SOP 02: Research Documentation and File Management

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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 Research & Innovation Webpage 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 Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded version are promptly withdrawn from use unless notified otherwise by the SOP Controller.

The definitive version of all Gloucestershire Hospitals NHS Foundation Trust 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&I website:

Research at our hospitals (gloshospitals.nhs.uk)

The Gloucestershire Hospitals NHS Foundation Trust wishes to acknowledge York Hospitals NHS Foundation Trust and University Hospitals Bristol NHS Foundation Trust who gave permission to use their templates in the development of these SOPs.

VERSION HISTORY LOG

This area will be updated with details of all changes made to the SOP whether due for full review or not.

Version	Details of Change	Date Implemented
1.0	Review and update along with reorganisation into the Gloucestershire R&D Consortium suite of SOPs previously SOP 09	01/11/2014
2.0	Update on HRA and electronic data	01/02/2017
3.0	Rebranding to GHNHSFT and updating of contact details	31/03/2018
4.0	Updating of Trust intranet link Updating of site file contents page to include: section on unblinding of treatment in a blinded trial GCP certificates within the CV section Clarification of source data/ use of source data forms Addition of electronic investigator site files	06/05/2021
5.0	Updating of Trust intranet link Updating of policy and document links Removal of fax policy and any references to using faxes Removal of e-communications and internet use policy which has been replaced by Acceptable use of information systems & equipment Clarification of current engagement with Electronic Patient Records Addition of non-CTIMP paper & e-ISF contents page appendices Addition of appendix detailing filing of documents on EDGE Addition of link to NIHR templates Addition of guidelines for filing patient research documentation into paper medical records Change of title of Trial Pharmacy File to Pharmacy Site File	31/03/2023
5.1	Removal of SOP categories and change of reference codes Updated format Updated references Changed R&D to R&I	03/01/2024

This SOP will be reviewed every two years unless changes to any relevant legislation require otherwise

Related Documents:

SOPs
SOP 03 - Training
SOP 04 - Informed Consent
SOP 05 - End of trial procedures – Close Down
SOP 10 - Hosting CTIMPs and other Clinical Trials
SOP 11 - Confirmation of capacity and capability
SOP 19 - Periodic Safety Reporting to Regulatory Authorities
SOP 20 - Adverse Event and Reaction Reporting
SOP 21 - Research Misconduct and Fraud
SOP 22 - Non-compliance and Serious Breaches
SOP 23 - Urgent Safety Measures
SOP 24 - Scientific Review
SOP 27 - Initiating Research - Sponsorship
SOP 28 - Application to the Trust for Sponsorship of a CTIMP
SOP 29 - Writing a protocol

Contents

1. Introduction, Background and Purpose

Maintenance of the correct and appropriate documentation in a manner suitable for managing the conduct of the trial and enabling evaluation by audit and inspection is essential for GCP compliance.

It must be possible to reconstruct the conduct of the trial at all stages from:

- set up (prior to patient recruitment),
- during patient recruitment and direct involvement
- for some time after its completion

from the documentation which is filed and retained within:

- the Trial Master File (TMF)
- Investigator Site File (ISF)
- Pharmacy Site File (PSF)Research and Development Study File (R&DSF)

from the perspective of:

- Sponsor/ CI
- PI and local research team
- Trust Research and Innovation Department (local research governance).

Trust policies and procedures must be adhered to in conjunction with this SOP and any that the Sponsor has written specifically for their trial. Any variations between SOPs from various sources should be discussed and decided upon before any trial activity starts at site.

2. Who should use this SOP?

All staff working on a trial should be familiar with the lay out and requirements of the file that is relevant to their role:

- Chief Investigators (CIs) and trial co-ordinators of clinical trials sponsored or co-sponsored by the Trust;
- Principal Investigators (PIs) and research staff at sites where multi-site studies sponsored or co-sponsored by the Trust are being run;

- R&I office personnel, who manage the sponsorship of trials on behalf of the Trust and support Trust hosted trials;
- PIs and research staff for externally-sponsored trials “hosted” by the Trust.

3. When this SOP should be used

This SOP must be referred to as soon as a trial is being considered for adding to the Trust trial portfolio. This will ensure that the necessary procedures to secure the quality of every aspect of the trial shall be complied with.

In accordance with Good Clinical Practice (GCP) the Sponsor should ensure appropriately qualified individuals are responsible for the overall conduct of the clinical trial, handling the data, verifying the data, conducting the statistical analyses, and preparing the trial reports.

The Sponsor should normally delegate data management within a clinical trial to the CI. Where the CI further delegates data management to another member of the research team this should be clearly outlined on the Clinical Trial Delegation Log.

For hosted trials, the PI or Local Collaborator (LC) is responsible for delegating roles and responsibilities at the participating site documented on the delegation log.

4. Trial Master File, Investigator Site File and Pharmacy Site File

4.1.1 Indexing TMF

The MHRA advise typically organising Sponsor files as follows:

Global level files	Documents in this file are relevant to the conduct of the trial at any site i.e. Investigator Brochure.

Country level files	Documents in this file are country – specific and are relevant to the conduct of the trial at any site in that country
Site level files	Documents in this file are specific to the conduct of the trial at a particular investigator site i.e., protocol signed by PI and delegation log

Potential document sources for the Sponsor TMF include:

- Trial pharmacovigilance documentation (SAE cases and reconciliation)
- Trial medication blinding/ unblinding process where applicable
- Trial specific IMP documentation (QP certification, certificates of analysis, shipping records)
- Regulatory documentation
- Trial contracts
- Clinical operations documentation
- Data management documentation
- R&I office documentation
- Vendor selection/ oversight documents
- Data management documentation
- Trial specific training records
- Trial specific computer system validation documentation
- Statistics documentation
- GDPR considerations

4.1.2 Indexing ISF (paper and electronic)

The Site File Index provided by the Sponsor/TU should be used. If, because of local requirements additional sections are needed to make essential documentation storage more practical, the Sponsor/TU will be informed of the proposed format and copies of the ISF or eISF provided with annotations.

