Standard Operating Procedures for Amendments, Urgent Safety Measures and Temporary Halt to a Trial

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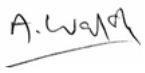
Author: Antony Walsh **Designation:** RES Research Governance Officer	*Signature* 	*Date* 25 August 2020
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[1] http://www.sussex.ac.uk/staff/research/governance

Acknowledgement , University of Keele

1. Purpose & Scope

1.1 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[2].

1.2 This SOP sets out the process for seeking approval for protocol amendments to Clinical Trials of Investigative or Medicinal Product studies (CTIMPs) for which the University of Sussex (US) has granted formal agreement to be the Sponsor. The sponsor is responsible for determining whether a proposed amendment to a research study is substantial or non-substantial. If the amendment is substantial, they are responsible for determining whether it should be submitted to the REC, the MHRA or both.

1.3 The process for implementing urgent safety measures (USM) and temporarily halting research studies sponsored by US is also outlined. An Urgent Safety Measure (USM) is a procedure which is not defined by the protocol that can be put in place with immediate effect without needing to gain prior authorisation by the REC (and MHRA where applicable), in order to protect clinical trial participants from any immediate hazard to their health and safety. Such safety measures may include a temporary halt to the study.

1.4 The scope of the document is for all schools at the University of Sussex, all members of staff with substantive employment and students registered at the University (including Brighton and Sussex Medical School) undertaking CTIMPs. The scope of the document includes anyone undertaking activities for a Clinical Trial on behalf of the University.

2. Introduction

2.1 An amendment is any change to the protocol or associated documents that were initially given a favourable ethical opinion by the REC (Research Ethics Committee) and/ or approved by the MHRA (Medicine and Healthcare Products Regulatory Agency) for studies that are CTIMPs.

2.2 There are two types of amendment; substantial or non-substantial. It is the sponsor's decision as to which category the amendment falls under. This document details the process of making amendments to a research study, as well as the process for taking urgent safety measures and temporarily halting a study.

2.3 An Urgent Safety Measure (USM) is a procedure which is not defined by the protocol that can be put in place with immediate effect without needing to gain prior authorisation by the REC (and MHRA where applicable), in order to protect clinical trial participants from any immediate hazard to their health and safety. Such safety measures may include a temporary halt to the study.

3. Responsibilities

Chief Investigator

3.1 The Chief Investigator (CI) is responsible for making a request to the University of Sussex to act as Sponsor and fulfilling the terms of the 'Conditions of Sponsorship Agreement' issued when the study has been formally accepted for Sponsorship. However, the University recognises that CIs may delegate this responsibility to another member of the research team with sufficient knowledge of the protocol and the overall management of the study.

3.2 The CI is responsible for submitting proposed amendments to the sponsor. Once it has been determined whether the amendment is substantial or non-substantial, the CI is responsible for submitting the amendment to the relevant parties.

3.3 The CI is responsible for ensuring that the research team at each participating research site has the amendment information and that any associated trial documents have been updated.

3.4 For non-CTIMPs, the CI is responsible for notifying the REC and any other relevant parties of USMs or any temporary halts of the study.

3.5 The CI will, however, remain ultimately responsible for any submissions made to the MHRA (Medicines and Healthcare Products Regulatory Agency), HRA (Health Research Authority) and an NHS Research Ethics Committee or to the Sponsorship Sub-Committee (SSC) (or any other body with research governance functions) on behalf of the study.

Sponsor

3.6 The sponsor is responsible for determining whether a proposed amendment to a research study is substantial or non-substantial. If the amendment is substantial, they are responsible for determining whether it should be submitted to the REC, the MHRA or both.

3.7 For CTIMPs, the sponsor is responsible for ensuring USMs and any temporary halts of the trial are reported to the MHRA, the REC and any other relevant parties within the required timeframes.

Principal Investigator (PI)

3.8 The PI is responsible for implementing amendments at their local research site.

3.9 If the PI is implementing an USM, they are responsible for notifying the sponsor immediately of this by emailing researchsponsorship@sussex.ac.uk.

