North Bristol NHS Trust

Standard Operating Procedure

Data Management

REFERENCE:	RI/QMS/SOP/017
VERSION NUMBER:	2.1
EFFECTIVE DATE:	28-03-18
REVIEW DATE:	28-03-20
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Document Version History

VERSION NUMBER	EFFECTIVE DATE	REASON FOR CHANGE
1.0	27-08-10	SOP renamed, updated in line with new template and recoded from ISOP-H01
2.0	28-11-16	SOP renamed from 'Essential Documents' to 'Data Management'. Clarification that Data Management Plan is required for CTIMPs. Appendices removed and uploaded to website separately

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DO NOT USE THIS SOP IN PRINTED FORM WITHOUT CHECKING IT IS THE LATEST VERSION

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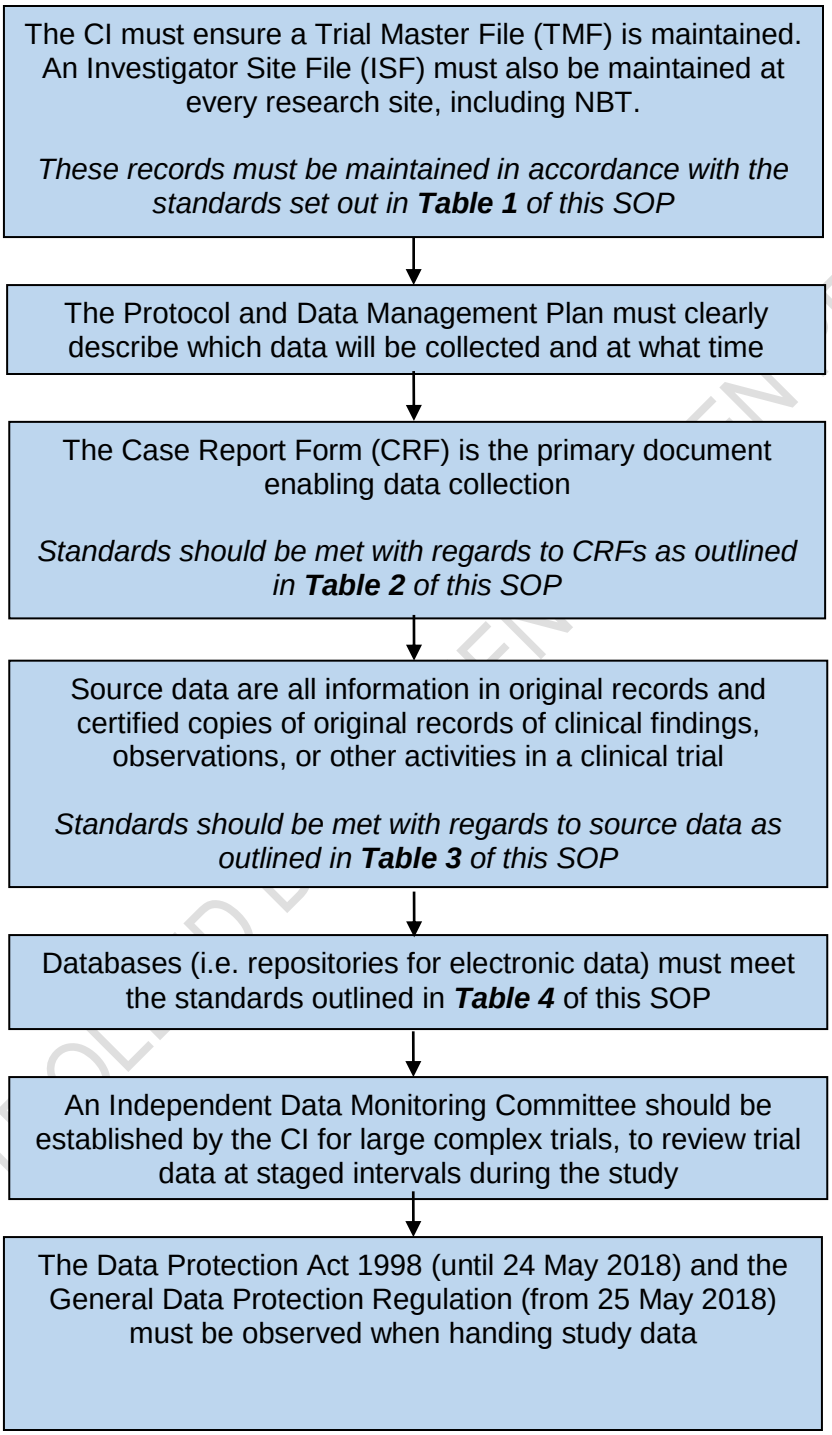
i. SOP Flowchart



