Standard Operating Procedure

STUDY DATA

SETTING Trustwide

AUDIENCE All R&D and research staff involved in collecting, entering, checking, correcting, transferring, and analysing data for UHBW sponsored trials

ISSUE This SOP relates to collecting, entering, checking, correcting, transferring, and analysing data generated by UHBW sponsored trials.

QUERIES Contact Research & Development (R&D) department on 0117 34 20233 or research@uhbw.nhs.uk

Document History

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Version Number	Reason for change
Original V1.0	N/A – original
V1.1	Minor update to clarify 'Protocol sign-off' in section 5.1
V1.2	Annual review – minor updates and clarifications.
V1.3	Annual review – minor updates and clarifications.
V1.4	Biennial review – minor updates and clarifications.
V2.0	New section on transfer of data
V2.1	Departmental name change from Research & Innovation to Research & Development. Updated throughout SOP as a minor amendment.
V3.0	Biennial review with a major amendment of the process to include use of proportionate DMPs for some non CTIMP research, and section on long term storage of data. Some minor updates such as removal of website links that no longer work, reference to guidance documents and updating the SOP in line with the UHBW SOP template.

1. Introduction

In accordance with Good Clinical Practice (GCP) 'All clinical trial information shall be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification' (Schedule 1, Part 2 (10) SI 2004/1031).

For clinical trials of investigational medicinal products, the need to be able to robustly defend the source of the data and the systems through which it passes until publication is paramount and is underpinned by the law through the Medicines for Human Use (Clinical Trials) Regulations (SI/2004/1031) and any amendments. Similarly, robust systems to document the effects of investigational medicinal products on human subjects must be in place.

The standards with which to comply with are also referenced in the MHRA Grey Guide (2012).

The data generated through research may be used to influence or drive changes in clinical practice. Therefore, the standards are in place to ensure that both robust data are generated, and patients are safe.

Data collection, processing, storage, transfer, and onward sharing must be done so in compliance with the Data Protection Act 2018

2. Purpose

The purpose of this SOP is to describe the standards required for collection, entry, checking, correction, transfer and analysis of data generated by UHBW sponsored research.

3. Scope

In Scope: Data systems and processes for Clinical Trials of Investigational Medicinal Products sponsored by UHBW. Data systems and processes for other research sponsored by UHBW.

Out of scope: Research sponsored by other organisations, hosted by UHBW.

4. Responsibilities

The R&D department has a responsibility as sponsor to ensure that staff delivering UHBW sponsored research are fully aware of the required data management standards which must be complied with and must maintain a level of sponsor oversight which is proportionate to the level of risk.

All research staff undertaking UHBW sponsored research who process data are responsible for ensuring the applicable data management standards are met as described in this SOP, the applicable regulations and with GCP.

5. Abbreviations and Definitions

Abbreviations	
CI	Chief Investigator
CRF	Case record/report form
DSA	Data Sharing Agreement
DMP	Data Management Plan
eCRF	Electronic Case record/report form
GDPR	General Data Protection Regulation
GCP	Good Clinical Practice
HRA	Health Research Authority
ICO	Information Commissioner Office
pCRF	Paper Case record/report form
R&D	Research and Development
RMF	Research Management Facilitator
RPM	Research Projects Manager
SAE	Serious Adverse Event
TMF	Trial Master File
UHBW	University Hospitals Bristol and Weston NHS Foundation Trust

Definitions	
CRF	Document used to record the required data as defined by the protocol for each participant throughout their participation in the study
Data Controller	'**controller**' means the natural or legal person, public authority, agency or other body which, alone or jointly with others, determines the purposes and means of the processing of personal data. (Taken from the Information Commissioners Office website: What are 'controllers' and 'processors'? | ICO)
Data Processer	'**processor**' means a natural or legal person, public authority, agency or other body which processes personal data on behalf of the controller (Taken from ICO website: What are 'controllers' and 'processors'? | ICO)
Data Management Plan	The main document that describes and defines all data management activities throughout the lifecycle of a research study
Data Validation	Checks on data quality
Data Verification	Checks on accuracy of data entered into a database

