STANDARD OPERATING PROCEDURE 16
Case Report Forms (CRFs)

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Contents

Revision Chronology:	Effective date:	Reason for change:
Version 4.0	07 March 2024	Minor update by the QA team to reflect implementation of 'Data Items List' Template to aid CRF cross checking and data minimisation.
Version 3.0	17 March 2022	Biennial review: Additional information about CRF annotation, a unit wide preventative action for ensuring appropriate access to data fields within the CRF. Replaced references to 'Database' with CDMS for consistency across SOPs. Slight amendment to flow to demonstrate that development of the CRFs often occurs alongside the programming of the CDMS. Multiple minor clarifications to text and expansion of the definition section.
Version 2.1	20 January 2020	Minor amendments to responsibilities for Trial Managers and Programming team. Change of order to process. Update to new format.
Version 2.0	20 March 2019	Biennial review: Rewrite with change to process flow. Addition of requirement for documented cross check of CRF with the protocol. Expansion of scope to include patient facing data collection forms.
Version 1.5	25 July 2016	Biennial review: Minor changes to guidance document and SOP text to include eCRFs. Change to new format.
Version 1.4	6 January 2014	Addition of process of generation, review and approval of documentation.
Version 1.3	5 March 2012	Format change to comply with SOP 1.
Version 1.2	1 February 2010	Biennial review. Web page links updated. Definition of source data and note re; design of CRF added.
Version 1.1	8 February 2008	Biennial review: Format change. Slight amendments to text.
Version 1.0	March 2006	

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1. Purpose and Scope

The purpose of this Standard Operating Procedure (SOP) is to inform Investigators and other study personnel of the process for development and implementation of tools to capture participant data and to do this in such a way to ensure accuracy, data verification and compliance with relevant data protection regulations. For more information about the development of a Clinical Data Management System (CDMS), refer to SOP 42 'CDMS Planning and Maintenance'.

2. Definitions

Case Report Form (CRF)	Form on which individual participant data required by the study protocol are recorded. It may be a paper document or a computer application, commonly a web-based portal system, where site staff enter data into an electronic case report form (eCRF). This type of system may be referred to as electronic data capture (EDC). For this procedure, the term CRF will be used to refer to all data capture tools, including participant questionnaires and diaries.
On entry validation	Automated check built into the application to ensure the validity or accuracy of a data item.
Clinical Data Management System (CDMS)	A tool used for the collection, tracking, processing, and storage of data used in clinical research. Where EDC will be used, entry of data occurs straight into the CDMS.
Source data	Source data is where a data point is first captured and is therefore the original record of information (e.g. hospital records, concomitant medication, laboratory results, ECGs, patient diaries, x-rays etc.)

3. Background

The CRF is usually used to record data copied from original (source) data such as medical notes, laboratory reports, scan reports etc. In some cases, the CRF can be the first and only document where data items are recorded and then the CRF becomes the source document; questionnaires or diaries completed by participants, for example. How these data are collected will directly impact on the quality of the data collected and therefore it is essential that the design of the CRF ensures that data collection is clear, precise and unambiguous. This will ensure consistency of data quality, ensure adequate collection of data is performed to be able to conduct final analysis as per protocol and ensure proper audit trails can be kept to demonstrate validity of the study data.

The analysis of the data and the compilation of reports will last for many months after data have been collected and the results of a study may also be audited or inspected a long time after the study has been completed, by which time the main protagonists involved in the study may have moved to other positions, thus it is imperative that CRFs are well designed, that the design process has a clear audit trail and that the CRF is well completed and appropriately archived.

4. Procedure

4.1 Responsibilities

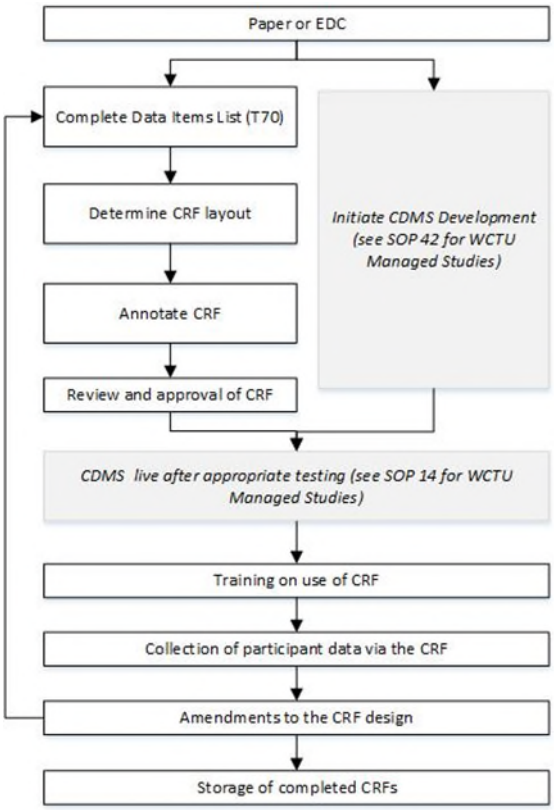
Chief Investigator (CI)	The Sponsor's Office in R&IS delegates overall responsibility for the design of CRF and ensuring that the CRF is designed to capture the required data and that the information gathered is appropriate to the aims of the study and will not adversely affect recruitment. Ensure validated questionnaires are used within the terms of the licence. The coordination of this process can be delegated but the CI retains overall responsibility and therefore final approval.
Statistician	Review of CRFs to assure that data collection will enable the analysis specified in the protocol.
Trial Manager (TM)/Coordinator (TC)	Coordinate the design of the CRF and acting on the instructions of the CI, statistician, and programmers**.**
Quality Assurance (QA)	Should be involved in the development and review of CRFs related to Serious Adverse Event (SAE) reporting.
Programmer	Program CRF in accordance with instructions from the study team. To check acceptability and logic for programming against requirements.

