Standard Operating Procedure

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<th>UM/UoM Monitoring/SOP13/4.0</th>
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<tbody>
<tr>
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<td>Monitoring of Clinical Trials</td>
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<tr>
<td>Author:</td>
<td>Dr Mohammed Zubair / Victoria Sheard</td>
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<tr>
<td>Reviewed by:</td>
<td>Dr Mohammed Zubair</td>
</tr>
<tr>
<td>Position:</td>
<td>Research Governance, Ethics and Integrity Manager</td>
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<tr>
<th>Version</th>
<th>Date</th>
<th>Reason for change</th>
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<tr>
<td>1.1</td>
<td>May 2014</td>
<td>Addition of version control statement for SOP</td>
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<tr>
<td>2.0</td>
<td>October 2015</td>
<td>Update of weblinks and office details</td>
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<tr>
<td>3.0</td>
<td>August 2016</td>
<td>Update of weblinks and office details</td>
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<tr>
<td>4.0</td>
<td>March 2018</td>
<td>Updated processes</td>
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UM/UoMMonitoring/SOP/4.0
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To access the most up-to-date version of this document please visit the University of Manchester Research Governance website: http://www.staffnet.manchester.ac.uk/services/rbess/governance/
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. A vendor assessment will also be requested from the delegated institution.

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 breakdown and detail who will undertake monitoring.

The frequency of monitoring to be undertaken will be determined by assessment of the study protocol in a risk based approach. This will usually be in the form of a risk assessment prior to the start of any study. Monitoring frequency needs will be assessed throughout the duration of the study as well as following monitoring visits or if new information or incidents arise.

2.0 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
• 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, processes 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:

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”:

<table>
<thead>
<tr>
<th>regulation</th>
<th>Refers to</th>
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<tbody>
<tr>
<td>3A</td>
<td>Sponsor’s responsibility for the investigator’s brochure</td>
</tr>
<tr>
<td>12 (1) and (2)</td>
<td>Requirement for authorisation and ethics committee opinion</td>
</tr>
<tr>
<td>13 (1)</td>
<td>Supply of IMP for the purpose of clinical trial</td>
</tr>
<tr>
<td>27</td>
<td>Conclusion of Clinical Trial</td>
</tr>
<tr>
<td>28 (1) to (3)</td>
<td>GCP and protection of clinical trial subjects</td>
</tr>
<tr>
<td>29 A</td>
<td>Conduct of Trial in accordance with trial authorisation etc.</td>
</tr>
<tr>
<td>29 A</td>
<td>Urgent safety measures</td>
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<tr>
<td>31A (1) to (3) and (5) to (10)</td>
<td>Trial master file and archiving</td>
</tr>
<tr>
<td>32 (1), (3) and (5) to (9)</td>
<td>Notification of adverse events</td>
</tr>
<tr>
<td>33 (1) to (5)</td>
<td>Notification of suspected unexpected serious adverse reactions (SUSARs)</td>
</tr>
<tr>
<td>34</td>
<td>Clinical trials conducted in third countries</td>
</tr>
<tr>
<td>35 (1)</td>
<td>Annual list of suspected serious adverse reactions (SARs) and safety report</td>
</tr>
<tr>
<td>36 (1)</td>
<td>Requirement for authorisation to manufacture or import investigational medicinal products</td>
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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.

3.0 Procedure
The University of Manchester is responsible for ensuring a monitoring plan is in place for each CTIMP/Medical Device study 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/Medical Device studies it sponsors/co-sponsors:
• All CTIMPs/Medical Device studies 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 Clinical Trials Management Group (CTMG) and the Research Governance, Ethics and Integrity Manager (Clinical Trials), regular monitoring reports will be submitted to the Research Governance, Ethics and Integrity Manager (Clinical Trials) either directly or via the CI. Schedules and scope for such reports will be agreed with co-sponsors. Such reports will be reviewed by the CTMG to maintain oversight of delegated activities.
• Where no adequate external monitoring arrangements exist, activities must be put in place by the CI in conjunction with the Research Governance, Ethics and Integrity Team to ensure all relevant information on the status of the trial is collected and subsequently reviewed.

