Standard Operating Procedure:

Case Report Form Development

# Purpose

This standard operating procedure (SOP) describes the processes for developing and implementing a case report form (CRF) for use in a clinical research project.

# Scope

The SOP is applicable to all clinical research sponsored by the University of Birmingham (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. This SOP also applies to clinical research approved by a UoB Research Ethics Committee (REC) that are 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 for all clinical trials, and any clinical studies where the CRFs are yet to be developed or are in draft form and are not going to be finalised within 3 months of the effective date.

For studies where CRFs are in draft and are to be finalised within 3 months of this document’s effective date or have been finalised and are in use, this SOP will be implemented prospectively following the next CRF update, and retrospectively where possible.

# Stakeholders

Note that where the UoB takes on the sponsor’s responsibility for CRF development, the UoB will delegate the majority of these duties to the chief investigator (CI) or to a clinical trials unit (CTU), who may delegate these duties further to their trials team(s). All delegation of duties will be documented (e.g. using the CI declaration and/or the Clinical Trial Task Delegation Log (UoB-SPO-QCD-001)).

* CI: the CI may delegate activities to members of their trial team, although evidence of CI involvement and approval is still expected and may not be delegated where ‘no delegation allowed’ is indicated. The 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 (PI), or the supervisor for postgraduate research students.
* Statistician. See also Statistics SOP (UoB-STA-SOP-001).

# Background and rationale

A CRF can be a printed or electronic document designed to record all the protocol-required information on each participant. A CRF can be the source data or used to transcribe from the source. The purpose of a CRF is to provide a standard, consistent, timely and structured way of capturing data in accordance with the protocol, which will allow for efficient and complete data processing, analysis and reporting. In addition, the CRF allows the CI to verify that the protocol is being followed.

A CRF helps to fulfil Principle 8 ‘Respect for Privacy’ in the UoB Principles of GCP for Clinical Research (UoB-GCP-POL-001) that states: “All information collected for, or as part of, the research project is recorded, handled and stored appropriately and in such a way and for such time that it can be accurately reported, interpreted and verified, while the confidentiality of individual research participants remains appropriately protected…”. A CRF can be a single document or a suite of documents that that may be created at different time points in the project.

# Process map



# Procedure

It is recommended that this SOP be used in conjunction with the Guide to CRF Development (UoB-CRF-QCD-001) as this document provides further guidance on how the requirements in this SOP can be potentially fulfilled.

## CRF design

1. The CI (or delegate) will decide the format of the CRF (i.e. paper or electronic).
2. For electronic CRFs (eCRFs), the CI (or delegate) will refer to the Data Management SOP (UoB-DMA-SOP-001) to ensure the appropriate development of the relevant study/trial systems.
3. The CI (or delegate) will develop the CRF based on the requirements of the protocol and the statistical analysis of the data. A defined list of critical data items may help when developing the CRF; see the Data Management SOP (UoB-DMA-SOP-001) for more information.
4. The CI (or delegate) will engage with experts, for example the statistician, study/trial coordinator, programmer, on developing the CRF. The CI (no delegation allowed) will ensure their expert advice is incorporated and the CI (or delegate) will ensure evidence of their engagement is filed in the S/TMF.
5. The CI (or delegate) will ensure gathering of any other data is kept to a minimum and is appropriate for the project, e.g. participant identifiers, visit dates, treatment information. Where additional data are planned to be collected, the CI (or delegate) will ensure that the S/TMF captures the requirement for additional data collection.
6. Where the CRF contains participant identifiable data, the CI (or delegate) will refer to the Essential Documents Development & Maintenance SOP (UoB-ESD-SOP-001) and Participant Engagement & Informed Consent SOP (UoB-PEI-SOP-001) to ensure the participant is appropriately informed about the processing and storage of their data. The CI (or delegate) will also ensure any personal data is collected and processed in accordance with the [Data Protection Act 2018](https://www.legislation.gov.uk/ukpga/2018/12/contents/enacted).
7. The CI (or delegate) will ensure CRF sections are finalised in a timely fashion to allow for real-time data collection, e.g. CRF sections relating to participant recruitment are finalised before recruitment is started.
8. Where a paper CRF (pCRF) is used, the CI (or delegate) will add the following information to each page:

* project ID
* site name/code
* participant’s unique identifier
* CRF section identifier, if applicable, e.g. ‘Visit 1’, ‘Adverse Events’
* CRF version number and version date (see Essential Documents Development & Maintenance SOP (UoB-ESD-SOP-001) for instructions on version numbering)
* CRF page number.

1. The CI (or delegate) will ensure that the CRF follows a standardised, logical order to allow for easy completion and facilitation in the data management, statistical analysis and reporting of the project. This will also help to minimise any data queries. Further guidance can be found in the Guide to CRF Development (UoB-CRF-QCD-001).
2. The CI (or delegate) will ensure that the terminology used in the CRF matches those used in other key documents, particularly in the categorisation of adverse events (see Adverse Event Reporting SOP (UoB-AES-SOP-001)).
3. For CTIMPs, the CI (or delegate) will ensure that the design of the CRF allows for the principal investigator (or delegate) to confirm the observations recorded in the CRF. For eCRFs, this can be in the form of an electronic signature being applied via the principal investigator’s (or delegate’s) specific user account.

* For all other clinical research, it is expected that this procedure is followed as a best practice.

