Standard Operating Procedure

Number: UM/UoM Substantial (& non) Amendments /SOP09/6.0
Title: Substantial and non-substantial amendments to Clinical Trials
Version: 6.0 (March 2018) Effective Date March 2018
Author: Dr Karen Schafheutle/ Victoria Sheard Review Date March 2020
Reviewed by: Dr Mohammed Zubair Approved By: Prof Deborah Symmons
Position: Research Governance, Ethics and Integrity Manager
Position: Chair of Clinical Trials Management Group
Signature: 

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Reason for change</th>
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<tbody>
<tr>
<td>2.0</td>
<td>January 2013</td>
<td>Update of weblinks and office details</td>
</tr>
<tr>
<td>3.0</td>
<td>April 2014</td>
<td>Addition of version control statement for SOP and additional reporting to Contracts team and Insurance office amendments</td>
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<tr>
<td>4.0</td>
<td>October 2015</td>
<td>Update of weblinks and office details Amendments to be reviewed by RGE&amp;I officer</td>
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<td>5.0</td>
<td>August 2016</td>
<td>Update of weblinks and office details</td>
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<tr>
<td>6.0</td>
<td>March 2018</td>
<td>Update in line with updated documentation</td>
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1.0 Background

The European Clinical Trials Directive 2001/20/EC (“the Directive”) was introduced to establish a standardised framework for good practice in the management of Clinical Trials throughout the European Community. The Directive sets out how clinical trials investigating the safety or efficacy of a medicinal product for use in humans must be conducted, and includes clinical trials involving healthy volunteers as well as small scale or pilot studies. The Directive also requires clinical trials to be conducted in compliance with the principles of Good Clinical Practice (GCP), with detailed standards subsequently published as the European Directive 2005/28/EC (usually referred to as “the GCP Directive”).

The Directive was transposed into UK law as the Medicines for Human Use (Clinical Trial) Regulations 2004, statutory instrument SI 2004/1031, which came into force on 1 May 2004. This statutory instrument and all its subsequent amendments (including SI 2006/1928, which transposed into UK law the GCP Directive), will be referred to as “the Regulations” in the rest of the document.

The Regulations are intended to protect the rights, safety and well-being of research participants in Clinical Trials of Investigational Medicinal Products (CTIMPs) and to harmonise, and make transparent, regulatory processes relating to clinical trials of medicines for human use.

In order to be compliant with the law, organisations conducting CTIMPs must have clearly documented Standard Operating Procedures (SOPs) covering all aspects of conducting Clinical Trials.

Amendments are changes that are made to the protocol, other essential documentation or other aspects of CTIMP/Medical Device arrangements after a favourable ethical opinion/HRA approval and/or approval by a regulatory body has been given. An amendment to a clinical trial can be either substantial or non-substantial.

This guidance applies when an amendment is required to any or all of the following

- The Clinical Trial Authorisation (CTA)
- The terms of the Research Ethics Committee (REC) application
- The terms of the HRA Approval Application
- The protocol
- Other trial documentation or particulars reviewed and approved by the Medicines and Healthcare products Regulatory Agency (MHRA) or main REC/HRA, during the initial or any subsequent reviews.
2.0 Purpose

This SOP relates to CTIMPs (i.e. all Trials which come under the Regulations, where The University of Manchester is the Sponsor or co-sponsor) or trials of Medical Devices. The requirements of this SOP should be applied as a minimum to such trials and in conjunction with all applicable University policies and procedures; and the policies and procedures of the relevant NHS Trust.

The purpose of this SOP is to define the process and procedures for submitting substantial and non-substantial amendments for CTIMPs/Medical Devices to the Sponsor(s), the main REC, the HRA and the MHRA; and for implementing the approved changes.

3.0 Roles and responsibilities

The Chief Investigator, or delegated individual, is responsible for notifying the Sponsor(s) of any planned amendments to a CTIMP/Medical Device throughout the life cycle of the trial.

It is the legal responsibility of the Sponsor(s) to decide whether an amendment is substantial.

Where the trial is not sole sponsored by The University of Manchester, planned amendments must be submitted to all co-sponsors.

For the purposes of this document the person responsible for managing amendments will be referred to as the Chief Investigator. However, this task may be delegated to another individual or organisation (e.g. Co-sponsor/PI/CTU). Where the SOP refers to the Chief Investigator it is also deemed to apply to any such delegated individual or organisation (as stated on the delegation log).

The clinical trial delegation log should clearly state the named individual responsible for managing amendments. All amendments must be submitted to the Sponsor(s) for review prior to submission to the main REC, HRA and MHRA.

Review and approval of amendments will be made on behalf of the Clinical Trials Management Group (CTMG) by a member of the Research Governance, Ethics and Integrity team and presented at the next meeting of the CTMG to avoid any delay of the trial. Where deemed necessary, amendment approval will be sought from CTMG prior to submission.

