STANDARD OPERATING PROCEDURE FOR THE MANAGEMENT OF AMENDMENTS TO STUDIES SPONSORED BY NHS FIFE

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1. PURPOSE

This SOP describes the procedure for the management of amendments to clinical research studies (Clinical Trials of Investigational Medicinal Products (CTIMPs) and non-CTIMPs) sponsored by NHS Fife and complies with the principles of Good Clinical Practice (GCP).

It is the responsibility of all researchers using this SOP to ensure they are using the latest version of it. The latest version is available via the Research & Development (R&D) page on the NHS Fife Intranet or, for guidance, contact the Trials Facilitator in the R&D Office, Queen Margaret Hospital, 01383 623623 (extension 20306).

2. APPLICABILITY

Unless otherwise specified in a clinical trial site agreement, this document applies to research sponsored or co-sponsored by NHS Fife or research where the Chief Investigator (CI) is employed by NHS Fife.

The document applies to CIs, Principal Investigators (PI), study staff and to all staff who manage, coordinate or advise on amendments.

3. POLICY

3.1 After a research study has received all necessary approvals, any subsequent amendments to the protocol or supporting documents must be submitted to the Sponsor's representative (R&D Research Coordinator) who will advise if the amendment is substantial or non-substantial and approve the amendment. A written Sponsor response must be obtained prior to further submission of the amendment unless it is an urgent safety measure.

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

3.2.1 Substantial Amendment

A Substantial Amendment is defined as an amendment to the protocol or any other supporting documentation that is likely to affect to a significant degree the:
1. safety or physical or mental integrity of the subjects of the trial
2. scientific value of the trial
3. conduct or management of the trial; or
4. quality or safety of any investigational medicinal product used in the trial.

Examples of substantial amendments include:

- changes to the design or methodology of the study, or to background information affecting its scientific value;
- changes to the procedures undertaken by participants;
- any change relating to 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 CI or key collaborator;
- a change to the insurance or indemnity arrangements for the study;
- inclusion of a new trial site (not listed in the original application) for a CTIMP;
- appointment of a new PI at a trial site for 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 Research Ethics Committee (REC) application.

3.2.2 Minor ('Non-Substantial') Amendments.

A minor amendment can be defined as a change to the details of a study which will have no significant implications for participants or for the conduct, management or scientific value of the study. Examples of minor amendments include:

- 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 CI's research team (other than appointment of key collaborators);
- changes to the research team at particular trial sites (other than appointment of a new PI 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.

3.3 The Health Research Authority has divided amendments into three categories:

- *Category A*: Has implications for, or affects, all participating NHS/HSC organisations hosting the research project *the*refore needs to be considered and may need change control ac*tions*
- *Category B*: Has implications for, or affects, specific participating NHS/HSC organisations hosting the research project. Only at these organisations does it need to be considered and any change control actions required
- *Category C*: Has 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.

  Note - Updated Investigator Brochure (IB; Clinical Trials of Investigational Medicinal Products (CTIMPs) only):
  Where the IB update, annual or otherwise, constitutes a non-substantial amendment for REC and MHRA and this is the only amendment (e.g. the update to IB does not give rise to updated pharmacy manual or protocol) the updated IB should not be submitted for categorisation. These amendments will always be category C and they will not be assessed by NHS/HSC if submitted. The IB should be provided to each participating NHS/HSC organisation.

4. PROCEDURE

4.1 Submission to Sponsor

The CI or delegate should notify the Sponsor, via e-mail to the R&D Research Coordinator, of their intention to make an amendment.

The email notification should specify which amendment(s) is to be made and should have the amended document(s) attached.

The R&D Research Coordinator will discuss with the CI or delegate, as appropriate, and confirm by email whether the amendment is substantial or non-substantial and to which parties the amendment requires to be notified.

The R&D Research Coordinator will re-assess the risk attached to the study as a consequence of the amendment, and will advise by e-mail the CI or delegate, and any other appropriate parties, of any change to the risk benefit analysis via an update to the Risk Assessment, if necessary.

Once a decision has been made on the nature of the amendment, the following procedures must be followed, depending on whether the amendment is substantial or minor.
Please note, the procedure will also differ if the study is a CTIMP (or gene therapy).

4.2 Reporting of Substantial Amendments - Non CTIMP Studies

Substantial amendments require a favourable opinion from both the REC and R&D **before** they can be implemented. The only exception to this is where urgent safety measures need to be taken.

4.2.1 Submission to the Research Ethics Committee

If advised by the R&D Research Coordinator that the amendment is substantial and that notification to the REC is required, the CI or delegate should create and complete a Notification of Substantial Amendment Form which can be generated from the Integrated Research Application System (IRAS) application (https://www.myresearchproject.org.uk) using the Amendment tab associated with the REC form.

For studies submitted using systems or procedures that pre-date IRAS, the CI or delegate can create a basic dataset in IRAS based on the information in the original application and this basic dataset can then be used to generate a Notice of Substantial Amendment Form.

The CI should electronically sign the Notification of Substantial Amendment Form and the form should be emailed to the REC, along with any updated documents, such as consent forms or protocols. The submission should include a covering letter detailing the list of documents sent, including version numbers and issue dates.

