Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Research Department

STANDARD OPERATING PROCEDURE

Research Department

Set up and Use of Case Report Forms for STH Sponsored studies

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Related SOPs	A108 Recording of research information in patient medical records A126 Sponsor Monitoring of STH Sponsored IMP Studies A127 Archiving of Essential Documents Generated During Clinical Research B131 Monitoring Visit of STH CTIMP studies C101 Document version control C118 Risk Assessment of STH sponsored CTIMPs		

Approved by (name & role)	Dipak Patel	**Date**	27 July 2017
Signature:	D Patel		

Standard Operating Procedure: Set up and Use of Case Report Forms for STH Sponsored studies

This SOP has been produced in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, Medicines for Human Use (Clinical Trials) Amendment Regulations 2006, ICH GCP and Research Governance Framework 2005. This SOP outlines the procedure for developing, finalising and using a study specific case report form (CRF) for studies where STH is the Sponsor.

Index

Background

GCP guidelines define the Case Report form (CRF) 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."

Under usual circumstances for STH Sponsored studies the CRF will be a paper record.

The purpose of the CRF is to fully document the conduct of the study at the participant visit level, to collect the data to answer the hypothesis formulated in the study protocol and to provide the safety data relating to the IMP. The CRF must also contain adequate data to allow for the reconstruction of the trial.

The CRF must be designed to ensure the precise collection of these data to allow for onward collation, analysis and reporting. Any discrepancy between the data required by the protocol and data collected will undermine confidence in the findings of the study.

As such the CRF must be clear, unambiguous and contain comprehensive instructions for completion.

It is the study sponsor's responsibility to ensure that an appropriate case report form is in place for the study which adequately performs the above functions. In practice this responsibility is often delegated to the study Chief Investigator (CI).

Whilst completion of CRF pages may be delegated by the Principal Investigator (PI) to appropriately trained member of the study team, it remains the responsibility of the PI to ensure the timely and accurate completion of CRF pages for each participant enrolled onto a study.

The CRF will standardise the collection of protocol defined study data including information about the

- study participant, including study eligibility, medical history and baseline data, including any stratification factors
- study intervention, including but not limited to randomisation details and the administration of IMP
- detail of the conduct and results of assessments / tests required to collect data on the study outcomes

- adverse event and concomitant medication recording where appropriate

The CRF collects the data which will be inputted into the study database which will be used for the statistical analysis of the project and then collated into the final study report and subsequent publications.

The contents of the CRF are the property of the study sponsor.

Where the CI team receiving the data and the PI team caring for the participant are not the same entity or where the CRF will otherwise be transferred to another entity, if consent to transfer of personal identifiable data (PID) is not explicit in the study participant information sheet and consent form, the CRF must not contain any PID.

Where it is the case that the CI team and the PI team caring for the participant are the same entity or the participant has explicitly consented to the transfer of their PID to another entity it is still good practice to store PID separately from the completed CRFs for each participant.

Study participants are identified on CRF pages by means of a study ID. Study ID is linked with personal identifiable data via the study enrolment log held in the Investigator Site File.

The CRF is completed by the investigator or other member of the research team as delegated in the study delegation log (eg research nurse or data manager) in a timely manner after each subject visit. Data entered into the CRF must be verifiable against data contained in source documentation except where the CRF directly collects source data. Where a CRF is designed to directly collect source data this should be explicitly confirmed in the study protocol and or study management arrangements; arrangements must be made for clinically relevant study data to be recorded in the medical records in timely fashion to facilitate participant care.

Direct access to the CRF must be made available to sponsor monitors and auditors or regulatory authorities for examination during monitoring, audit and regulatory inspection. The same people will also need access to the documentation containing the source data from the trial for verification of the data entered into the CRF.

The completed CRFs must be stored safely and securely on site during the trial. Following the end of the trial the CRFs must be archived with other Essential Documents for the trial according to sponsor and local SOPs. Adequate fire precautions must be operational in the building.

