STANDARD OPERATING PROCEDURE FOR PREPARING AND MAINTAINING CASE REPORT FORMS (CRFs) FOR USE IN CLINICAL RESEARCH

SOP NUMBER:	**Fife R&D SOP21**
AUTHOR:	**Julie Aitken**
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1. PURPOSE

This document describes the procedure for designing, completing and correcting Case Report Forms (CRFs) in NHS Fife and complies with the principles of Good Clinical Practice (GCP).

It is the responsibility of all researchers using this SOP to ensure they are using the latest version of it. The latest version is available via the R&D pages on the NHS Fife Intranet (www.nhsfife.org/research). For guidance, contact the R&D Department via fife-uhb.randd@nhs.net.

2. APPLICABILITY

This document applies to clinical research studies sponsored or co-sponsored by NHS Fife.

This SOP is intended for use by researchers, study co-ordinators, research nurses and any other NHS Fife staff who design CRFs and complete CRFs for NHS Fife Sponsored studies. Responsibility for the compilation of CRFs may be transferred to individuals outside NHS Fife but this must be done using a formal appropriate clinical study contract.

3. POLICY

3.1 A CRF is defined in ICH CGP as 'a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject'.

3.2 The use of a CRF is mandatory for a Clinical Trial of an Investigational Medicinal Product (CTIMP) and is highly recommended for all other studies.

3.3 The CRF can be produced and designed by the study team or this may be outsourced to an external third party.

3.4 The CRF must be designed to collect only the information required to meet the aims of the study and to ensure the eligibility and safety of the participant.

3.5 All CRFs must be completed in accordance with current GCP Guidelines.

4. PROCEDURE

4.1 General

4.1.1 Any changes to the CRF template made during a study must be documented. The CRF must be version controlled (see R&D WI37 on Version Control) and all versions of the CRF must be retained within the Study Master File (SMF), and Investigator Site File (ISF) for multicentre studies.

4.1.2 Each page of a paper CRF must be numbered and include the version number and date.

4.1.3 Each CRF page must include the Study Reference Number and Protocol Title (or acronym).

4.1.4 CRFs must not record personal identifiable information. A unique ID must be allocated for each participant and recorded in the CRF. If approved by the Chief Investigator (CI), the CRF may record other identifiers on each page, such as site (for multicentre studies), participant initials, dates of birth or visit numbers, in accordance with GDPR.

4.1.5 There must be clear evidence that the CI and/or a statistician have approved the CRF template prior to use.

4.1.6 Paper CRFs must be stored in a secure location and available for monitoring purposes whilst the study is active.

4.1.7 Where possible electronic CRFs (eCRFs)/Electronic Data Capture (EDC) must utilise upper and lower limits for variables to minimise the risk of data entry error.

4.1.8 eCRFs must be retained on a secure server with limited access as per the sponsorship risk assessment. Read-only access to eCRFs must be available to the monitors/auditors. This can be organised by completion of a System Access Form available from eHealth and found in the Business Systems section in Quick Links on the NHS Fife Intranet.

4.1.9 CRF completion must be a delegated task from the CI or Site Principal Investigator (PI) and documented in the Delegation of Duties & Signature Log (Doc Ref 13-01).

4.2 Design of the CRF

4.2.1 CRF design depends on the type of data being collected. Generally, the following guidelines must be adhered to:

- The CRF must be consistent with the protocol.
- CRF pages must be arranged in order of participant visits.
- The arrangement of the data fields must be clear, logical and user friendly. It must not be open to misinterpretation.
- There must be no unnecessary duplication.
- Consideration must be given to layout of paper CRFs in relation to database/eCRF data entry.
- Space for free text is discouraged unless this is a specific requirement of the

protocol.

- Where possible, tick box options must be provided rather than the opportunity for free text. Tick box options must be exhaustive e.g. with an option for 'Other' or 'N/A' (Not Applicable) if appropriate. Where 'Other' is an option, the CRF must provide a data field to collect more specific information.
- For variables where the actual value is captured, the number of boxes provided must be adequate and, if appropriate, reflect the number of decimal places.
- The unit of measurement must be specified.Laboratory values must be entered without conversion from printed reports. If conversions are necessary e.g. in multicentre studies where units of measurement differ, space must be made available on the CRF for the original figure, the conversion factor (this may be pre-printed) and the converted result.

4.3 CRF Pages and Data to be Recorded

4.3.1 The data to be collected on the CRF will document participant eligibility, treatment, outcomes and endpoints as defined in the protocol. These data must include the following:

- Inclusion/exclusion page where the investigator can sign to confirm that the participant is eligible to participate in the study. The Inclusion/Exclusion criterion must be clear and unambiguous.
- Reason if ineligible
- Date of Informed Consent
- Adverse events
- Serious Adverse Events
- Withdrawal/completed study form, including space for CI or PI signature to verify that all data are complete and accurate

4.3.2 If any of the CRF will be used as source data, e.g. participant questionnaires this must be determined and documented, in the SMF or ISF as appropriate, prior to the start of the study,. 'Source Data' is defined as *"all information in original records (and certified copies of original records) of clinical findings, observations or other activity in a clinical trial essential for the reconstruction and evaluation of the trial. Source data are contained in source documents". Examples of source data include:*

- Signed informed consent forms
- Hospital records
- Clinical charts
- Laboratory reports

Where a CRF is considered a source document (e.g. for electronic questionnaire-based studies) mechanisms must be built in to ensure that checks are in place to minimise the chances of error when completing the questionnaire.