4.2 When?

Design of CRFs should be initiated alongside protocol development and implemented CRFs should always reflect the current version of the protocol. For studies managed by Warwick Clinical Trials Unit (WCTU), CRF design should be appropriately reviewed and approved prior to the live CDMS being released.

4.3 How?

Process for development of the CRF is summarised below, see subsections for more information.



4.3.1 Paper or EDC

Consideration should be made at study outset as to whether paper or EDC will be used and the potential advantages and disadvantages for the study. Where EDC is used, paper CRFs (pCRFs) will often need to be created as a backup in case of system failures or in situations where an individual's signature is required who does not have individual access to the CDMS application.

4.3.2 Complete Data Items List

- Template T70 should be completed using the protocol to ensure all data items required to safely deliver the trial and analyse the primary and secondary outcomes.
- This template provides key documentation about the cross check with the protocol and aids the concept of data protection by design by encouraging the minimisation of data.
- Excessive data capture that is surplus to data analysis can also increase resource requirements, reduce accuracy /completeness and ability to identify non-compliance.
- This form can then be used to develop the CRF content.
- At the point of CDMS release, the content of the CRF should align to the outcomes and analysis specified in the current approved version of the protocol.

4.3.3 Design layout of CRF

- For participant facing data capture forms such as questionnaires or diaries, ethical approval is required in line with the guidance in SOPs 5 (1) 'Gaining initial ethical approval for research studies' & 6 'Amendments to approved study documents'.
- Where validated questionnaires are to be used, applications for permissions or licences should be considered early on. Evidence of permissions should be filed in the Trial Master File (TMF). Where a validated questionnaire will be collected using different methods, more than one licence may be required.

- Where non-validated CRFs are to be used, consideration should be made in the design to the appropriateness of the language and layout to make sure they are intuitive to complete.
- It is recommended that the programming team are consulted at an early stage to determine what is and is not possible to ensure the most efficient design.
- Throughout the development process, appropriate **version control** should be used to document and reconstruct the development process. Decimal increments should be reserved for each draft revision and whole integers for final approved documents. Further information is available in guidance document **SOP 45: Document Management**.
- CRF templates are available upon request from the WCTU QA Team.

4.3.4 Annotation of the CRF

- Annotation of the CRF can facilitate the CDMS design along with the Data Items List. This process can help ensure that all validation and access requirements have been considered.
- Annotations can be a simple set of notes on each field and should be retained in the Trial Master File (TMF) as evidence that these considerations have been applied.
- The table below lists the considerations for each table or field in the CRF during the annotation process. For each field, consider the points in the table below.

Access	On entry validations
• Does access need to be restricted to certain roles? • Does the protocol, ethics application or PIS state that certain people will not see data? • Does the requirement for robust blinding mean information should be restricted?	• Variable length • Variable format • Coding requirements • Variable constraints • Skip logic

4.3.5 Review and approval of CRF

- Draft document(s) should be circulated for review to all relevant parties who have knowledge or experience sufficient to comment on the content.
- Version control, and tracked changes should be used to coordinate the review process. If possible, a CRF review meeting may be held in order to agree the final CRF.
- The Chief Investigator must approve all significant changes to the CRF prior to submission to ethics (where it is applicable for participant facing CRFs) and implementation.
- All CRFs should have appropriate review before they are approved. Minimum suggested reviewers are listed in the table below.

Role	Scope of review
Statistician	To check that all the required data are being collected and in the correct format to be able to conduct the analysis as per the approved protocol. To ensure validations are appropriate.

Clinically qualified investigator(s):	To ensure all data are being collected in line with the clinical data flow and that items are included to ensure effective monitoring of participant safety. To ensure validations are appropriate and data collection is adequate and not excessive.

Other appropriate reviewers include, but are not limited to:

Quality Assurance: specifically in relation to the SAE reporting CRFs.