The completed CRFs must be archived with the Trial Master File at the end of the study in accordance with STH Research Department SOP A127.

Acronyms

CRF	Case report Form
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
PID	Personal Identifiable Data

Standard CRF abbreviations

ND	Not done
NA	Not applicable
NK	Not known
NAD	No abnormality detected
NCS	Not clinically significant

Definitions

CTRU/CRO	A Clinical Trials Research Unit / Contract Research Organisation contracted to manage a trial on behalf of the trial sponsor
Case Report form	A paper document or electronic system designed to record/input all of the protocol required information to be reported for each trial subject.
Source documentation	Original records or certified copies that contain clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. At STH this is usually the participant's medical record or for healthy volunteers, a file of raw data. Occasionally it may be appropriate to record source data directly into the CRF, with arrangements made for clinically relevant study data to be recorded in the participant medical record. However the CI/sponsor would need to design the CRF with this purpose in mind
Baseline Data	Always includes confirmation of Inclusion / exclusion criteria, usually requiring sign off by an investigator to confirm eligibility. May also include data on demographics, medical history, baseline laboratory data, vital signs, physical examination and ongoing medications
Efficacy Data	Records of data resulting from assessments specific to the primary, secondary and other outcomes as set out in the protocol for the study
Safety Data	Ongoing records of vital signs, physical examinations, laboratory investigations performed for safety reasons and adverse events
Intervention Compliance Data	Records of medication (IMP and NIMP) prescription and/or administration and return (where applicable), concurrent/concomitant medications. Withdrawal or end of study records.

Procedure

A) CRF design for all STH sponsored studies.

Whilst the design of a CRF for a study may be delegated to a member of the study team the ultimate responsibility for ensuring that the CRF collects all the necessary data for the study lies with the Chief Investigator. The CI or delegate designs the CRF for the study according to the following criteria:

1. The CRF must be clear, unambiguous and contain comprehensive instructions for completion.
2. Only data identified in the protocol must be collected in the CRF. It is unethical to collect excessive secondary information which is not specified in the protocol or other study documentation submitted for ethical review.
3. Participants must be identified on CRF pages by means of a study ID. Study ID must be linked with personal identifiable data via the study enrolment log held in the Investigator Site File.
4. The data collected in the CRF will feed the population of the study database. In designing the CRF the investigator should consider whether any necessary coding of data should be done by the study team at the point of completing the case report form from source data or by data managers at the point of transferring CRF data to the study database.
    a. At either time-point the study team member responsible for coding the data will need a comprehensive and explicit guide for how to code the data containing all the pre-defined codes to be used.
5. The order of the CRF should follow the assessment sequence as outlined in the protocol. The inclusion of a table of events in the protocol can be a useful tool for identifying what assessments are needed at each study visit.
6. Each CRF page must be uniquely identifiable to the study, the site (for multi-centred studies), the trial subject and the visit time point. Therefore each page of the CRF must contain:
    a. Identification of trial (This will be the STH reference number. This should be prepopulated in CRF template).
    b. Other study identifiers may include the CI, the study sponsor, the trial acronym, IRAS number. (These should be prepopulated in CRF template).