Sponsorship Sub-Committee

3.10 The SSC is responsible for reviewing and approving applications for amendments to

Sponsorship on behalf of the University before any notifications to external bodies. The Sub-Committee allows for the use of Chair's action on a case-by-case basis when the CI can make a robust case that waiting for the next Sub-Committee meeting date will be detrimental to the study. In all instances, the Sub-Committee receives details of any approved business between meeting dates to maintain its oversight.

4. Procedure

4.1 The Chief Investigator (CI) or delegated individual is required to submit an application for an amendment to Sponsorship. The nature of the amendment (Substantial or Non-Substantial) determines how the SSC will review the amendment request. The sponsor will then determine whether the amendment is substantial or non-substantial and if substantial, whether it should be submitted to the REC, the MHRA (for CTIMPs) or both.

How to determine whether the amendment is Substantial or Non-Substantial

4.2 The HRA provides the following guidance on the distinction between different categories of amendment[2].

a. Examples of substantial amendments:

- changes to the design or methodology of the study, or to background information likely to have a significant impact on its scientific value;
- changes to the procedures undertaken by participants;
- changes likely to have a significant impact on the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study;
- significant changes to study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheets for relatives or carers;
- a change of sponsor(s) or sponsor's legal representative;
- appointment of a new chief investigator
- a change to the insurance or indemnity arrangements for the study;
- inclusion of a new trial site (not listed in the original application) in a CTIMP;
- appointment of a new principal investigator at a trial site in a CTIMP;
- temporary halt of a study to protect participants from harm, and the planned restart of a study following a temporary halt;
- a change to the definition of the end of the study;
- any other significant change to the protocol or the terms of the REC application.

[2] https://www.hra.nhs.uk/approvals-amendments/amending-approval/examples-of-substantial-and-non-substantial-amendments/

IRAS also provides information on 'Amendments for projects conducted in NHS/HSC' https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx

b. Examples of non-substantial amendments:

- minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications;
- updates of the investigator's brochure (unless there is a change to the risk/benefit assessment for the trial);
- changes to the chief investigator's research team
- changes to the research team at particular trial sites (other than appointment of a new principal investigator in a CTIMP);
- changes in funding arrangements;
- changes in the documentation used by the research team for recording study data;
- changes in the logistical arrangements for storing or transporting samples;
- inclusion of new sites and investigators in studies other than CTIMPs;
- extension of the study beyond the period specified in the application form.

4.3 The Research Governance Officer can receive initial queries on processes– researchsponsorship@sussex.ac.uk.

When to request an amendment

4.4 Following NHS Research Ethics Committee approval, all research should comply with the protocol approved by the HRA and the approving NHS Research Ethics Committee.

4.5 Changes to the research activity from the approved protocol may only occur when approval has been:

- granted by the HRA and the NHS REC (substantial amendments) or
- when the HRA confirms receipt of the Notification of Non-Substantial/Minor Amendments

Applying for an amendment – the Sponsorship Sub-Committee

4.6 Applicants should be aware of meeting dates and submission deadlines as indicated on http://www.sussex.ac.uk/staff/research/governance/sponsorship/applysponsorship so that amendments can be considered.

Non-Substantial Amendments

4.7 Applicants should complete use the HRA Amendment[3] tool and send together (taking into account the latest HRA procedures) with any relevant supporting documents to

[3] https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool

researchsponsorship@sussex.ac.uk.

4.8 The email should briefly explain the reason for the request. The CI (or the delegated member of the research team) should submit the modified study documents, showing both the previous and new wording, with the form. The SSC cannot review and decide on applications that are incomplete or missing the required minimum documentation.

Substantial Amendments

4.9 A substantial amendment is a change that is likely to have a significant impact on the safety or physical or mental integrity of the clinical trial subjects or the scientific value of the clinical trial.

