Guidance on the Design and Maintenance of a Case Report Form when setting up a Sponsored Medicines and Healthcare products Regulatory Agency regulated study

Contents

1. Definitions

A Case Report Form (CRF) is '*A data acquisition tool designed to record protocol-required information to be reported by the investigator to the sponsor on each trial participant*.' (ICH GCP E6 R3 Glossary).

It is the tool for the collection of all clinical research data on each individual participant in a clinical trial.

When designing case report forms, the General Data Protection Regulations (GDPR) and Data Protection Act (DPA) 2018 must be taken into consideration.

2. Responsibility

The Sponsor delegates the responsibility of designing the CRF to the Coordinating Investigator (CI). The CI may delegate the responsibility to a suitable member of their team but must maintain oversight of the design process

3. CRF Design

Please take into consideration the following points below when designing the CRF for your trial. The principles laid out in this guidance document apply to both paper CRFs and e-CRFs.

4. Patient identifiable data vs anonymised data

The definitions given below are taken from NHS Digital Code of Practice on Confidential Information (May 2025), which can be downloaded from the NHS Digital website.

Confidential information	"*information which is in a form that identifies any individual to whom the information relates or enables the identity of such an individual to be ascertained, or any other information in respect of which the person who holds it owes an obligation of confidence*."
Anonymised data	"*data that has been converted into a form that does not identify individuals and where identification is unlikely to take place*,"
Pseudonymised data	"*data that has been de-identified so that a coded reference or pseudonym is attached to a record to allow the data to be associated with a particular individual without that individual being identified*"

5. General information

The CRFs must only capture data required by the protocol or by regulations and established guidelines. This can include data to support the objectives of the protocol, data to demonstrate compliance to the protocol regulations and Good Clinical Practice (GCP) to monitor the safety of the participant.

It is important that the CRFs do not collect any additional data that is not defined by the study protocol or applicable guidelines.

CRFs should be clear, concise, and easy to use.

The CI or delegate is responsible for the design and development of the CRFs. Instructions should be given to all participating locations on how to complete the CRF to ensure that data is collected in a standardised format and meets the requirements of the DPA.

A CRF completion guide may be useful in a multi-centre study. As per Joint Research Management Office (JRMO) Standard Operating Procedure (SOP) 46: Location activation and JRMO SOP 38b: Trial data management systems, a training log should exist to document that CRF training has been completed.

The local Investigator at each site should make sure site staff entering data on the CRF have been delegated to do so by signing them off on the delegation log.

6. CRF Development

The following points should be considered when designing a CRF:

• CRFs SHOULD NOT contain any participant identifiable information. When participants are entered/randomised onto a study, they should be allocated a code number known as the patient identifier which can include their initials alongside an allocated number generally pertaining to their entry onto the study.

• If using participants' initials, the first letter of the patient's forename, middle and surname constitute their initials (e.g., John Edward Smith, the initials JES should be utilised). If the patient does not have a middle name, simply use a dash (e.g., William Knight, the initials W-K should be utilised).

• CRFs should be appropriately versioned and dated If there are changes to be made to these documents, the version number and date should be updated accordingly, especially in the case of a protocol modification that may lead to changes in the design of the CRFs.

• CRFs should be consistent with the protocol.

• CRFs must capture all visits and procedures that the protocol requires including questionnaires, participant diaries and telephone follow-ups. This should include the dates that they take place on.

• CRFs must accurately capture dates and doses of Investigational Medicinal Product (IMP) administration, including dose calculations and escalations where applicable.

• Avoid duplication of data collection (e.g. collecting the participant's age and their date of birth).

• Wherever possible avoid free text.

• Where possible use tick box or drop-down options. Where appropriate, implement an "Other" option with a field for the user to enter more information.

• For numerical data, the number of boxes/spaces given should reflect the site of the data to be captured. There should be no blank spaces left on the CRF once completed.

• Units of measurement should always be provided where applicable.

• Sometimes unit conversions are necessary (e.g., in multi-site studies local laboratories may use different units of measurement). In such cases the CRFs should provide space in which the conversion can be documented, with the original figure alongside the conversion factor.