   c. Site identification (multicentre trials only).
   d. Unique participant identification. There must be a consistent approach between the CRF, the protocol, drug accountability forms, randomisation schedule, consent form and study enrolment log in how participants are referenced (eg all documents might use a three-digit code referred to as an enrolment ID). Where participants are allocated more than one study identifier (eg a screening number and a randomisation number) it must be clear on each document which number is required and the study enrolment log must include both numbers so that a central link between the numbers is maintained.
   e. Visit number (This should be prepopulated in CRF template unless the same template is used for multiple visits).
   f. The date of the assessment/visit (need only be recorded once for each visit except where dates differ, eg scans performed on a different day to the study visit).
   g. CRF page number (in the footer, prepopulated in CRF template unless the same page is used more than once for the same participant).
   h. Version number / date of CRF version (in footer: This should be prepopulated in CRF template).
7. For studies where adverse event data is to be collected the CRF for each visit should include a field to specify whether the participant has suffered any adverse events since the previous visit (i.e. a yes/no box). Collection of this data is generally required for CTIMPs unless explicitly stated in the protocol. The details of adverse events should ideally be collected on a separate adverse events page which details the data for all adverse events occurring for that participant throughout the study. This helps ensure consistency in data recording and avoids problems with discrepancies in the recording of adverse event data between visits. A template adverse events CRF page is available.
8. For studies where changes to concomitant medications are to be collected the CRF for each visit should include a field to specify whether the participant has had any changes to concomitant medications since the previous visit (i.e. a yes/no box). Collection of this data is generally required for CTIMPs unless explicitly stated in the protocol. The details of concomitant medications should ideally be collected on a separate concomitant medications page which details the data for all concomitant medications for that participant throughout the study. This helps ensure consistency in data recording and avoids problems with discrepancies in the recording of concomitant medications data between visits. A template concomitant medications CRF page is available.
9. The CRF must be prescriptive in the data to be entered. For example:
   a. fields must specify how they should be completed to avoid confusion (eg dd/mmm/yyyy).
   b. The CRF must make it clear when numerical data is required by providing boxes in which to record each digit. In doing so it is also possible to prescribe the accuracy to which data needs to be recorded (eg providing boxes for recording data to one or two decimal places).
   c. The CRF must specify the units in which the required data should be recorded (eg mg, mm/hg or °C).
   d. Provision of multiple choice items is a good way of ensuring that the recorded responses can be matched with codes when data is entered into the study database.
   e. Free text fields should only be used when more specific fields are not appropriate since a free text field does not give the completer any guidance as to what type of response is required or the required level of detail.
   f. If free text fields are required, it is good practice to give guidance with regards to the above.
10. The CRF should provide fields for the person entering the data to sign and date to confirm who entered the data and when. It is suggested that there should be a minimum of one signature field for each study visit (required for CTIMPs), more may be appropriate where it is likely that the CRF will be completed by more than one person within each visit
11. The CRF should ideally require the Principal Investigator to sign the completed CRF for each participant once that participant is completed and/or withdrawn so that the PI can confirm that the CRF data is complete and accurate. This sign off is required for CTIMPs since the responsibility for the provision of complete and accurate data in the CRF ultimately lies with the PI.

12. The Chief Investigator must consider whether it is appropriate for any of the study data to be recorded directly onto the CRF. For example it is common for participant completed questionnaires to form part of the CRF.
13. If the CI decides that it is appropriate for any of the study data to be recorded directly onto the CRF then the CI should detail this in the study protocol. When source data is recorded directly onto the CRF it is generally necessary (except with the possible exception of questionnaire responses which have no clinical relevance) to place a copy of the completed CRF in the medical records in order that relevant clinical data is readily available to those treating the participant. In this case since the CRF is the only record of clinically relevant data it is important that such copies of completed CRFs are inserted into the medical record in a timely fashion. The original CRF must be retained by the investigator team for use in data entry and for subsequent archiving.
14. The research team may record research source data directly into the medical record or they may develop a proforma on which to collect source data during the study visit prior to transcription of this data to the study CRF. Where such a source data collection worksheet exists as a separate entity to the CRF then the source data worksheet must always be routinely filed in the medical record.

B) CRF review and approval for STH sponsored CTIMPs not managed by a CTRU/CRO

STH generally requires STH sponsored multicentre CTIMPs to be project managed by a CTRU or CRO. Where a CTRU/CRO is responsible for the project management of an STH sponsored CTIMP including the design and approval of the trial CRF then the responsibility for the design and approval of the CRF will be formally delegated to the CTRU/CRO and the CTRU/CRO will follow their own processes and SOPs and this section of this SOP will not apply.