4.10 The notification of amendment for a CTIMP to the SSC requires the following:

a) a signed cover letter, including:

- in its subject line, the EudraCT number and the sponsor reference with the title of the trial and the sponsor's amendment code number allowing unique identification of the substantial amendment.
- a highlighted indication of any special issues related to the amendment and indication where the relevant information or text is in the original application
- identification of any information that: might impact on the risk to trial participants;

b) the Amendment Tool, and a description of the amendment:

- an extract from the amended documents showing previous and new wording in track changes, as well as the extract only showing the new wording;
- if the changes are so widespread or far-reaching that they justify an entire new version of the document, a new version of the entire document. In this case, an additional table should list the amendments to the documents. In this list researchers should group together identical changes. The new version should feature the date and an updated version number.

c) supporting information including, where applicable:

- summaries of data,
- an updated overall risk/benefit assessment,
- possible consequences for subjects already included in the trial,
- possible consequences for the evaluation of the results;

4.11 Applicants should complete use the HRA Amendment[4] tool and send together (taking into account the latest HRA procedures) with any relevant supporting documents to researchsponsorship@sussex.ac.uk. The email should briefly explain the reason for the request.

[4] https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool

4.12 Amendments requiring notification to the MHRA should also be accompanied by the Annex 2 Substantial Amendment form. This is available under the 'Annex 2' tab of the Amendment Tool which is enabled only when the information entered into the amendment tool tab indicates that an Annex 2 notification is required.[5]

Submitting requests for amendments to the SSC

4.13 Applicants should be aware of SSC meeting dates and submission deadlines as indicated on http://www.sussex.ac.uk/staff/research/governance/sponsorship/applysponsorship .

4.14 It is up to the sponsor of the clinical trial to assess whether a substantial amendment requires authorisation, or an ethical opinion from an NHS REC, or both. General guidance on the matter can be consulted at https://www.hra.nhs.uk/approvals-amendments/amending-approval/examples-of-substantial-and-non-substantial-amendments/

4.15 The CI or his research team may not implement amendments until the MHRA, NHS REC and the HRA grants approval.

Review by the Sponsorship Sub-Committee

4.16 For all studies, it is the responsibility of the sponsor to determine whether an amendment is substantial or non-substantial.

4.17 The SSC shall review and decide whether to grant approval to both substantial and non-substantial amendment requests. By exception, the Chair of the SSC can review and approve amendment requests with the Research Governance Officer on behalf of the SSC. The amendment requests will be reported to the next SSC meeting for note.

4.18 There are three main decision outcomes from the SSC:

- **Full approval of the application as submitted** - The Research Governance Officer will issue a letter confirming the approval.
- **Provisional approval** pending the addressing of issues identified.
- **Rejected** with comments.

[5] Refer to the on-screen guidance when completing this form. The Annex 2 form will need to be signed. This can be done by either adding in an image of the signature to the excel form prior to locking the form, or you can print, sign and scan the pdf. When complete, click 'Lock for submission' which will generate a locked pdf copy of the completed Annex 2 form. Save this to your computer ready for upload later. Alternatively it can be downloaded from the EudraCT website at http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm.

4.19 The SSC can request further information and/or documentation of the CI as necessary. The CI (or nominated individual) may need to be available to answer any additional questions raised by the SSC.

Granting of approval

4.20 The Sponsor will issue a letter of approval of all requests for amendments indicating the nature of the amendment and version numbers of supporting documents associated with the amendment.

4.21 Once Sponsor approval has been granted, the CI (or delegated member of the research team) should submit the amendment to the approving REC via the HRA's online amendment submission portal[6] :

https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Online-Submission

Sponsor's Right to withdrawal of Sponsorship

4.22 In line with its responsibilities as a recognised Sponsor of research, the University may withdraw Sponsorship that it has granted if there has been a breach of the 'Conditions of Sponsorship Agreement' or if matters come to light through the study that have significant legal, regulatory, financial or reputational consequences to the University.