1. PURPOSE AND SCOPE

The purpose of this SOP is to describe the standards required for collecting, maintaining, verifying, correcting, transferring, and analysing data generated by NBT sponsored CTIMPS.

For CTIMPs, the standards defined in The Medicines for Human Use (Clinical Trials) Regulations 2004 apply, along with those described in ICH GCP. The data generated through research may be used to influence or drive changes in clinical practice. The standards are in place to ensure that both robust data are generated and patients are safe. The need to be able to robustly defend the source of the data and the systems through which it passes until publication is thus paramount, and robust systems to document the effects of investigational medicinal products on human subjects must be in place.

A substantial amount of documentation is generated before, during and after undertaking any research project. It is important that such documentation is complete, legible and easily accessible at any time for monitoring, audit or inspection. In accordance with ICH GCP the Sponsor should ensure appropriately qualified individuals are responsible for the overall conduct of the research study, handling the data, verifying the data, conducting the statistical analyses, and preparing the study reports. For NBT sponsored studies, these responsibilities are delegated to the CI.

All documents for NBT sponsored studies should be created and used in line with NBT research SOPs. The development of patient facing documentation and the Protocol should be in line with the HRA guidance.

2. DEFINITIONS/ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMP	Data Management Plan
ICH GCP	International Conference on Harmonisation Guidelines for Good Clinical Practice
IDMC	Independent Data Monitoring Committee
ISF	Investigator Site File
NBT	North Bristol NHS Trust
PI	Principal Investigator
R&I	NBT Research & Innovation Office
Sponsor	The individual, company, institution or organisation, which takes on ultimate responsibility for the initiation, management (or arranging the initiation and management) of and/or financing (or arranging the financing) for that research
TMF	Trial Master File
TSC	Trial Steering Committee

3. WHO SHOULD USE THIS SOP

This SOP should be used by the CI of NBT sponsored CTIMPs as well as any research staff involved in collecting, entering, checking, correcting, transferring and analysing data for NBT sponsored CTIMPs.

Although this SOP is aimed at NBT sponsored CTIMPs, the principles are also applicable for all research undertaken at NBT.

For studies sponsored by NBT, it is expected that the CI ensures clear plans for data management are generated in addition to this SOP.

4. WHEN SHOULD THIS SOP BE USED

This SOP should be used before, during, and after conducting CTIMPs sponsored by NBT, to determine the standards required for collecting, maintaining, verifying, correcting, transferring, and analysing data generated.

5. PROCEDURE

5.1. Maintaining the Trial Master File (TMF) and Investigator Site File (ISF)

ICH GCP defines documentation as: *"all records, in any form (including, but not limited to, written, electronic, magnetic and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct and/or results of a trial, the factors affecting a trial, and the actions taken."*

Essential documentation are *"documents which individually and collectively permit the evaluation of the conduct of a study and the quality of the data produced".* The 'essential documents' are therefore the minimum required documents to be maintained during any research project.

There are essential documents collected before, during, and after a clinical trial**.** The specific documents to be maintained for each project will vary and it is therefore important that the specific essential documents for individual projects are considered on a case-by-case basis in collaboration with R&I.

The Trial Master File (TMF) and Investigator Site File (ISF) represent the standard filing system for the storage of essential documentation; The CI should set up and maintain the TMF (at NBT, the TMF and NBT's ISF can be one and the same file) and the PI at each trial site should set up and maintain a separate ISF. The Site File Template available on the NBT website should be used to determine the appropriate content/structure of these files. Standards for maintaining the TMF and ISF are outlined in Table 1.