If a Sponsor does not provide a Site File/ Site File Index then the Trust proforma template will be used (based on NIHR templates – Appendix 2a 2b non- 2c and 2d)

4.1.3 Indexing R&I Study Files

The Trust indexes for both paper files and electronic files should be used for all types of research (see Appendix 9)

4.2 Essential Documents

Essential documents are those records created from following trial procedures as well as those listed in guidance relating to the conduct of the trial and should be retained to demonstrate compliance with ICH GCP (see Appendix1).

Below are listed the minimum essential documents listed in E8 of GCP Guidelines:

- Investigator's Brochure
- Signed protocol and amendments, if any, and sample case report form (CRF)
- Information given to trial subject
    - Informed consent form (including all applicable translations)
    - Any other written information
    - Advertisement for subject recruitment (if used)
- Financial aspects of the trial
- Insurance statement (where required)
- Signed agreement between involved parties e.g.:
    - investigator/institution and sponsor
    - investigator/institution and CRO
    - sponsor and CRO
    - investigator/institution and authority(ies) (where required)
    - investigator/institution and external support department e.g. Cobalt Health for radiology

- Dated, documented approval/ favourable opinion of Trust R&D department (Institutional Review Board) and Independent Ethics Committee (REC) of the following:
    - protocol and any amendments
    - CRF (if applicable)
    - Participant Information Sheet/ Informed Consent Form(s)
    - any other written information to be provided to the subject(s)
    - advertisement for subject recruitment (if used)
    - subject compensation (if any)
    - GP letter (if applicable)
    - any other documents given approval/ favourable opinion
- Trust R&I department (Institutional Review Board) and Independent Ethics Committee (REC) composition
- Regulatory authority (MHRA) Authorisation/ approvals
- HRA
- Notification of protocol (where required)
- Curriculum Vitae and/ or other relevant documents evidencing qualifications of investigator(s) and sub-investigator(s)(signed and dated, updated annually)
- GCP certificates
- Normal values/ range(s) for medical / laboratory/ technical procedure(s) and/ or test(s) included in the protocol, (signed and dated by Laboratory Manager)
- Medical / laboratory/ technical/ procedures/ tests
    - certification or
    - accreditation or
    - established quality control and/or external quality assessment or
    - other validation (where required)
- Sample of label(s) attached to investigator product container(s)
- Instructions for handling of investigational product(s) and trial – related materials (if not included in protocol or Investigator's Brochure)
- Shipping records for investigational product(s) and trial related material(s)

- Certificate(s) of analysis of investigational product(s) shipped
- Decoding procedures for blinded trials
- Master randomisation list
- Pre-trial monitoring report
- Trial initiation monitoring report

The list above is not exhaustive and has some key omissions, below are some or all of which will be required to demonstrate GCP compliance:

- IMP handling
    - Qualified Person (QP) certification,
    - green-light document to release and ship IMP(s)
- electronic database documentation
- trial specific training given by PI to research staff
- centralised records relevant to a number of trials
    - written procedures
    - staff training records
    - maintenance and calibration records of equipment used in a trial

Therefore, an assessment of all activities carried out within a trial will be undertaken to determine whether they need to be documented to enable reconstruction of the trial conduct from the paperwork alone. Consideration will also be given to centrally stored electronic data, for example, Trust Mandatory Training/ other staff training records. These must be stored in accordance with Trust IT policies and guidelines and site file notes placed in the Trial Master File, Investigator Site File and Pharmacy Site File to indicate how these may be accessed by appropriately authorised Trust staff.

5. Source data, CRF and e-CRF

5.1 Source data

Patient information where it is recorded for the first time is defined as source data. Trial participants' notes, hospital / clinical records in any format (paper or electronic) are source documentation for source data. Any format used must

permit the reconstruction of the clinical care given to the participant and describe participant-specific events that have occurred during the conduct of the trial. Where copies are provided, they must be certified by the provider.

Key events to be recorded in trial participants' notes include the following below. Participants' notes can be electronic and paper-based. Currently the electronic system is used for inpatient medical records apart from the paper-based trial documentation, for example completed patient consent form, GP letter, Patient Information Sheet which are filed in the paper medical notes. Paper-based medical notes are used for outpatients

- Eligibility decision and any required supporting information not available elsewhere within the notes (signed and dated by PI Co-investigator or delegated member of the research team). Eligibility decision remains responsibility of a medic for a CTIMP trial
- Provision of subject information sheet/ invitation to consider the trial (including version and date)
- Receiving informed consent (including version and date)
- Randomisation or trial entry, including trial identification.
- Trial visits or follow up phone calls required by the protocol
- Treatment and dosing decisions, including changes to concomitant medication
- Reconfirmation of consent
- Any trial–related decisions relating to the clinical care of the subject
- Adverse events, their seriousness, causality and severity
- Withdrawal, termination or end-of trial involvement including any protocol defined follow up.

Where trial specific templates are provided by the Sponsor or devised by the research team to capture trial specific information, completed sheets should be retained within the hospital notes and blank versions filed in the site file. (See appendix 12)

The definition of source data must be agreed with the Sponsor during trial set up and documented so that future Sponsor monitoring for Source Data Verification purposes can be facilitated with the minimum of additional work for the research team.

The recording of data will be:

- Completed contemporaneously
- Signed and dated by the person making the entry. This may be wet ink signature or an appropriately controlled electronic signature.
- If retrospective entries or annotations are made then these should be obvious and will be signed and dated with the date the entries where added – electronic entries must have a clear audit trail
- All entries must include the details of the staff involved in the consultation and are countersigned where decisions have been made by staff other than the person making the entry. For example, a nurse is making the entry about dosing when the clinician decides to amend the dose – this then will need to be countersigned by the treating clinician.
- Where data is stored centrally on a trust computer system, the clinician must still be able to demonstrate that they have assessed these reports during the course of the trial.

5.2 Case Report Forms (CRFs) and electronic – Case Report Forms (e-CRF)

CRFs should be completed according to the specifications of each study by a delegated member of the research team, who has received training on the data collection requirements of the specific trial / study. CRFs should be completed in a timely fashion and, where possible within one month of the event taking place, unless another time frame is specified in the protocol (see Appendix 8 for Trust guidelines on completion CRFs). Access to eCRF systems must be in place for the PI as well as the research nurses/ co-ordinators and data officers.