Urgent Safety Measures

4.23 Appropriate urgent safety measures (USM) may be taken to protect participants from any immediate hazard to their health and safety. If a PI (Principal Investigator) or CI (Chief Investigator) instigates an USM rather than the sponsor, then the sponsor must be notified immediately so that it can be assessed and reported immediately within the required time frames.

4.24 The Clinical Trial Unit at the MHRA must be telephoned and the issue discussed with the safety scientist immediately. The USM should be implemented straight away and the Sponsor (researchsponsorship@sussex.ac.uk), the MHRA and the REC must be informed in writing within 3 days of implementing the USM via a notification of substantial amendment form. The approving REC shall be notified by a telephone call immediately in the first instance.

4.25 The substantial amendment should include details of the measures taken, the reason for them and any supporting documentation. It should also set out the plan for further action. The funder should be updated on all developments and actions as soon as possible. NHS R&D offices of participating sites should also be notified of the USM in line with their local policies.

4.26 If applicable, relevant oversight committees such as the Data Monitoring Committee should review the USM and report any recommendations to the relevant parties.

[6] https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool

Temporary Halt of Trial

4.27 If a temporary halt of a CTIMP is required, whether it is the whole trial or a single investigator site, the sponsor will notify the MHRA and the REC immediately, at least within 15 days from when the trial was halted. The notification will be made by substantial amendment explaining what has been halted (e.g. stopping recruitment and/or interrupting treatment) and the reasons behind this. This does not include trials that are halted temporarily for logistical reasons.

4.28 To restart the trial, a further substantial amendment will be submitted to the MHRA providing evidence that the restart is safe. If the trial is not restarted then an end of trial declaration form should be submitted within 15 days of the decision to prematurely terminate the trial (see SOPRG09a End of CTIMP Research Study) including a brief explanation of the reasons for ending the trial prematurely. It is important that there is documentation of the decision to prematurely terminate the trial.

5. Training

5.1 This is a 'read and understand' SOP. Please note that the Research Ethics, Integrity and Governance Team discourages the retention of hard copies of SOPs and can only guarantee that the most up-to-date version is on the University website.

6. Abbreviations

AE	Adverse Event
CI	Chief Investigator
COA	Compliance Oversight Advisor
CRF	Case report form
CRN	Clinical Research Network
CRO	Clinical Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DCF	Data Clarification Form
DSUR	Development Safety Update Report
eCRF	Electronic Case report form
EDC	Electronic Data Capture
EU	European Union
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMO	Genetically Modified Organism
GTAC	Gene Therapy Advisory Committee
HRA	Health Research Authority

HSC	Health and Social Care
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
IVD	In Vitro Diagnostic
JCRO	Joint Clinical Research Office
LIP	Local Information Pack
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal Investigator
PAF	Portfolio Application Form
PPI	Patient and Public Involvement
PVG	Pharmacovigilance Manager
QA	Quality Assurance
R&D	Research and Development
REC	Research Ethics Committee
RM(ATIMPS)	Regulatory Manager for ATIMPS
RM(P)	Regulatory Manager (Pharmaceuticals)
SI	Statutory Instrument
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SRA	Sponsor Regulatory Advisor
SSC	Sponsorship Sub-Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TM	Trial Manager
TMF	Trial Master File
US	University of Sussex
USM	Urgent Safety Measure

7. Cross Referenced SOPs

SOPRG01a Sponsorship Approval of CTIMPs
SOPRG033 Archiving Paper Trial Documents for US as a Sponsor

8. References

Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, SI 1031
http://www.legislation.gov.uk/uksi/2004/1031/contents/made

ICH Good Clinical Practice

https://www.ich.org/page/efficacy-guidelines

Good Clinical Practice Guide MHRA/ Stationery Office (Great Britain), London: 2012

NIHR Clinical Trials Toolkit - http://www.ct-toolkit.ac.uk/

Clinical trials for medicines: manage your authorisation, report safety issues (December 14)

https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues

EudraLex - Volume 10 - Clinical trials guidelines

https://ec.europa.eu/health/documents/eudralex/vol-10_en