Health Economist: to check that all the required data is being collected and in the correct format to be able to conduct the planned health economic analysis.

Senior Project Manager: it is strongly recommended that the Senior Project Manager reviews CRFs in order to facilitate consistency and lessons learnt across the portfolio.

Only after CRFs have been reviewed and approved as per the process above, can the CDMS be released.

For **WCTU managed studies**, documentation of appropriate review and approval of CRFs should be captured via the Q-Pulse electronic Quality Management System (eQMS). For colleagues external to WCTU who do not have access to the eQMS, sign off should occur using appropriate email approval following the guidance in **G33**.

4.3.6 Training on use of CRF

Training requirements should be considered for those completing CRFs. Completion guidance for CRFs and any associated CDMS tools should be created either as part of the CRF itself or as part of an approved working instruction or study manual; see SOP 34 'Generation, review and approval of trial specific working instructions'. Any training requirements for members of the WCTU study team should be added to the Data Management Plan (DMP) if relevant. Individual access to the CDMS should only be granted after documentation of appropriate training.

4.3.7 Collection of participant data via the CRF

CRFs are based on 'source data' and should be completed as soon as the source data becomes available.

The source data should remain in a participant's medical records in such a way that it can be easily retrieved (even years after completion of the study) in case of an audit or regulatory inspection. The participant's medical file should state that they have been a participant in a clinical study.

Data reported on the CRF that are derived from source documents should be consistent with the source documents, or the discrepancies should be explained e.g., via Data Clarification Forms (DCF) or explanatory notes filed with the CRF.

4.3.7.1 CRFs that are also source data

Where the CRF is the source document (e.g., information collected by a researcher directly from the participant and not recorded elsewhere or data that is collected via participant questionnaires or diaries) then the training of the persons collecting and recording those data (using clearly documented procedures) is crucial (ICH GCP sections 4.9 and 5.5) and data items for which this is acceptable should

be clearly documented in the protocol. CRFs that are completed from direct interviews with participants or completed by participants themselves in situations where medical notes are not a relevant source, should be detailed in the protocol along with the strategy for obtaining any missing data from these forms.

The format in which CRFs should be received by the study office should be clear and investigator sites should retain a contemporaneous copy where possible. This can be achieved by photocopying or scanning prior to sending to the coordinating centre. There may be some situations where this is not possible, e.g., where participants are completing questionnaires directly from home or where CRFs are completed at study interventions that do not occur in a healthcare setting. If this will occur, then this should be clearly documented in the protocol.

4.3.8 Amendments to CRF design

- Where an amendment to any part of a CRF is required, the process described in section 4.3.5 should be followed for its review and approval. It is good practice to prepare a summary of the changes, so that those undertaking the review can easily identify what changes have been made and to store this along with justification of the change in the TMF.
- There should be a change control process in place to enable confirmation that investigator sites are aware of, and have understood the changes where there have been significant amendments. For eCRFs consider any re-training needs, for pCRFs consider how you will monitor to ensure correct versions are being used.
- Consideration should be given to the implementation date of an updated CRF, particularly when an eCRF is to be used following ethical review. Update DMP and any associated Trial Specific Working Instructions to reflect any changes in requirements to the management of the data. This should be done in line with SOP 15(1) 'Data Management' and SOP 34 'Trial Specific Working Instructions'.

4.3.9 Storage of completed CRFs

Completed pCRFs at investigator sites should be kept in an appropriate repository of the Investigator Site File (ISF) whilst the study is ongoing. The Principal Investigator (PI) or delegate at site is responsible for archiving the Investigator Site File, including copies of the CRFs once the site has been notified to archive. If data is collected via EDC, then this should be accessible to sites until the data is locked. Upon archiving a copy of the data provided by each investigator site should be provided by the Sponsor to the site for archiving. For WCTU managed studies, WCTU will notify sites to archive investigator site files. Investigator sites should be sent copies of eCRFs for their site in a suitable format upon archiving to ensure the PI has access to the information that was provided by the site.

CRFs held at Warwick Clinical Trials Unit must be stored securely and accessed only by authorised personnel.

For more information on storage of CRFs, see SOP 20, 'Closing Research Study Recruitment Sites' and SOP 23'Archiving'.

List of abbreviations

CI	Chief Investigator
CDMS	Clinical Data Management System
CRF	Case Report Form
DCF	Data Clarification Form
DMP	Data Management Plan
eCRF	electronic Case Report Form
eQMS	electronic Quality Management System
EDC	Electronic Data Capture
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ISF	Investigator Site File
pCRF	Paper CRF
PI	Principal Investigator
QA	Quality Assurance
R&IS	Research and Impact Services
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TM/TC	Trial Manager/Trial Coordinator
TMF	Trial Master File
WCTU	Warwick Clinical Trials Unit

Templates and Associated Guidance

T70 – Data Items List

G33 – Email approval guidance