3.1 Monitoring
The extent of monitoring will be based on the outcome of an initial risk assessment of the clinical trial, following a risk based approach. 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/Clinical Trials Unit (CTU) and will usually be defined in an agreement. Monitoring will take place centrally and/or on-site.

When monitoring activities are delegated to trained staff at a CTU, local processes will be followed with regards to adequate staff training, development of monitoring plans and scheduling.
of visits. All organisations delegated such activities will have previously completed a vendor assessment and obtained Sponsor approval via CTMG. The Sponsor requires review, input and sign off into all proposed monitoring plans.

Monitoring plans are expected to include the following checks as a minimum as well as a provision for triggered and escalated monitoring, and any study specific requirements. Triggered monitoring may be in relation to the timing of the first on-site visit or downstream of any halts, deviations or breaches to the trial:

- Consent and Eligibility
- Delegation Logs
- Study Endpoints
- Other Data (SDV)
- IMP Management
- Safety (Reporting of AEs)
- Implementation of Amendments
- Investigator Site File / Pharmacy Site File

### 3.2 Preparation for a Trial Monitoring Visit

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

1. Review the Trial Master File (TMF), and identify any incomplete or missing documentation. This should include all regulatory documents and approvals.

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 local PI to make the ISF 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 adherence and drug accountability checks. Contact pharmacy to check what the accountability arrangements are if not known.

5. Ensure that necessary clearance (possibly Honorary Research Contract for non-NHS employees) is in place prior to visit.

6. Ensure relevant access to buildings and passwords has been obtained beforehand

The monitor should have an understanding of the protocol and all relevant governance requirements as well as an awareness of any conditions in place following ethical or regulatory approval and any amendments to the study prior to the visit.

### 3.3 Trial Monitoring Visit – the monitor should:

1. Take all necessary precautions to adhere to the Data Protection Act 1998 as well as any local/Trust policies.
2. Work through the monitoring plan 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 at least 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 there any Suspected Unexpected Serious Adverse Reactions (SUSARs); were 
they reported within the required timeframes; have SAEs been reported to other PIs; has the IMP 
supplier been contacted; and have all the listed SAEs and SUSARs been reported to the MHRA, 
main REC and the Sponsor.
5. Check on the site and pharmacy files at each visit. The files and the documents contained 
within these files should be checked with care for validity and version control with focus on any 
amendments.
6. Pharmacy visits largely consist of checking the pharmacy site file and maintaining a good 
rappor with pharmacy colleagues.
7. At the end of the monitoring visit feedback should be given to the local PI.

3.4 Findings arising from Monitoring Visit
Following both on-site and central monitoring, a monitoring report will be completed. Findings 
from the monitoring visit will be disseminated to the site, CI and Sponsor. Any corrective and 
preventative actions which have been identified must also be discussed with the PI 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 ISF. Minor incidents and issues across all 
elements of the trial should be reported to the Sponsor via the monthly and quarterly Sponsor 
reporting channels. Where deemed serious/necessary the Sponsor should be approached 
outside of this reporting timeframes. These will be reviewed and actioned by the Research, 
Governance, Ethics and Integrity team. Where resolution cannot be made CTMG will be 
consulted.

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 Investigating Concerns about the 
Conduct of Research. As part of this process the relevant NHS R&D Trust may also be informed.

4.0 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)
- UK Policy Framework for Health and Social Care Research
- Clinical Trials Toolkit information on monitoring, which can be accessed here: 
- Guidance on submission of substantial amendments to the MHRA, please see 
  https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-
safety-issues
5.0 References:

- UK Policy Framework for Health and Social Care Research
- UK Clinical Trial Regulations
- http://www.ct-toolkit.ac.uk/