R&I will retain electronic records relating to research governance and sponsorship, but are not required to retain Case Report Forms (CRFs) or other source documentation.

Storage	Documents contained in the TMF/ISF may include original regulatory approvals and confidential information. The files should therefore be stored in a secure place with restricted access. Documents may be kept in separate folders, files or cabinets but the TMF/ISF must indicate specifically where these are stored. Currently, there are no guidelines relating to the storage of documents in electronic format. It is good practice to print and retain hard copies of this information. Electronic copies should be password-protected or stored in a password-protected folder or drive for backup purposes. Direct access to all data must be provided for quality control and quality assurance reviews (e.g. monitoring and audit) or regulatory inspection.
Quality	All documents must be complete and legible so that they may be easily accessed and understood by monitor, auditors and inspectors.
Version Control	A system should be in place for version control of documents. It is recommended that a chronology of amendments is kept on file that records all the amendments submitted and the documents that they relate to. Old version of documents should be retained on file alongside the new versions and old versions clearly marked as no longer being used. Information on amendments can be found in SOP on Research Study Amendments (RI/QMS/SOP/003).

Table 1: Standards that should be met when maintaining the TMF and ISF

5.2. **The Protocol**

The protocol must clearly describe which data will be collected, and at what time points. Further requirements for protocol design are outlined in the SOP on Writing a Protocol for CTIMPs (RI/QMS/SOP/008).

R&I must sign off the protocol prior to any regulatory submissions, including amendments, in accordance with the following SOPs: Applying for North Bristol NHS Trust Sponsorship (RI/QMS/SOP/007) and Research Study Amendments (RI/QMS/SOP/003). The Chief Investigator must sign off the Protocol either through wet ink signature or electronic, upon receipt of HRA Approval.

5.3. **Data Management Plan**

A robust Data Management Plan (DMP) is required for all CTIMPs. The DMP must be approved by the Sponsor prior to study initiation and as required during the course of the trial.

Data management will be included as a standing agenda item at the trial management meetings between the Sponsor and Trial Manager, and will be checked as part of monitoring. The DMP should be reviewed at least every 12 months.

In the case of non-CTIMPs, the Sponsor will take a proportionate risk-based decision regarding the need of a separate formal DMP, taking into consideration whether there is sufficient information in the Protocol.

The DMP should specify the following information:

- Where the Reference Safety Information (RSI) is located, i.e. Investigational Brochure or SmPC.
- How data will be collected, clarified, stored and analysed with reference to the database lock process and audit trails.
- How eligibility of participants is assessed and documented.
- How trial related information is provided to participants and documented.
- The requirements for baseline data to be obtained and documented, and the implications if this is not adhered to.

An R&I recommended DMP template is available on the NBT website (www.nbt.nhs.uk/research). If an alternative DMP template is to be used, approval by the Sponsor is required.

5.4. **Case Report Forms (CRFs)**

A CRF is *"a printed, optical or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each [research] subject."* The CRF is the primary document enabling collection of data. Standards that should be met with regards to CRFs are outlined in Table 2.

Design	The CRF must be designed by the CI before the research begins. It should be designed to only collect data as required in the protocol and nothing more, to comply with data protection requirements. CRFs may be paper or electronic. Original paper CRFs form part of the trial master file, as an essential document. Any electronic CRF collection systems must be verified in accordance with the Computer System Validation & Backup SOP (RI/QMS/SOP/015). Any verification of data which must be done by particular members of the research team (e.g. inclusion/exclusion criteria and safety data by medically qualified staff) must be evidenced. For paper CRFs, this would usually take the form of a signature and date; for electronic CRFs, this may be carried out by means of audit software incorporating particular logins, or documented separately within the source data. The CRF and any amended versions must be signed off by R&I prior to implementation.
Validation	The CRF should be reviewed by a range of staff to ensure ease of data collection and inputting, and all data is collected in line with the planned aims and objectives. Any changes to the CRF should be documented clearly and stored in the TMF. The amended CRF should be signed off by the Sponsor and Chief Investigator before implementation.
Completion	The recording of data on the CRF should be performed by the PI at each trial site, however this responsibility may be delegated to other members of the team if appropriately trained. Paper CRFs should be completed in ink and data fields should not be left blank. Where there is no data to record in certain fields they should be marked Not Applicable (N/A) or No Data (N/D).

