Humber Health Partnership

CRF SOP

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This page details the version history and the main changes made for each new version.

Version Log		
Version number and date	**Author**	**Details of significant changes**
Version 1, 16.10.12	J H Pacynko J Illingworth	First SOP approved by R&D Committee on 15.10.12
Version 2, 01.02.18	S Moffat J H Pacynko	Removal of what the CRF should record, replaced by instructions for investigators to use the current CRF template/guide. Addition of the following wording to Section 5: Any information that would routinely be expected to appear in a patient's casenotes should continue do so during the study to ensure the care of the patient is maintained. The casenotes should provide sufficient information to allow the investigator to enrol the patient in the trial in compliance with the protocol. Source documents should be: ➢ Accurate ➢ Legible ➢ Contemporaneous ➢ Original ➢ Attributable ➢ Enduring ➢ Available and accessible. Sponsor assessment of eCRF/database prior to greenlight.
Version 3, 18.02.21	S Moffat	3 yearly review carried out and the following changes made: Numbering of sections updated. Section 4, point 4.2 Addition of "All third party providers will be subject to a Sponsor vendor assessment in order to assess suitability prior to the signing of contracts. A fully signed contract with the vendor must in place prior to Sponsor Greenlight. Refer to R&D GCP SOP 19 – Vendor Selection, Assessment, Contracting and Oversight SOP."
Version 4, 12.06.2024	G Constable	Replaced reference to R&D with RDI. Section 6, 'Electronic CRFs' added in line with current practice and guidance.
Version 5, Draft		Structural and formatting updates to improve readability and consistency

		Clarification of responsibilities for investigators, research staff, and R&D personnel Updated terminology to reflect ICH E6(R3) concepts (e.g., critical-to-quality factors, proportionate processes, data governance expectations) Strengthened requirements for electronic systems, metadata, audit trails, and validation Updated archiving and retention wording to reflect current regulatory requirements Minor editorial corrections and alignment with current Trust templates

Please note for definitions of acronyms refer to Appendix 1 of Management of SOPs. Refer to Appendix 2 of Management of SOPs for the standards to which clinical trials that investigate the safety and/or efficacy of a medicinal product are conducted.

All the HHP RDI GCP SOPs are available at:
https://www.hey.nhs.uk/research/researchers/gcp-sops-for-hey-sponsored-ctimps/

1 Purpose

1.1 CRF is an acronym for Case Report Form which is a pharmaceutical term referring to study subject data collection forms. There is usually one CRF per subject.

1.2 The CRF is used to gather and submit study data and must reflect the investigations described in the study protocol.

1.3 CRFs act like a checklist to ensure that the information collected from subjects' study visits is complete and standardized and adheres to the protocol. In effect the CRF is the 'working' protocol.

1.4 CRFs are part of the essential documents which make up the Trial Master File (ICH GCP 8.3.14). The TMF must at all times contain the essential documents relating to the clinical trial (UK CT reg 31A (3)).

1.5 This SOP covers the content, design and format of CRFs and the importance of documenting study visits in the casenotes and source data verification.

2 Who should use this SOP

2.1 This SOP should be used by:

- All research staff involved with HHP-sponsored CTIMPs – Chief/Principal Investigator, co-investigators, research nurses, clinical trial assistants, project managers, clinical trial co-ordinators, data managers, administrators etc.
- Clinical trials pharmacy staff – technicians and pharmacists.
- All HHP R&D staff who manage the sponsorship of HHP-sponsored CTIMPs.
- Research staff involved with HHP-sponsored non-CTIMPs may find this SOP a useful guide, although the SOP will need to be adapted for the non-CTIMP trial.
- Research staff involved with clinical trials sponsored by an external organisation where the sponsor has no SOP for the CRF. HHP R&D SOPs are defaulted to in this case.

3 CRF content, design and format

3.1 The CRF must be designed by the Chief/Principal Investigator or delegated person as soon as the protocol has been finalised. The CRF must reflect exactly the inclusion and exclusion criteria, the investigations and the schedule of investigations described in the protocol.

3.1.1 CRF design must incorporate a risk-proportionate approach. The Chief/Principal Investigator must ensure that the CRF captures data that are critical-to-quality (CtQ) for participant safety, rights, and the reliability of trial results. Non-essential data collection should be avoided to minimise burden and reduce avoidable complexity

3.2 Investigators should use the CRF template/guide produced by RDI. This is available from the R&D Monitor or QA Manager. There are clear instructions at the beginning of the template to help in the design of a CRF.

