York Foundation Trust R&D Unit
Standard Operating Procedure
R&D/S09

Set Up and Management of Research Studies

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the R&D Unit's website and/or Q-Pulse for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.

The definitive versions of all R&D Unit SOPs appear online. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the R&D Unit website: www.northyorksresearch.nhs.uk/sops.html and/or Q-Pulse

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	Date:	18th July 2017
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	Signature:	Signed copy held by R&D Unit
	Date:	18th July 2017

This SOP will normally be reviewed every 3 years unless changes to the legislation require otherwise

Version History Log

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of significant changes
1.0	12th July 2007	
2.0	21st October 2009	Version History log added. Front page box updated. SOP renumbered and renamed. Coverage extended – SOP no longer exclusively aimed at Alliance Trust sponsored CTIMPs; may now be used in externally sponsored CTIMPs where appropriate
3.0	14th November 2011	Broadened applicability to research studies of all types. Addition of Source Data Location List, File Note Template, File Note Log and Screening/Enrolment Log. Minor typographical changes and cross referencing of SOPs. Addition of University of York to Section 2; minor related modifications.
4.0	18th August 2017	Removal of references to the North and East Yorkshire R&D Alliance. Change of author.

Contents

1 Introduction, Background and Purpose

This SOP establishes a procedure for setting up and managing research studies. In relation to studies of all kinds it supports compliance with the Research Governance Framework for Health and Social Care; in relation to clinical trials of investigational medicinal products (CTIMPs) it supports compliance with the UK Clinical Trial Regulations.

In general, the practices required for high quality conduct of research are similar, whatever type of study is involved. Where particular actions are required for some studies only, such as CTIMPs, this is stated in the SOP.

To avoid complexity, the terminology of 'Trial Master File' / 'Investigator Site File' is used throughout, rather than 'Study Master File' for studies that are not trials.

2 Who Should Use This SOP

This SOP should be used by all staff involved in research studies sponsored, co-sponsored or hosted by the Trust

Separate sections deal with sponsored/co-sponsored and hosted studies.

A separate SOP (R&D/S91) provides detailed guidance for R&D Unit staff involved with setting up Sponsored studies in the Trust.

3 When this SOP Should be Used

This SOP should be followed when setting up, initiating, running or providing services for a research study.

This SOP ends at the point where the Medicines and Healthcare Products Regulatory Agency (MHRA) and / or the Research Ethics Committee (REC) have to be informed that the study has terminated. Study Close-Out and procedure for notifying the regulatory authorities of the end of the study are covered in specific SOPs (see Section 7).

Where an external Sponsor has specific SOPs for the trial, or issues Investigator Site Files in a particular format, the Sponsor's arrangements take priority, provided they enable compliance with the UK Clinical Trial Regulations and / or the Research Governance Framework as applicable. Applicability of SOPs should be established and documented when any study is initiated at the Trust Site.

4 Setting up a Trust sponsored or co-sponsored Study

4.1 Organise the Trial Master File / any Investigator Site Files

The CI is responsible for setting up the Trial Master File (TMF) which contains all the 'essential documents' (in accordance with ICH-GCP) relating to the study. These are documents that are generated before the study commences, during the study and after the study has finished. The CI must

prepare the TMF, with the required contents page and numbered sections with dividers, before initiation of the CI Site.

For a multi-site study each Site must have its own Investigator Site File (ISF), containing copies of all the essential documents including those that are Site-specific. The CI is responsible for ensuring each Site has a file prepared before Site initiation. This may be delegated to the Site PI, but it is preferred practice for the CI to prepare all ISFs and supply them to the participating Sites.

For the contents and layout of the TMF/ISF see the Contents of TMF/ISF Form referenced in Section 7.

It is often convenient for some of the contents of the TMF/ISF to be kept by Trust departments such as Pharmacy or Laboratories. The essential requirement is that all the documents a particular Site should have are within that Site. They need not all be in the same lever-arch file or in the same location within the Site, but it must be possible to assemble the whole TMF/ISF immediately if required for monitoring or inspection. All files should contain numbered sections with file dividers as set out in the Contents of TMF/ISF Form; where some sections are empty because the corresponding section is used in a file held by another department at the Site, a cross-referencing file note must be inserted using the appropriate template (see Section 7).

An important part of Site Initiation is verification that the TMF/ISF is in place and that there are satisfactory arrangements for secure storage of study documentation.