1. Study set up
   1.1. The Chief Investigator (CI) or delegate identifies what data must be collected at each study visit and documents this clearly in the study protocol.
   1.2. The CI or delegate drafts the CRF template following the guidance in section A of this SOP. The CI retains ultimate responsibility for ensuring that the CRF captures all of the data necessary for the study in a format suitable for subsequent analysis.

   1.3. The CI or delegate submits the CRF template to the R&D Coordinator, for review.
   1.4. The R&D Coordinator reviews the CRF template against the study protocol and other supporting documents and completes the CRF Assessment Checklist.
   1.5. Where the R&D Coordinator review indicates that major revision is necessary the R&D Coordinator returns the CRF Assessment Checklist to the CI for revision of the CRF.
   1.6. The CI or delegate submits the revised CRF template to the R&D Coordinator for further review.
   1.7. Where the R&D Coordinator has assessed that the CRF template complies with all the items on the CRF Assessment Checklist or the necessary revisions are minor the R&D Coordinator forwards the CRF template and the CRF Assessment Checklist to the R&D Risk Assessment Lead or delegate for review.
   1.8. The R&D Risk Assessment Lead or delegate reviews the CRF template in conjunction with the protocol, other supporting documents and CRF Assessment Checklist providing feedback to the CI or delegate where necessary.
   1.9. R&D Risk Assessment Lead or delegate informs the CI or delegate and the R&D Coordinator when the CRF is satisfactory (ie has passed Sponsor review).

   1.10. The Risk Assessment Lead verifies that the Study Management Arrangements form and/or protocol specifies where source data for the study will be recorded. Arrangements for the recording of source data and, where relevant the transfer of source data to the medical record, will be verified at the Site Initiation Visit.
      1.10.1. The STH research team may choose to develop a proforma on which to collect source data during the study visit prior to transcription of this data to the study CRF. Where such a source data collection worksheet exists as a separate entity to the CRF then the source data worksheet template does not need to be reviewed

by the STH Research Department or recorded on the Version Control Tracking Sheet since it does not constitute a CRF.

1.11. The R&D Coordinator includes the approved version of the CRF in the sponsor Version Control Tracking Sheet. Sponsor approval for the CRF template is confirmed when the R&D Coordinator issues the Version Control Tracking Sheet listing the CRF template version as an attachment to the Confirmation of Capability and Capacity / Sponsor Green Light email to open the study.

1.12. The R&D co-ordinator uploads the finalised CRF template to Alfresco (section 9.1) and files a paper copy of the CRF in the R&D master file.

1.13. The CI or delegate files a copy of the finalised CRF template in the TMF and ISF and ensures the finalised version of the CRF is available for completion by the study team.

2. Amendments to the CRF after study set up.

2.1. The CI identifies the need for amendments to the CRF. These may be in relation to a protocol amendment or may be an amendment to the CRF alone to correct inconsistencies either within the CRF of between the CRF and the protocol.

2.1.1. Where a protocol amendment is necessary the CI must consider whether this will necessitate changes to the CRF.

2.1.1.1. The CI or delegate submits the proposed revision to the R&D Coordinator for review and approval prior to use.

2.2. The R&D Coordinator reviews the proposed revision in conjunction with any related protocol amendment in line with procedures for assessment of amendments described in SOP C118, referring the review to the Risk Assessment Lead or delegate where necessary.

2.3. The R&D Coordinator includes the approved version of the CRF in the sponsor Version Control Tracking Sheet. Sponsor approval for the updated CRF template is confirmed when the R&D Coordinator issues the Version Control Tracking Sheet listing the CRF template version as an attachment to the Confirmation of Continued Capability and Capacity / Sponsor Green Light email for the amendment.

2.4. The R&D co-ordinator uploads the approved updated CRF template to Alfresco and files a paper copy of the CRF in the R&D master file.

2.5. The CI or delegate files a copy of the updated approved CRF template in the TMF and ISF and ensures that the new version of the CRF is available for completion by the study team and that the study team is notified and trained as appropriate.