6. File management

TMF, ISF, TPF and R&DSF should all be maintained contemporaneously. All documents must be filed in date order from most recent date to oldest date.

Copies of all correspondence between the site staff, Sponsors and trial participants must be retained. This includes printing off emails, with highlighting of pertinent information or adding numbering to the documents so that it is easier to reconstruct the flow of information.

The research team must check whether a trial participant has more than one set of notes within the Trust, for example general hospital notes and departmental specific notes (maternity, oncology (RTH notes), ophthalmology). Notification that the patient is a participant in a trial must be included in all paper notes so that all health care teams are alerted to the patient's involvement in a trial. Currently unable to use an alert in the electronic medical records that a patient is in a trial in the electronic medical records system. R&I are in discussion with the EPR team regarding this.

7. Format

The format of the documentation and its storage will be agreed with the Sponsor at trial set up. It therefore may be that the ISF is all paper based, or a combination of paper and electronic, or completely electronic.

Where a Sponsor provides an ISF format this should be used; if one isn't provided then the Trust proforma should be given to the Sponsor for sign off by them and used throughout the life of the trial. (See Appendix 2a and 2b)

8. Version Control

Systems should be in place for version control of documents. A chronology of amendments will be kept on file that records all the amendments submitted and

the documents that they relate to. Old versions of documents should be retained on file alongside the new versions with the old versions, clearly marked as superseded. Documents should be filed clearly in all folders chronologically, including correspondence whether the file is electronic or paper based.

9. Storage

Documents contained in the TMF, ISF and R&DSF may be original regulatory approvals and confidential information. The files should therefore be stored in a secure place with restricted access. A locked drawer, cupboard or dedicated room is recommended, depending on the size of the project. Electronic ISF should be held on a GHNHSFT server. The exact location of the e-ISF will be agreed by the specific research delivery team. The information regarding the electronic R&I files and information held on EDGE will be found in appendix 9 and appendix 10 respectively.

Before, during and after the conduct of the research, it is useful to bear in mind the archiving of the documentation. Documentation may need to be retrieved at a future stage and so a catalogue or index of documents should be maintained to ensure this process is not burdensome. (Further details are given in the SOP 05 End of Trial Procedures and Close Down and SOP 06 Trial Archiving.)

a. Where a study is not submitted electronically, digital versions of the documents should be requested from the sponsor and an Electronic Folder set up as above.

b. If the documents are not available electronically at all the paper copies provided will be scanned and stored in the usual manner.

c. The cover and spine of the physical R&I file should contain the same information as recorded on the R&I Number Allocation List. The physical R&I files ceased to be used from 1st April 2015 and all further documents from this point are stored electronically.

10. References

Records management - B0259 (sharepoint.com)

Clinical and non clinical information systems management policy - B0676 (sharepoint.com)

Health records - https://intranet.gloshospitals.nhs.uk/departments/corporate-division/health-records/

Maternity Health records - MB0556 (sharepoint.com)

Information Governance Policy - B0413 (sharepoint.com)

Data Quality- B0406 (sharepoint.com)

Consent Policy - A0297 (sharepoint.com)

IT Security - B0591 (sharepoint.com)

Acceptable Use of Information Systems & Equipment - B0742 (sharepoint.com)

Quality Assurance and Quality Improvement Process - B0679 (sharepoint.com)

EMA guidance to assist sponsors and investigators to comply with the requirements of the Clinical Trials Regulation (EU) No 536/2014. Guideline on the content, management and archiving of the clinical trial master file (europa.eu)

EMA expectation on source data - Guideline on computerised systems and electronic data in clinical trials (europa.eu)

MHRA position statement - https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/470228/Electronic_Health_Records_MHRA_Position_Statement.pdf

NIHR GCP supporting templates - Course: GCP Supporting Templates (nihr.ac.uk)

Appendix 1: GCP Guidelines E8

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.1	INVESTIGATOR'S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	INFORMATION GIVEN TO TRIAL SUBJECT - INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent	X	X
	- ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
8.2.5	INSURANCE STATEMENT (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X

8.2.6	SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.: - investigator/institution and sponsor - investigator/institution and CRO - sponsor and CRO - investigator/institution and authority(ies) (where required) -investigator/institution and external provider of support eg Cobalt Health and radiology	To document agreements	 X X X	 X X (where required) X
8.2.7	DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - subject compensation (if any) - any other documents given approval/ favourable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)	 X	 X

8.2.8	INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION	To document that the IRB/IEC is constituted in agreement with GCP	X	X
8.2.9	REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL (where required)	To document appropriate authorisation/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
8.2.10	CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and/or ranges of the tests	X	X
8.2.12	MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s) , and support reliability of results	X (where required)	X

8.2.13	SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
8.2.14	INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
8.2.15	SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
8.2.16	CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.2.17	DECODING PROCEDURES FOR BLINDED TRIALS	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
8.2.18	MASTER RANDOMISATION LIST	To document method for randomisation of trial population		X (third party if applicable)
8.2.19	PRE-TRIAL MONITORING REPORT	To document that the site is suitable for the trial (may be combined with 8.2.20)		X

8.2.20	TRIAL INITIATION MONITORING REPORT	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X

Appendix 2 Suggested Site File Contents (paper and electronic)

2a)

Investigator Site File Contents (CTIMP)