The CI / PI responsible for work at any particular Site is responsible for ensuring that all essential documents are reconciled from wherever they are held for archiving at the end of the study.

4.2 File Notes

File notes should be used cautiously. A useful file note has the following parts: A problem is identified, a procedural change is identified for preventing recurrence, and this procedure is then instituted. It is important to remember that once a file note is written it becomes a study record and it cannot be retracted.

A file note template (see Section 7) is available for download. All file notes should be signed and dated by the individual with knowledge of the event leading to the file note and authorised by the PI (or Sponsor when more appropriate). File notes should be referenced in a file note log (see Section 7) within the TMF/ISF and signed copies distributed to separate files (e.g. Sponsor File, Pharmacy File) where appropriate. Cross referencing file notes indicating the location of documents within the TMF do not require PI authorisation.

4.3 Document Control

All study documents should be dated and version controlled throughout study set-up and during the study. Any amendment to a study document should generate a new version with an appropriate date. It is advised that version numbers, dates and a study identifier (including the IRAS number) should be

on each page of study documents (e.g. in the page header or footer); Amendments Checklist and Amendments Log should be used to manage amendment implementation process (see Amendments and CRF Design and Completion SOPs referenced in Section 7).

4.4 Personnel – Training

The CI is responsible for:

- appointing research personnel, if necessary, at the Chief Investigator Site and arranging training they need (including GCP training in CTIMP studies);
- attending and participating fully in training sessions (including Site Initiation where applicable) to ensure all personnel are trained on the Protocol and relevant Standard operating Procedures:
- selecting PIs and participating sites for a multi-site study;
- ensuring that any PIs at participating Sites are fully trained on, and familiar with, the Protocol. If possible, it is recommended that CIs visit the Site or arrange for PIs to visit the CI Site for training. At minimum there should be a teleconference;
- giving the Monitor or Study Co-ordinator any support required for effective Site Initiation at all participating Sites, as they join the study (see Monitoring SOP referenced in Section 7).

The PI at a participating Site is responsible for:

- appointing research personnel if necessary, or making arrangements for support from a research network team or similar, at the Site and arranging any training they need (including GCP training in CTIMP studies);
- attending and participating fully in training sessions (including Site Initiation where applicable) to ensure self and all Site personnel are trained on the Protocol and relevant Standard Operating Procedures:
- seeking further training on the Protocol or any other aspect of study conduct if they identify gaps in their knowledge.

The TMF/ISF should contain documentary evidence that all personnel are qualified by education, training and experience to perform their tasks on the study. CVs, evidence of electronic SOP training in Q-Pulse and GCP training records must be filed up to date, as must all Site Initiation and Monitoring Reports.

4.5 Delegation of Authority and Signature Log

This must be kept up to date in the TMF/ISF, using the form provided (see Section 7). All significant tasks such as taking consent, establishing participant eligibility, prescribing or dispensing IMP, or carrying out particular medical procedures should be specifically delegated by the CI or PI to those who have the necessary education, training and experience. This includes familiarity with the Protocol and GCP.

Formal delegation arrangements also apply to delegation of the responsibilities allocated in this SOP. Where, for example, this SOP gives responsibility to the CI for tasks such as setting up the TMF or checking

equipment s/he may formally delegate this to a study co-ordinator or other member of staff. See Delegation SOP referenced in Section 7.

4.6 Source Data Location List

Source data are information in original records and certified copies of clinical findings, observations or other data necessary for the reconstruction and evaluation of the study. Source documents serve to document the existence of participants and to substantiate the integrity of the data collected. The provision and maintenance of adequate source documentation also ensures that other health care professionals are fully informed about a patient's participation in a study.

To enable the Monitor to verify the data collected for the study, the location of source data should be clearly stated in the Protocol and it is the CI's responsibility to ensure that this is consistent across all study sites. This may simply state that all source data will be found as hard copy in one patient health record file kept by participating NHS Trust(s). For convenience the list should also be kept in the TMF/ISF. An example source data location list form is available (See Section 7). This is used to identify source data locations and indicate what records will need to be accessed during the study for source data verification (SDV). This information will guide monitors, auditors and regulatory inspectors to the source data.

Where study participants are patients the source data will usually be the patients' hospital or GP records; however care should be taken at the outset to list any departures from this – for example, separate study-specific records kept for healthy volunteers, portable records held by maternity patients or patients with chronic conditions, electronic records of imaging or blood test results, participant diaries.