4.3.3 The CRF can also include:

- Participant Initials, date of birth, participant demographics (e.g. age, gender, and ethnicity) and participant identifiable data such as name, address, postcode, CHI-number (but only where this has been approved by a REC and/or Caldicott Guardian)
- Relevant medical history
- Results of physical exam

- Baseline data as per protocol
- Primary and secondary endpoints
- Randomisation/registration form
- Dosing and compliance
- Concomitant medications
- A glossary of abbreviations
- End of Treatment form (end result of study)
  - Death
  - Relapse / recurrence
  - Follow-ups

4.4 CRF Sign-off

4.4.1 The CRF design (master copy) must be reviewed and signed off by the CI and study statistician (if applicable) before use in the study.

4.4.2 The CI is responsible for ensuring that there are enough CRFs at all participating sites.

4.5 CRF Completion

4.5.1 CRFs must be completed according to the specifications of each study and only by those authorised to do so in the Delegation of Responsibility and Signature Log (Doc Ref 13-01).

4.5.2 The CRF must be completed as soon as possible after each participant assessment.

4.5.3 Permanent blue or black ink must be used, with enough pressure to ensure any copies are clear.

4.5.4 If CRFs are printed on carbonless duplication paper, a suitable separator must be inserted under the page being completed.

4.5.5 All data fields must be completed. Any missing data must be explained e.g. '*unknown', 'missing', 'test not done'* and not left blank.

4.5.6 All entries must be accurate, legible and verifiable with the source data (e.g. the medical record).

4.5.7 For laboratory values outside the laboratory's reference range or some other range pre-identified in the study protocol, or if a value shows significant variation from one assessment to the next, the significance (if any) must be noted along with a record of action taken, e.g. a letter was sent to the participant's GP. A copy of the letter must be kept in the participant's medical records or study records, as appropriate.

4.6 Training in CRF Completion

4.6.1 Clear instructions or training must be given to all relevant staff on how to complete the CRF so as to ensure that data are collected in a standardised fashion.

4.6.2 CRF training must be documented by a training log and/or meeting minutes.

4.6.3 Where appropriate, a CRF completion guide can be developed for use in a multicentre study.

4.7 Verifying Against Source Data

4.7.1 CRFs must always match with source data; discrepancies must be clearly noted and the reason explained.

4.7.2 Data with personal identifiers stored with the CRF e.g. copies of ECGs, Laboratory Reports, must be clearly identified with the following information:

- R&D Ref number
- Participant ID
- Visit Number

4.8 Corrections

4.8.1 Paper CRFs:

- Incorrect entries in paper CRFs and Source Data must be crossed out with a single line so that the incorrect entry is still legible.
- The correct data must be entered.
- The correction must then be initialled and dated.
- An explanation of the reason for the correction must be documented if it is not obvious why the change was made.
- Correction fluid must not be used.

4.8.2 Electronic CRFs:

Corrections must be subject to an audit trail to enable the following to be tracked:

- Which data point has been amended
- Who entered the original data
- When the original data was entered
- Who changed the data
- What data was changed
- When the data was changed
- Why the data was changed

4.9 Storing and Accessing CRFs

4.9.1 Completed CRFs must be stored when not in use in a locked secure storage area.

4.9.2 Access to CRFs must be restricted to the investigators, monitors, study staff, relevant NHS Fife staff, and regulatory authorities (see R&D SOP35 for more information on archiving).

5. ASSOCIATED DOCUMENTS

Doc Ref 13-01 - Delegation of Responsibilities & Signature Log
R&D SOP35 - Archiving Clinical Research Data
R&D WI37 - Version Control of Clinical Research Study Documentation

6. ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Forms
CTIMP	Clinical Trial of Investigational Medicinal Product
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
ISF	Investigator Site File
PI	Principal Investigator
R&D	Research and Development
SMF	Study Master File
SOP	Standard Operating

7. REFERENCES

World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.
(https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/)

Medicines for Human Use (Clinical Trials) Regulations 2004.
(http://www.legislation.gov.uk/uksi/2004/1031/contents/made)
It is assumed that by referencing the principal regulations, all subsequent amendments made to the principal regulations are included in this citation.

8. DOCUMENT HISTORY

Version Number	Edited by (job title)	Effective Date	Details of Revisions Made
1	Julie Aitken R&D Trials Facilitator	02/02/2015	Adapted from TASC SOP19, version 6, effective date 01/09/2014)
2	Julie Aitken R&D Trials Facilitator	26/02/2019	Reformatted in line with current SOP template, and to reflect current practice, including the use of eCRFs.

9. APPROVAL

APPROVED BY	Date
Professor Alex Baldacchino, Research & Development Director, NHS Fife Signature: 	26/02/2019