



Standard Operating Procedure

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Version	Date	Reason for change
1.1	May 2014	Addition of version control statement for SOP
2.0	October 2015	Update of weblinks and office details
3.0	August 2016	Update of weblinks and office details

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1.0 Background

The EU Good Clinical Practice (GCP) Directive 2001/20/EC was introduced to establish standardisation of research activity in Clinical Trials throughout the European Union. It was transposed into UK law as the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) which came into force on 1st May 2004. The Medicines for Human Use (Clinical Trials) Regulations together with subsequent amendments will be referred to as the Regulations in the rest of this document.

According to the National Institute of Health Research (NIHR), the purpose of monitoring is a system of ongoing checks to detect faults and failures and to fix them. The purpose of monitoring a clinical trial is to ensure that the rights and well-being of human subjects are protected; the reported study data are accurate, complete, and verifiable from source documents; the conduct of the study complies with the latest and approved versions of the protocol, complies with Good Clinical Practice (GCP), and with all applicable regulatory requirements. It is the responsibility of the sponsor to monitor a study. Where monitoring activities have been delegated to external parties, the sponsor remains accountable.

An audit of a clinical trial is a retrospective check of the study, and as defined by the NIHR this involves a “systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor Standard Operating Procedures (SOP), GCP, and the applicable regulatory requirement(s)”.

Monitoring for a CTIMP will usually be undertaken by the Sponsor or co-sponsor responsible for Parts 4 and 5 of the UK Clinical Trials Regulations, Good Clinical Practice and Pharmacovigilance respectively, and/or by a member of the study team. Where a contracted external monitor is to be used, it is important that before any monitoring takes place, a contract must be in place to cover the role and responsibilities of the monitor. The Delegation of Responsibility document will detail who will undertake monitoring.

How often monitoring will be undertaken will be determined by the assessment of the study protocol. This will usually be in the form of a risk assessment prior to the start of any study. Monitoring needs will be assessed throughout the duration of the study and following monitoring visits or should new information or incidents arise.

1.1 Purpose

This SOP outlines when and how the University will undertake monitoring, what form the monitoring will take and how often it will be conducted.

Monitoring must verify that:

- The rights and well-being of patients are protected

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- Ensure the safe use of medicines
- Ensure that safety data is detected, recorded and reported
- All reported trial data is accurate, checked for completeness, and must be verified from source documents
- That the conduct of the clinical trial is in compliance with the most recently approved protocol
- The trial team are suitably qualified and trained with up to date GCP training

The purpose of this SOP is to define the standards, process and procedures expected by The University of Manchester in relation to the monitoring of CTIMPs, of which it is sole or co-sponsor.

The monitoring process described in this SOP is intended to ensure that a CTIMP sponsored/ co-sponsored by The University of Manchester conforms to:

1. The UK Medicines for Human Use (Clinical Trials) Regulations 2004, SI 2004/1031, (please look it up, <http://www.opsi.gov.uk/si/si2004/20041031.htm>)
2. The UK Medicines for Human Use (Clinical Trials) Amendment Regulations 2006, SI 2006/1928,
3. The UK Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006, SI 2006/2984.
4. The UK Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008, SI 2008/941.

Compliance with the relevant regulations is essential. Non-compliance is an offence under UK Regulation 49. **“Any person who contravenes any of the following provisions (...) shall be guilty of an offence”:**

<i>regulation</i>	<i>Refers to</i>
3A	Sponsor's responsibility for the investigator's brochure
12 (1) and (2)	Requirement for authorisation and ethics committee opinion
13 (1)	Supply of IMP for the purpose of clinical trial
27	Conclusion of Clinical Trial
28 (1) to (3)	GCP and protection of clinical trial subjects
29	Conduct of Trial in accordance with trial authorisation etc.
29 A	Notification of serious breaches
30 (2)	Urgent safety measures
31A (1) to (3) and (5) to (10)	Trial master file and archiving
32 (1), (3) and (5) to (9)	Notification of adverse events
33 (1) to (5)	Notification of suspected unexpected serious adverse reactions (SUSARs)
34	Clinical trials conducted in third countries

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35 (1)	Annual list of suspected serious adverse reactions (SARs) and safety report
36 (1)	Requirement for authorisation to manufacture or import investigational medicinal products
42	Obligation of manufacturing authorisation holder
43 (1) and (6)	Qualified persons

Non-compliance could mean that a person could be personally guilty of an offence under the regulations.