6. Procedure

6.1 Protocol

- For **all studies sponsored by UHBW**, the protocol must clearly describe which data will be collected, at what time points, where it will be stored and how it will be used.
- The protocol or IRAS form should document the data custodian for the study. For UHBW sponsored studies it is expected that the Chief Investigator or an appropriate delegated other (e.g. data manager) acts as data custodian. This will be discussed prior to submission of the application for approval to the Research Ethics Committee and Health Research Authority (HRA).
- The version of the protocol in use must be signed off by the sponsor. 'Sign-off' constitutes one or all of the following: electronic signature on the protocol; wet ink signature on the protocol; authorisation on the application for approval to the Research Ethics Committee and HRA.

6.1.1 Information Sheets and Consent forms

- In line with the General Data Protection Regulations, it is vital that use of data is transparent. Information Sheets and Consent forms must therefore include as much information as possible around intended processing and use of any data for the research study. Further information on this can be found on the HRA website: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-detailed-guidance/transparency/
- The Information Sheet should also detail who is identified as data controller for the research study. Where sponsor, this will be UHBW however in some circumstances it may be appropriate to act as joint data controller with another organisation (e.g. if co-sponsor or where an external trials unit is managing a UHBW sponsored study). The Research Projects Manager (RPM) or Research Management Facilitator (RMF) will advise on this prior to any submission to the Research Ethics Committee and HRA.

6.2 Data Management Plan

- For **UHBW sponsored CTIMPs** a *Data Management Plan (DMP)* (*TMPL_041*) must be completed. This document will provide an overview of the data flow processes for the study as well as detail all of the data management activities for a study. The sponsor's DMP template must be used unless an alternative is agreed with the sponsor.
- The DMP is a live document that may change throughout the duration of a study. The first version should be sent to the Research Projects Manager (PRM) for review during study set up. The RPM will ensure that adequate data management is described and liaise with the Trial Manager to finalise the document. The DMP must be stored in the Trial Master File (TMF). Any amended versions will also need to be reviewed by the RPM prior to finalisation and all versions stored in the TMF.
- For **other UHBW sponsored research** a risk-based decision should be made regarding the need for a DMP, an abridged DMP or other document agreed by UHBW as sponsor. The detail provided in each section should be proportionate to the size and complexity of the study. Refer to *TMPL_041 Data Management Plan* or if agreed by UHBW as sponsor, an alternative data management plan template may be used.

6.3 Data Protection Impact Assessment (DPIA)

A DPIA must be completed where a type of processing is likely to result in a high risk to the rights and freedoms of individuals taking part in the study. This is the responsibility of the sponsor, as data controller, and must be done prior to processing of personal data. This may be done in conjunction with other organisations where there is more than one data controller and with input from the Information Governance team at UHBW. Refer to **https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/what-law-says/data-privacy-impact-assessments/**

Further information can also be found in GD_034 Data related regulations DPIA and DSAs

6.4 Data Sharing Agreements

For UHBW sponsored research where we hold the grant a separate Data Sharing Agreement will be required in addition to any collaboration agreement to set out clearly the data controller and processer relationships. This is separate to any required standard site agreements (where the site is usually the data processer) which includes data processing and sharing terms . Note for these studies a separate DPIA is not usually required (as agreed with the UHBW Information Governance team.

