St George's University Hospitals NHS
NHS Foundation Trust

Standard Operating Procedure (SOP)
Preparation and maintenance of the Trial Master File (TMF)

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SOP Chronology

SOP Version Number:	Reason for Change:	Author:
V1.0	Original Version	Zuhur Balayah
V2.0	Review of Original Version	Ira Jakupovic
V3.0	Responsibility of TMF maintenance transferred to CI and study team. New SOP format.	Debbie Rolfe
v4.0	Correction of typos	Lucy Parker
V5.0	New Logo and Trust name Addition of Sponsored Device and International CTIMPs. Change of title to HORG	Debbie Rolfe

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1. Background

The requirement to maintain a set of essential documents within the Trial Master File (TMF) comes from ICH GCP guidelines. ICH GCP is an internationally recognised standard for the initiation, conduct, recording and reporting of clinical research involving human participants, particularly drug trials. The principles of GCP were adopted in UK law in the Medicine for Human Use (Clinical Trials) Regulations 2004, which implement the European Clinical Trials Directive 2001/20/EC that was established to achieve standardisation of research activity in Clinical Trials throughout the European community. As a consequence, it is a legal requirement to maintain a TMF for all Clinical Trials of Investigational Medicinal Products (CTIMPs) within the scope of the Regulations.

For the purposes of this SOP the maintenance of trial related documentation will be applied to both CTIMPs and non-CTIMPs studies sponsored by St Georges.

2. Joint Research and Enterprise Office (JREO) Policy

All JREO SOPs will be produced and approved in accordance with the JREO SOP on SOPs and must be used in conjunction with local NHS Trust and St George's policies and procedures.

The JREO acts as the representative of both St George's University of London (SGUL) and St George's University Hospital's NHS Foundation Trust (SGHT). St George's will be the official name used on all SOPs to represent both institutions acting as clinical trials Sponsor.

3. Scope

The purpose of this SOP is to inform the Investigator and any nominated members of the research team on how to prepare and maintain a Trial Master file (TMF) throughout the lifetime of a study and to ensure that the filing system utilising the appropriate TMF index supplied by the JREO is used appropriately.

4. Definitions

4.1 Trial Master File (TMF)

The TMF is a file which contains all the essential documents that demonstrate that the trial has been conducted in accordance with regulatory requirements and ICH GCP. The TMF is set up at the start of a study and is archived at the end of the study for a set

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period of time which will be defined either in the protocol or Clinical Trials Agreement The TMF will contain essential documents which enable both the conduct and quality of the trial to be evaluated. The

Case Report Forms (CRFs), the Pharmacy Site File (PSF), Laboratory Manuals, where applicable, are all part of the TMF. However, during the active phase of the study they may be held separately within the appropriate departments. Responsibilities for the maintenance of each of these files may be delegated to appropriately placed/qualified study team members although the ultimate responsibility for their maintenance and upkeep will lie with the Chief Investigator (CI). The TMF and any of the subsections, e.g. PSF, must be made available for monitoring and audit purposes throughout the lifetime of the study. The TMF may also exist electronically and will be referred to in this SOP as 'eTMF'.

4.2 Investigator Site File (ISF)

An ISF is an Investigator Site File. This file is provided to each participating site (along with a Pharmacy Site File, if applicable) at the Site Initiation Visit. It contains all the information site staff will need to conduct the clinical trial at the site. The ISF forms part of the TMF, and will be made available for monitoring and audit purposes throughout the study.

4.3 Sponsor Site File (SSF)

The SSF is the file held in the JREO Office. Documents generated throughout the project development phase prior to study start will be retained in the SSF and e-TMF. The SSF will contain documentation to facilitate sponsor oversight of all aspects of the study e.g. regulatory submissions, pharmacovigilance and financial arrangements.

5 Responsibilities

5.1 Chief Investigator (CI)/Principal Investigator (PI) or lead Investigator

The CI or PI at St Georges is responsible for preparing and maintaining all the study files that form the TMF throughout the lifetime of the study.

For multicentre trials that are sponsored by St Georges , the PI at the respective sites will be responsible for the preparation and the subsequent maintenance of the ISF in accordance with the requirements of St Georges, the institution and any local requirements.