All CTIMPs sponsored or co-sponsored by The University of Manchester will be monitored in a manner that meets the requirements of the standards set out in this SOP. Monitoring may be conducted by the Sponsor and/or co-sponsor or may be contracted out to external organisations. Where monitoring is to be contracted out to external organisations, The University of Manchester will ensure arrangements are in place that ensure it retains oversight.

Additionally, this SOP will also outline when and how the University will undertake auditing, what form the auditing will take and how often.

1.2 Procedure

The University of Manchester is responsible for ensuring a monitoring plan is in place for each CTIMP it sponsors. The University has nominated the Clinical Trials Management Group to oversee the conduct and management of all non-commercial clinical trials sponsored/co-sponsored by The University of Manchester.

The University of Manchester will require the following minimum standards to be achieved for all the non-commercial CTIMPs it sponsors/co-sponsors:

- All CTIMPs sponsored/co-sponsored by The University of Manchester will be audited at least once during the lifetime of the trial
- Where adequate external monitoring arrangements exist (to be determined by the Chair of the CTMG and the Research Governance, Ethics and Integrity Officer (Clinical Trials), regular monitoring reports will be submitted to the Research Governance, Ethics and Integrity Officer (Clinical Trials) either directly or via the CI. Schedules and scope for such reports will be agreed with co-sponsors.
- Where no adequate external monitoring arrangements exist, the CI will be responsible for ensuring that the trial is self-monitored using The University of Manchester's Self-Assessment Questionnaire (see Annex 1) or a modified form to collate relevant information on the status of the trial.

Monitoring

The extent of monitoring may be based on the outcome of an initial risk assessment of the clinical trial. Monitoring therefore must be proportional to the overall objective and design of the clinical study and will be agreed at the outset of the trial between the Sponsor(s) and the Chief Investigator/CTU and will usually be defined in an agreement.

Preparation for a Trial Monitoring Visit

Before visiting a site in order to monitor the trial, the monitor will complete the following steps in sequence:

1. Review the Sponsor Trial Master File, and identify any incomplete or missing documentation. This should include all regulatory documents.
2. Notify the PI, research nurse and pharmacist that monitoring will be undertaken in advance and, where appropriate, arrange a mutually convenient time for the monitoring visit. Ask the CI to make the TMF available on the day of the monitoring visit.
3. Request that medical notes, Case Report Forms (CRF) and, if required, Site Files (Investigator and Pharmacy) are made available.
4. Pharmacy visit may involve drug accountability checks and drug adherence calculated. Contact pharmacy to check what the accountability arrangements are if not known.
5. Ensure that necessary clearance (possibly Honorary Research Contract in non- NHS employed) is in place prior to visit.

Trial Monitoring Visit

1. Take all necessary precautions to adhere to the Data Protection 1998 law as well as any Trust policies.
2. Work through the monitoring tool in a systematic manner.

Consent forms should be checked for validity and accuracy. For subsequent visits only those consent forms completed since the last visit need be checked.

3. Source data verification (SDV) for the first visit should be a full 20% random sample; all documents need to be checked as per the patient notes' page of this monitoring tool.
4. Check whether any Adverse Events (AEs) have occurred, and whether the AEs were reported correctly; were any Suspected Unexpected Serious Adverse Reactions (SUSARs); reported within the required timeframes; have SAEs been reported to other PIs; has the IMP

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supplier been contacted; and have all the listed SAEs and SUSARs been reported to the MHRA and the main REC?