3.3 The template will need to be modified for each study to reflect the protocol. CRFs must not include data fields that are not required by the protocol or critical to trial quality. Unnecessary data collection should be avoided.

3.4 The current template is available as Working Instruction 04 on the Y drive in Y:\Research\GCP SOPs & forms\Working instructions.

3.5 CRFs for HHP -sponsored trials are frequently in paper format. If CRFs are to be in electronic format, investigators must ensure that there will be an audit trail in place to record any changes made to the data so that there is a clear record of who made the change, when, what the new value is and what the old value was. Electronic CRFs must retain all relevant metadata, including timestamps, user identification, and system-generated audit trails, in accordance with ICH GCP and data governance expectations. The eCRF will also need to be validated prior to use. Electronic CRF systems must comply with ICH GCP requirements for computerised systems, including user access controls, system security, backup and recovery processes, and documented procedures for system failure and technical support. The EMA eCRF reflection paper on expectations for electronic source documents used in clinical trials should be adhered to which is available on the EMA website: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004385.pdf. Guidance from the MHRA can be found here (although it is recommended to review MHRA for further updates to this guidance): https://www.gov.uk/government/publications/oversight-and-monitoring-of-investigational-medical-product-trials/oversight-and-monitoring-activities

3.6 It has encouraged that CRFs avoid 'tick' boxes as a data collection and instead opt for boxes that require specific values. This includes the eligibility criteria checklist; by requiring values to be added to these boxes on the CRF it functions as an additional check from the study team member recruiting this participant.

4 CRF review, confidentiality and security

4.1 As part of quality assurance checks prior to Sponsor Greenlight, the QA Manager or R&D monitor will review the CRF and send any comments back to the investigator. This prevents modifications to the CRF after the study has started.

4.2 Any eCRF/database being used from a third party vendor should be assessed for suitability by the Sponsor prior to any commitment to use it. All third party providers will be subject to a Sponsor vendor assessment in order to assess suitability prior to the signing of contracts. A fully signed contract with the vendor must in place prior to Sponsor Greenlight. Vendor assessments must confirm that the electronic system meets ICH GCP expectations for validation, security, user management, audit trails, and data integrity controls. Refer to R&D GCP SOP 19 – Vendor Selection, Assessment, Contracting and Oversight SOP.

4.3 When creating the CRF it is important to respect patient confidentiality by keeping the CRF anonymous and only referring to patient's initials and study number on each form.

4.4 The only place in the Investigator Site File that there should be patient identifiable data is on the signed informed consent forms and on the Patient Identification List (ICH GCP 8.3.21), and in the Pharmacy Site File on prescription forms.

4.5 Once the CRF has been created, the database/spreadsheet should be designed to store the information collected in the CRFs. The database must support the full data life cycle,

including data capture, review, correction, transfer, finalisation, retention, and destruction, with all steps traceable through metadata and audit trails. For details on the database/spreadsheet requirements, data entry, data validation, data protection, database lock etc refer to the R&D GCP SOP 13 - Data Management SOP.

4.6 CRFs must be stored during the study in a secure but accessible location. An ideal location is a lockable filing cabinet or cupboard in an office kept locked when not in use.

4.7 CRFs must be archived with the Investigator Site File for the period required by applicable regulatory requirements (e.g., typically a minimum of 25 years for UK CTIMPs), or longer if specified in the protocol or sponsor procedures.

4.8 If the study is multi-centre, Principal Investigators should keep original or certified copies of CRFs in the Investigator Site File (or with the file) for the duration of the study and archiving.

4.9 Investigators must have timely access to the data generated at their site to support ongoing participant care, safety review, and oversight responsibilities.

5 Documenting study visits in casenotes and source data verification

5.1 A study participant may see a variety of clinicians, GPs and other health care professionals over the course of the study. It is important that the data from a patient study visit is written clearly into casenotes so that other clinicians and health care professionals are informed of any relevant results or information that may affect the patient's ongoing medical care.

5.2 Any information that would routinely be expected to appear in a patient's casenotes should continue to do so during the study to ensure the care of the patient is maintained.