6.5 CRF

- The CRF should be designed to support collection of the data required by the protocol,and may be paper (pCRF) or electronic (eCRF). See *GD_007 Key elements to be considered in the design of a CRF.*
- It is good practice to include a wide range of staff in CRF design review. The CRF should be reviewed against the protocol to ensure all necessary information is captured and to ensure that the design and flow of the questions allows good quality data collection so that the data tables generated support the planned data analysis.
- The CRF and any amended versions must be signed off to confirm that the CRF is collecting all of the data required by the protocol. UHBW as sponsor delegates this sign off to the CI.
- Original CRFs form part of the TMF, as an essential document. Provision must be made for sites to retain a copy of the CRF at site, independent of the sponsor, in order to ensure that the sponsor cannot manipulate the site data. If eCRFs are in use, this might be by using worksheets to collect data ('shadow' CRFs) or providing copies of the data back to site on DVD/CD at the end of the trial.
- Verification of data done by members of the central and local research teams (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 eCRFs, this may be carried out by means of audit software incorporating particular logins,or could be documented separately within the source data.

6.6 Source Data

- Source data is the first place that a piece of information is recorded, prior to transcription into a CRF. Source data can take many forms and must remain at the location at which it was

generated. Refer to *GD_008 Key elements to include in source data* for further information. Types of source data include handwritten and typed paper and electronic notes, clinical systems, hard copy or electronic images. On occasion, the CRF may act as the source data.

- It should 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.

6.7 Authorising changes to the data

- 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 who is permitted to authorise the changes, 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 only be authorised by the CI.

6.8 Database

- 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, provided it meets the standards described in *SOP_011 Validation and Backup of Computer Systems*. Please note for CTIMPs an excel spreadsheet is not recommended. 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.
- 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).
- As more data is 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 (e.g. initial and last name).
- Further information on databases can be found in GD_33 Guidance on databases and required approvals

6.9 Data entry

- Entry of data into the database should be performed by fully competent staff who are appropriately qualified and have received any necessary training.
- Data entry may occur during or after each participant's visit or at the end of the study.
- The data should be entered as recorded on the CRF without modification.

6.10 Quality control

- Systems to ensure that data entry is accurate or that errors are identified and corrected must be in place. This can be supported in a number of ways:
    - Dual data entry, and discrepancy checking of the two entries
    - Using consistency/logic checks to ensure expected answers are entered – e.g. blood results fall within expected reference ranges, ages match dates of birth, etc;

  - Source data verification - quality checks carried out against the source data in patient records and against CRF entries.
- If the mechanism of carrying out these checks is not automated, checks must be documented when they are completed. For automated checks, an audit trail must be available. Records of checks and audit trails must be retained as part of the essential documents in the TMF.

- Data held on the database may be validated or monitored/reviewed centrally in order to ensure that the data are complete and accurate. This can be done in a number of ways, including review of print-outs and comparison either across visits, or with paper CRFs to ensure consistency and accuracy. For more complex trials, this may be done using consistency/logic checks as described above. All checks must be documented fully. Any queries which are generated as a result of this process must be addressed with the PI (or delegate) in order to resolve the query and make changes to the data. These must be documented fully.

6.11 Reconciling clinical and pharmacovigilance databases

- If serious adverse events recorded are on a separate pharmacovigilance database they must be matched with the clinical research database. For long/complex studies this should be conducted throughout the lifecycle of the study; for simpler, short studies with low numbers of SAEs this can be carried out at the end of the study.
- As part of the DMP, an approach to reconciling the SAE data must be agreed at the start of a trial.

6.12 Data coding

- Data coding may be appropriate for larger trials. Plans for management of coding should be incorporated into the data management plan.

6.13 Final data quality

- It is good practice to check the final data quality of a database prior to lock. For small, low risk trials it might be appropriate to combine a number of checks which might have been conducted throughout the data management process into this final check. However, there is a risk in this approach that the time lapse since collection of the data makes clarification of any queries that arise more difficult. Any decision around the approach should be documented at the study start.
- A data quality check is an assessment of a proportion of the data, comparing it to the data in the paper CRF. That proportion may be 100% when it relates to primary endpoint data, or lower for other data. A threshold of 'acceptable' error rates should be agreed, below which further checks should be carried out until the quality is deemed to be acceptable. The process of identifying and resolving errors must be documented. For eCRFs the checks should have been completed via source data verification earlier in the process of data management, unless a different approach has been agreed in the DMP.