5. Check on the site and pharmacy files at each visit. The files and the documents contained within should be checked with care for validity and version control.

6. Pharmacy visits largely consist of checking the pharmacy site file and maintaining a good rapport with our pharmacy colleagues.

7. At the end of the monitoring visit feedback should be given to the CI. .

Findings arising from Monitoring Visit

Where a monitor finds suspicion of research misconduct, fraud or breach of GCP, this will be dealt with in accordance with the University Code of Practice for Dealing with Complaints of Misconduct in Research, as part of this process the relevant NHS R&D Trust may also be informed.

Following the monitoring visit, a monitoring report will be completed. Findings from the monitoring visit will be discussed with the CI. Any corrective and preventative actions which have been identified will also be discussed with the CI and a timeframe for remedial action will be discussed. Where there have been any deviations from the protocol or other issues these should be filed in the TMF.

Further information and documentation/guidance related to this SOP:

- Directive 2001/20/EC
- Directive 2005/28/EC
- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 1031)
- The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (SI 1928)

All the above can be accessed via/ downloaded from the MHRA website:

<http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/ImplementationoftheClinicalTrialsDirectiveintheUK/index.htm>

- The Research Governance Framework for Health and Social Care: Second Edition, 2005, which can be accessed via/downloaded from:
http://www.dh.gov.uk/en/Aboutus/Researchanddevelopment/AtoZ/Researchgovernance/DH_4002112
- Clinical Trials Toolkit information on monitoring, which can be accessed via/downloaded from
http://www.ct-toolkit.ac.uk/route_maps/map_landing.cfm?cit_id=248

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- Guidance on submission of substantial amendments to the MHRA, please see <http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/MakingclinicaltrialsubmissionstotheMHRA/index.htm>.

References:

RGF 2nd Edition

UK Clinical Trial Regulations

http://www.ct-toolkit.ac.uk/_db/_documents/Trial_MP.pdf

Annex 1

SELF-ASSESSMENT QUESTIONNAIRE FOR RESEARCHERS - non-commercial Clinical Trial of an Investigational Medicinal Product (CTIMP) which is sponsored or co-sponsored by the University of Manchester

This information required in this form should be maintained continuously during the trial in the Trial Master File (TMF)

Project Details	
Full Project Title:	
EudraCT Number	
REC Ref:	
Principal Investigator:	
Funding body	
Sponsor(s):	
This self-assessment questionnaire covers the period between _____ and _____	

***Please circle**

1. Trial Status: Please indicate the current status of the trial and record the associated dates accurately

In set-up?	Yes/No	What is the proposed/actual start date: _____
Recruiting?	Yes/No	What is the proposed/actual date that the first patient will be/was recruited? _____
		What is the proposed/actual end-date for recruiting? _____
In follow-up? (no extension)	Yes/No	When is the proposed/actual end-date of follow-up?: _____
Extended?	Yes/No	When is the proposed/actual end-date of follow-up?: _____
Completed?	Yes/No	What is the actual/proposed completion date: _____
Terminated?	Yes/No	What was the actual termination date: _____

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2. Patient Recruitment (across all sites)

- a. Overall recruitment target (as approved by the NHS REC & MHRA)? _____
- b. Overall number of patients recruited so far (i.e. enrolled/active participation)? _____
- c. Of your target recruitment , what percentage have you recruited to date? _____
- d. How many patients are in the treatment phase? _____
- e. How many patients have completed the trial treatment? _____
- f. How many patients are in the follow-up (i.e. the post treatment) phase?

- g. How many patients have withdrawn from the trial? _____
- h. What are the version numbers of the most recent Patient Information Sheet,
Consent form _____
GP letter _____
- i. Do you have evidence that these are the version numbers in current use at all sites? _____
- j. Where are the completed trial Case Report Forms (CRFs) stored? _____

3. Site Approvals

- a. How many sites have been given NHS R&D approval to date? _____
- b. Is there a signed site agreement (between the Sponsor and the Site R&D Office) in the TMF for each site? **Yes/No**

4. Trial Management

- a. What is the location at which the TMF is maintained?

