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Case Report Forms

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Version	Date	Reason for Change
Version 1.0	03 Jul 2006	Annual review
Version 2.0	25 Jun 2007	Annual review
Version 3.0	26 Jun 2008	Annual review
Version 4.0	08 Feb 2010	Formation of Research Governance and Integrity Team
Version 5.0	14 Jul 2011	Annual review
Version 6.0	30 Nov 2012	Annual review
Version 7.0	18 Feb 2015	Scheduled review
Version 8.0	25 Oct 2017	Scheduled review
Version 9.0	19 Oct 2020	Scheduled Review Template removed and administrative changes to SOP. JRCO name change to RGIT.
Version 10.0	10 Aug 2022	Update made to the Trial eCRF
Version 11.0	05June 2023	Added information on EDC System provided by Imperial College for Non-CTIMP Studies. Minor changes to the SOP.
Version 12.0	20 Mar 2024	Scheduled Review

Table of Contents

1. PURPOSE

The purpose of this guide is to aid in the design of paper Case Report Forms (CRFs). CRFs are the official instrument to collect data from clinical trials and are a key component of quality assurance and control. It is aimed at researchers, trial coordinators, research nurses and any other staff who design CRFs for a study. Some guidance on Electronic CRFs (eCRFs) is also provided at the bottom of this SOP.

2. INTRODUCTION

CRFs are used to collect data generated for a trial subject, in accordance with the protocol, during their participation in a trial. They also ensure compliance with regulatory requirements. A CRF should collect only appropriate trial data, in an appropriate format, as set out in the protocol and for anticipated analyses. Data collection more than that required by the protocol and analysis plan is undesirable.

Excessive data capture, that is surplus to data analysis, only increases the resources required for data input and verification. Contrary, if too little data are requested this could result in some essential data not being captured or protocol non-compliance going unnoticed. Therefore, the CRF should be designed with detailed reference to the trial protocol and there should be a documented review of consistency of the CRF with the trial protocol requirements. Collaboration with a trial statistician is recommended.

In accordance with GDPR, trials should be adhering to data minimisation when designing Study CRFs. Any patient data which is not strictly required should not be included on the CRFs (e.g., Patient initials should not be captured on a CRF if Subject ID is sufficient to identify which participant the CRF belongs to).

Standard CRFs usually include the following forms/fields:

- Field for an unambiguous subject identity code and visit date on each page
- Entry form (collects screening/baseline data/demographics)
- Confirmation of eligibility/data used to assess eligibility (list of inclusion and exclusion criteria)
- Randomisation/registration form (Appendix 2)
- Treatment form (doses, AEs, concomitant medications and other interventions)
- During and post-treatment data for the primary and secondary endpoints
- Safety data (i.e., vital signs)
- Death
- Relapse / recurrence
- Serious Adverse Event (Appendix 3)
- Follow-ups
- End of Treatment form (final visit: trial completion/withdrawal)
- Field for the approval of the data by the principal investigator or authorised delegates

3. PROCEDURE

3.1. General Principles

Each CRF should be dated and have a clear version number. Any changes to the final CRFs used during a trial should be documented.

The CRF layout should have a logical ordering that follows the schedule of clinic visits, should ask unambiguous questions and should be consistent with the protocol. Thought should be given in advance as to whether any data collected on the CRF can be validated through monitoring of the original source document if required or if the CRF is the source document.

CRFs should be reviewed and signed off by the Chief Investigator and Trial Statistician if available before they are used in the trial. It is good practice for data managers, monitors, CRAs and research nurses to view the CRFs prior to sign off as they will have a clear perspective.

Consideration may also be given to ensuring that the CRF captures the times of time-dependent events, so that confounding factors are recorded and assessed. For example, the timing of blood sampling is key to pharmacokinetic (PK) analysis and this information needs to be captured, ideally in the CRF.

Ideally a well-designed CRF will remind the principal investigators at local sites to perform specific evaluations. Research nurses or monitors can verify that the protocol is being followed and compared with source documents, and the database developer will be able to build in edit checks to help with data management and analysis.