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The CI will be ultimately responsible for ensuring that updated documentation is provided to any participating sites, support departments and where necessary the JREO as guardians of the SSF. The CI may of course delegate this task to the Study co-ordinator. Responsibilities must be agreed and clearly defined at study start

Upon receipt of a TMF/SSF status report it will be the responsibility of the CI to collaborate with the JREO to provide highlighted missing essential documentation for filing.

The CI will ensure that the TMF will be made available for the purposes of monitoring, audit or inspection and will be held in a suitably secure location.

5.2 The Joint Research and Enterprise Office (JREO)

The JREO will be responsible for the set up and upkeep of the Sponsor Site File. Where the JREO is responsible for the initiation of any trial related activity during the lifetime of the study, a copy of any essential documentation will be provided to the CI for filing in the trial TMF within 3 working days.

Throughout the lifetime of the study the lead Research Governance Officer (RGO) and where appropriate for CTIMP studies the Clinical Trials Monitor (CTM) will be responsible for the maintenance and upkeep of the SSF.

The TMF and SSF will be reviewed periodically to ensure presence of correct versions of essential documentation. The TMF/SSF review will be co-ordinated by the JREO and undertaken by the assigned CTM or where appropriate the lead RGO. Any missing documentation will be noted on a TMF/SSF status report included within the routine monitoring visit or SSF review. A copy of the report will be provided to the CI and where appropriate the lead RGO/CTM.

6 Procedure

6.1 JREO Procedure Sponsored CTIMPs

a) Upon notification of a CTIMP proposal the JREO will provide the CI with a copy of the TMF index JREODOC0004 for sponsored CTIMPs.
b) The JREO will set up a paper CTIMP Sponsor Site File (SSF) using the JREO CTIMP file index JREODOC0066 and will also set up a full electronic SSF using the same filing reference locations.

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c) The JREO will maintain the SSF and provide copies of any documentation generated via the JREO as required for the TMF to the Chief Investigator or delegated Study team member within 3 working days. Examples of such documentation generated by the JREO during the lifetime of a study include MHRA submission, Archiving procedure, Open to Recruitment Letter and monitoring reports.

d) Upon receipt of any study related documentation for the trial SSF generated by the Study team, the JREO will ensure it is filed both physically and electronically according to the JREO site file index. Documents not provided electronically will be scanned in a compressed pdf format. Examples of documents that may be generated via the Study team include Annual Progress reports and Patient Information Sheets.

e) Upon receipt of the Final study report and confirmation from the CTM that all outstanding queries are resolved following TMF review the SSF will be archived together with the TMF following JREOSOP0016.

6.2 Investigator Procedure – Sponsored CTIMPS

a) The Chief Investigator or delegated study team member will obtain a copy of the TMF index JREODOC0004 and throughout the lifetime of the study ensure all documents generated are stored according to the index (see Appendix 1) provided in a secure location.

b) The Investigator will ensure the TMF is available at all times to the Research Governance Team for the purposes of monitoring, audit or inspection.

c) The Investigator will ensure that the TMF reflects all the most relevant study related information and that all superseded documents are stored and marked as such (clearly identifiable as superseded by a strike through line, initialled and dated). Any important relevant communications should be printed and stored within the correct indexed section to enable restructure of any important trial events at any given point in time.

d) The Investigator will provide documentation indicated as required by the sponsor or as requested following a TMF review, to the JREO team within 3 working days. e) At the end of the study and/or close out visit and upon resolution of any outstanding queries the TMF must remain intact and will be prepared for archiving following JREOSOP0016 by the Investigator.