The Sponsor expects the CI/Trial team to maintain a log of all amendments processed. This log should be stored within the TMF. In addition, an amendment log and associated action/update should be introduced into all documents as amendments are required.
4.0 Procedures

4.1 Classification of amendment

A non-substantial amendment can be defined as a change to the details of a study which will have no significant implications for participants, for the conduct of the study, its management or scientific value. Non-substantial amendments do not have to have prior authorisation, but must be recorded and be available upon request for inspection by the Sponsor(s) or authorised external agency both centrally and at the trial site(s). For CTIMPs, it is expected that the Sponsor is notified using Annex 1.

All other amendments are substantial amendments. Substantial amendments (except for urgent safety measures) (see Section 4.2) require a favourable opinion from the main REC, HRA Approval and approval from the MHRA, before the amendment can be implemented:

The Chief Investigator should complete all sections of the Amendment Assessment form (Annex 1), including those relating to the classification of the amendment and actions required, and submit to the Sponsor for review and approval. This should be at least 10 working days before the planned submission of the amendment (if substantial) to the main REC, HRA or MHRA. This is mandatory for Substantial Amendments. Where applicable, sign off from the relevant Clinical Trial Unit (CTU) member or trial statistician is required before submission to the Sponsor.

Upon review of the form, the Sponsor may require changes to the ‘Amendment classification’, ‘Type of Notification required’ and ‘Actions required’. The updated amendment should then be resubmitted to the Sponsor.

Substantial amendments will be shared with the University Insurance Office and the University Contracts team if applicable.

4.2 Substantial amendments

Amendments may arise from changes to the terms of the CTA, REC approval or HRA approval, changes to the protocol of the trial or from information becoming available that requires changes to be made to the scientific documents produced and used in support of a trial.

Amendments are to be regarded as substantial where they are likely to have a significant impact on one or all of the following:

- the safety or physical or mental integrity of the subjects
- the scientific value of the trial
- the conduct or management of the trial, or
- the quality or safety of any IMP/Device used in the trial
Arrangements must be in place for taking appropriate **urgent safety measures**, i.e. measures that have to be taken to protect participants against any immediate hazard (e.g. from events relating to the conduct of the trial or the development of the investigational medicinal product (IMP)), and may include termination of the trial. Please refer to the relevant **SOP11: Urgent Safety Measures. All other substantial amendments must receive MHRA and REC/HRA authorisation as necessary before the amendment is implemented.**

**Examples of substantial amendments**, from EU guidance, are given below.

- **Amendments related to the protocol:**
  - Purpose of trial
  - Design of trial
  - Informed consent
  - Recruitment procedure
  - Measures of efficacy
  - Schedule of samples
  - Addition or deletion of tests or measures
  - Number of participants
  - Age range of participants
  - Inclusion criteria
  - Exclusion criteria
  - Safety monitoring
  - Duration of exposure to the investigational medicinal product(s)
  - Change in dosage of the investigational medicinal product(s)
  - Change of comparator
  - Statistical analysis
  - Temporary halts

- **Amendments related to the trial arrangements:**
  - Change of the principal investigator or addition of new ones (NB this means the lead investigator in each centre)
  - Change of the coordinating investigator
  - Change of the trial site or addition of new sites
  - Change of Sponsor or legal representative
  - Change of the Clinical Research Organisation (CRO)/Clinical Trials Unit (CTU) assigned significant tasks
  - Change of the definition of the end of the trial
• **Amendments related to the IMP/Device:**
  o Addition to stability data/change of expiry date
  o Change of formulation
  o Additional toxicology data
  o Change to route of synthesis

# Addition of a new site should be sent to the MHRA as a substantial amendment but for NOTIFICATION ONLY. This notification does not attract a fee. There is no requirement to wait for a response from the MHRA but the submission will be acknowledged. Please note Patient Identification Centres are not classed as research sites and thus do not require to be processed as a substantial amendment,

• **Changes to investigational medicinal product quality data concerning:**
  o Change of name or code of IMPs
  o Immediate packaging material
  o Manufacturer(s) of active substance
  o Manufacturing process of the active substance
  o Specifications of active substance
  o Manufacture of the medicinal product
  o Specification of the medicinal product
  o Specification of excipients where these may affect product performance
  o Shelf-life including after first opening and reconstitution
  o Major change to the formulation
  o Storage conditions
  o Test procedures of active substance
  o Test procedures of the medicinal product
  o Test procedures of non-pharmacopoeial excipients

• **Changes to non-clinical pharmacology and toxicology data where this is relevant to the ongoing trials (i.e. altered risk: benefit assessment). For example data concerning:**
  o Results of new pharmacology tests
  o New interpretation of existing pharmacology tests
  o Result of new toxicity tests
  o New interpretation of existing toxicity tests
  o Results of new interaction studies

• **Changes to clinical trial and human experience data where this is relevant to the ongoing trials (i.e. altered risk: benefit assessment). For example concerning:**
  o Safety related to a clinical trial or human experience with the investigational medicinal product
  o Results of new clinical pharmacology tests
  o New interpretation of existing clinical pharmacology tests
o Results of new clinical trials
o New interpretation of existing clinical trial data
o New data from human experience with the investigational medicinal product
o New interpretation of existing data from human experience with the investigational medicinal product

4.3 Sponsor’s approval

The Sponsor and Chief Investigator will counter-sign the amendment approval form to confirm the exact amendments approved. A copy of the form will be held by the Sponsor in the sponsor file. Another copy is to be kept in the Trial Master File.