The CI or delegate must make any changes to the amended documents as requested by the REC and resubmit the documents to REC as necessary.

4.2.2 Submission to R&D

For multi-site studies, the CI or delegate must submit the Notification of Substantial Amendment Form, amended documents and covering letter to NHS Research Scotland Permissions Coordinating Centre (NRSPCC). NRSPCC will then advise local R&D Offices if the amendment is Category A, B or C (See 3.3 above). If Category C, NRSPCC will also advise directly the person who made the submission, by email. The email from NRSPCC must be subsequently forwarded to the R&D Research Coordinator.

For single-site studies, the CI or delegate must submit the Notification of Substantial Amendment Form, amended documents and covering letter to NHS Fife R&D Office.

When all necessary approval(s) are in place, sites will issue their individual R&D Management Approval Letters.

The CI or delegate must file all correspondence relating to the amendment in the Trial Master File and must retain all versions of study documents relating to the amendment.

If the study is multi-site, the CI must send a copy of all approval letters and a copy of the approved amended documents to Site PI(s) for retention within the Investigator Site File (ISF).

4.3 Reporting of Substantial Amendments - CTIMPs

4.3.1 Submission to MHRA and REC

If advised by the R&D Research Coordinator that the amendment is substantial and that notification to the Medicines & Healthcare products Regulatory Agency (MHRA) and REC is required, the CI or delegate should create and complete a European Union Drug Regulating Authorities Clinical Trials (Eudract) Notification of Substantial Amendment Form which can be generated from the IRAS application (https://www.myresearchproject.org.uk.) using the amendment tab associated with the MHRA form. The CI should electronically sign the Eudract Notification of Substantial Amendment Form and this should then be submitted along with any amended document(s) to, as appropriate, the REC and/or the MHRA via the Common European Submission Portal (CESP - http://cesp.hma.eu/home/index).

The Substantial Amendment Form must summarise the change(s) and briefly explain the reasons in each case. It is important that the form is completed 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
- Covering letter to REC and/or MHRA including a list of documents sent with version numbers and dates.

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.

The original IRAS MHRA Form should be updated in its entirety at the occasion of such a substantial amendment notification to MHRA. Details of any previous amendment(s)(non-substantial and/or substantial but notified to REC only) should be clearly noted in the documentation and differentiated from the substantial amendment being made.

Further information can be found in the document 'Submitting a CTA application to the MHRA' found at:
(http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/ManagingyourCTA/Amendments/Generalinformation/index.htm)

Substantial amendments cannot be made following the Declaration of the End of the Trial, unless the MHRA has approved the withdrawal of the Declaration and the re-opening of the trial.

4.3.2 Submission to R&D

The same procedure should be followed as in 4.2.2

4.4 Reporting of Non-substantial Amendments - Non CTIMP Studies

4.4.1 Notifying the REC

If advised by the R&D Research Coordinator that the amendment is non-substantial, the CI should notify the REC (for information only) by email.

4.4.2 Notifying R&D

The CI or delegate should submit all amended documents with a covering letter as in 4.2.2.

4.5 Reporting of Non-substantial Amendments - CTIMPs

4.5.1 Notifying the REC

The same procedure should be followed as in 4.4.1.

4.5.2 Notifying MHRA

The CI or delegate should notify the MHRA of any non-substantial amendment(s) if/when next submitting a subsequent Notification of Substantial Amendment Form via CESP.

4.5.3 Notifying R&D

The same procedure should be followed as in 4.4.2

4.6 Reporting of Amendments - Gene Therapy Research

The same processes as in sections 4.3 and 4.5 above for CTIMPs should be followed for Gene Therapy studies, with the CTIMP Substantial Amendments Form sent to the Gene Therapy Advisory Committee (GTAC): http://www.hra.nhs.uk/resources/applying-to-recs/gene-therapy-advisory-committee-gtac/

4.7 Reporting of Amendments - MHRA Device Studies

MHRA Devices must be notified of **any** proposed changes to the investigation (not just those classed as substantial amendments for the purposes of ethical review) and the CI must wait for a letter of no objection from MHRA Devices to be received before any changes are implemented. This includes any changes requested by the REC. Failure to provide this notification could result in the manufacturer being liable to prosecution.

When notifying the MHRA of any changes, the following information must be provided in writing:

- the MHRA reference number for the trial;

- details of the proposed change(s) to the clinical investigation plan or the design of the device;
- the reason for the change(s); and
- a signed statement by or on behalf of the manufacturer that the proposed change(s) do not predictably increase the risk to the patient, user or third party.

Notifications should be sent directly to MHRA devices: (http://www.mhra.gov.uk/Howweregulate/Devices/Clinicaltrials/index.htm).

Amendments to device studies must be submitted to the REC and R&D as 4.2 and 4.4 above.

