Queen's University Belfast

Research and Enterprise

Standard Operating Procedure
Research Governance

Title:	**Amendments to Protocols and Essential Documentation**		
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* For all University sponsored research that has been approved by a National Research Ethics Committee
\# For all other University sponsored research involving human participants

Revision Log

Previous Version number	Date of Review/Modification	Reason for Review/Modification	New Version Number
Final v 1.0	10/11/09	Annual Review	Final v 1.0
Final v 1.0	17/08/11	Annual Review/ Update following MHRA GCP Inspection	Final v 2.0
Final v 2.0	21/08/2012	Periodic Review	Final v 3.0
Final v.3.0	06/10/2014	Periodic Review	Final v 4.0
Final v 4.0	19/09/2016	Periodic Review	Final v 5.0

1. Purpose

This Standard Operating Procedure (SOP) describes the procedure to be followed when amendments are made to a study protocol that has previously received a favourable ethical opinion, or been authorised by the Medicines and Healthcare products Regulatory Authority (MHRA).

The primary focus of this SOP is for clinical trials of Investigational Medicinal Products (IMP).

2. Introduction

2.1 An amendment is any deviation from, or change(s) to the study protocol or other essential documentation during the life of the study. An amendment can be either minor or substantial in nature.

A minor amendment is one that has no significant implications for a research participant, or alters the management or conduct of the study. Examples of minor amendments include:
Correcting typing errors, minor clarifications of essential documents, changes to the research team (other than the Chief Investigator, or in the case of a multi-centred trial a Principal Investigator), changes in funding arrangements, changes in the documents used by the research team to record study data, changes in the logistical arrangements for storing or transporting samples, extensions of the IMP-Trial's study period, or the inclusion of new sites in site specific assessment (SSA) exempt studies.

A substantial amendment is an amendment to the protocol or other supporting documentation, where they are likely to have a significant impact on one or more of the following:

- The safety or physical or mental integrity of participants of the study;
- The scientific value of the trial;
- The conduct or management of the trial;
- The quality or safety of any investigational medicinal product used in the trial.

2.2 Examples of substantial amendments, as outlined in the Department of Health and Medical Research Council Clinical Trials Toolkit include:

2.2.1 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 of dose of the investigational medicinal product(s);
- Change of comparator;
- Statistical analysis.

2.2.2 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 CRO assigned significant tasks;
- Change of the definition of the end of the trial.

*Addition of a new site for UK trials only, does not have to be sent to the MHRA.

2.2.3 Amendments related to the IMP:
For example:

- Addition to stability data/change of expiry date;
- Change of formulation;
- Additional toxicology data;
- Change to route of synthesis.

2.2.4 Changes to investigational medicinal product quality data concerning:

- Change of name or code of IMPs;
- Immediate packaging material;
- Manufacturer(s) of active substance;
- Manufacturing process of the active substance;
- Specifications of active substance;
- Manufacture of the medicinal product;
- Specification of the medicinal product;
- Specification of excipients where these may affect product performance;
- Shelf-life including after first opening and reconstitution;
- Major change to the formulation;
- Storage conditions;
- Test procedures of active substance;
- Test procedures of the medicinal product;
- Test procedures of non-pharmacopoeia excipients.

It is a legal requirement for trials involving IMPs to comply with the procedures specified in this SOP.

3. Scope

This SOP applies to all studies for which the University is acting as Sponsor.

4. Responsibilities

4.1 Chief Investigator

It is the legal responsibility of the Sponsor to determine if an amendment is substantial or not. It becomes the responsibility of the CI to ensure that the appropriate organisations and regulatory bodies are advised of amendments, once approval has been given from the Sponsor(s).

5. Procedure

5.1 Reporting Substantial Amendments in Clinical Trials of Investigational Medicinal Products

All substantial amendments need to be considered by, the main Research Ethics Committee that originally approved the study, the University and the Health Trusts, if appropriate. The REC needs to approve all substantial amendments. For changes to participant information sheet(s) and consent form(s) only it is advisable to apply first to the REC and then inform the MHRA, rather than submitting parallel notifications.