Arrangements for ensuring the availability and security of all source data records must be carefully considered and recorded in the source data location list.

4.7 Standard Operating Procedures

The default position is that R&D Unit Standard Operating Procedures will be used for studies sponsored or co-sponsored by the Trust. ,Any departure from this must be agreed in advance and recorded in the TMF/ISF – for example, in co-sponsored studies, by specific agreement between the representative(s) of the co-sponsors and a participating Site, or where study specific SOPs are used for processes unique to the study. Study-specific SOPs must meet similar standards to the applicable R&D Unit SOP (see Section 7) and enable compliance with the Research Governance Framework and / or the Clinical Trial Regulations.

4.8 Equipment

Any equipment needed for the study should be clearly identified, sourced and regularly checked. This may include fridges or freezers used for storage of IMP or samples, scales used for weighing participants, equipment used for medical procedures. All such equipment should have an asset code from the EME department and be properly calibrated and maintained throughout the study, as per manufacturer's recommendations. The CI or Site PI is responsible for ensuring this is done and supporting information and evidence is kept in the TMF/ISF.

4.9 Pharmacy and IMP supply

The CI should contact the relevant Pharmacy Department (where applicable) to make arrangements for manufacture, importation, purchase and labelling of IMP supplies, and for randomisation systems, as required. Requirements will vary from study to study, and specific Pharmacy Standard Operating Procedures should apply to these processes.

In multi-site studies, pharmacy arrangements at participating sites will have been included in contract negotiations leading to completion of the study agreement. During the final run-up to Site Initiation the Site PI is responsible for ensuring appropriate communication takes place with the local Pharmacy and with the Pharmacy at the CI site..

CIs and Site PIs should be aware that participant recruitment will not be allowed at any Site until all necessary Pharmacy arrangements are in place at that Site and the IMP supplies have been obtained and are confirmed as ready for dispensing. This will be clearly notified by the by the R&D Unit when Capacity and Capability is confirmed.

4.10 Other involved departments

As for the Pharmacy arrangements described in 4.9, the Chief Investigator should contact any involved departments, such as Laboratories or Radiology, to make arrangements for their involvement in the study. External sub-contractors should be contacted by the CI with the involvement of the R&D Unit, who will ensure that all contracts are completed prior to study commencement.

In multi-site studies, Site PIs should have discussions with local service support departments and any local sub-contractors, the latter in conjunction with local R&D Departments to ensure contracts are in place at the right time.

CIs and Site PIs should be aware that participant recruitment must not take place at any Site until all necessary departmental and sub-contractual arrangements are in place and written confirmation is given by the Site.

Investigators setting up studies involving laboratories or imaging should refer to the relevant SOPs (see Section 7).

5 Setting up an externally-sponsored study

5.1 Organise the Investigator Site File

Some external Sponsors will provide the ISF ready for use, or give detailed instructions for how they wish the File to be assembled. In such cases the Sponsor's requirements must be followed, and the PI is responsible for ensuring this is done.

In all other cases the PI is responsible for setting up the ISF which contains all the 'essential documents' (in accordance with ICH-GCP) relating to the study These are documents that are generated before the study commences, during the study and after the study has finished. The PI must prepare the ISF, with the required contents page and numbered sections with dividers, before Site initiation. In these cases, for the contents and layout of the ISF see the Content of ISF Form referenced in Section 7.

It is often convenient for some of the contents of the ISF to be kept by departments such as Pharmacy. The essential requirement is that all the documents a particular Site should have are within that Site. They need not all be in the same lever-arch file or in the same location within the Site, but it must be possible to assemble the whole ISF immediately if required for monitoring/audit or inspection. All files should contain numbered sections with file dividers as set out in the Content of ISF Form; where some sections are empty because the corresponding section is used in a file held by another department at the Site, there should be a file note in the file to provide a clear statement of where all parts of the documentation at Site are to be found.

An important part of Site Initiation is verification that the ISF is in place and that there are satisfactory arrangements for secure storage of study documentation.

5.2 File Notes

File notes should be used cautiously. A useful file note has the following parts: A problem is identified, a procedural change is identified for preventing recurrence, and this procedure is then instituted. It is important to remember that once a file note is written it becomes a study record and it cannot be retracted.

A file note template (see Section 7) is available for download. All file notes should be signed and dated by the individual with knowledge of the event leading to the file note and authorised by the PI. File notes should be referenced in a file note log (see Section 7) within the ISF and signed copies distributed to separate files (e.g. Sponsor File, Pharmacy File, University Department File) where appropriate. Cross referencing file notes indicating the location of documents within the ISF do not require PI authorisation.

