STANDARD OPERATING PROCEDURE FOR RESEARCH

Amendments to Research Projects

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SOP SUMMARY

This Standard Operating Procedure (SOP) describes the procedure for making amendments, both substantial and minor, to research studies. It gives a summary of the procedures for submitting/reporting to the Health Research Authority (HRA), the Medicines and Healthcare products Regulatory Agency (MHRA), and the Gene Therapy Advisory Committee, if required.

The Trust monitors the implementation of and compliance with this policy in the following ways:

Monitoring of implementation and compliance with this procedure will be undertaken by the Executive Medical Director, Research manager, Research lead, R&D department staff and R&D group.

Services	Applicable	Comments
Trustwide	✓	
Essex MH&LD		
CHS		

ESSEX PARTNERSHIP UNIVERSITY NHS FOUNDATION TRUST

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1. PURPOSE

This Standard Operating Procedure (SOP) describes the procedure for making amendments, both substantial and minor, to research studies. It gives a summary of the procedures for submitting/reporting to the Health Research Authority (HRA), the Medicines and Healthcare products Regulatory Agency (MHRA), and the Gene Therapy Advisory Committee, if required.

It is recommended that researchers view the guidance for submitting amendments at the following web addresses:

Health Research Authority
(HRA)
http://www.hra.nhs.uk/resources/after-you-apply/amendments/

Medicines and Healthcare products Regulatory Agency (MHRA)
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/index.htm

Gene Therapy Advisory Committee (GTAC)
http://www.hra.nhs.uk/about-the-hra/our-committees/gtac

2. BACKGROUND

Amendments are changes made to a protocol, other essential documentation or aspects of a research study's arrangements (such as changes to key members of the research team; i.e. Principal Investigator), after a favourable ethical opinion and approval by the regulatory body has been given.

3. INTRODUCTION

An amendment to a research project can be either **substantial** *or* **minor (non-substantial)** in nature.

Study documentation must be version controlled and dated. All research protocols/documents should have a clear version number and date in order to maintain accurate records and audit trails. Version numbers and dates will therefore be amended along with the document. Best practice is for version numbers and dates to be listed on each page.

4. TYPES OF AMENDMENT

4.1 Amendment to a clinical trial authorisation

This type of amendment only applies to the Sponsor/s of a CTIMP.

An “amendment to a clinical trial authorisation” is defined broadly in the Clinical Trials Regulations as an amendment to any of the following:

I. the terms of the request for clinical trial authorisation from the MHRA
II. the terms of the REC application
III. the protocol
IV. any other particulars or documents submitted with the applications to the MHRA or the main REC.

4.2 Substantial Amendment

Defined as an amendment to the protocol or any other supporting documentation that is likely to affect, to a significant degree, the:

I. safety, physical or mental integrity of the subjects of the trial
II. scientific value of the trial
III. conduct or management of the trial or
IV. quality or safety of any investigational medicinal product used in the trial.

All substantial amendments should be notified to the MHRA (if a CTIMP) and Research Ethics Committee (main REC or MREC) that gave a favourable opinion.

Examples of substantial amendments include:
1. Amendments relating to the protocol:

- purpose of trial
- design of trial
- recruitment procedure
- measures of efficacy
- schedule of samples
- addition or deletion of tests or measures
- number of participants
- age range of participants
- inclusion and 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

2. Amendments to other study documentation:

    - participant information sheet
    - consent form
    - questionnaires
    - letters of invitation
    - letters to GPs or other clinicians
    - information sheets for relatives or carers

3. Amendments related to the trial management and co-ordination including changes to the:

    - Principal Investigator (PI) or addition of new ones (NB this means the lead investigator in each centre)
    - co-ordinating investigator
    - trial site or addition of new sites (NB: addition of a new site should be sent to the MHRA as a substantial amendment but for notification only.)
    - sponsor or legal representative
    - CRO assigned significant tasks
    - definition of the end of the trial

4.3 Minor ('Non-Substantial') Amendment

Defined as a change to the details of a study that will have no significant implications for participants or for the conduct, management or scientific value of the study.

Examples of minor amendments include:

- correction of typographical errors in the study documentation
- minor clarifications to the protocol
- extension of the study beyond the period specified in the application form
- the research team (apart from changes to CI or PI)
- funding arrangements
- inclusion of new sites in SSA-exempt studies;
- the documentation used by the research team for recording study data (i.e. case report forms)
- the arrangements for storing or transporting samples

5. PROCESS

It is the responsibility of the Sponsor to determine whether an amendment is substantial or non-substantial If an amendment is required, the CI must first determine whether it is substantial or not. Once this decision has been made, the following procedures must be followed. (If you are unsure how an amendment should be classified, you can seek advice from the Research & Development Office or the Local Research Ethics Committee.)