6.14 Locking and unlocking the database

- Database locking is the process by which the database 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 a risk-based approach should be taken when deciding how to do this.

- Unlocking the database should take place only under exceptional circumstances,and requires due consideration by the sponsor and consultation with the statistician. 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.

6.15 Release of the final database/datasets

- Data should be extracted securely from the locked database to carry out the final analysis. The process to do this should be adequately described documenting how the data will be protected from alteration. Only the minimum amount of data required to undertake the final analysis should be made available to those undertaking the analysis. 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.

6.15 Transfer of data

- A Data Sharing Agreement should be put in place where data is transferred between organisations. The model non-commercial agreement (MnCA) or the Organisation Information Document (OID) are usually sufficient for data sharing between a participating site and the sponsor.
- Data sharing must be compliant with data protection legislation, including the Data Protection Act 2018 and UK GDPR.

6.16 Onward sharing of data for other research studies

- During set up of the research study, it should be considered whether the data collected should be made available at the end of the study for other researchers (e.g. creating a data resource). If so, this should be discussed with UHBW as sponsor and fully detailed in the initial application to the Research Ethics Committee and HRA. Any data sharing must be compliant with applicable regulations, e.g. the Data Protection Act 2018 and in line with participant consent.

6.17 Storage of data

Long term storage arrangements of study data after the study has ended must be documented within the DMP, agreed by sponsor and have REC and HRA approval as applicable. This should include how and who would share data after the study ends for further research.Any amendments to long term storage arrangements require REC and HRA approval (as applicable) and the DMP updated. All arrangements must comply with applicable data protection legislation (e.g. on security and long term access arrangements) and any other requirements as described in SOP_015 Archiving of research documents.

7. Dissemination and training in the SOP

This SOP will be disseminated to applicable research staff (including R&D) and will be available on the R&D website.

Plan Elements	Plan Details
The Dissemination Lead is:	Research Operations Manager
Is this document: A – replacing the same titled, expired SOP, B – replacing an alternative SOP, C – a new SOP:	A – replacing the same titled, expired SOP

If answer above is B: Alternative documentation this SOP will replace (if applicable):	N/A
This document is to be disseminated to:	All applicable research staff (including R&D)
Method of dissemination:	For major updates to the SOP dissemination will be: 1. To Chief Investigators of UHBW Sponsored CTIMPs 2. Research Unit leads across UHBW 3. Head of Research Governance at UoB (where SOP is applicable) All updates (major and minor to the SOP) will be: 1. Updated on the trust Document Management System 2. Updated on the R&D website 3. Cascaded in the R&D e-bulletin
Is Training required:	All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP. The personal training log of the individual (and the Investigator Site File/Trial Master File if required) should be completed to document that the content of this SOP has been read and understood as described in *SOP_007 Research Training UHBW*

REFERENCES	• Medicines for Human Use (Clinical Trials) Regulations (SI/2004/1031) and any amendments • MHRA Grey Guide (2012). • General Data Protection Regulation • Data Protection Act 2018 • HRA: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-detailed-guidance/transparency/
RELATED DOCUMENTS AND PAGES	• GD_007 CRF design: Key elements • GD_008 Source data: Key elements to include, with dates • SOP_007 Research Training • SOP_011 Validation and Backup of Computer Systems • SOP_015 Archiving of Research Documents • TMPL_041 Data Management Plan • These can be found on the R&D section of UHBW's website: http://www.uhbristol.nhs.uk/research-innovation/

AUTHORISING BODY	Trust Research Group
SAFETY	N/A
QUERIES AND CONTACT	Research & Development Department on 0117 34 20233 or research@uhbw.nhs.uk
AUDIT REQUIREMENTS	R&D departmental Quality Management System audits are undertaken annually.