5.3 Document Control

All study documents should be dated and version controlled throughout study set-up and during the study. Any amendment to a document should generate a new version with an appropriate date.. It is advised that version numbers, dates and a study identifier should be on each page of study documents (e.g. in the page header or footer). Amendments Checklist and Amendments Log should be used to manage amendment implementation process (see Amendments and CRF Design and Completion SOPs referenced in Section 7).

5.4 Personnel - Training

The PI is responsible for:

- appointing research personnel if necessary, or making arrangements for support from a research network team or similar, at the Site and arranging any training they need (including GCP training in CTIMP studies);
- attending and participating fully in training (including Site Initiation where applicable) to ensure self and all Site personnel are trained on the Protocol and relevant Standard Operating Procedures.
- seeking further training on the Protocol or any other aspect of study conduct if they identify gaps in their knowledge.

The ISF should contain documentary evidence that all personnel are qualified by education, training and experience to perform their tasks on the study. CVs, SOP Training Logs and GCP training records must be filed up to date, as must all Site Initiation and Monitoring/Audit Reports.

5.5 Delegation of Authority and Signature Log

This must be kept up to date in the ISF. All significant tasks such as taking consent, establishing participant eligibility, prescribing or dispensing IMP, or carrying out particular medical procedures or laboratory tests should be specifically delegated by the PI to those who have the necessary education, training and experience. This includes familiarity with the Protocol and GCP.

5.6 Source Data Location List

To enable the Monitor/Auditor to verify the data collected for the study, the location of source data should be clearly identified. PIs should seek clarification at Site Initiation and keep a list in the ISF. Where study participants are patients the source data will usually be the patients' hospital or GP records; however care should be taken at the outset to list any departures from this – for example, separate study-specific records kept for healthy volunteers, portable records held by maternity patients or patients with chronic conditions, electronic records of imaging or blood test results, participant diaries. An example source data location list form is available (see Section 7).

5.7 Standard Operating Procedures

The ISF should include details of which Standard Operating Procedures are to be applied. It is the PI's responsibility to secure clear agreement about this with the Sponsor during Site Initiation. If the Sponsor wishes to apply its own, Clinical Trial Regulations / Research Governance Framework compliant SOPs, copies should be provided for the ISF. In default, R&D Unit Standard Operating Procedures will apply to all studies conducted in the Trust.

5.8 Equipment

Any equipment needed for the study should be clearly identified, sourced and regularly checked. This may include fridges or freezers used for storage of IMP or samples, scales used for weighing participants, equipment used for medical procedures. All such equipment should have an asset code from the EME department and be properly calibrated and maintained throughout the study, as per manufacturer's recommendations. The PI is responsible for ensuring this is done and supporting information is kept in the TMF/ISF.

5.9 Pharmacy and IMP supply

The details of Pharmacy arrangements will vary from study to study and these will have been agreed during contract negotiations leading to completion of the clinical trial agreement. During the study initiation phase the PI should discuss the study with the local Pharmacy and ensure that appropriate communication takes place between the local Pharmacy and the Sponsor or Sponsor's representative on IMP supply, dispensing, storage and related issues.

PIs should be aware that participant recruitment will not be allowed until all necessary Pharmacy arrangements are in place and the IMP supplies have

been obtained, ready for dispensing. This situation will be clearly notified by the R&D Unit when Capacity and Capability is confirmed.

5.10 Other involved departments

As for the Pharmacy arrangements described in 5.8, PIs should have discussions with local service support departments and any local sub-contractors in conjunction with the R&D Unit to ensure contracts and arrangement are in place at the right time.

PIs in the Trust should be aware that participant recruitment will not be allowed until all necessary departmental and sub-contractual arrangements are in place.

6 Running the Study

The requirement for all staff involved in running a CTIMP, whether a CI, a PI, other research team member or staff in a service department, is to work to the standard set by the UK Clinical Trial Regulations. For non-CTIMPs the Research Governance Framework for Health and Social Care applies. Each member of staff should undertake GCP training before commencing work on a clinical trial of an investigational medicinal product (CTIMP), preferably face to face GCP training. GCP training should be updated as deemed appropriate by the study Sponsor and/or York Teaching Hospital NHS Foundation Trust.