4.8 Reporting of Amendments - Administration of Radioactive Substances Advisory Committee

In addition to submissions made to the REC, MHRA (if required) and R&D, the Administration of Radioactive Substances Advisory Committee (ARSAC) must be notified for information of any changes to the administration of radioactive materials during a study, such as:

- Dose changes
- New modalities
- New classes of study participant

These changes will normally meet the criteria for notifying substantial amendments to the REC (or Gene Therapy Advisory Committee (GTAC)). ARSAC must be provided with a copy of the Notice of Substantial Amendment when this is submitted to the REC, together with any supporting documentation (e.g. protocol, patient information sheets).

For a multi-site study, it is not necessary for the ARSAC certificate holder at each site to notify ARSAC; the ARSAC certificate holder at the lead site or the trial co-ordinator can provide a single notification. ARSAC will contact certificate holders if further information is required and/or the changes could affect existing certification.

5. IMPLEMENTATION OF AMENDMENTS

5.1 Amendments can only be implemented when all approvals have been received in writing (except for Urgent Safety Measures - see section 6 below).

5.2 For multi-site studies, the CI must ensure that the amendment is not implemented at sites until each Site PI receives written local NHS R&D management approval in writing.

5.3 The CI or delegate must log all amendments, including non-substantial amendments, in a study-specific Amendments Log (Doc Ref 20-001) and, if the study is multi-site, must advise PI(s) to do so. All logs will be examined by a Clinical Trial Monitor or another appropriate Sponsor representative. Logs should clearly identify which Site they refer to.

5.4 The CI is responsible for ensuring that all changes, substantial or non-substantial, to all study-specific documents - protocol, PIS, ICF, Invitation Letter, GP Letter, Participant Diary, Questionnaire, Case Report Form (CRF) and any other are subject to version control (refer to WI37(Fife) - Version Control of Clinical Research Study Documentation).

5.5 The CI and/or PI must ensure that all research staff are familiar with any new documentation and trained in new procedures/interventions with appropriate amendment to their training logs.

5.6 One original copy of any superseded versions of study documents must be retained in the TMF and/or ISF. All other copies of previous versions must be destroyed,
5.7 The CI must ensure that all Protocol versions are appropriately signed and dated by all pertinent study staff.

6. URGENT SAFETY MEASURES

An Amendment **must not** be implemented prior to all approvals being received in writing unless it is in relation to an Urgent Safety Measure.

There must be arrangements in place for taking appropriate Urgent Safety Measures to protect participants against any immediate hazard where new events relating to the conduct of the study are likely to affect the safety of the subjects. In many studies, the individual best able to take such measures would be the CI or another identified person or organisation, rather than the Sponsor directly. The protocol should identify the specific individual(s) who accept(s) this responsibility. Otherwise, the Sponsor remains directly responsible.

Any safety measures, such as temporarily halting the study, may be taken without prior authorisation from the MHRA and/or REC but must be reported to the MHRA, Ethics Committee, Sponsor and R&D Departments.

7. ASSOCIATED DOCUMENTS & REFERENCES

WI37(Fife) - Version Control Of Clinical Research Study Documentation

Doc Ref 20-01- Amendment Log

World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.
(https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/)

Medicines for Human Use (Clinical Trials) Regulations 2004.
(http://www.legislation.gov.uk/uksi/2004/1031/contents/made)
It is assumed that by referencing the principal regulations, all subsequent amendments made to the principal regulations are included in this citation.

UK Policy Framework for Health and Social Care Research
https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/.

European Commission - Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1, (2010/C 82/01).
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52010XC0330%2801%29.

Substantial amendments to your clinical trial authorisation: General information
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/ManagingyourCTA/Amendments/Generalinformation/index.htm.

IRAS Online Substantial Amendment Form
https://www.myresearchproject.org.uk/help/Contents/BlankPdfForms/NoticeOfAmendmentForm.pdf).

IRAS Guidance – Amendments
https://www.myresearchproject.org.uk/help/hlpamendments.aspx

8. ABBREVIATIONS

ARSAC	Administration of Radioactive Substances Advisory Committee
CI	Chief Investigator
GTAC	Gene Therapy Advisory Committee
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File
MHRA	Medicines and Healthcare Products Regulatory Agency
NRSPCC	NHS Research Scotland Permissions Coordinating Centre
PI	Principal Investigator
REC	NHS Research Ethics Committee
R&D	Research and Development
SOP	Standard Operating Procedure
TMF	Trial Master File

9. DOCUMENT HISTORY

Version Number:	Edited by (job title):	Effective Date:	Details of Revisions Made:
1.0	Julie Aitken R&D Trials Facilitator Allyson Bailey R&D Commercial Manager	10/11/2014	Adapted from TASC SOPs 26 (v3.0) and 30 (v1.0)
2.0	Julie Aitken R&D Trials Facilitator	07/09/2016	Revised to cover NHS Sponsored studies only and updated to reflect changes in procedure for R&D review of multi-centre studies and change in reporting procedures to MHRA via CESP.
3.0	Julie Aitken R&D Trials Facilitator	04/10/2018	Minor changes only

10. APPROVAL

APPROVED BY	Date
Professor Alex Baldacchino, Research & Development Director, NHS Fife Signature: 	4th Oct 2018

Appendix 1: Amendments flowchart