The CRF package that is circulated to all local sites should include:
- General instructions
  - Use permanent Black ink when completing
  - Complete all items
  - Provide glossary of abbreviations
  - Contact information
  - Procedure for corrections and amendments
- CRF study schedule
- Checklist and section dividers, preferably by visit

3.2. Design Guide

For ease of completion:
- Provide definitions
- Specify units if appropriate
- Avoid requesting unnecessary calculations
- Consider grading visual analogue scales

For ease of understanding:
- Avoid double negatives
- Ask explicit questions
- Use absolutes if possible. For examples when describing levels of pain, use:
  None, Mild, Moderate, Severe;
  rather than: Better, Same, Worse

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- Give constant baselines for comparisons
- Avoid compound questions

3.2.1. Layout

Keep adequate amounts of free space on the CRF page. Ensure alignment, margins, spacing and fonts are consistent throughout the CRF booklet. Margins should be large enough to accommodate hole punching/binding.

As much as possible, align text to the right with boxes to the left or centred so it is easily understood which tick box is associated to which question:

	Yes	No
Married?	☐	☐
Driving licence?	☐	☐
Any children?	☐	☐
Good health?	☐	☐

Layout of CRFs should allow for ease of completion, as well as ease of data entry. Things to look for with data entry include adding dropdown choices/menu onto a database, grouping same type of data together on the same form (e.g., dropdown answers together), numeric together and alpha numeric together.

3.2.1.1 Header

The header of each CRF should include:
- Name of study or study number
- Subject identification number
- Site/centre number (if not included in the subject number)
- Name of form
- If CRF goes to 2 pages, indicate page 1 of 2 and 2 of 2

It is easier to access this vital information when looking through a stack of CRFs if located in the upper right-hand corner

<Name of study>	**<subject ID number>** ☐☐ - ☐☐
<NAME OF FORM> (PAGE 1 OF 2)	☐

3.2.1.2 Footer

Signatures and dates should be included at the bottom of each CRF. Each CRF should include the "address to return form to" on the bottom of the form:

Completed by:	Date completed:
Please return to: <Trial Coordinator>, Imperial College AHSC, <address>	

3.2.2 Data Collection

For data analysis purposes, avoid unnecessary textual data, pictorial data and obtaining data from diary cards. Provide choices for each question, this makes it easier at analysis.

Provide units to ensure comparable values and provide instructions to reduce misinterpretations.

Collect raw data rather than calculated data (e.g., for age, collect birth date and visit date). When collecting toxicity data, it is more valuable to have the exact value of the blood result, (e.g., haemoglobin 5.2 g/dl) rather than a CTCAE toxicity grade of 3.

There are different types of data collection responses:
- **Open**: text, number, alpha numeric
- **Closed**: Check box, multiple choice
- **Combination**: open and closed
- Analogue / rating scales

3.2.2.1 Open
Avoid free text if possible as it is almost impossible to analyse. For date / time, add characters to boxes to ensure that the dates are collected in a uniform fashion (MMM/DD/YYYY). This is especially important with international trials.

3.2.2.2 Closed
Provides a list of options (e.g., yes/no). Checkbox is the clearest option. If using coding, be consistent across all CRFs(e.g., 'Yes' is always 1, 'No' is always 2).

This is the best choice for collecting and analysing data.

3.2.2.3 Combination
Generally used with closed type questions when one of the possible responses is 'Other', or 'Specify'. This information could be used for future studies as it gives the investigator additional options.

3.2.2.4 Analogue/rating scales
Use only validated instruments (e.g., Quality of Life). They are used to measure one's perception of a situation.

Text boxes should have a consistent design throughout (e.g., utilise box combing, box dividing or free text areas (avoid if possible)).

Box combing: |⎵⎵⎵⎵⎵⎵⎵⎵⎵⎵⎵|

Box dividing: ☐☐☐☐☐☐☐

Free text: _____

Use a standardised answer mode throughout all the CRFs, e.g.:

Married?	Yes / (No)	**by circling**
Driving licence?	<u>Yes</u> / No	**by underlining**
Any children?	~~Yes~~ / No	**by deleting**

Good health?   Yes ☐ /No √   **by ticking a box**

Smoker?   Yes (Y) / No (N) N   **by using a code**

Tick boxes tend to be the easiest to complete and utilise for data entry.

3.3.   Completing CRFs

No fields should be left blank. **ND** (not done) should be used if data is unavailable either because a measure was not taken or test was not performed. **N/A** (not applicable) should be used if a measure was not required at the time point the form relates to. **NK** (not known) should be used if the data is unknown and every effort has been made to find the data. CRFs should be signed by all site personnel completing the CRF. The Principal Investigator at the local site is responsible for the accuracy of the CRF.