3. Monitoring and audit

3.1. The PI is responsible for ensuring that each CRF is completed accurately and in a timely manner on an ongoing basis throughout the course of the study.

3.2. Completion of the CRF for an STH sponsored IMP study will be monitored in line with STH Research Department SOPs A126 and B131. The designated monitor (usually the STH Research Department R&D Co-ordinator) identifies which participants are to be reviewed at the visit and informs the PI or delegate, providing details of what is to be reviewed (ie source data files, medical records, CRFs).

3.3. The PI or delegate obtains those documents requested and makes these available for the agreed monitoring/audit visit.

3.4. The monitor reviews the completed CRFs following appropriate sponsor monitoring templates in order to verify that:

3.4.1. The protocol is being followed.

3.4.2. The CRF pages are being completed in a timely fashion by appropriately delegated study staff and according to best practice.

3.4.3. The CRF data is internally consistent and credible.

3.4.4. The CRF contains accurate data when verified against source documentation. *NB in the case of trials which are not project managed by an external CTRU/CRO the task of ensuring the accuracy of both data recorded in the study CRF and in the study database against source data is largely delegated to the CI team. The delegation of this responsibility will be agreed in the Study Management Arrangements form which will be signed by the CI before the study opens.

4. Study closure
   4.1. The PI or delegate undertakes a final review of each CRF for accuracy and signs off as complete on as each participant completes their involvement.
   4.2. The CI or delegate uses the data inputted from the CRF to the study database to perform pre-agreed analysis of study results as set out in the protocol and any associated statistical analysis plan.
   4.3. The CI or delegate ensures that the TMF and CRFs are securely stored both during and after the trial and are archived for the appropriate period in accordance with SOP A127.

C) Procedure: CRF completion – all STH sponsored studies

1. The STH Principal Investigator is ultimately responsible for the completeness and accuracy of all participant data recorded in the CRF. The PI may delegate the task of CRF completion to suitability qualified members of the study team, recording this delegation in the study delegation log. Only study staff who have the appropriate delegation documented in the study delegation log and who have completed any necessary CRF training should undertake the task of CRF completion.

2. The PI or delegate ensures they are using the current version of the CRF template for the study. For STH sponsored CTIMPs the version of the CRF in use must be approved by the study sponsor (STH Research Department) or the delegated CTRU.

3. The PI or delegate completes the CRF according to the following criteria:
   a. Always refer to the study protocol and other study documents (eg management arrangements form, study specific SOPs) before completing forms. The protocol will specify the data to be recorded in the CRF at each visit.
   b. The protocol or other study document will specify whether the CRF is intended to be used as a data collection tool during the visit, whereby source data is recorded directly in the CRF or whether the source data is to be recorded directly in the medical record, with the CRF completed subsequently by drawing study data from the source documents. It is essential that the study team member(s) conducting the visit and completing the CRF understand where the source data for the study is to be recorded. See also section D below regarding recording of clinically relevant information in the medical records.
   c. Entries must be written clearly in black ballpoint pen.
   d. Write clearly ensuring that the entries are legible to others.
   e. Ensure that the 'header' information on each page is completed consistently.
   f. Always populate every field on each CRF page (unless indicated otherwise). Use standard abbreviations to account for missing data. Standard abbreviations are given in the Standard CRF abbreviations section above.
   g. Other than standard abbreviations avoid abbreviations and acronyms, unless they are standard medical abbreviations which are known to be acceptable or are listed as acceptable in the relevant study documents.
   h. Completely fill in each box using leading '0's if needed.
   i. Record complete dates, making it clear where data is not available (i.e. if you know the month and year, but not the day, record- NK/04/05).
   j. Record data in the format required by the CRF (for example for dates the required format may be 11/04/14; 11 APR 14; or 11 APR 2014 or another format).
   k. Use the correct units as specified in the CRF and/or protocol / study manual
   l. Ensure adverse events and medications for these are recorded completely, accurately and consistently across the study visit pages, AE pages, study medication pages and concomitant medication pages.
   m. To amend incorrect data on a CRF page,
      i. score through the error with a single line,
      ii. do not obscure the original entry,
      iii. do not use correction fluid,
      iv. write the correct data nearby,
      v. initial and date each amendment.

n. Ensure that all CRF pages are signed and dated where indicated by the person completing the form.