	The precise completion of CRFs is vital to preserving confidence in the findings of the project and therefore any discrepancies between the data required and the data collected or the source data should be minimised and explained. Any changes or corrections to a CRF or entries within them should be dated, initialled and explained (where necessary) and should not obscure the original entry. There should be an agreed system and process in place for authorising changes to data. The CI should agree with the research team what changes are acceptable, and document this. For example, the CI may agree that any member of the research team can amend clear transcription errors where the source data have not been transcribed correctly into the paper CRF. Other items, such as medical assessments and safety data changes should be authorised by the CI. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data recorded in the CRFs. CRFs should be completed at the earliest opportunity, contemporaneously with collection of source data wherever possible.
Review	The PI should regularly review the CRFs and source documents to identify any discrepancies or deviations from protocol. Protocol deviations should be documented and explained in accordance with the SOP on Managing Breaches of Good Clinical Practice or the Protocol (RI/QMS/SOP/012). The review of each CRF and source documents should be documented by the PI.
Storage	The CI must ensure provision is made for trial sites to retain a copy of the CRF at site. Direct access to data must be provided for quality control and quality assurance reviews (e.g. monitoring and audit) or regulatory inspection.

Table 2: Standards that should be met with regards to CRFs

5.5. **Source Data**

Source data are all information in *original* records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the clinical trial. Source data are the first place that a piece of information is recorded.

Source data are contained in source documents (original records or certified copies). Source documents are considered essential documents that serve to certify compliance with ICH GCP and regulatory requirements.

Standards that should be met with regards to source data are outlined in Table 3.

Identifying source documentation	Prior to a trial commencing at a trial site, the PI at that site should identify what constitutes source documents at that site, and must record this on a Source Data Form. Source documentation may include (but is not limited to): hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches,

	photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. On occasion, the CRF may act as the source. Source data may be captured initially into a permanent electronic record. In this context 'permanent' means that all changes in the data are recorded in an audit trial (the minimum standard for this is a record of who made the change and when).
Source documentation verification	It must be possible to establish that the source information for data collected in the CRF existed at the appropriate point in time. That is, electronic systems used to record source data should have appropriate audit software providing the date, or be saved in a version controlled manner, and paper records should include a date and signature.
Source data retention	Source data must remain at the location at which it was generated. The location of all source data records should be documented to allow quick access. Direct access to data must be provided for quality control and quality assurance reviews (e.g. monitoring and audit) or regulatory inspection.

Table 3: Standards that should be met with regards to source data

5.6. **Databases**

A database is a repository for electronic data. Databases vary widely, depending on the size, type and complexity of the research being carried out. For a simple, small study, an excel spreadsheet can be used. At the other end of the spectrum are complex databases which have automated audit software and consistency checking capability, as well as the ability to generate data queries.

Standards that should be met with regards to databases are outlined in Table 4. The CI is delegated responsibility for setting up and managing databases for recording trial data. These must meet the standards described in the SOP on Computer System Validation & Backup (RI/QMS/SOP/015).

Design	A database must reflect the CRF so that the data required by the protocol can be collected. The chief investigator must check that the database meets the needs of the study by reviewing and testing it, and documenting that the database meets the required specifications (user acceptance testing). The database must have suitable audit trail functionality. See SOP on Computer System Validation & Backup (RI/QMS/SOP/015). Points to consider include: ease of setting up and maintaining data entry screens; the ability for more than one user to use the system at the same time; and the ability to store and retrieve all data required for the study efficiently. If there is blinding involved in the trial, the system must allow this to be maintained.
Data entry	CRF data queries should be raised and resolved before entering data in the