3.4.   Corrections to data entry

As a rule, corrections to data recorded on CRFs should always be handled at the local site. Exceptionally, the Chief Investigator or Trial Coordinator could correct the data entered on a CRF if this is agreed in writing or verbally AND a copy of the changed CRF is then sent to the local site.

Corrections should be made by drawing a single line through the incorrect item and should not obscure the original entry. All corrections should be dated and initialled. Tippex must not be used.

When completing a query, attach an amended copy of the CRF and return either by post or fax to the coordinating centre.

3.5.   Electronic data capture

Electronic data capture (EDC) allows sites to transcribe subject details directly onto a web-based database, thus saving time and trees. EDC offers an advantage as it ensures a standardised format for data entry and can code events. Possible disadvantages include training of staff at local sites, ensuring all staff have access to the internet and the need for a paper backup in case of system failure.

Imperial College Academic Health Science Centre (AHSC) has implemented a Clinical Trial eCRF that will allow for the design and use of EDC. OpenClinica V4.0 is a fully GCP compliant, cloud-hosted system. eCRFs are designed in-house by the Clinical Data Systems (CDS) Team (OpenClinica | Faculty of Medicine | Imperial College London (Last Cited: 10Mar2023). This system is mandatory and should be considered the College's default choice for all Imperial College AHSC sponsored clinical trials of an IMP. For further information , please contact the CDS team: cds_services@imperial.ac.uk or click on the following link: Clinical Data Systems | Faculty of Medicine | Imperial College London (Last Cited: 10Mar2023).

Any requests to opt out from using OpenClinica as the EDC system in an Imperial College AHSC sponsored clinical trial of an IMP will need to be discussed with RGIT early in the sponsorship review stage, including RGIT vendor assessment of the suggested alternative EDC and its provider.

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For Non-CTIMP Studies, Research Electronic Data Capture (REDCap) is a popular data collection tool with a simple web-based interface designed for clinical researchers to manage their study data collection needs. Please note however, that the software is provided for the purposes of non-commercial research only and the research activity must be led by an Imperial College CI. The software installation is not validated to Good Clinical Practice (GCP) standards and is therefore not suitable for CTIMP (drug) studies or studies requiring MHRA regulatory compliance. For further information, please click on the following link: Electronic data capture systems | Research and Innovation | Imperial College London (Last Cited: 10Ma 2023).

4. CRF DATA FOR PROTOCOL NON-COMPLIANCE

Non-compliance checks are not easily built into the CRF design, but considerations may be given to include a dedicated CRF field for non-compliance due to predefined reasons plus a comments field for site staff to record other, unclassified, non-compliance.

Unstructured data recorded in the comments fields are, however, difficult to categorise and therefore it is recommended that methods such as CRFs logs are used instead to capture non-compliance data.

Although non-compliance may be noted by the monitor or site personnel and documented in the monitoring visit reports, in the file notes or in a log, if the method of documentation is unstructured, there is a risk that some non-compliance may be omitted. For this reason, it is then recommended that non-compliance is collated centrally and must be documented and provided to the statistician and medical writer.

Non-compliance can hence be captured through the data validation process, when computer edit checks or contemporaneous validation of eCRFs can highlight departures from the protocol.

5. REFERENCES

Medicines for Human Use (Clinical Trials) Regulations 2004 (Legislation.gov.uk (Last Cited: 10Mar2023)).

ICH E6 (R2) Good clinical practice - Scientific guideline ICH E6 (R2) Good clinical practice – Scientific guideline | European Medicines Agency (europa.eu) (Last Cited: 10Mar2023).

OpenClinica | Faculty of Medicine | Imperial College London (Last Cited: 10Mar2023).

Clinical Data Systems | Faculty of Medicine | Imperial College London (Last Cited: 10Mar2023).

Electronic data capture systems | Research and Innovation | Imperial College London (Last Cited: 10Ma 2023).

6. APPENDICES

The following Appendices list the following Templates associated to this SOP which can be found on the SOP, Associated Documents & Templates page.

Appendix 1: Example CRF sign-off sheet – RGIT_TEMP_016
Appendix 2: Example randomisation form – RGIT_TEMP_017