# 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 printed, optical, or electronic document designed to record all the protocol required information to be reported to the sponsor on each study subject.' ICH GCP section 1.11

It is the tool for the collection of all clinical research data on each individual subject 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 Chief 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 the Department of Health Confidentiality NHS Code of Practice November 2003, which can be downloaded from the Department of Health web site

| Patient identifiable information: | Key identifiable information includes:<br>• patient's name, address, full post code, date of birth;<br>• pictures, photographs, videos, audiotapes or other images of patients;<br>• NHS number and local patient identifiable codes;<br>• Anything else that may be used to identify a patient directly or indirectly. For example, rare diseases, drug treatments or statistical analyses which have very small numbers within a small population may allow individuals to be identified. |
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| Anonymised Information | This is information which does not identify an individual directly, and which cannot reasonably be used to determine identity. Anonymisation requires the removal of name, address, full postcode and any other detail or combination of details that might support identification. |
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| Pseudonymised Information | This is like anonymised information in that in the possession of the holder it cannot reasonably be used by the holder to identify an individual. However, it differs in that the original provider of the information may retain a means of identifying individuals. This will often be achieved by attaching codes or other unique references to information so that the data will only be identifiable to those who have access to the key or index. Pseudonymisation allows information about the same individual to be linked in a way that true anonymisation does not. |

## 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, 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 sites on how to complete the CRF to ensure that data is collected in a standardised format and meets the requirements of the data protection act.

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

The PI 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 patient identifiable information – When Patients 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.

• Patients' 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 amendment 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 – for example collecting the patient'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. Please remember that 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 Principal Investigator (PI) (if multi-site) 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 subject in their care

## 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 in multicentre studies, site 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 – for example when confirming eligibility – extra space should be given for the assessor to countersign the form.

• CRF pages should be sequentially arranged in order of patient 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 medication
    o Treatment Form/Dosing and Compliance data (including dose escalations, reductions and modifications)
    o Withdrawal/Completed study form
    o Death
    o Study visits and follow-ups forms (including the date of each visit or procedure)
    o Principal Investigator sign off statement

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

    Relevant Medical History
    o Patient 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 meets 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 subject'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 lead site on a regular basis.
     • In the case of multi-centre studies, ensure that all original CRFs are sent to the coordinating centre for data management personnel to review. Copies should be made and retained at the site.
     • 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 site to respond to.

## 11. Amendments

When amendments are made to the protocol, the CI should assess whether the CRFs should be updated. Updated CRFs should be provided to all sites 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

All CRFs

     • No sections of a CRF should be left blank. If some data is unavailable at the time of completion, then 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 trial delegation log.

Consideration for Paper CRFS

Permanent ink should be used in the completion 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.