5.3 The casenotes should provide sufficient information to allow the investigator to enroll the patient in the trial in compliance with the protocol.

5.4 The minimum information required in casenotes is:

- Clearly written date, brief study title and visit number to confirm the subject is in the study.
- Date patient given patient information sheet
- Version number of Patient Information Sheet
- Date of consent
- Version number of Informed Consent Form
- Date of screening
- Medical history, concomitant diseases and medication including study medication, and
- any changes in concomitant diseases and medication at subsequent visits.
- Anything which is relevant to the ongoing care of the subject;
    a. Relevant results and study medic's assessment of these results.
    b. Brief description of any AEs with start & stop times/dates and any significant test results or a medical summary of events if more appropriate.
- Any other relevant details.

5.5 At the site initiation visit, the study monitor may prepare a study casenotes sheet with the investigator to make it easier and quicker for investigators to complete the required and relevant information in the casenotes.

5.6 It is usual practice for study data to be recorded in the patients' casenotes before transferring the data to the CRF. Patients' casenotes are referred to as source documents and include X-rays, MRI scans, ECG printouts, lab reports, coroner's reports etc. Source is the original entry.

5.7 The purpose of source documents in clinical research is to document the existence of the subject and substantiate the integrity of the trial data collected (ICH GCP 8.3.13).

- Source documents should be:
- Accurate
- Legible
- Contemporaneous
- Original
- Attributable
- Enduring
- Available and accessible.

5.8 During a monitoring visit, the RDI monitor will check the CRF against the source data in patients' casenotes. This is known as source data verification (SDV). Source data verification will be conducted using a risk-proportionate approach, focusing on data that are critical-to-quality and essential for participant safety and trial reliability.

6 Electronic CRFs (eCRFs)

6.1 The use of eCRFs have gained popularity within clinical trials as they allow direct remote entry into the clinical database and the trial has an EDC trail.

6.2 The processes and mechanisms of data input, data clarification and data flow have changed with advancing computer system technology.

6.3 The eCRF is a computer system and therefore should be validated whether it is a trial-specific build using a commercial 'off-the-shelf' system or a bespoke system for the trial requiring full computer system validation. The CRF design is part of the specification process for the system build. The validation process highlighted in *R&D GCP SOP 19 Vendor assessment and WI 24 CSV review checklist* should be followed. The validation of this system should include the encryption of data transmission to protect against unauthorized access and perform a User Acceptance Test to ensure the eCRF meets all functional requirements.

6.4 The use of these computer systems should accommodate unique, individual logins with password protection. A user log should be available showing all individual login credentials and show an audit trail for changes to user rights throughout a study (this should be reviewed as part of monitoring visits). The eCRF may require electronic or digital signatures for sign-offs where applicable therefore the login credentials should be secure and not shared between study teams (this should be scrutinised in the CSV, see *6.3*). The assessment of user-logins should be made in the monitoring visits where applicable.

6.5 The eCRF should incorporate role-based access to particular areas. This can be useful, for example, to confirm the eligibility of a trial subject, where only users registered as medically

qualified doctors would have access. A user access list should be reviewed at monitoring visits and should have its own dedicated audit trail to show changes to user access throughout the study. No user should have access to change their own access level unless this access is specifically granted to 'super-users' who control the data management system. These 'super-users' should not perform any data input.

6.6 It is crucial that a thorough and comprehensive audit trail is activated at the set up phase of the trial and is activated-throughout the study. Using the audit trail it should be possible to reconstruct each study visit. This includes showing any corrections to the data captured at the trial visits.The design of the electronic system should ideally include a prompt for any corrections being made to give a justification as to why this correction is being made, when and who is making the change.

6.7 Consideration should be given to the archiving of eCRFs when the study has concluded. This could include a download of an independent certified copy of the data onto the investigators computer or other electronic storage device (CD or memory stick, for example). For transcribed data, the investigator must have the source data at site and be able to compare the provided data with the source to confirm its accuracy. Refer to R&D GCP SOP 13 - Data Management SOP where applicable.

6.8 It is critical that back-up plans are in place for if the electronic system is not available with paper equivalents available. This process should be validated prior to use and discussed with the site during SIV.

7 Implementation

7.1 Implementation of this SOP will conform to the process outlined in R&D SOP 01 Management of SOPs.