1. Introduction

The purpose of this Standard Operating Procedure (SOP) is to standardise the approach for designing Case Report Forms (CRFs) for research sponsored by the University Hospitals of Leicester NHS Trust (UHL).

The UHL sponsors a wide range of research ranging from simple qualitative studies to complex highly regulated Clinical Trials of Investigational Medicinal Products (CTIMPs) and CE and Non CE Marked Medical Device studies. It is recognised that the CRF requirements will vary accordingly. The type of CRF used needs to be proportionate to the risk associated with the study and this will be determined during the Sponsor Risk Assessment process. Where possible the services of a Clinical Trial Unit (CTU) should be used for CRF (and database) production, however, the principles of CRF design are the same irrespective of the complexity or size of the study.

2. Scope

This SOP applies to all research studies sponsored by the UHL.

3. Definition

The data collection tool or CRF may be a paper CRF (pCRF) which can be a very simple paper document ranging from one page to a folder of pages. It may also be a computer application where the data are entered into an electronic case report form (eCRF), which is commonly in a web based portal system or, less frequently, on a standalone electronic device. The type of CRF used will vary according to the requirements of each individual study. The Chief Investigator in collaboration with the Sponsor will need to decide which system is most suitable for each particular trial. More information on the specifications for eCRFs can be found in the Data Management SOP S-1031 UHL.

4. CRF Design

CRF design must be guided by the requirements of the protocol and the planned statistical analysis of the trial data. This principle remains the same whether the CRF is in paper or electronic format. The CRF needs to be appropriately structured with each study visit clearly defined. A CRF Template is available for use (Appendix 1) as well as a CRF Guidance document (Appendix 2).

The following would be considered key elements for a CRF (some may not be applicable – this depends on the type of trial):

- Field for unambiguous, anonymised subject identity code on each page (non-patient identifiable data)
- Field for visit date on each page
- Field for confirming continued consent on each visit
- Field per visit for initials of person completing CRF
- Screening and baseline visit(s)
  - -Subject demography
  - -Disease characteristics of the subject
  - -Medical and medication history and physical examination
  - -Data used to assess eligibility (list of inclusion and exclusion criteria)

- -Confirmation of eligibility with a space for CI / PI signature to confirm eligibility (or medically qualified delegate)*
- -Initial data for the primary and secondary endpoints
- Subject randomisation
- Trial visits
  - -During and post-treatment data for the primary and secondary endpoints
  - -Data to assess compliance with the protocol and the (IMP) treatment regimen
  - -Exploratory or health outcome data not related to the main end-points
  - -Safety data
- Final visit (trial completion/withdrawal)
- Adverse events/adverse device effects
- Concomitant medications and other interventions
- Serious adverse events/ serious adverse device effects forms Field for the signature indicating approval of the final data by the CI or PI
- Drug accountability/ Device accountability

* For Clinical Trials of Investigational Medicinal Products (CTIMPs) where any eligibility are confirmed there must be evidence of who performed this confirmation to verify that the final decision to enter a subject into a trial was made by a medically qualified doctor. This must also be reflected in the Delegation of Authority and Signature Log.

4.1 Timing

CRF design can be performed simultaneously with the development of the protocol or following finalisation of the protocol. Whichever approach is used, there should be a process in place for adequate version control during the drafting process and once the CRF is finalised. The CRF needs to be reviewed by the Sponsor and finalised prior to the first site initiation visit.

4.2 Amendments to the CRF Post-Finalisation

Often, during a study a protocol amendment may be required and as a result, changes to the CRF (and database) may be necessary. It is expected that where this applies, amendments to the database and CRF are made during the approval process for amendments and the Sponsor informed. There must also be a clear audit trail detailing changes that have been made.

All changes must be version controlled.

5. CRF Review and Approval

The CRF should be designed with detailed reference to the protocol capturing all, and only, the information required by it. Appropriate personnel, including the person who will be analysing the data, should review the CRF to ensure that:

a) The appropriate data are being collected
b) The data are consistent with the trial protocol

Reviews must be retained and evidenced within the Trial Master File.

The CRF does not need to be a signed document, however it is recommended that there is documented evidence of approval of the final version (and any amendments) by relevant personnel to ensure that it is fit to collect the data required so that the objectives of the study are met.

NB: For CTIMP Studies the Sponsor Green Light will not be given until the CRF has been finalised.

6. CRF Completion Guidelines

For large, complex or multi-centre trials it may be useful to compile a CRF completion guideline which would typically include advice on:

- Date format and partial dates
- Time format and unknown times
- Rounding conventions
- Trial–specific interpretation of data fields
- Definitions and guidance for completion of trial-specific activities/ procedures
- Entry requirements for concomitant medications (generic or branded names)
- Which forms to complete when
- What to do in certain scenarios, for example when a subject withdraws from the trial
- Missing/incomplete data
- Completing SAEs and reporting SAEs
- Repeat laboratory tests
- Protocol and GCP non-compliances/ deviations

7. Source Data

While the CRF is normally used for transcribing data from the source data, there may be circumstances where the CRF has data directly recorded into it, meaning that at least part of the CRF is a source document. In these circumstances such data should be listed as source data in the trial protocol and the Source Data schedule completed which can be found as Appendix 5 to SOP S-1007 UHL, or otherwise documented as source data and confirmed by the Sponsor.

8. Data Recording Tools for Trial Subjects

Occasionally data are entered by the trial subjects themselves (or their carers) into paper or electronic diaries/self-assessment questionnaires. Where this is the case it is recommended that diaries are designed to facilitate data collection by taking into account possible infirmities of the subjects, such as difficulty in writing or eyesight problems. The recorded data may have a high level of importance – for example, they may be an end-point for a trial recording pain or asthma symptoms. This will be identified at the risk assessment stage. Consideration must be given to the importance of the subject recorded data and appropriate control processes implemented to ensure the robustness of the data.

If paper diary data are to be entered into a database by a separate data management facility, the diaries must be checked to ensure there are no subject identifiers present prior to removal from the investigator site and a copy should be retained by the Investigator.

9. Worksheets and CRFs

There are situations where trial-specific observations or tests are not performed routinely on site and therefore to avoid missing data, use of a worksheet may be warranted. This may be particularly important for studies with high throughput and/or time-dependent data requirements such as vital signs in an intensive therapy unit setting. In these instances the worksheets should be version controlled to ensure they are updated in line with any amendments to the protocol (e.g. eligibility criteria, additional data points). When worksheets are used as source data they must be retained and filed with patient notes.

10. Responsibilities

	Responsibility	Undertaken by	Activity
1	Sponsor / CI	Head of Research Operations or delegate & CI	Decide and document what type of CRF will be appropriate during the Sponsor Risk Assessment & Sponsor review
2	CI or delegate	CI or delegate	Design the CRF in accordance with the protocol specifications.
3	Statistician (or other person analysing the data) and other relevant personnel	Statistician (or other person analysing the data) and other relevant personnel	Review the CRF to verify the appropriate data are being recorded and to ensure consistency with the protocol. Document and retain evidence of this review.
4	Chief Investigator	Chief Investigator or delegate	Ensure the accuracy, completeness, legibility and timeliness of the data recorded in the CRF.
5	Chief Investigator	Chief Investigator or delegate	In the event of a protocol amendment, perform a review of the CRF and ensure appropriate changes are made and version controlled.

11. Supporting Documents and Key References

SOP S-1035 Appendix 1 & 2

SOP S-1031

12. Key Words

Research, Innovation, Volunteers, Participants, CTIMPs, Trials, CRF, GCP, Case Report Forms, CE Marked, TMF

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