

# Standard Operating Procedure CCTU/SOP013

## Case Report Form Design

### 1. Scope

This Standard Operating Procedure applies to staff of the Cambridge Clinical Trials Unit Chief Investigators and their trial teams working on Trust-Sponsored CTIMPs or clinical studies coordinated by the CCTU.

### 2. Purpose

The purpose of this SOP is to standardise the procedure for designing paper CRF to be used in conjunction with a separate database on which the data is ultimately stored. This is distinct from an electronic CRF used for electronic data capture directly into a database. However the level of detail required in an annotated paper CRF is identical to the level of detail needed to specify a database.

### 3. Definitions and Abbreviations

The headings below contain the definitions of terms and meaning of abbreviations used within the document.

Common abbreviations and definitions can be found in CCTU/INF001 Common Abbreviations and Definitions.

#### 3.1. Definitions

| Term            | Definition  |
|-----------------|---|
| Trust-Sponsored | Sponsored by Cambridge University Hospitals NHS Foundation Trust (CUH) or sponsored by CUH jointly with The University of Cambridge |

#### 3.2. Abbreviations

| Abbreviation | Meaning   |
|--------------|---|
| CRF          | Case Report Form                                    |
| eCRF         | Electronic Case Report Form                         |
| CTIMP        | Clinical Trial of Investigational Medicinal Product |
| MHRA         | Medicines and Healthcare products Regulatory Agency |
| CI           | Chief Investigator                                  |
| PI           | Principal Investigator                              |
| CDASH        | Clinical Data Acquisition Standards Harmonisation   |

### 4. Undertaken by

Clinical Trial Coordinators, Statisticians, Data Managers, Programmers, CIs, and designees responsible for the design of CRFs.

## 5. Items Required

Final REC and MHRA approved version of the trial protocol  
CCTU/SOP001 Pharmacovigilance Process for the CCTU  
CCTU/SOP002 Pharmacovigilance Process for Investigator  
CCTU/FRM001 Serious Adverse Event Reporting Form  
CCTU/FRM003 Pregnancy Reporting Form  
CCTU/FRM004 Other Important Safety Issues Reporting Form

## 6. Summary of Significant Changes

More clarity in section 7.1

## 7. Method

The following sections provide a description of the processes to be followed when implementing this document's procedures.

### 7.1. General Principles

- The CRF must be finalised prior to the start of the trial and before any site is opened for recruitment
- The CRF (and amendments) should be developed in collaboration with the Statistician, Data Manager, Programmer and CI/PI
- An annotated CRF or Database Specifications must be finalised prior to the start of the trial before any site is opened for recruitment
- The annotated CRF must provide all the information needed to complete the Database Specifications (CCTU/SOP0026, CCTU/FRM029, CCTU/FRM030, CCTU/FRM031, CCTU/FRM032, CCTU/FRM034)
- The CRF and the database should be developed in parallel
- After finalisation of the CRF, any changes deemed necessary must be discussed with the Data Manager and/or Programmer and the Statistician before they are made
- A change in the CRF is likely to involve a change in the database
- Each form must be dated and version controlled. Each version change must be documented in the version control log in the TMF
- The CRF should only collect trial data as set out in the associated clinical trial protocol
- Unless explicit consent and/or ethical approval is granted, only non-identifiable patient data should be collected in the CRF. For example, the patient's hospital number should not be collected in the CRF as it can be directly linked to the patients' medical records compromising patient confidentiality
- The CRF should be designed to ensure compliance with the protocol and regulatory requirements using questions, for example:  
*Does the patient meet the eligibility criteria? Yes/No*
- All inclusion/exclusion criteria questions must be exact quotations from the protocol

- The CRF should be approved by the Chief Investigator, Data Manager, Clinical Trial Coordinator and Statistician prior to use