	database. The process for managing data queries should be specified in the DMP. Data entry should be completed by trained delegated staff. Data should be entered in a format that allows for analysis, e.g. coded. Clinical data also needs to be coded for recording of all adverse events. Plans for coding must be incorporated into the DMP. To reduce errors, data should be checked. This may involve double entry checking (if sophisticated systems that allow for this are in use) or visual checking the database against CRFs. Records of checks and audit trails must be retained as part of the essential documents. Predicted timelines for inputting the data across sites should be included in the DMP, with a contingency plan should these timelines not be met. The Sponsor should be informed if the contingency plan is drawn upon, with regular reviews of the action.
Validation	Post-entry computer tests should be undertaken, for example by running lists of all missing values will be listed, or all values outside of pre-defined range. Logical checks should also be performed to check for implausible data. Post-entry checks should be defined before the study starts in the DMP. Records of checks and audit trails must be retained as part of the essential documents
Change control	As more data are entered, or changes are made it is important that an audit trail of the changes is available, so that previous versions of the datasets can be accessed if necessary. For sophisticated databases, the mechanism may be by using the database software to record changes to data fields and the associated logins that carried out the change(s); for a simpler database this might be by saving subsequent copies with a version number and date and a form of identification of the person who modified the file (eg initial and last name).
Management	The CI should ensure there is a specific SOP for managing the study database. There must be adequate backup for the data.
Access	The database should be secure, with appropriate password-protected access to prevent unauthorised access to the data, with a list identifying those individuals permitted to make changes to the data.
Data Lock	Database locking is the process by which it is declared and identified as final. No changes to the data should be made once the database has been locked, and arrangements should be put in place to control access to the data and protect it. The files should be protected from editing and deleting, and the decision about the approach to doing this should be made in a risk based way. Unlocking the database should take place only under exceptional circumstances, and requires agreement from R&I and trial statisticians. Written approval for data unlocking, the justification, the changes that will be made and the impact on the analysis must be recorded in the trial master file prior to unlocking.
Data Release	Data should be extracted from the locked database to carry out the final analysis. The process to do this should be adequately described. Test extracts may be made, and these must be stored in a separate location to the extracted datasets on which the analysis will be performed.

Table 4: Standards that should be met with regards to databases

5.7 **Publication Plan**

A publication plan should be created as a standalone document or included within the DMP to ensure suitable dissemination of the results. This should include the publication of non-significant results and lessons which have been learnt from any errors during the development or delivery of the study.

5.8 **Independent Data Monitoring Committee (IDMC)**

For large complex trials, the CI should establish an Independent Data Monitoring Committee (IDMC) to carry out reviews of trial data at staged intervals during the study. The role of the IDMC is review the interim results and determine whether or not there are any safety issues or any reason why the study should not continue.

The data reviewed by the monitoring committee should be as up to date as possible and should be validated up to the point of the interim analysis to ensure it is of sufficient quality.

The membership of the committee should include experienced trial investigators, statisticians and clinicians; all of whom must be independent to the research team. The results should be reviewed at regular intervals as sufficient data accumulate.

If there is a Trial Steering Committee (TSC) for the study, the IDMC would normally make their recommendations for action through them.

5.9 **Data Protection**

During the entire data management and validation process it is essential that all study data are kept in accordance with the terms of the Data Protection Act 1998 (until 24 May 2018) and the General Data Protection Regulation (from 25 May 2018).

6 DISSEMINATION AND TRAINING

SOPs will be distributed in accordance with the SOP on Preparation of Research SOPs (RI/QMS/SOP/001).

This SOP and any associated templates and forms will be uploaded to the Trust website (www.nbt.nhs.uk/research) and the Managed Learning Environment (MLE) system on the Trust intranet shortly after having been released.

All staff whose activities are subject to this SOP should ensure that they read and understand the content of this SOP.

The training log within the Investigator Site File/Trial Master File should be completed to document that members of staff have read and understood the content of this SOP.

7 RELATED SOPS AND DOCUMENTS

- The following R&I documents are available on the NBT website: www.nbt.nhs.uk/research

RI/QMS/SOP/003	Research Study Amendments
RI/QMS/SOP/007	Applying for North Bristol NHS Trust Sponsorship
RI/QMS/SOP/008	Writing a Protocol for CTIMPs
RI/QMS/SOP/012	Managing Breaches of Good Clinical Practice or the Protocol
RI/QMS/SOP/015	Computer System Validation & Backup