1. The CI (or delegate) will identify in the protocol or in a separate document where sections of the CRF will be used as source data. See Protocol Development Tool for non-CTIMP & Studies (UoB-ESD-QCD-003) or the Protocol Template for CTIMPs (UoB-CLN-PRO-QCD-002).
2. Where participants are expected to complete questionnaires, the CI (or delegate) will ensure the questionnaires are approved by the REC. Where validated questionnaires are available, the CI (or delegate) will use them in accordance with their licences/permissions. Where questionnaires are being created specifically for the project, the CI (or delegate) will ensure the language used within them is at a suitable level for the participant population.
3. As a minimum, the CI (no delegation allowed) will approve the final version of CRFs relating to items required for the statistical analysis of the data. The CI may delegate this duty for any other CRFs. The CI (or delegate) will file evidence of these approvals in the S/TMF.

* For CTIMPs, it is expected that there is also documented evidence of the statistician’s approval. Where appropriate, this procedure could also be applied in non-CTIMPs/clinical studies to support best practice.

## CRF Implementation

1. The CI (or delegate) will inform the site staff of the CRF to be used, and file evidence of this communication in the S/TMF.
2. The CI (or delegate) will assess if any training is required on the CRF. Where training is required and subsequently provided, the CI (or delegate) will ensure the training is documented. See also Training SOP (UoB-TRN-SOP-001).
3. The CI (or delegate) will ensure the correct version of the CRF is being used by the sites upon receipt of the completed CRFs. If incorrect, the CI (or delegate) will notify the site accordingly.

## CRF amendments

1. When amendments are needed to the approved CRF, the CI (or delegate) will make the necessary amendments and change the version number of the new CRF or sections thereof.

* For CTIMPs, the CI (or delegate) will keep a record of the changes made to the CRF template and where required, the rationale for any changes to data items which affect the statistical analysis (if not self-evident, for example amending a typographical error).

1. The CI (no delegation allowed) will approve any changes to the CRF where these relate to items required for the statistical analysis of the data, before implementing these changes to the CRF. This approval must be documented and filed within the S/TMF.

* For CTIMPs, it is expected that there is also documented evidence of the statistician’s approval. Where appropriate, this procedure could also be applied in non-CTIMPs/clinical studies to support best practice.

1. Once the amended CRF is approved, the CI (or delegate) will repeat the steps for CRF implementation (see points 15-17).
2. For amended pCRFs, the CI (or delegate) will also instruct sites to keep one copy of the superseded version of the CRF in the investigator site file, and to destroy any other blank copies of the superseded version of the CRF.

* For CTIMPs, the CI (or delegate) will ensure this communication is filed in the TMF.

## CRF completion

Note: if using a pCRF, it is expected that the sites are instructed to send the original completed CRFs to the coordinating centre and to keep a copy at site. The original may be kept at site if sending the CRF electronically (i.e. via fax).

1. The CI (or delegate) will track CRF returns (if applicable) and process the completed CRFs as detailed in the Data Management SOP (UoB-DMA-SOP-001). CRFs are expected to be completed, and if applicable, sent to the coordinating centre, in a timely manner to enable trend analyses to occur.

# List of expected outputs

* CRFs containing the items required to report on the project, as defined in the S/TMF.
* Documented evidence within the S/TMF confirming the CI’s approval (and statistician’s for CTIMPs) of the CRFs, and for any subsequent amendments where changes relate to items required for the statistical analysis of the data.
* Documented evidence that sites have been informed about the CRFs or subsequent amendments before use.
* Where applicable, evidence of training provided to site staff on the CRFs or subsequent amendments.
* CRFs completed (and with evidence of the principal investigator’s (or delegate’s) confirmation of the data for CTIMPs), and if appliable sent to the coordinating centre, in a timely manner.
* For CTIMPs, a record of any changes made to the CRF template and where required, the rationale for any changes to data items which affect the statistical analysis.

# Related documents

* UoB-AES-SOP-001 Adverse Event Reporting
* UoB-CLN-PRO-QCD-002 Protocol Template - CTIMPs
* UoB-CRF-QCD-001 Guide to CRF Development
* UoB-DMA-SOP-001 Data Management
* UoB-ESD-QCD-003 Protocol Development Tool for non-CTIMPs and Studies
* UoB-ESD-QCD-004 Protocol Template for non-CTIMPs and Studies
* UoB-ESD-SOP-001 Essential Documents Development and Maintenance
* UoB-GCP-POL-001 UoB Principles of GCP for Clinical Research
* UoB-PEI-SOP-001 Participant Engagement and Informed Consent
* UoB-SPO-QCD-001 Clinical Trial Task Delegation Log
* UoB-STA-SOP-001 Statistics
* 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

* Data Protection Act 2018: <https://www.legislation.gov.uk/ukpga/2018/12/contents/enacted>
* Good Clinical Practice Guide compiled by the Medicines and Healthcare products Regulatory Agency (MHRA). First edition published in 2012.

# Abbreviations and definitions

| Term | Description |
| --- | --- |
| AE | Adverse event |
| Case report form (CRF) | A printed or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each participant. |
| CI | Chief investigator |
| CTIMP | Clinical trial of an investigational medicinal product |
| CTU | Clinical trials unit |
| eCRF | Electronic case report form |
| GCP | Good clinical practice |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| pCRF | Paper case report form |
| PI | Principal investigator |
| REC | Research ethics committee |
| SOP | Standard operating procedure |
| S/TMF | Study/trial master file |
| UoB | University of Birmingham |

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