or delegate) will ensure a clear audit trail of the documents submitted to the approval bodies (the submission package) and approval letters is maintained in the S/TMF, with a copy of the relevant documentation in the investigator site file (ISF).
3. The CI (or delegate) will review and authorise necessary Essential Documents and any amendments obtained from the REC, HRA and relevant regulators prior to research project initiation.

Implementation

1. The CI (or delegate) will distribute the approved documentation to the site PI(s).

* Where a version control log is used (see UoB-CLN-ESD-QCD-006 Version Control Log for a template), ensure this is kept up to date when documents are designed or amended during project set-up, conduct and following project closure.

1. For CTIMPs, the CI (or delegate) will distribute the latest version of the protocol to the laboratory academic lead (LAL) of any laboratories storing or analysing trial samples. See also UoB-CRL-SOP-001 Laboratory Set-Up and Management.
2. The CI (or delegate) will obtain evidence that the site PI(s) agree(s) to work to latest approved version of the research project protocol (either via signing the protocol signature page or via a confirmation of receipt document with a statement to that extent), and the PI (or delegate) will ensure all relevant site staff are notified about the approved documentation.
3. The CI (or delegate) will ensure site staff are appropriately trained in the protocol and other essential documents prior to site initiation and they are appropriately trained on any changes to the research project following the implementation of amended essential documents. See also UoB-SMA-SOP-001 Investigator Site Management (current under development) for details on the site initiation process.
4. The CI (or delegate) will ensure copies of the essential documents are added to the ISF, and any previous versions are marked in the ISF as superseded.
5. The CI (or delegate) will instruct the site to remove any previous versions of the essential documents in any working files.
6. Where required, the CI (or delegate) will forward approved versions to third parties, e.g. IMP manufacturers.
7. The CI (or delegate) will complete any amendments in accordance with UoB-SET-SOP-001 Project Setup.

Filing and archiving of essential documents

1. The CI (or delegate) will ensure that all records created by clinical research procedures and all documents listed in guidance relating to the conduct of the research project are filed in the S/TMF which is held by the Sponsor and archived for the specified period.
2. Where the UoB takes on the sponsor’s responsibility for S/TMF maintenance and archiving and for clinical research approved by a UoB REC, the CI is delegated this duty. The CI (or delegate) will ensure that:

* Where documents are stored or archived elsewhere (e.g. laboratory analysis forms), ensure reference is made in the S/TMF describing the location of these documents.
* Where laboratory analysis forms part of the end point analysis the related analytical data and supporting records must be filed in the S/TMF, or a reference is made in the S/TMF describing the location of these documents (as stated above).
* Key emails, including decision processes are filed in the S/TMF to ensure documents can be accessed.
* Each site maintains an ISF, separate to the S/TMF as this will contain patient identifiable information such as the participant identification log, which should not be held in the S/TMF.
* For CTIMPs, as a minimum, all relevant documents as listed in [Section 8 of the ICH Guidelines for GCP E6(R2) (PDF – 693 KB)](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf) are filed in the TMF. See also UoB-CLN-ESD-QCD-001 Essential Documents Checklist for guidance of what should be held in the TMF and ISF.

1. When preparing for archiving, the CI (or delegate) will follow the procedures detailed inUoB-ARC-SOP-001 Archiving.

# List of expected outputs

* Evidence of dated essential documents with version control.
* Evidence that, where signatures are required on essential documents, these are in ink and dated, or using appropriate electronic signatures where the names and date of signatures are clearly specified and attributed to the signatures.
* A version control log.
* Where appropriate, evidence of the use of a reputable translation service provider for translation of essential documents with the process of translation documented appropriately.
* Documented evidence of internal review of all draft versions of essential documents.
* Documented evidence within the S/TMF confirming the CI’s approval of the final version of the protocol, PIS/ICF and CRF and for any subsequent amendments.
* Evidence that essential documents have been reviewed and approved by the REC and HRA (and MHRA for CTIMPs), and a clear audit trail is provided in the S/TMF and LMF (where appropriate), with copies in the ISF file and any previous versions marked as superseded.
* A protocol.
* PIS and ICF (in accordance with the protocol).
* Where human tissue is to be collected, the ICF outlines where it will be collected, stored, shipped to, and processed and what will happen to samples at the end of the research.
* CRF
* Evidence of confirmation of receipt of approved essential documents by the PI(s) and documented agreement to work with the latest approved version of the protocol.
* IB (for CTIMPs).
* Other research project specific essential documents (where applicable).
* Evidence that any correspondence to participants is on headed paper (in the UK) and forms part of the essential documents.
* Evidence of essential documents being submitted to RGT and all relevant bodies for review and approval.
* Evidence of distribution of essential documents to site PIs and evidence of their agreement to work to and distribute that version.
* Essential documents added to the ISF.
* Evidence that site staff are appropriately trained in the protocol and other essential documents prior to site initiation and following subsequent amendments.
* Superseded copies of essential documents to be marked as such in ISF, S/TF and LMF.
* Removal of previous versions of essential documents from any working files.
* Copies of approved versions of essential documents circulated to third parties as appropriate, e.g. IMP manufacturers.
* For CTIMPs, evidence of distribution of protocol to LAL(s).
* Evidence of retention and archiving of all essential documents and research project records for the specified period and in accordance with UoB-ARC-SOP-001 Archiving.
* For any documents stored elsewhere, reference is made in the S/TMF to where these are located.