### 7.2. Guideline of Contents

- The Data Manager will identify all the data collection requirements necessary as defined in the clinical trial protocol
- The CRF should collect sufficient data to support analysis of the protocol's objectives
- Depending on the data required by the clinical trial protocol, a standard CRF document might include, but is not limited to, the following pages:
  - Front Cover Sheet
  - Randomisation/registration form
  - Eligibility form
  - Baseline/screening form
  - Treatment form (treatment, doses, administration routes, reductions)
  - Patient Completion (documenting the date, reason and circumstances for the cessation of visits or data collection due to withdrawal, death, progression or other)
  - Medical History (including relapse/recurrence form)
  - Concomitant Medication
  - Adverse Event
  - Serious Adverse Event forms as per CCTU/SOP001 Pharmacovigilance Process for the CCTU, CCTU/SOP002 Pharmacovigilance Process for Investigator
  - CCTU/FRM001 Serious Adverse Event Reporting Form
  - CCTU/FRM003 Pregnancy Reporting Form
  - CCTU/FRM004 Other Important Safety Issues Reporting Form
  - Follow-up forms
  - Patient Withdrawal
  - Death form
  - Investigator sign-off
- Any CRF, most importantly for any multi-centre trial, should be accompanied by CRF completion guidelines providing general instructions to ensure data quality
- A copy of the CRF completion guidelines should be maintained in the appropriate section of the TMF
- These guidelines should be version controlled
- Details of how and when the CRF should be returned should also be included

### 7.3. CRF Design

All CRF pages must be designed with:

- the same format to provide consistency
- a standard header and footer on each page
- adequate amounts of free space on the CRF page to aid readability
- a consistent and linear format to ease completion

### 7.3.1. Header

The header should include:

- Short title or number of the trial and logo (if applicable)
- Title or unique ID number of the form
- Site reference (name or number)
- Three patient identifiers
  - Patient's Trial ID
  - Patient's Initials
  - Patient's Date of Birth

### 7.3.2. Footer

The footer should include:

- Space for Investigator and/or designee's signature (the signatory must be on the delegation log for that site)
- Space for the date of signature
- CRF version number and date
- Page number and total page number for the form if applicable
- Also if possible the address and details of where the forms must be returned

### 7.3.3. Main Page Content

- The CRF layout should have a logical ordering that follows with the schedule of visits as defined in the clinical trial protocol
- The CRF layout should allow for ease and clarity of data entry in order to limit the number of data queries
- Questions should be grouped into sections with headings indicating their content e.g. In/Exclusion criteria, haematology results
- Question instructions should be clear, succinct, appropriately located and presented in the same manner and position (if possible) across forms
- The format of questions must provide standardised answers that aid completion
- Questions should be constructed in the yes/no format or with a set list of options wherever possible, to limit errors and collection of unnecessary or ambiguous data
- Where a list is not exhaustive an 'other' option should be included with space for free-text comments, only if appropriate, and should be avoided if feasible
- Design format should:
  - Avoid collecting free text
  - Ask explicit questions
  - Avoid double negatives in the questions
  - Provide pre-coded answer options to ease the analysis e.g. "yes"/"no"/ "Not applicable"/ "Not known" "Please specify"
  - Indicate if a question can have one answer or multiple answers
  - Use absolute, rather than comparative, questions, e.g.: None, Mild, Moderate, Severe; rather than Better, Same, Worse

- Collect raw data rather than calculated data, e.g. for age, collect birth date
- Collect dates in a uniform fashion (DD/MM/YYYY)
- Pre-specify the choice of units wherever possible e.g. mg, ml, cm etc.
- Avoid requesting unnecessary calculations
- Ensure consistency across the CRF booklet (units, terminology etc.)
- Avoid duplication of data e.g. gender only needs to be collected at screening as this is unlikely to change during the course of the trial
- Where appropriate give the option to report "ND" (not done) or "UNK" (Unknown) to avoid ambiguity in questions left blank
- If missing data is anticipated for key questions (e.g. primary endpoint) then provide questions that record the reason why the data is missing

### 7.4. Visit Schedule

A visit schedule that documents which forms will be used at which visits must be produced as per Database Development CCTU/SOP026 and Visit Schedule Specification (CCTU/FRM029).

