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

SOP NUMBER:	**Fife R&D SOP20**
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1. PURPOSE

This SOP describes the procedure for the management of amendments to clinical research studies 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 NHS Fife StaffLink, EDGE and the R&D section of the NHS Fife website (www.nhsfife.org/research). For guidance, contact the R&D Department via fife.randd@nhs.scot.

2. APPLICABILITY

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 (PIs), clinical research staff and all staff who manage, coordinate or advise on amendments to research Sponsored by NHS Fife.

3. POLICY

3.1 After a research study sponsored by NHS Fife has received all necessary approvals, any subsequent amendments to the protocol or supporting documents must be submitted to the Sponsor's representative via the R&D Approval Team (fife.fiferesearchapprovals@nhs.scot) who will advise on the submissions process-and approve or acknowledge the amendment as required once it has been categorised and any required regulatory approvals are in place.

A written response must be obtained from the Sponsor's representative prior to further submission of the amendment, unless the amendment is an urgent safety measure.

3.2 An amendment to a research project can be either **substantial** *or* **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 participants of the study
2. Scientific value of the study

3. Conduct or management of the study

Examples of substantial amendments include:

- changes to the design or methodology of the study, or to background information affecting its scientific value i.e. as a result of interim study data which reveal unexpected beneficial or harmful effects (e.g. following the interim analyses of study data, updated safety analyses, reports from the Study Monitoring Committee or any other changes which may require further evaluation;
- 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;
- 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 Non-Substantial Amendments.

A non-substantial 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 non-substantial amendments include:

- minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications;
- changes to the CI's research team (other than appointment of key collaborators);
- changes to the research team at particular study sites;
- 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;
- 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 therefore 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.

3.4 All amendments for research projects (with the exception of tissue bank and research databases) must use the IRAS Amendment Tool and be submitted online when authorised and locked by the R&D Approvals Team. For full guidance on how to complete the Amendment Tool go to: http://www.myresearchproject.org.uk/help/hlpamendments.aspx

Research Tissue Banks (RTB) and Research Databases (RDB) require review by an NHS REC, but do not need NHS R&D approval and are notified to R&D Offices for information only. For amendments to tissue banks and research databases, researchers should continue to use the Notice of Substantial Amendment Form generated in IRAS in order to notify substantial amendments to the REC.

4. PROCEDURE

4.1 Submission to Sponsor

4.1.1 The CI or delegate should notify the Sponsor, via e-mail to the R&D Approvals Team (fife.fiferesearchapprovals@nhs.scot), 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.

4.1.2 The R&D Approvals Team will discuss with the CI or delegate, as appropriate, and confirm by email whether the amendment is acceptable and advise on submission process if required.

4.1.3 The R&D Approvals Team will re-assess the risk attached to the study as a consequence of the amendment, and, if necessary, 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.

4.1.4 Once Sponsor approval in principle has been given, the Amendment must be submitted using the online IRAS Amendment Tool for REC and R&D Approvals as outlined below.

4.2 Reporting of Substantial Amendments

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

The CI or delegate should create and complete an online Amendment Tool which can be generated from the Integrated Research Application System (IRAS) (https://www.myresearchproject.org.uk/help/hlpamendments.aspx). The Amendment Tool will state whether or not the amendment is substantial or non-substantial and what type of review will be required.

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 complete the online Amendment Tool.

Details for submission of the online Amendment Tool can be found at: https://www.myresearchproject.org.uk/help/hlpamendments.aspx.

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, following submission of the Online Amendment Tool, amended documents and covering letter will be made available to the 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 NHS Fife R&D Approvals Team.

For single-site studies, the CI or delegate must submit the online Amendment Tool, amended documents and covering letter which will then be notified via NRSPCC to NHS Fife R&D Approvals Team.

When all necessary approval(s) are in place, sites will issue their individual Local Management Approval Letters or e-mail acknowledgement.

The CI or delegate must file all correspondence relating to the amendment in the Study 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).

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 Management Approval or acknowledgement in writing.

5.3 The CI or delegate must log all amendments, including non-substantial amendments, in a study-specific Amendments Log (Doc Ref 20-01) and, if the study is multi-site, must advise PI(s) to do so. 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 Fife R&D WI37 - 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 SMF 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

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

6.2 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.

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

7. ASSOCIATED DOCUMENTS & REFERENCES

Doc Ref 20-01- Amendment Log

Fife R&D WI37 - Version Control of Clinical Research Study Documentation

IRAS Online Amendment Tool and Guidance:
https://www.myresearchproject.org.uk/help/hlpamendments.aspx#NHS-HSC-REC

8. ABBREVIATIONS

CI	Chief Investigator
ICF	Informed Consent Form
IRAS	Integrated Research Application System
ISF	Investigator Site File
NRSPCC	NHS Research Scotland Permissions Coordinating Centre
PI	Principal Investigator
REC	NHS Research Ethics Committee
R&D	Research and Development
SMF	Study Master File
SOP	Standard Operating Procedure

9. DOCUMENT HISTORY

Version Number:	Edited by (job title):	Effective Date:	Details of Revisions Made:
1	Julie Aitken R&D Trials Facilitator Allyson Bailey R&D Commercial Manager	10 Nov 2014	Adapted from TASC SOPs 26 (v3.0) and 30 (v1.0)
2	Julie Aitken R&D Trials Facilitator	07 Sept 2016	Revised to cover NHS Fife 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	Julie Aitken R&D Trials Facilitator	04 Oct 2018	Minor changes only
4	Aileen Yell R&D Research Coordinator	28 Jan 2021	References to MHRA and CTIMPs removed as NHS Fife does not currently Sponsor CTIMPs. Reference to process for using IRAS Amendment Tool added.

10. APPROVAL

APPROVED BY	Date
Professor Alex Baldacchino, Research & Development Director, NHS Fife Signature: 	28 Jan 2021