For all CTIMPs, substantial amendments must be notified to the Main REC/HRA and the MHRA using the European Commission form “Notification of a Substantial Amendment to a Clinical Trial on a Medicinal Product for Human Use to the Competent Authorities and for Opinion of the Ethics Committees in the Community”, at
https://ec.europa.eu/health/files/...10/substantial_amendment_notification_form_.doc

The form should be signed by the named applicant.

Trial teams MUST notify all sites expected to consider both the amendment and continued permission with details of the amendment and amended documentation. If there are no objections, the amendment and associated documents may be implemented following approval from MHRA/REC (or acknowledgement of receipt of letters of approval).

Trial teams must also provide the Sponsor (the Research Governance, Ethics and Integrity Manager (Clinical Trials), 2nd Floor Christie Building, The University of Manchester, Oxford Road, Manchester, M13 9PL / clinicaltrials@manchester.ac.uk) with the following documentation for inclusion in the Sponsor File:
• Main REC/MHRA approval/acknowledgement of receipt of letters
• Signed and dated copies of the amended documentation

Further to this, CIs/Trial teams should detail all amendments in Sponsor Quarterly/Monthly reports requested by the Sponsor.

5.0 References:

• 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)  
The above can be accessed via/downloaded from the MHRA website:  
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Implem
entationoftheClinicalTrialsDirectiveintheUK/index.htm

• Clinical Trials Toolkit information on ‘Substantial Protocol Amendments’, which can be accessed via/downloaded from: http://www.ct-toolkit.ac.uk/routemap/substantial-amendments/

• Guidance from the HRA on amending an approval: https://www.hra.nhs.uk/approvals-
amendments/amending-approval/

• Guidance on submission to REC can be accessed via the IRAS website at  
https://www.myresearchproject.org.uk/help/AmendmentGuidance.aspx

• 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

6.0  Appendices

• Annex 1: Amendment Assessment Form (Sponsor Notification)
**Amendment Assessment**

*Please use in conjunction with the UoM SOP on Substantial and non-Substantial Amendment*

| Trial title: |  |
| Sponsor ref number (R code): |  |
| EudraCT number: |  |
| Chief Investigator: |  |
| Amendment number: |  |

**1.0 Classification of amendment(s)**

*Please select the classification of the amendment and provide a brief description below:*

<table>
<thead>
<tr>
<th>Substantial</th>
<th></th>
<th>Substantial amendment affecting:</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>A The safety or physical or mental integrity of the subjects of the trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B The scientific value of the trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C The conduct or management of the trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D The quality or safety of any investigational medicinal product (IMP)/device used in the trial</td>
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*Please select one or more categories from above:*

| A | B | C | D |

| Non-substantial |  | Please provide justification: |  |

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UM/UoM Substantial (non) Amendments/SOP09/6.0
This document/SOP is a controlled document.
Any printed version of this document may not be current. It is the responsibility of colleagues to ensure that the most recent version of the document is accessed and the procedures stated within the document followed.

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/
2.0 Changes to be amended

<table>
<thead>
<tr>
<th>Document/s to be amended (including current version and date - Please include page number where relevant)</th>
<th>Details of amendment (including proposed version and date)</th>
<th>Classification*</th>
</tr>
</thead>
<tbody>
<tr>
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*Please indicate S = substantial amendment or NS = non-substantial amendment for each document/change listed
3.0 Actions required

*Please state if there are any resulting actions required e.g. change to risk assessment status, contractual or monitoring arrangements*

<table>
<thead>
<tr>
<th>Potential Change to:</th>
<th>Action Required:</th>
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<tbody>
<tr>
<td></td>
<td><em>Please detail or state N/A</em></td>
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<tr>
<td>Risk Assessment</td>
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<tr>
<td>Contract/s</td>
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<td>Monitoring</td>
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<td>Insurance</td>
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<tr>
<td>Design and Analysis (Requires statistical review)</td>
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<tr>
<td>Other</td>
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4.0 Type of notification required

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<td></td>
<td>REC information only □</td>
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<tr>
<td>HRA</td>
<td>HRA approval required □</td>
</tr>
<tr>
<td></td>
<td>HRA information only □</td>
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5.0 Sponsor Approval

Following sign off, approval is given on behalf of the Sponsor for this amendment to be notified to the MHRA/REC/HRA (as appropriate) for the trial identified on page 1 of this form.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
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<tbody>
<tr>
<td>Chief Investigator</td>
<td>......................................................</td>
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</tr>
<tr>
<td>CTU (as required)</td>
<td>......................................................</td>
<td>..../..../.....</td>
</tr>
<tr>
<td>Sponsor</td>
<td>......................................................</td>
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