SECTION	TITLE	CONTENT/COMMENTS	SIGN & DATE WHEN COMPLETE
1	Protocol / amendments	• Current protocol • Protocol amendments • Historical protocols • Unblinding instructions and contact details (when applicable)	
2	Sample CRF/ QLQ Diary Cards	If too bulky to put in file place file note in this section stating where it can be found	
3	Regulatory approval documentation		
4	Site signature /responsibility log		
5	Curriculum Vitae GCP certificates	CVs for all research personnel listed in the signature/responsibility log GCP training specific to the level of freedom to act	
6	Patient Identification form Patient recruitment /screening form		
7	Sample of current and all historical Patient Information / Informed Consent form and GP Letter Completed patient Information and Informed Consent Forms		
8	Correspondence	File in chronological order all correspondence to/from the coordinating research body. File email communication Include a separate section here for newsletters	
9	Minutes from Initiation meeting Monitoring logs Notes of telephone calls	If the study is not monitored state this in a file note in this section Document telephone call in relation to agreements or significant discussions regarding trial administration, trial conduct, adverse events or protocol violations	
10	Blank serious adverse event forms and guidelines for their completion		
11	Notification of serious adverse events and/or safety reports	By Investigator to co-ordinating research body By co-ordinating research body to Investigator By co-ordinating research body to regulatory authorities (if this will not be supplied place a file note stating this)	
12	Randomisation details	Instructions (if applicable)	

13	Instructions for handling trial medication and trial related materials Shipping records	This responsibility is normally that of the clinical trial pharmacist if this is the case place a file note in this section stating this	
14	Clinical Laboratory	Laboratory normal reference ranges (including revisions) Laboratory certificate(s)	
15	Contracts	Investigator Commitment Statement/Study Acknowledgement Indemnity Confidentiality Clinical Trial Agreement including financial details. Completed and signed FDA 1572 form (if applicable) Financial disclosure letter (if applicable)	
16	Investigator's Brochure Safety alert letters/Updates		
17	Completed Data Queries		
18	Study Training Materials		
19	Miscellaneous (specify)…….		

AFTER THE COMPLETION OF THE TRIAL THE FOLLOWING MUST BE ALSO FILED IN THE SITE FILE

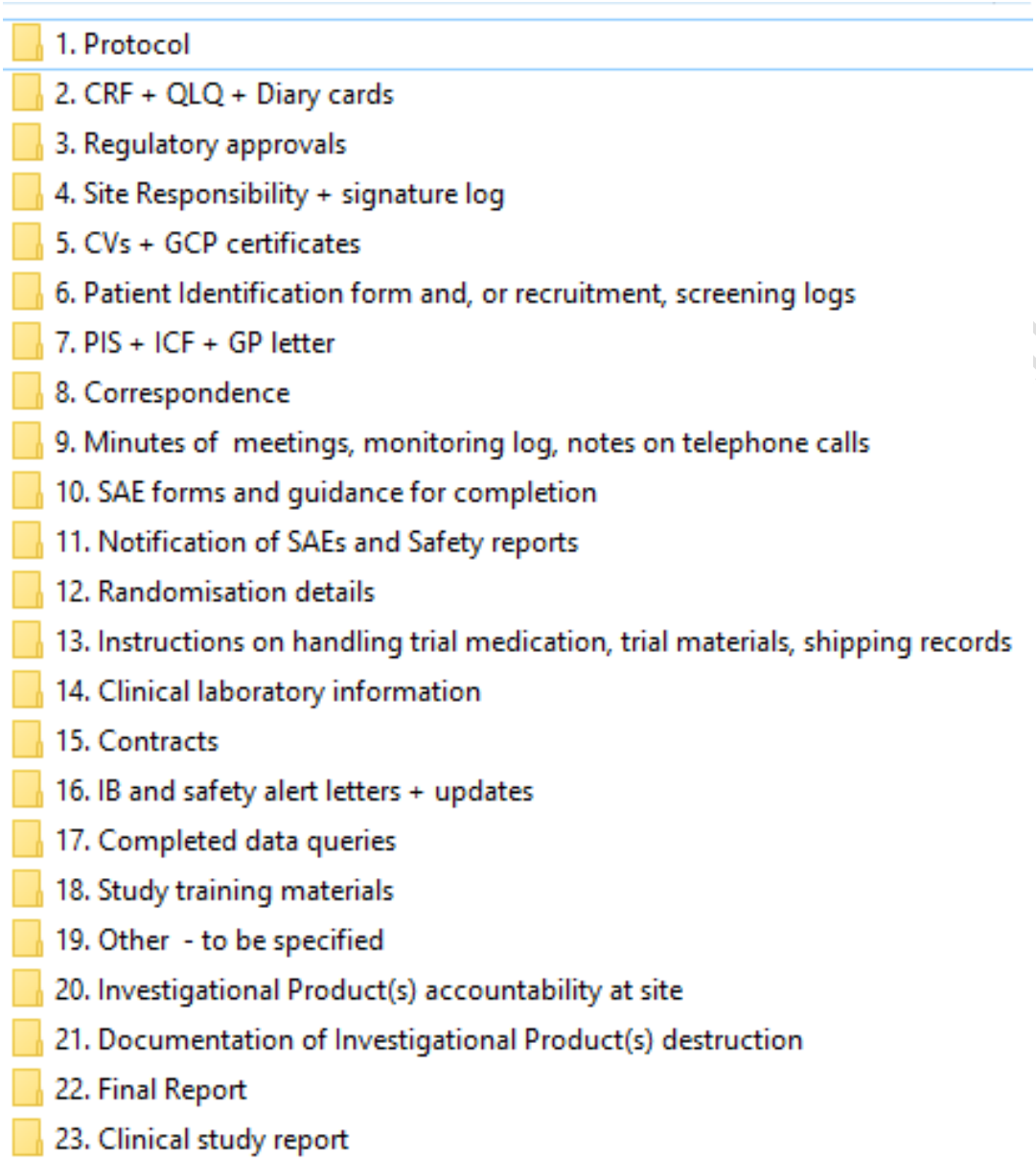
20	Investigational product(s) accountability at site	This will be with the clinical trials pharmacist	
21	Documentation of Investigational product destruction	If destroyed at site this will be with the clinical trials pharmacist	
22	Final report	From Investigator to REC	
23	Clinical study report	To document results and interpretation of trial	

2b) Investigator's Site File (ISF) Contents (non-CTIMP)