6.3 JREO Procedure for Sponsored NON-CTIMP studies or hosted studies

a) The assigned RGO, upon notification of a proposed project will create both an electronic folder to represent the study eSponsor File and a physical file to reflect the index JREODOC0025. Where appropriate any protocol related documents will be uploaded as

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they are received to facilitate the management, approval and the subsequent safe conduct of the study.

b) The JREO will provide the CI with a copy of the index JREODOC0025 Governance/Investigator Site File index (appendix 2) for non-CTIMP studies upon request
c) The RGO will also provide a copy of the Host site permission letter to be filed in section 8 of the Site File.
d) The RGO will also provide copies of any documents throughout the lifetime of the study to the Investigator e.g JREO Amendment approval email, copies of financial contracts, copy of insurance certificate where applicable and as required.
e) The RGO will also ensure that both the physical study file and the eTMF is also kept current and up to date by efficient filing. For documents not provided electronically – then scan as compressed pdf.file and upload into the eTMF File. Examples of documents that may be generated via the Study team e.g. Annual Progress reports, Patient Information Sheets.
f) Upon receipt of the Final study report and confirmation from the RGO or where appropriate the sponsor that all outstanding queries are resolved following the close out visit that the JREO study file will be archived together with the ISF following JREOSOP0016.

6.4 Investigator Procedure Non CTIMP studies

a) The lead Investigator will ensure that any documentation generated in the lifetime of the study is filed according to the Study file index (an example is in appendix 2 – JREDOC0025) or according to the file index as supplied by the study sponsor in the Investigator Site File.
b) The lead Investigator will ensure that the ISF is available at all times for the purposes of monitoring, audit or inspection.
c) The lead investigator will ensure that any important correspondance received electronically is filed in the relevant section of the ISF.
d) The lead Investigator will ensure that any protocol related activity in respect of amendments or Annual Progress Reports are provided to the JREO in a timely fashion within 3 days of generation or upon request.
e) The investigator will ensure that the ISF reflects all of the most relevant study related documentation and that where required documentation is signed and checked where appropriate.

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f) At the end of the study and/or close out visit and upon resolution of any outstanding queries the ISF must remain intact and will be prepared for archiving following JREOSOP0016 by the Investigator for sponsor studies or under the instruction of the sponsor where studies have been hosted by St George's.

6.5 JREO Procedure for Sponsored Devices

a) Upon notification of a Device proposal the JREO will provide the CI with a copy of the TMF index JREODOC0082 for Sponsored Device Investigations.
b) The JREO will set up a paper CTIMP Sponsor Site File (SSF) using the JREO Device file index JREODOC0082 and will also set up a full electronic SSF using the same filing reference locations.
c) For Maintenance of the TMF and exchange of documentation refer to 6.1

6.6 Investigator Procedure for Sponsored Devices

a) Refer to 6.2

6.7 JREO Procedure for Sponsored International CTIMPs

a) Refer to 6.1 using JREODOC0076 International TMF index

6.8. Investigator Procedure for Sponsored International CTIMPs

a) Refer to 6.2

7 References

ICH GCP E6

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and as amended

EU Clinical Trials Directive 2001/20/EC

JREOSOP0016 Archiving of Clinical Trials at St Georges

8 Appendices

8.1 : CTIMP File Index

8.2 : Governance/Investigator Site File index JREODOC0025

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Appendix 8.1 example of CTIMP File Index

EudraCT number:		R&D number:	
Trial Acronym/Short Title			
Chief Investigator (CI):		Lead RGO:	

Table of content:		Yes	N/A
1.	**Sponsorship**		
1.1	Risk Assessment Questionnaire		
1.2	Sponsorship In Principle Letter		
1.3	Final Sponsorship Letter		
1.4	Insurance/Indemnity Policy		SGH studies
1.5	Peer Review (if applicable)		
1.6	Open to Recruitment letter		
1.7	Sponsor correspondence		
2.	**Agreements**		
2.1	IMP supply agreement	TMF	
2.2	Pharmacy Agreement (if applicable)	PSF	
2.3	Technical Agreement (if applicable)	TMF	
2.4	Laboratory Service Agreement	TMF	
2.5	CRO agreement	TMF	
2.6	Memorandum of Understanding (MoU)	TMF	
2.7	Funding agreements		
2.8	Annual Report to Funding organization (if applicable)		
2.9	Grant application(s)/award(s)		
2.10	Delegation of Duties Signed Agreement (DDSA)		
2.11	Other agreements		
3.	**Protocol**		
3.1	Final Approved Protocol		
3.2	Superseded Protocols		
3.3	Protocol reviews/meetings		
3.4	Draft protocols	TMF	
3.5	Log of Protocol Deviations		
4.	**Study Team documentation**		
4.1	Protocol and amendment(s) training log	TMF	
4.2	Protocol training materials e.g. presentations and attendance log	TMF	
4.3	JREO SOP read log (also for subsequent versions)	TMF	
4.4	Study Staff delegation & duties log	TMF	
4.5	Signature log	TMF	
4.6	CVs and GCP certificates for all staff on study delegation log	TMF	
4.7	Team meetings -minutes	TMF	
5.	**Subject/Patient Information**		