Many R&D Unit SOPs are relevant to particular elements of study duties, such as those on Informed Consent, or Safety Reporting. As set out above staff should, at the beginning of the study, be aware of the Standard Operating Procedures to which they are working. Some general guidance points are pertinent here, and should be observed in all cases:

1. The CI has overall responsibility for the study and Site responsibility for all work done at the Chief Investigator Site – delegation must not mean abdication;
2. A Site PI has responsibility for all work done at the participating Site – delegation must not mean abdication;
3. All other staff must only work within the delegation arrangements documented in the TMF / ISF Delegation of Authority and Signature Log;
4. The study must be carried out strictly in accordance with the current version of the protocol as approved by MHRA and / or the REC and / or HRA. Working outside this – for example be recruiting a few extra participants – can have serious consequences, including invalidating the study insurance.
5. For a CTIMP, the tasks of:
    - explaining the study to a potential participant so that they understand the risks and objectives; and
    - determining that a particular participant meets all eligibility criteria and is suitable for the study;

    should only be delegated to medically-qualified personnel, whose signatures should confirm their involvement.
6. After screening and/or randomisation, the participant's code/ID number should be entered in a Screening and Enrolment Log (see Form referenced

in Section 7). The Enrolment Log must be retained at site and archived at the end of the study.

7. There must be a complete audit trail of all activity undertaken for the study – sufficient to allow the study to be recreated from the paperwork; and the paperwork should be ready for monitoring/audit or inspection at any time. It follows that:
    - TMF / ISF maintenance must be meticulous;
    - Any events or decisions not otherwise provided for should be recorded in dated and signed file notes;
    - Any corrections that need to be made to the documentation should be made so that the original entry is not obliterated – a correction entry should be made, with the date of the change and signature of the person making it.
    - Regular team meetings should be held involving staff working on the study at a particular Site; these should be minuted or notes should be made of all significant decisions and follow-up actions.
8. All staff should be aware of the responsibility to report Serious Adverse Events and Serious Breaches (see specific SOPs referenced in Section 7).
9. If there is any doubt about any aspect of setting up or running a research study in the Trust it is essential to seek advice from the R&D Unit. It is important to note that some Sponsor instructions may occasionally contravene or conflict with local processes or arrangements. In this eventuality, investigators and research teams must ensure they seek advice or guidance from the R&D Unit.

Additional Reading

For a detailed step by step guide to setting up and managing a CTIMP reference may be made to the Clinical Trials Toolkit website www.ct-toolkit.ac.uk. This website provides one route map that takes researchers through the stages of planning a new trial and another one for managing a trial. When clicking on the various stages along the route map further detailed information about each stage is provided.

7 Related SOPs and Documents

All York Foundation Trust R&D Unit SOPs and Guidance documents are related to Set Up and Management of Research Studies and the full list of them should be checked; however the following are of particular direct relevance:

R&D/S03	Delegation of Tasks for Trust Sponsored Research Studies
R&D/S04	Breaches of GCP or the Study Protocol
R&D/S05	Research Related Adverse Event Reporting Procedure for CTIMP Studies (including reporting of a pregnancy)
R&D/S06	Reporting Requirements During Research Studies
R&D/S07	Implementing Amendments for Research Studies NOT Sponsored by the Trust
R&D/S08	Monitoring of Trust Sponsored Research Studies
R&D/S14	Local New Study Set-Up: Capacity & Capability Assessment
R&D/S21	Study Close-Out: Clinical Trials of Investigational Medicinal Products (CTIMPs) and other research studies
R&D/S25	Providing and Documenting Training for Researchers
R&D/S26	Preparation, Review and Approval of Study-Specific Standard Operating Procedures for Research
R&D/S28	Quality Assurance
R&D/S63	Contracting with Laboratories to undertake Research
R&D/S64	Setting up Research Studies Involving Imaging (including studies using Ionising Radiation)
R&D/S71	Auditing of Research Studies and Processes
R&D/S74	Making Amendments to Trust Sponsored Research Studies
R&D/S81	Case Report Form (CRF) Design and Completion
R&D/F11	Investigator Site File Contents (Hosted studies)
R&D/F16	Study Delegation and Signature Log
R&D/F18	Amendment Checklist (Research Teams)
R&D/F58	Source Data Location List
R&D/F59	File Note Log
R&D/F71	Screening Log
R&D/F95	Trial Master File Contents List (Trust Sponsored Studies)
R&D/F110	Enrolment Log
R&D/F118	Amendment Log
R&D/T20	File Note Template