Section	Title	Content / guidance notes
1	Study personnel and contact list	• Names and contact details for key stakeholders, e.g. sponsor, chief investigator (if applicable), clinical research organisation, central laboratory etc. (if applicable) • CVs for all research personnel listed in the delegation of duties log
2	Protocol	• Current approved protocol (signed and dated) • Protocol amendments / superseded protocols (most recent on top)
3	Contracts and agreements	• Clinical Trial Agreement(s) (if applicable) • Indemnity and insurance documentation • Vendor contract(s) (if applicable)
4	Approvals and authorisations *(may be appropriate to separate individual approvals into specific sections)*	• Integrated Research Application System (IRAS) application • Research Ethics Committee (REC) application / correspondence • Study-specific approvals e.g. ARSAC - *sponsor will advise on which additional approvals are required* • Study-specific local approvals e.g. Biological Safety (if applicable) – *sponsor will advise on which additional approvals are required* • Capacity and Capability (Research and Innovation / R&I) approval
5	Approved documentation	• Current version of the Patient Information Sheet / Informed Consent Form / GP Letter
6	Delegation of duties log	• Completed Delegation of duties log, signed by PI
7	Study-specific training	• Completed training records or file note describing location of training documentation (e.g. training records are held centrally)
8	Screening and recruitment	• Subject Screening Log • Subject Enrolment Log • Subject Identification Log • Signed Informed Consent Forms

Section	Title	Content / guidance notes
9	Safety reporting	• Blank serious adverse event, pregnancy reporting form(s) and completion guidelines (if applicable) • Notification of reporting to REC (if applicable)
10	Case Report Form and data collection	• Sample Case Report Form, data collection forms, version and date • Any additional data collection forms e.g. Quality of Life questionnaires, patient diary cards *If the CRF is too large, include a File Note stating location e.g. electronic version held on shared drive*
11	Laboratory	• Evidence of retained tissue samples (if any)
12	Correspondence	*File in chronological order, most recent on top.* • Include any correspondence related to significant discussions around trial administration, trial conduct, adverse events or study issues / deviations / breaches • Minutes from meetings • Telephone call summaries / records
AFTER THE COMPLETION OF THE TRIAL THE FOLLOWING MUST BE ALSO FILED		
If applicable	Clinical study report	• Final report(s) including those to the REC • Any publications

c) Electronic Investigator Site File (CTIMP)



2d) Electronic Investigator Site File (Non-CTIMP)

1. Protocol
2. CRF + QLQ
3. Regulatory approvals
4. Site responsibility + signature log
5. CVs + GCP certificates
6. Patient identification form and, or recruitment, screening logs
7. PIS + ICF + GP letter
8. Correspondence
9. Minutes of meetings, monitoring logs, notes on telephone calls
10. SAE forms and guidance for completion
11. Notification of SAEs and safety reports
12. Randomisation details
13. Clinical laboratory information
14. Contracts
15. Completed data queries
16. Study training materials
17 Other – to be specified
18. Final Report
19. Clinical study report

Appendix 3 Site file note

File Note

Study:	**Principal Investigator:**
Date:	**Time:**

Print Name .....

Signature ..... Date. .....

Role ……..

Appendix 4 Trial Specific Training Log

[Study Title] Training Log

Topic	Date	Training given by	Training given to

Appendix 5 Study Specific Tracking Log

SIGNATURE						
DATE RETURNED						
SIGNATURE						
LOCATION						
DATE TAKEN FOR USE						
VERSION						
DOCUMENT						

Appendix 6 Trial Specific Treatment Allocation Log

Treatment Allocation Log

Study:	Patient ID:

Date	Treatment	Dose	Comments

Appendix 7: Appointment Checklist

Patient Details

STUDY: _____

STUDY ID: _____

Appointment Date						
Time						
Visit No						
Medical/Dr						
Annual Review						
Notes						
Bloods						
Meds						
PFT						
ECG						
Echo / CIMT						
Exam - Eye / E.Photos						
Transport						
Interpreter						
GP letter						
In Diaries						
Comments						

Appendix 8: CRF completion guidelines

Case Report Forms should be completed as soon as possible and no more than a month after the trial participant's visit or sooner if stipulated by the Sponsor.

Paper CRF'S

- Always check you are using the **correct version** number of the CRF.

1. Always use a **black ink** ballpoint pen.

2. Writing should be in **block capitals** wherever possible and only written in the designated box or lined area.

3. If the CRFs are printed on carbonless duplication paper, always make sure that a suitable separator is inserted under the form being completed. In addition, it is important to ensure that the bottom copy is legible before sending the top copy to the Trials Office. If necessary, a copy of the top copy should be made and retained. If the CRFs are only written on standard paper then ensure photocopies are kept. However photocopies of Quality of Life questionnaires should not be made and retained at site unless stipulated in the protocol.

4. Ensure all entries are **accurate, legible** and **verifiable** with the source data in the medical record and that data is entered in accordance with CRF completion guidelines for that particular trial.

5. Where source data forms (SDF's) are used to collect the information required for a CRF it is important not to rely on this data solely but also to check all other forms of information such as notes, Electronic Patient Records (EPR) correspondence, clinic sheets, , laboratory results, Trak, or other relevant hospital system. Where protocol visits are widely spaced, for example three monthly, all the information for the time between visits should be reviewed. Any discrepancies between the source data form and other information should be discussed with the person responsible for completing the SDF.

6. Any discrepancies with source data should be checked with a member of the medical team and an explanation of the significance should be noted in the CRF and/or patient's medical records. For laboratory values outside the laboratory's reference range or some other range agreed with the study Sponsor, or if a value shows significant variation from one assessment to the next, this should be commented on and the significance noted in the CRF and/or patients medical records.

7. **Never over-write an entry**. Corrections should be made as instructed by the TU, below are listed some examples:

    - Corrections should be made on the data query forms sent out by the Trials Unit (TU) and not on the retained copy of the CRF unless stipulated by the TU. If the retained copy is amended/updated this must be recopied and sent

to the TU to ensure that they have the most up to date version. Ensure any amendments to the CRF's are signed and dated.

- In some cases, CRF's are amended by the TU (some trials have an SOP in place to make self-evident correction) these amended CRFs are sent from the TU and should be attached to the relevant CRF.