• Each set of entries made on the CRF should be signed and dated by the individual completing the CRF. Such individuals should be trained on the protocol and should be delegated responsibility for CRF completion on the study delegation log. The CI or the local Investigator (if multi-location) should then review the data entered into the CRF, validating their review with a signature and date of review on each CRF for every study participant.

7. Considerations for CRF Layout

CRFs should be well aligned, and the arrangement of data fields should be clear, logical and user friendly. Alignment, margins, spacing and fonts should be consistent.

• All CRF pages should be paginated and include headers and footers with the study code and participant code on every page, and in multicentre studies, location identifier codes should also be used.

• There should be space for the person completing the CRF to sign and date the page. When expert medical assessments are required (e.g. when confirming eligibility) extra space should be given for the assessor to countersign the form.

• CRF pages should be sequentially arranged in order of participant visits.

• If in paper format, consider how the pages will be stored in a file or bound into a booklet. Ensure that the margins are wide enough.

• Sections can be separated using dividers.

8. Mandatory fields and forms

• When creating the CRF for Barts Health NHS Trust (Barts Health) and Queen Mary University of London (Queen Mary) Sponsored Medicines and Healthcare products Regulatory Agency (MHRA) Regulated studies, the following forms are mandatory and can only be omitted with permission from the GCP manager:

- o Eligibility criteria
- o Informed Consent details (date, version etc.)
- o Adverse Event Reporting form
- o Concomitant medications
- o Treatment Form/Dosing and Compliance data (including dose escalations, reductions and modifications)
- o Withdrawal/Study completion form
- o Death
- o Study visits and follow-ups forms (including the date of each visit or procedure)
- o Local Investigator sign off statement

• Additionally, the following forms are recommended for all studies, and mandatory if required by the protocol:

- o Relevant Medical History
- o Participant Demographics
- o Physical Examination and results
- o Baseline data
- o Randomisation/registration
- o Relapse/recurrence
- o End of Treatment form
- o Laboratory data, Electrocardiograms, etc

9. CRF Signing Off and Training

• The CRF should be reviewed and signed off by the CI and the study statistician. The CI and Statistician should check if:

o Sufficient data is being collected to answer all study research questions.
o All data points outlined in the protocol are being collected.
o No data points are being collected that are not outlined in the protocol.
o CRF design complies with the GDPR, DPA and GCP.

• There should be a clear, consistent procedure for the completion and correction of the CRF pages. This can be provided within a training session or written instructions.

10. CRF Completion and management

There should be fixed timelines for CRF completion after each participant's visit, so that data entry is completed on a regular basis.

• In the case of multi centre studies, copies of the CRFs should be sent to the coordinating centre on a regular basis for data management personnel to review. Originals should be retained at the location.
• If the coordinator becomes aware of a data discrepancy documented on the CRF, the coordinator should raise a query using an email or data clarification form for the location to respond to.

11. Modifications

When modifications are made to the protocol, the CI should assess whether the CRFs should be updated. Updated CRFs should be provided to all locations and filed in the Trial Master File (TMF) and the Investigator Site Files (ISF). Superseded CRFs should be marked superseded and retained in the TMF/ISF.

12. CRF Completion

• No sections of a CRF should be left blank. If data is unavailable at the time of completion, explain why e.g., 'unknown', 'missing' or 'test not done'.
• Ensure that the data entered corresponds with the source data (e.g., Medical Records, ECG, and Laboratory Results), and that it is legible.
• Where source data is found to be incorrect, it should be corrected by a suitable person.
• If there are laboratory results outside of reference ranges or if a value shows marked variation from one assessment to the next, the significance of these results should be assessed and documented on the CRF. Each set of entries made on the CRF should be signed and dated by the individual completing the CRF. The person completing the CRF must be delegated the responsibility on the study delegation log.

<u>Consideration for paper CRFS</u>

Permanent ink should be used to comple of the CRFs. Blue or black ink should be used.

• If a data point needs to be corrected, the following procedure must be followed:

o Cross out the incorrect entry with a single line so that the incorrect entry is still legible
o Enter the correct data next to the original
o Initial and date the correction
o If not obvious, explain the correction and why it was made.
o The original data must never be obscured, and correction fluid must never be used.