The Notification of an Amendment Form must be used to notify the MHRA and main REC. Using the Integrated Research Application System (IRAS) a notice of substantial amendment form can be created www.myresearchproject.co.uk. Ensure that this form is completed using plain language and comprehensible to a lay person.

An updated Clinical Trial Application form should be submitted if there are changes to the information originally submitted to the MHRA.

5.1.1 Format and content of notification

The notification of a substantial amendment should include the following information:

- Covering letter, including reason for qualification as a substantial amendment.
- Application form: that contains:
  (i) Identification of Clinical Trial (title, EudraCT number, sponsor's protocol code number);
  (ii) Identification of applicant;
  (iii) Identification of the amendment (sponsor's amendment number and date). One amendment could refer to several changes in the protocol or scientific supporting documents;
  (iv) A description of the amendment and the reason for it.
- An extract of the modified documents showing previous and new wording, where applicable.
- The new version of modified documents where the changes are so widespread and/or substantial that they justify a new version, identified with updated number of version and date.
- Supporting information including, where applicable:
  (i) Summaries of data;
  (ii) An updated overall risk benefit assessment;
  (iii) Possible consequences for subjects already included in the trial;
  (iv) Possible consequences for the evaluation of the results.
- Where applicable, if a substantial amendment changes the core data or the full application form data set (according to national requirements) in the XML file (computer file) accompanying the initial application for the trial, the sponsor should submit a revised copy of the XML file with the Notification of Amendment, incorporating amended data. The application for substantial amendment should identify the fields to be changed, by attaching a print out of the revised form showing the amended fields highlighted.

5.1.2 Notification to Competent Authority

The MHRA will review the amendment and should issue an opinion within a maximum of 35 working days from receipt of a valid submission.

Following assessment the applicant will be notified of:

- Acceptance of the amendment
- Acceptance of the amendment subject to conditions
- Grounds for non-acceptance of the amendment

Only when the amendment has been accepted, without conditions, can it be implemented.

Where the study involves international sites the substantial amendment should also be submitted to and approved by the relevant competent authority and national ethics committee in each country before the amendment can be implemented in that country.

Notification to Research Ethics Committee

The REC which approved the clinical trial must consider the substantial amendment, normally within 35 working days of receipt of a valid submission. Any amendment cannot be implemented until it has received a favourable ethical opinion.

Notification to NHS Organisations

For multi-site trials, the process for review of amendments by NHS R&D offices involves the categorisation of amendments into Category A, B or C and also a 35 working day default approval of amendments for NHS organisations.

For single site studies within Northern Ireland, the normal local Trust arrangements for notification, consideration and approval of substantial amendments apply.

5.2 Minor amendments

Minor amendments do not have to be approved by the MHRA or UK REC. However, they should be recorded and if appropriate included in the next update of the Investigators Brochure. They should also be available on request for inspection at the trial site and/or sponsors premises as appropriate.

For all studies, it is best practice to notify the REC of any minor amendments. It is however necessary to submit all minor amendments for NHS approval.

5.3 Urgent Safety Measures Amendments

Urgent safety measures must be taken in order to protect research participants against any immediate hazard to their health or safety. The protocol should identify who is responsible for taking urgent safety measures, which in many studies will be the CI.

Safety measures, such as halting the trial, may be taken without prior authorisation from the MHRA, REC. However, the CI must telephone the MHRA and REC and follow it up with a written report within three days.

In the event of a trial being temporarily halted the MHRA and REC must be notified within 15 days. The trial may not be recommenced until a favourable opinion has been received and the MHRA has not raised any grounds for non-acceptance of the recommencement.

6. References

Medicines and Healthcare products Regulatory Agency website, last accessed September 2016.
https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#apply-to-change-your-trials-protocol-or-documentation
EudraLex - Volume 10 Clinical trials guidelines. Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (135 KB) (revision 1 of February 2006) (accessed October 2014)

Department of Health Clinical Trials Toolkit (accessed 14 September 2016), http://www.ct-toolkit.ac.uk/