- If it becomes apparent that data has been omitted or entered incorrectly in a manner which will not trigger the Trial Unit to issue a data query then the Trial Unit should be advised of the correct data in the format which they specify e.g., by email. Original CRFs should not be amended unless instructed to do so.

- Cross out the incorrect entry with a single line so that it is still readable. Never use correction fluid or obliterate entries made on the CRF. Enter the correct data and initial and date the correction.

8. The procedure to be followed for the resolution of data queries should be agreed with the study sponsor / TU and these should be completed by site staff in a timely fashion.

9. The CRF must be **signed** where indicated, by the Principal Investigator or designee (as appropriate) to assert that he/she believes they are complete and correct.

10. CRFs should be kept in a **secure location** during the course of the study. When CRFs have been completed they should be filed in a secure location with a file note in the site file to say where they are stored. When the study is closed to both recruitment and data collection CRFs should be archived, or stored according to the protocol.

Electronic CRFs

- **Training** should be completed as designated by TU before entering any electronic data.

- The SOP provided by the TU for inputting data/answering discrepancies / amending data should be adhered to.

- Discrepancies should be answered in a timely fashion in accordance with trial SOP.

- All data must be **saved prior to logging out**, as unsaved data will be lost.

- Electronic CRF data should be verified by a nominated person/trained member of staff to certify that the completed data is correct and in accordance with the patients' source data, as stipulated in trial SOP.

In General

- Ensure data entry is as complete as possible without omissions for both paper and electronic CRFs. **It is impossible for personnel doing the data entry to interpret blank spaces. If data is unavailable write, for example, '*unknown', 'missing', 'test not done',*** etc as defined by CRF Completion Guidelines (if applicable). Avoid using the ambiguous phrase, *'not available'*.

- Unless requested by the protocol, CRF or TU, laboratory values should be entered without conversion from printed reports even if in multi-centre study units of measurement differ from centre to centre, this applies to both paper and electronic CRFs. The units used should be specified where they differ from those shown on the CRF. If hard copies of laboratory values are required protocol, measures should be followed in terms of removing personal identifiable information such as the patient's full name.

11. The patient's identity should remain as confidential as possible at all times, providing only data requested by the TU. A record must be kept by the Investigator of patients in the study consisting of the patient's full name and study number; this is the Subject Identification Log.

Appendix 9 R&I Governance Study File Guidelines

1. **Allocation of unique identifiers**
   Immediately upon receipt of a new application, the study details will be added to the R&I allocation list for the appropriate Trust(s) as stored on the RDSU Shared Network Drive

   The R&I Reference is generated sequentially. For example, YY_XXX_GHT, where YY denotes the year of submission and XXX is a sequential number starting from 001. The Trust acronyms are:

   Gloucestershire Hospitals NHS Foundation Trust - GHT,
   Research running across several or all the Gloucestershire NHS Trusts will be suffixed with MTS (Multi-Trust Study)

2. **Naming Electronic folders**
   Each folder will use the following format:
   R&D Reference_BRIEF TITLE/ACRONYM
   For example 23/001/GHT_TEST

3. **Organising electronic folders on the shared IT drive GLNT199 (RDSU)**
   The electronic folder for trials in feasibility/ set up and delivery stages will be filed as follows:
   - PROJECTS
   - folder for the year of submission
   - TRUST acronym

4. **Sub folders within each electronic folder**
   R&I – all governance documentation including:
   - Trust Approval Letter
   - Support Department approvals/agreements
   - Local SSI Application/OID form
   - IRAS Application form
   - CVs/Good Clinical Practice certificates
   - Sponsor Letters
   - Indemnity Certificates
   - Investigator Brochures
   - Clinical Trial Agreements
   - Original Ethics Favourable Opinions/Amendment prior to R&I Approval
   - MHRA Clinical Trial Authorisations/Amendments prior to R&I Approval
   - HRA Approvals prior to R&I approval

   Current Study Documents – One set of the current, approved protocol and patient documentation. Superseded documents will be moved to the SUPERSCEDED folder within this folder

   Finance – all details of study funding will be stored here

For commercially sponsored trials the NIHR Costing Template **MUST** be included in this folder.

For academic trials details of any income or expenditure/SoECAT will be stored here.

Amendments After Initial C&C approval– To be organised within subfolders named by the REC amendment reference number and date. It will include the Amendment Approval Notification (letter or email)

Honorary Contracts/Letters of Access – Copies of relevant Research Passport and associated documentation along with copies of Honorary Contracts and Letters of Access will be stored here.

Correspondence – any pertinent correspondence relating to the study. Finance correspondence should be saved to the finance sub-folder.

Serious Adverse Events/ Adverse Events – Details of SAEs and any AEs that require reporting to the R&I Office will be recorded on EDGE

Governance Breaches – Details of any governance breaches.

5. Where a study is not submitted electronically, electronic versions of the documents should be requested from the sponsor and an Electronic Folder set up as above.

6. If the documents are not available electronically then the paper copies provided will be scanned and stored as for all research submissions.

Appendix 10:

Project and Project Site Files
Guidelines on how to upload documents to the EDGE Portfolio Management System

In order to maintain a clean data structure and approach to file storage, R&I use the EDGE Portfolio Management to upload and store study documentation. This should mirror the documents that are saved to the electronic R&I folder. This allows those researchers without RDSU drive access but with EDGE access to view these documents.

For more details on using and accessing EDGE please refer to the R&D SOP 12 - Trial Management on EDGE.

For documentation uploaded to EDGE there is a clear file structure.