NB - the procedure will also differ according to whether the study is a CTIMP, gene therapy, or other healthcare research.

5.1 Reporting Substantial Amendments

Substantial amendments require a favourable opinion from the main REC and the MHRA (CTIMPs) **before** they can be implemented. The only exception to this is where urgent safety measures need to be taken (see section 5.4)

5.1.1 CTIMPS (Clinical Trials of Investigational Medicinal Products)

5.1.1.1 Who?

Under the Clinical Trials Regulations, the sponsor of a clinical trial of a medicinal product may make an "amendment to a clinical trial authorisation", other than a "substantial amendment", at any time after the trial has started. Amendments that are not substantial (referred to in these SOPs as "minor amendments") do not need to be notified to MHRA or REC, but should be notified to the HRA. This can be done by submitting a Non-Substantial Amendment form to hra.amendments@nhs.net.

Where the amendment is substantial, the sponsor is required to submit a valid notice of amendment both to the MHRA and to the REC that gave the favourable opinion of the trial. Where there is more than one sponsor for the research, "the sponsor" refers to the sponsor that has been designated to take responsibility for all matters relating to amendments.

5.1.1.2 How?

The European Commission has issued guidance on amendments as part of the "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of a trial" (ENTR/CT1). Annex 2 to the guidance prescribes a "Notification of Amendment form" (the "EU Notification of Amendment") to be used in all member states for notification both of the competent authority and the ethics committee. The sponsor must indicate on the form whether the amendment requires authorisation by the competent authority, or a favourable opinion from the ethics committee, or both. In some cases, the amendment may be for information only of one or other agency.

Annex 2 is available from the European Medicines Evaluation Agency (EMEA) website: http://ec.europa.eu/health/documents/eudralex/vol-10/

A substantial amendment to a CTIMP must be reported to MHRA and main NHS REC approving the study **before** the amendment is actioned. The form structure is protected and only permits responses in the appropriate boxes. The form should be submitted by the Chief Investigator (CI), or another person or organisation authorised by the sponsor.

Annex 2 should summarise the change(s) and briefly explain the reasons in each case, using language comprehensible to a lay person.

Other documents required in the submission are:

- Description of the amendment
- Reasons for the proposed amendment
- Copy of the proposed changes to the protocol or any other documents demonstrating both the previous and new wording.
- Supporting data for the amendment, including any change to the risk benefit analysis

Where the modified documents (e.g. protocol) are lengthy, it is acceptable for extracts to be provided or for the changes to be listed in a separate document. The CI may also include other supporting information, such as a summary of trial data, an updated safety analysis or a report from a trial monitoring committee. Where the amendment could significantly affect the scientific value of the research, further evidence of scientific and/or statistical review should be provided.

When the REC and MHRA have confirmed that they have no objections to the amendment, and HRA have categorised the amendment, the CI, Sponsor or appropriate representative must inform R&D Departments. All amended documents and supporting information must be forwarded in order for the R&D department to provide amendment approval.

If the amendment has affected the protocol significantly, the Sponsor may be required to amend the Clinical Trial Agreement. Any agreement or financial amendments must be dealt with through the R&D department.

5.1.2 Gene Therapy Research

As 5.1.1 but with Annex 2 form sent to GTAC.

5.1.3 All Other Research (Non-CTIMPS)

5.1.3.1 Who?

For all non CTIMPs research, the CI should complete the IRAS substantial amendment form and submit via email to the NHS REC which gave a favourable opinion, along with any updated documents e.g. consent form or protocol, copying in the HRA: hra.amendments@nhs.net. A copy must also be sent to the R&D Department if Essex Partnership NHS Foundation Trust is the research sponsor.

5.1.3.2 How?

Substantial amendments to non-CTIMP studies should be notified to the REC that gave a favourable opinion using the “Notice of Amendment form” on IRAS.

Following submission of the NoA form on IRAS, HRA review will occur parallel with REC review. The HRA will categorise the amendment within 5 days and assess for compliance with HRA approval. The applicant should then send the

amendment and the categorisation information to participating NHS organisations (study delivery team, R&D office, and LCRN where applicable). The HRA will email the applicant again following the NHS REC opinion of the amendment and outcome of HRA assessment. This must be shared with the Trust along with associated documentation. The Trust can then provide amendment approval, if required according to the HRA categorisation of the amendment. If the amendment has affected the protocol significantly, the Sponsor may be required to amend the Clinical Trial Agreement. Agreement changes or financial amendments must be dealt with through the R&D department.