# Related documents

* UoB-ARC-SOP-001 Archiving
* 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-QCD-004 Informed Consent procedure for site staff
* UoB-CLN-ESD-QCD-006 Version Control Log
* UoB-CLN-PRO-QCD-002 Protocol Template for CTIMPs
* UoB-CRG-QCD-001 Sponsor Review Tool
* UoB-CRL-QCD-001 Setting up a Laboratory Master File
* UoB-CRL-SOP-001 Laboratory Set-Up and Management
* UoB-CRT-CRF-SOP-001 Case Report Form Development
* UoB-CRT-NCTM-QCD-001 Non-CTIMPs and Studies Protocol Template
* UoB-GCP-POL-001 UoB Principles of GCP for Clinical Research
* UoB-PEI-SOP-001 Participant Engagement and Informed Consent
* UoB-SET-SOP-001 Project Setup
* UoB-SMA-SOP-001 Investigator Site Management

Note the UoB QMS documents can be found on the [Clinical Research Compliance Team (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 the RGT ([researchgovernance@contacts.bham.ac.uk](mailto:researchgovernance@contacts.bham.ac.uk)).

# References and frameworks

* European Committee, 2006. Recommendations on the content of the trial master file and archiving: <https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/v10_chap5_en.pdf>
* HRA approval process: <https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/hra-approval/>
* HRA Combined review: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/<https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/>
* HRA Consent and Participant Information Guidance: <http://www.hra-decisiontools.org.uk/consent/docs/Consent%20and%20PIS%20Guidance.pdf>
* HRA informing participants and seeking consent: <https://www.hra.nhs.uk/planning-and-improving-research/best-practice/informing-participants-and-seeking-consent/>
* HTA Code of Practice A - Guiding Principles and the Fundamental Principle of Consent: <https://content.hta.gov.uk/sites/default/files/2020-11/Code%20A.pdf>
* ICH Guidelines for GCP E6(R2): <https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf>
* IRAS Amendment Tool guidance: https://www.myresearchproject.org.uk/help/hlpamendments.aspx<https://www.myresearchproject.org.uk/help/hlpamendments.aspx>
* MHRA guidance on clinical trials for medicines; applying for authorisation in the UK: <https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk>
* Spirit 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents: <http://www.spirit-statement.org/wp-content/uploads/2013/01/SPIRIT-Checklist-download-8Jan13.pdf>
* UoB CI Declaration: <https://intranet.birmingham.ac.uk/finance/documents/public/rgt/Internal-CI-Agreement-UoB-sponsor-UK-study-non-CTIMPs-V1.docx>
* UoB How the University uses your data: <https://www.birmingham.ac.uk/privacy/index.aspx>
* UoB Information Classification Standard: <https://collaborate.bham.ac.uk/it/itas/Published/Standards/Information%20Classification%20Standard.pdf>

# Abbreviations and definitions

| Term | Description |
| --- | --- |
| CI | Chief investigator |
| CRF | Case report form |
| CTA | Clinical trial authorisation |
| CTIMP | Clinical trial of an investigational medicinal product |
| CTU | Clinical trials unit |
| GCP | Good Clinical Practice |
| HRA | Health Research Authority |
| HTA | Human Tissue Authority |
| IB | Investigator brochure |
| ICF | Informed consent form |
| IMP | Investigational medicinal product |
| IRAS | Integrated Research Application System |
| ISF | Investigator site file. See ‘Site file’. |
| LAL | Laboratory academic lead |
| LMF | Laboratory master file |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NIMP | Non-investigational medicinal product |
| PI | Principal investigator |
| PIS | Participant information sheet |
| QP | Quality person |
| REC | Research ethics committee |
| RGT | Research Governance Team |
| RSI | Reference safety information |
| Site file | The site file contains all the 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). |
| SmPC | Summary of product characteristics |
| SOP | Standard operating procedure |
| SS&DL | Site signature and delegation log |
| Study/trial master file (S/TMF) | The study/trial master file consists of essential documents kept at the sponsor (or delegate) 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. |
| 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).