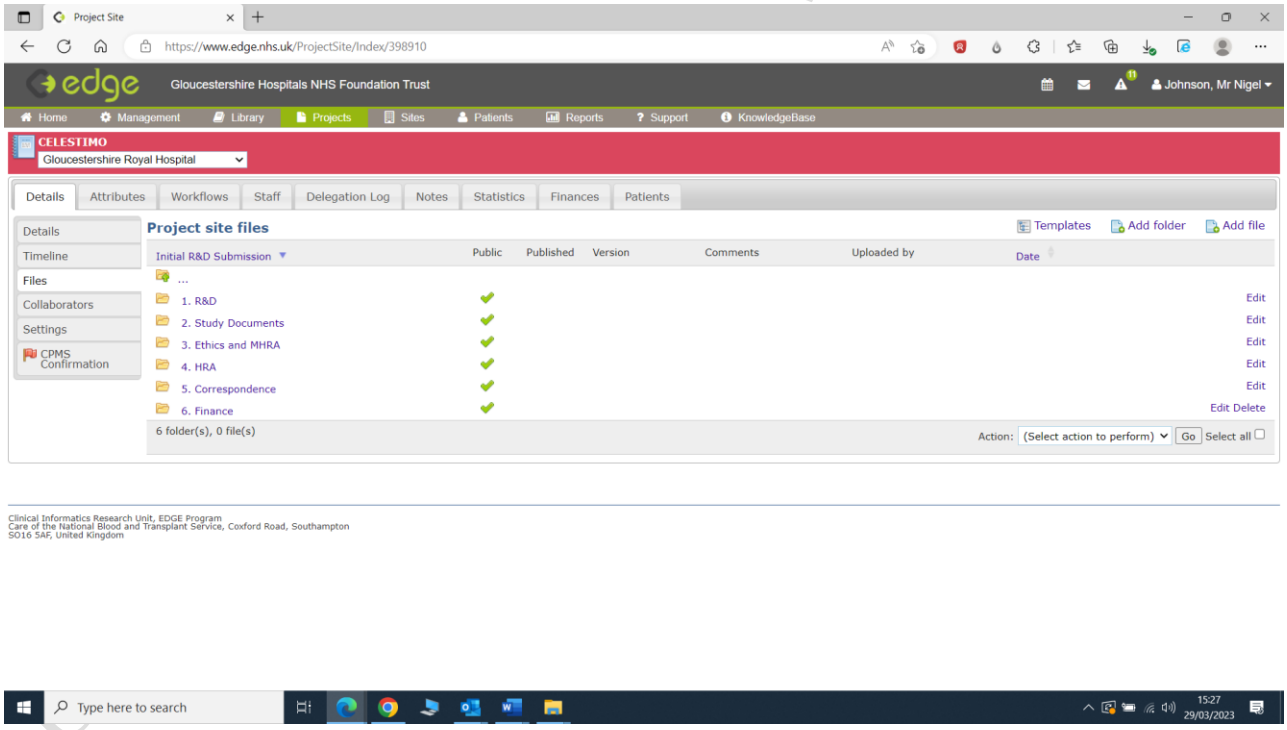
Following receipt of a Local Information Pack documentation that has been saved to the electronic R&I folder should be uploaded to EDGE.

It should be saved in the following format:

All documentation related to the study can be stored in the Files section on EDGE.

Study documents should be pertinent to the relevant study. Documents not related to the individual study should not be included in the folder.

A main folder will be created called 'Initial R&D Submission'.



Within the 'initial R&D Submission' folder there should be 6 sub folders.

1. R&D
2. Study Documents

3. Ethics and MHRA
4. HRA
5. Correspondence
6. Finance

Within this folder the following documents can be saved. The list is not comprehensive.

1. R&D

- Study Contract/OID
- Insurance information
- Sponsor letter
- CV of Principal Investigator
- GCP of Principal Investigator
- Email of C&C Approval

2. Study Documents

- PIS
- ICF
- STUDY Protocol
- CRFs
- Investigator Brochure/SPCs
- Other documents- Participant Diaries-if applicable
- Superseded documents- if the above documents are superseded during the set-up process due to a study amendment- then those documents should be moved to this sub folder.

3. Ethics and MHRA

- Original REC favourable opinion
- Original REC Covering Letter
- Original MHRA acceptance (if applicable)
- Original MHRA covering Letter
- All pre-approval amendments that follow the original REC/MHRA Approval

4. HRA

- Initial assessment letter
- HRA letter
- All pre-approval amendments that follow the original HRA Approval
- IRAS application

5. Correspondence

- Important email trails
- Correspondence related to set-up
- Email showing receipt of Local Information pack and study selection date
- Email confirming Greenlight for study to commence

6. Finance

- SoeCATt/ICT Download
- Income distribution sheet

- Email correspondence related to finance and income

It may be applicable to add the following sub folders to EDGE.
Honorary Contracts/Letter of Access – for those studies where a letter of access or Honorary Contract is required- documentation related to this should be uploaded. These would include:

- CV of LOA or HC Applicant
- Research Passport of LOA applicant -applicable to NHS Staff
- Letter of Access signed by the Head of R&I

How to upload documents to EDGE.
Documents should be uploaded in the following way:

Click Add file
Click Select file
Find the folder you want to upload to EDGE
Click select file and you should be able to download
Click on public and upload the file
The file should now be successfully uploaded.

Study Amendments
Once the study has received Local Trust Approval/Capacity and Capability any subsequent amendments should be saved in a separate folder for amendments. These should contain the following:

- Folder for each amendment after C&C
- Contract amendments

All amendment documentation should be saved to EDGE in the following format, for example;
Within the amendments folder there should be sub folders for every subsequent amendment.
Amendment 1
Amendment 2
Within each sub folder there should be sub folders for the following: see screenshot below.

1. R&D
2. Study Documents
3. Ethics and MHRA
4. HRA
5. Correspondence

Documents should be saved as per the guidance for uploading documents to the Initial R&D Submission folder.

1.