5.2 Reporting Minor Amendments

5.2.1. Who?

A CI, Sponsor or authorised representative can make a non-substantial amendment at any time but must keep records.

5.2.2 How?

Amendments not requiring NHS REC approval can be submitted by email to hra.amendments@nhs.net using the Non-Substantial Amendment Form, available at: http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/preparing-amendments/

The process will then be as above in section 5.1, except without parallel REC review and permission.

5.3 Procedures for reviewing substantial amendments

5.3.1 HRA

The HRA will categorise the amendment and inform the applicant within 5 days. The applicant should then send the amendment and the categorisation information to participating NHS organisations (study delivery team, R&D office, and LCRN where applicable).

5.3.2 MHRA

Upon receipt of the Annex 2 form, the MHRA will review and should issue an opinion within a maximum of **35** days from the receipt of a valid form. However, if the MHRA is overburdened, this may be delayed beyond the 35 day deadline as set out in the Medicine for Human Use (Clinical Trials) Regulations 2004. The MHRA states in the acknowledgement letter that

"*It is the Authority's intention within 35 days of the date of receipt of the request, to notify you, where appropriate, by either setting out the grounds for not accepting the proposed amendment of accepting the application for amendment with or without conditions. If you are not sent either notice then the amendment can be made*."

However, although the MHRA state this on their standard letter, it may be prudent to wait for their approval.

5.3.3 GTAC

GTAC should review the amendment and issue an opinion within a maximum of 35 days, similar to the REC and MHRA guidelines.

5.3.4 R&D

The need for a response from R&D is determined by the HRA categorisation of an amendment. This categorisation is completed once for each amendment submission; and when applicants receive the correspondence confirming the category it will contain instructions about how to proceed.

Categories:

A - Implications for, or affects, all participating NHS/HSC organisations hosting the research project.
B - Implications for, or affects, specific participating NHS/HSC organisations hosting the research project.
C - No implications that require management or oversight by the participating NHS/HSC organisations hosting the research project. However the amendment should still be submitted for information.

If an amendment is categorised as A or B (with EPUT as one of the Trusts affected), then the R&D office will assess and notify the HRA if there is an objection to the amendment. If not, then following HRA approval, the R&D office will notify the Sponsor representative and PI that there are no objections to the study continuing with the proposed changes.

Note that subject to the three conditions below, amendments can be implemented 35 days after notification to the NHS Trust:

1) The amendment may not be implemented until and unless all required regulatory approvals have been provided, including REC favourable opinion and confirmation of HRA Approval for the amendment. Sponsor representatives must provide regulatory approvals to the research management support offices and local research teams at the Trust.

2) The amendment may not be implemented if the Trust informs the Sponsor representative within the 35 day period that they require additional time to consider the amendment, until the Trust provides notification that the considerations have been satisfactorily completed.

3) The amendment may not be implemented if the Trust informs the Sponsor representative that it is no longer able to undertake this study.

If the above are all met, the amendment can be implemented immediately. There is no need for Sponsor representatives to receive a letter of confirmation from the Trust that the amendment can be implemented, as the intended date of implementation is communicated through the above process. However, Sponsor representatives may be able to implement this amendment ahead of the 35 day

deadline, if all necessary regulatory approvals are in place and the Trust has confirmed that the amendment may be implemented ahead of the 35 day date.

5.4 Urgent Safety Measures

If unexpected events relating to the conduct of the trial or the development of the IMP occur, there must be arrangements in place for taking appropriate urgent safety measures to protect participants against any **immediate** hazard. In many studies, such measures are best taken by the CI or another identified person/organization, rather than the Sponsor directly. The protocol should identify the individual(s) who accept this responsibility; otherwise the Sponsor remains directly responsible. Safety measures, such as temporarily halting the trial, may be taken without prior authorisation from the MHRA but must be reported to MHRA and REC (see CLPG19 SOP 16 - Safety Reporting in Externally Sponsored Clinical Trials).

6. REFERENCES

Health Research Authority
www.hra.nhs.uk

Medicines and Healthcare Products Regulatory Agency
https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

Gene Therapy Advisory Committee
http://www.hra.nhs.uk/resources/applying-to-recs/gene-therapy-advisory-committee-gtac/

European Clinical Trials Database
https://www.clinicaltrialsregister.eu/

Integrated Research Application System (IRAS)
https://www.myresearchproject.org.uk/