4. Where an eCRF is in use log-ins must not be shared by members of the study team. Each member of the study team requiring eCRF access must complete any relevant training in order to be issued with their own individual log-in. It is good practice that more than one person is trained in access and navigation of the software, to cover unexpected and planned absences.

5. The Principal Investigator is responsible for the accuracy of the data reported in the CRF. Where the CRF requires it, the PI must sign and date the CRF to certify accuracy, completeness and legibility of the data reported in the CRF.

D) CRF storage and access – all STH sponsored studies

1. The PI is responsible for ensuring the security and accessibility of all the study essential documents including the completed CRFs. The PI also has a duty to ensure that clinically relevant data generated during research is made available to others caring for the participant in the medical record. The PI or delegate exercises these responsibilities in the following way:

2. Where the CRF collects source data the completed CRF forms both an essential document which must be archived with the site file at the end of the trial and also clinical data which is relevant to the participant's clinical care. As such it is essential that following the participant visit during which the source data has been entered directly into the CRF, CRF pages containing clinically relevant participant data are photocopied and copies inserted into the medical record to enable all concerned with participant care to have access to clinically relevant data. Where this is impractical then an entry may be made into the participant medical record to record clinically relevant data from the visit with this entry being clearly marked as retrospective so that it is clear that the entry in the CRF is source and the entry in the medical record is secondary.

3. Where the CRF does not collect source data CRF entries must be completed in a timely fashion following the study visit. This would usually be within one week of the study. The PI or delegate must ensure that CRF data entries are consistent with the source data and that each data entry in the CRF is verifiable in source documents.

4. The CRF must be stored safely and securely on site during the trial in a locked, secure area when not in use where confidentiality can be maintained. Adequate fire and flooding precautions must be operational in the building.

5. Ideally the research data collected in the CRF should be stored separately to other documents which may identify the participant. The identity of the participants must be retained in the signed consent forms and the study enrolment log. However contact details for the participants should be removed from the Essential Documents prior to archiving and filed in the participant medical notes..

6. Where the CRF is sent off-site for data entry or other purposes a copy of the completed CRF must always be retained at site.

7. Sponsor auditors or regulatory authorities must be given access to the CRF when such access is requested by prior request.

8. At the end of the trial the completed CRFs must be archived with the site file according to STH Research Department SOP A127.

Appendix 3 Documents Associated with the SOP

	Document	S-drive	Website	Author/owner
1	STH Adverse Event CRF page	S:\General\Research Governance\Pharmacovigilance\Adverse events	No	AL
2	STH Concomitant Medications CRF page	S:\General\Research Governance\Generic Case Report Form\Data Collection Tool\original generic forms	No	AL
3	STH Guidelines and Template for Single Centre Internal Management and Monitoring of CTIMPs	S:\General\Research Governance\Monitoring documents\STH sponsored CTIMPS\Risk assessment	No	EW
4	STH sponsored CTIMP CRF pages checklist	S:\General\Research Governance\Monitoring documents\STH sponsored CTIMPS\Risk assessment	No	EW
5				
6				
7				
8				

Appendix 4 SOP revisions and history

SOP number & version	Effective date	Reason for change	Author
THIS SOP			
C128, V1.0	01 Sept 17	Replaces SOP A112 to include guidance for design and completion of case report forms and to align the CRF creation and review process with changed sponsor processes for risk assessment and management of CTIMP studies	EW
PREVIOUS SOPs			
A112	03 Aug 05	Not applicable	AL