### 7.5. Annotated CRF or Database Specification Documents

To enable the construction of a database, an annotated CRF, or equivalently a set of Database Specification Documents, must be produced. It is not acceptable to commence data collection with a paper CRF before the annotated CRF or Database Specification Documentation is produced. The annotated CRF is one way to *represent* some of the information required to design a database as specified in Database Development CCTU/SOP026. The Database Development CCTU/SOP0026 gives details of the roles and responsibilities for producing and approving the required documentation. If desired, the annotated CRF can be replaced with Database Specifications Documentation:

- CRF/eCRF Specification (CCTU/FRM0030)
- Question Validation Specification (CCTU/FRM0031)

If the annotated CRF is preferred then the information must allow these documents to be completed. In summary, this information includes but is not limited to:

- Question Name: as per CDASH requirements where applicable
- Question Label: free text briefly describing the question
- Question Type: integer, real, date/time, categorical, text
- For any categorical questions, the possible values the question can take

#### 7.5.1. Format of the Questions

- Integers could be, for example, ##9; meaning at least 1 digit, but up to 3 possible
- Reals could be -##9.9##; giving the number of compulsory and optional number of digits before and after the decimal point and allowing negative numbers
- Dates could be dd/mm/yyyy and times can be hh:mm:ss or hh:mm

- Text should be given a realistic maximum length that only allows for appropriate data collection, 250 is the maximum character length possible.
- Details of any external look-up database to be used. For example MedDRA coding of adverse events, laboratory normal ranges
- Any activation conditions that must be met before a question can be completed, for example the subject ID and visit date must be completed and eligibility confirmed before a subject can be randomised

### 7.5.2. Status of the question

- Mandatory: where a question must be completed to allow a form to be saved and considered as complete
- Optional: where a question can be left uncompleted and will not be considered as missing data
- "Blank": neither of the above
- Any validation requirements to check the validity of data and issue warnings or rejections of data. For example upper and lower bounds, checking that dates are not in the future

### 7.6. CRF Amendment

- To comply with regulatory requirements a Database must be fully specified and tested as per Database Development CCTU/SOP026. Any changes to a paper CRF will require a new version of the specification documents and a repetition of the testing process. Consequently, a CRF should not be changed unless absolutely necessary
- Any amendments to the CRF must be documented
- The new version of the CRF must be consistent with the protocol
- An amendment must be designed in collaboration with the Statistician, Data Manager and/or Programmer then approved by the CI or delegate. This is to achieve consistency with the approval process of the original CRF
- If applicable the Trial Specific data management plan and the CRF completion guidelines must be updated to reflect any changes
- Any amendments that are made to the CRF need to be documented and approved on a CRF Approval Form CCTU/FRM034, before any changes to the database may be made
- If problems arise with a CRF
  - New guidelines or a memorandum should be issued to all those using the form to ensure that the completion requirements are clear
  - Any problems and the action taken to remedy them should be recorded in the Trial Master File

### 7.7. CRF Archive

- The CRF forms part of the Trial Master File
- All approved versions of the CRF and CRF Approval Forms must be filed in the Trial Master File
- The CRF should be archived with the TMF according to the CCTU/SOP006

## 8. Monitoring compliance with and the Effectiveness of this Document

### a. Process for Monitoring compliance and Effectiveness

As part of routine monitoring visits, audit and inspection

### b. Standards/Key Performance Indicators

This process forms part of a quality management system. Documents are reviewed every two years

## 9. References

The Institute of Clinical Research, 2008, Abbreviations used in Clinical Trials.

## 10. Associated Documents

CCTU/SOP006 Archiving

CCTU/SOP026 Database Development

CCTU/FRM034 CRF Approval Form

CCTU/FRM029 Visit Schedule

CCTU/FRM030 CRF/eCRF Specification

CCTU/FRM031 Question Validation Specification

CCTU/FRM032 Study Parameters

CCTU/FRM034 CRF Approval Form

## 11. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

## 12. Disclaimer

It is the user's responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

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