Appendix 11

Sample of Worksheet

Next appointment due	Gloucestershire Hospitals NHS NHS Foundation Trust

INCYTE 313

A Phase 3 Randomized, Double-Blind, Placebo-controlled Study of the combination of PI3Kδ Inhibitor Parsaclisib and Ruxolitinib in Participants with Myelofibrosis

Trial Number & Initials		MRN	
Date of Visit		Week	
Is the participant willing to continue? ☐ YES ☐ NO			Date of birth

Please ask the participant if there is anything they would like to make us aware of that might assist with their care

Dosing diary given to participant? ☐ YES	

DRUG COMPLIANCE			
Dosing diary reviewed?	☐ YES ☐	No, reason	
Correct dose taken?			
Total number of tablets returned	Parsaclisib/placebo		Ruxolitinib
Is the participant aware of any specific missing or incorrect doses from what was prescribed? ☐ No ☐ Yes			

TRANSFUSION HISTORY STATUS			
Transfusion history date			
Blood component (please circle)	Packed red blood cells	Platelet transfusion	Other, specify
Reason for PRBC/platelet transfusion	Anemia	Thrombocytopenia	Other, specify
Quantity and units/bags			

PHYSICAL EXAMINATION			
Was a full physical exam performed? ☐ Yes ☐ No, reason			ECOG
Was participant monitored for CMV? ☐ Yes ☐ No			
Has the participant taken antibiotics prophylaxis for PCP/PJP?			☐ Yes ☐ No
Has the participant reported signs of other viral or bacterial infections?			☐ Yes ☐ No

Status of edema compared to baseline, please circle: Improved / Same as Baseline / Worsened
Status of ascites compared to baseline, please circle: Improved / Same as Baseline / Worsened
Any interventions performed since last visit related to edema? YES / NO
Any interventions performed since last visit related to ascites? YES / NO

VITAL SIGNS TIME TAKEN -			
Pulse (beats/min)		Blood pressure (mmHg)	
Temperature (°C)	Respiration rate		Weight

SPLEEN PALPATION			
Was manual palpation of the spleen performed?		☐ Yes ☐ No, reason	
Was the spleen palpable? ☐ Yes ☐ No			
Spleen length from the left costal margin to the point of greatest splenic protusion			cm

PTO

LABORATORY INVESTIGATIONS - SERUM CHEMISTRY, HEMATOLOGY & COAGULATION, PREGNANCY TEST				
Have laboratory investigations been carried out? ☐ Yes ☐ No, reason				
PERCENTAGE RESULTS - % neuts = abs neut/total WBC , then X100 to get percentage.				
Neutrophils				
Basophils				
Monocytes				
Eosiphils				
Lymphocytes				
Have laboratory assessments been reviewed by clinician? ☐ Yes ☐ No, reason				
Pregnancy test - urine or serum? YES / NO / N/A			Kit number	

CENTRAL LAB SAMPLES
Lipid panel (overnight fast) required at week 12
Virology CMV required at weeks 4 and 8

PK PLASMA WEEK 4 ONLY
Kit number
Date & time of dose of parasaclisib/placebo prior to the predose PK sample
Date & time of dose of ruxolitinib prior to the predose PK sample
Date & time of meal prior to the predose PK sample
Contents of meal prior to the predose PK sample
Date & time of dose of ruxolitinib after PK sampling completed
Date & time of dose of parsaclisib/placebo after PK sampling completed
Did the subject have a snack/meal at this visit? No ☐ Yes ☐ date & time -

TRANSLATIONAL SAMPLES - WHERE TAKEN, PLEASE SPECIFY TYPE, TIME TAKEN AND SPECIMEN ID
Plasma correlative
Whole blood correlative DNA
Whole blood for PBMC
Whole blood correlative RNA

Completed by	**Designation**		**Date**
Verified togther with AE & Conmed form by	**Designation**		**Date**
			To be filed in the medical notes

Appendix 12

Guidelines on filing patient research documents in paper medical records and ISF

The following is not exhaustive but should act as a guide for the main documents. Refer to the Sponsor/ISF index for further details as locations may differ according to instructions from the Sponsor.

- **Paper notes alerted and stamped as described in page below**
- **Original clinical history sheet filed in the clinical record section of MRN notes. If other types of notes in use for example oncology (RTH) a copy will be placed in the clinical record section and any spare space crossed through to prevent any further addition being made to the copy.**
- **Correspondence including GP letter should be filed in the correspondence section.**
- **Copy of consent form and Patient Information Sheet filed in the legal section.**
- **Original signed and dated Patient Information Sheet (if using) and original consent form in the ISF.**
- **Case Report Forms filed in the ISF or a file note placed in the relevant section of the ISF documenting where the Case Report Forms are being stored.**
-

Gloucestershire Hospitals NHS Foundation Trust

Appendix 13: Schematic view of types of research documentation storage

(these are examples not definitive for all types of research – refer to HRA clinical trials toolkit)

Sponsor/CI

Trial Master File
Paper : Electronic

All documentation as specified in the contents pages:

- Documentary evidence of Trust Sponsorship/ co-sponsorship
- Funding
- Protocol development/ peer review
- Regulatory submissions
- Reporting schedules
- Monitoring Schedules
- IMP QP process
- Unblinding processes
- Independent data monitoring committee
- Trial management committee
- Trial supplies
- Laboratory accreditations
- Investigator Selection

Principal Investigator

Investigator Site File
Paper: Electronic

All documentation as specified in the contents pages:

- Where sponsor uses a generic contents page and a section is not relevant, a site file note must be put in specifying the section is left empty intentionally
- Where a Sponsor does not provide an ISF then the generic Trust one (App 2a) should be used and sections not required have a Site File note completed
- Where a Sponsor has agreed for the site to use an eISF but not provided one the standard format should be used (App 2b) and folders not required annotated as not applicable (n/a)

Trust Medical Records

Patient Notes
Paper : Electronic

Key research specific documents:

- Patient Information Sheet
- Informed Consent Form
- GP Letter
- Source data forms
- Notes will be marked with and ALERT sticker on the outside and details of TRIAL PATIENT -notes to be retained. The entry is signed and dated with the date the patient entered the study and the date notes cannot be destroyed before if know. Sponsor provided trial stickers can be used if dated/signed as described above.
- Electronic notes currently do not have a trial alert tab. This is being reviewed by the Electronic Patient Records team.
-

Trust Pharmacy

Pharmacy Site File

IMP specific information:

- Order/delivery receipts
- Accountability logs
- Temperature logs for refrigerators
- Unblinding information
- Specimen(s) of electronic prescription
- Pharmacy specific work sheets
- Pharmacy specific SOP(s)