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5.1	Final Approved **Patient/Subject Information Sheet** (PIS)/(SIS)		
5.2	Final Approved **Informed Consent Form** (ICF)		
5.3	Final Approved GP Letter		
5.4	Superseded PIS,CF and GP letter		
5.5	Other study related information & documentation		
6.	**Research Ethics Committee**		
6.1	REC Application		
6.2	Validation letter including REC composition		
6.3	Provisional REC approval (if applicable)		
6.4	Response to conditions of approval (if applicable)		
6.5	REC Favorable Opinion Letter		
6.6	Annual Progress Reports (APRs)		
6.7	End of Trial Notification		
6.8	Final Report Notification inc. supporting documents		
6.9	Related Correspondence		
7.	**Medicines and Healthcare products Regulatory Agency (MHRA)**		
7.1	CTA application		
7.2	MHRA Acknowledgement Letter		
7.3	Notice of Acceptance Letter (and/or Non-acceptance Letter)		
7.4	Response to MHRA remarks (if applicable)		
7.5	Declaration of the End of Trial (DET)		
7.6	MHRA's DET Acknowledgement		
7.7	Final Report to MHRA inc. supporting documents		
7.8	Related Correspondence		
8	**Protocol deviation & Violation**		
8.1	Protocol deviation log		
8.2	Serious breach notification(s) and related correspondence		
9	**Amendments**		
9.1	Log of Amendment(s)		
9.2	Annex 2 and supporting documents (as submitted to REC and MHRA)		
9.3	Acknowledgement Letter		
9.4	Amendment **Ethics** approval letter		
9.5	Amendment **MHRA** approval letter		
9.6	Amendment **R&D** approval email/letter		
9.7	Related Correspondence		
10	**Investigational Medicinal Product (IMP)** **(File note 10.6-10.17 to be kept in PSF whilst study open)**		
10.1	Investigational Medicinal Product Dossier (IMPD) or simplified IMPD		
10.2	Investigator Brochure (IB)		
10.3	Summary of Product Characteristics (SmPC)		
10.4	SmPC Checking log	**PSF/TMF**	

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10.5	Previous versions of IMPD, SIMPD, IB & SmPCs	PSF	
10.6	Manufacturing Authorization License (MA(IMP)) (if applicable)	TMF	
10.7	IMP Label Template (sample approved by MHRA)		
10.8	Certified QP release statement (if applicable)	PSF	
10.9	Certificate of Analysis (CoA) (if applicable)	PSF	
10.10	TSE Certificate (if applicable)		
10.11	IMP Shipment Record	PSF	
10.12	IMP Prescription Template	PSF	
10.13	Temperature Log Template	PSF	
10.14	Temperature Deviation Log (if applicable)	PSF	
10.15	Dispensing procedure	PSF	
10.16	IMP Accountability Log Template	PSF	
10.17	IMP Destruction Log Template	PSF	
10.18	Master Randomization List	TMF/PSF	
10.19	Treatment allocation	PSF	
10.20	Decoding Procedure for Blinded Trials signed/agreed by pharmacy (if applicable)	TMF/PSF	
10.21	Related Correspondence	TMF/PSF	
11	**Pharmacovigilance**		
11.1	Adverse Events (AE) Logs		
11.2	SAE reports		
11.3	SUSAR reports		
11.4	Urgent Safety Measures		
11.5	Participant 24hr contact cards		
11.6	Notification of Safety Information to Investigators		
11.7	MHRA and REC Development Update Safety Reports (DSURs)		
11.8	Related Correspondence		
12	**Data Management and Statistical analysis/output**		
12.1	Final version of trial CRF(s)		
12.2	JREO review and approval of final version of CRF		
12.3	Previous version of trial CRF(s) (if applicable)	TMF	
12.4	Instructions for completion (if applicable)	TMF	
12.5	Data queries	TMF	
12.6	Computerised system/ Data base assessment		
12.7	Statistical Review		
12.8	Interim Data Analysis (if applicable)		
12.9	Related Correspondence		
13	**Monitoring**		
13.1	Completed Risk assessment		
13.2	Monitoring Plan		
13.3	Monitoring Visit log		
13.4	Intent to monitor correspondence		
13.5	Trial Site Initiation Report/Letter		
13.6	Pharmacy Initiation Report/Letter		
13.7	Sponsor Monitoring reports		
13.8	Close-out study report		