- b. Please list the date and version number of the latest protocol? _____
- c. Please list the date and version number of the protocol which has been appended to the contract in the TMF?

- d. Have there been any substantial amendments in the last 12 months? **Yes/No**

Please list all amendments and reports submitted and approvals obtained in the past 12 months in the table overleaf, and to which organisation(s) this information was passed on to. You must have evidence to support your replies:

Submissions & Reports	Date of Approval/ Document	Is there evidence in the TMF of submission to each of these organisation(s)?									
		NHS Ethics		Sponsor(s)		MHRA		NHS R&D Sites		Is a copy available in the TMF?	
		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Substantial amendments (list each one separately)											
Annual Progress Report											
Annual Safety Report											
SUSARs (list each one separately)											

e. Is expenditure on this project within the original budget? **Yes/No**

f. Has the trial been monitored? **Yes/No**

g. Which organisation monitored the trial and when?

h. Has the trial been audited? **Yes/No**

i. Which organisation audited the trial and when?

j. Do you have, in your TMF, a record of the number of body fluid/tissue samples collected and the site of storage? **Yes/No/Not applicable**

k. Please list the contractual obligations to the funder (s) (e.g. submission of annual report)

Do you have written evidence that all contractual obligations have been met? **Yes/No**

5. Data security

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- a. Are the IT systems used to receive, store, process, transmit and archive trial data compliant with the following University standard operating procedures (available on the clinical trials website)?

SOP for Computerised Systems for Clinical trials **Yes/No**

SOP for IT Security and Encryption **Yes/No**

- b. Has a trial-specific Data Management SOP been drawn up in accordance with the University SOP for Data Management? **Yes/No**

- c. Has a trial-specific System Level Security Policy document been drawn up In accordance with the University SOP for System Level Security Policy? **Yes/No**

- d. Are there copies of all the above SOPs in the TMF? **Yes/No**

6. Safety Reporting

(i) SAEs

Period for which information required is: From _____ to _____

- a. Which sponsor is responsible for pharmacovigilance? _____

- b. How many SAEs have been reported in the above period (from all sites) _____

- c. How many SAEs in total have been reported in the study to date (from all sites)? _____

- d. Have all these SAEs been recorded in line with the protocol? **Yes/No**

- e. Have all these SAEs been reported to the appropriate Sponsor(s)? **Yes/No**

(ii) SUSARs

Period for which information required is: From _____ to _____

- a. How many SUSARs have been reported in the above period (from all sites) _____

- b. How many SUSARs in total have been reported in the study to date (from all sites)? _____

- c. Have these SUSARs been recorded in line with the protocol? **Yes/No**

- d. Have these SUSARs been reported to all the Sponsors? **Yes/No**

- e. Has a summary report, in the agreed format, been submitted to the University of Manchester in the above period? **Yes/No**

7. Trial Team Personnel and Training

****Delegation of responsibilities log**

- a. Have new members or new responsibilities been added to the Trial Team? **Yes/No**

- b. Is there a copy of the signed CV and GCP certificate for each team member

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- in the TMF (dated within the last two years of the date on this form)? **Yes/No**
- c. Have any changes to the IMP been checked with pharmacy? **Yes/No/Not applicable**
- d. Have all members of the Trial team accessed and read the University of Manchester Research Standard Operating procedures (SOPs)? **Yes/No**

****Please send a copy of the current delegation log with this completed questionnaire**

Any other issues

Please include all information regarding problems with the trial and use this space to expand and clarify your answers

--

Form Completed by:	
Delegated Role:	
Date Completed:	
Copy of Current Delegation Log Enclosed	Yes/No

Please return the completed form to Research-governance@manchester.ac.uk by the _____
and retain a copy in the TMF