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13.9	Related Correspondence		
14	**AUDITS and INSPECTIONS**		
14.1	Correspondence of Intent to Audit		
14.2	Audit Follow up		
14.3	Regulatory Inspections		
14.4	Related correspondence		
15	**Central Laboratories**		
15.1	List of External Laboratories	TMF	
15.2	STG Evaluation / assessment	TMF	
15.3	Laboratory Accreditation Certificates	TMF	
15.4	Normal Reference Ranges	TMF	
15.5	Sample Shipment Record(s)	TMF	
15.6	Record of retained body fluids	TMF	
15.7	SOPs/Instruction manuals for trial specific procedure(s)	TMF	
16	**Publications**		
16.1	Presentation(s) related to current results	TMF	
16.2	Publication(s) related to current results	TMF	
17	**Trial Specific Documentation**		
17.1	Trial Specific SOPs (if applicable)	TMF	
17.2	Trial Specific SOP Deviation Form (if applicable)	TMF	
17.3	Trial Specific SOP reading log	TMF	
18	**Trial Committees**		
18.1	Meeting Agendas and Minutes	TMF	
18.2	Trial Management Group (TMG)	TMF	
18.3	Data Monitoring Committee (DMC)/Independent DMC	TMF	
18.4	Trial Steering Committee (TSC)	TMF	
19	**Correspondence**		
19.1	Emails/Letters	TMF	
19.2	Notes	TMF	
19.3	Trial Activity Sheet	TMF	
20	**Archiving Arrangements**		
20.1	Archiving Procedure	TMF	
20.2	Archiving Personnel Details	TMF	
21	**Site Specific Documentation** Please assemble Section 21 for **each site** detailed in section 21.1 participating in the trial (*i.e.* Section 21.2, 21.3 *etc.*)		
21.1	List of all trial sites (multicentre trials only)		
Participating Trial site Name and Identifier :			
21.2	Site suitability checklist (signed off by JREO)		
21.3	Site Contact Details	TMF	
21.4	Clinical Trial Site Agreement (CTSA)	TMF	
21.5	Site Set up documents checklist	TMF	
21.6	St George's site activation/initiation confirmation	TMF	
21.7	Site Specific Information Form (signed and dated)	TMF	
21.8	R&D Host Approval and subsequent amendment approvals	TMF	

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21.9	Protocol approval page and subsequent amendments (signed and dated)	TMF	
21.10	Site Pharmacy Arrangements (if different)	TMF	
21.11	St George's Recruitment Update (completed)	TMF	
21.12	Monitoring reports (if applicable)		
21.13	Audit Certificates (if applicable)		
21.14	Site correspondence	TMF	
21.15	SAE logs		
21.16	Protocol deviation logs	TMF	

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Appendix 8.2 JREO Governance/Investigator Site File Index

Section	Received Complete	Contents
1.		Annual Reports/ End of Study
2.		Miscellaneous/ Correspondence QA checks
3.		Amendments (Submission & Approval Documents)
4.		Approvals (CGL/BM/MHRA/REC/R&D)
5.		Finance (Award Letter/Costings/ Insurance/Contract)
6.		SSI Form
7.		REC AND R&D Forms (Sponsor Letter where appropriate)
8.		Protocol (and Peer Review if applicable)
9.		Associated Documents (PIS/ICF/GP Letter etc)
10		Personnel (CV's etc)

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