York and Scarborough Teaching Hospitals NHS Foundation Trust R&D Unit
Standard Operating Procedure
R&D/S74

Making Amendments to Trust Sponsored Research Studies

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the R&D Unit's website and/or Q-Pulse for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.

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This SOP will normally be reviewed every 3 years unless changes to the legislation require otherwise

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Version History Log

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of significant changes
1.0	14th November 2011	Previous R&D/CTIMP/S07 split into three separate SOPs (S07, S74 and S75)
2.0	1st January 2012	Administrative change
3.0	13th May 2013	Removal of references to the North and East Yorkshire R&D Alliance. Change of author.
4.0	24th August 2017	
5.0	15th July 2019	Change of link to R&D website.

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Contents

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1 Introduction, Background and Purpose

This SOP describes the procedure for:

- making amendments to the protocol, other essential documents[1] or study arrangements;
- updating the Investigator's Brochure or SmPC in a clinical trial of an investigational medicinal product (CTIMP);
- obtaining approvals for these changes where required;
- notifying changes to regulatory authorities;
- the exception for urgent safety measures;
- implementing amendments at Site(s);
- notifying other individuals, departments or organisations involved in the study that these changes have been made.

2 Who Should Use This SOP

This SOP is aimed at:

- Chief Investigators (CIs) of research studies sponsored or co-sponsored by the Trust;
- Principal Investigators (PIs) and research staff at sites where multi-site studies sponsored or co-sponsored by the Trust are being run;
- R&D Unit staff.

In this SOP the Trust means:

- York and Scarborough Teaching Hospitals NHS Foundation Trust

3 When this SOP Should be Used

This SOP should be used:

- when an amendment to a Trust sponsored study is required;
- when an Investigator Brochure (IB), or Summary of Product Characteristics (SmPC)is updated for a CTIMP;

For Urgent Safety Measures – refer to the SOP referenced in Section 6.

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[1] "essential documents" are defined in the UK Clinical Trial Regulations governing clinical trials of investigational medicinal products: "… documents … which (a) enable both the conduct of the clinical trial and the quality of the data produced to be evaluated; and (b) show whether the trial is, or has been, conducted in accordance with the applicable requirements of Directive 2001/83/EC, the Directive, the GCP Directive and Commission Directive 2003/94/EC".

4 Procedure(s)

4.1 Amendments and their classification

Amendments are changes made to a research study after approval has been given.

Amendments can be made to the protocol, other essential documentation or other aspects of a study's arrangements. All research documents should have a clear version number and date in order to maintain accurate records and audit trails. Any amendment to a research protocol or study documentation, whether substantial or minor, should have a concordant amendment to the date and version number.

An amendment can be either **substantial** *or* **minor (non-substantial)** in nature. The classification decisions must be made by the Sponsor although advice may be sought from the Research Ethics Committee (REC) for non-CTIMP studies.

The current guidance published on the Health Research Authority (HRA) website (see Section 6) should be applied. For CTIMPs additional information is available in the European Commission document also referenced in Section 6.

4.1.1 Substantial amendments defined

A Substantial Amendment is defined by the Clinical Trials Regulations as an amendment to the protocol or any other supporting documentation that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial;
- The scientific value of the trial;
- The conduct or management of the trial; or
- The quality or safety of any investigational medicinal product (IMP) used in the trial.

The same definition of "substantial amendment" applies for non-CTIMP studies.

The following changes would normally be regarded as substantial:

1. Changes to the design or methodology of the study, or to background information, likely to have a significant impact on its scientific value
2. Changes to the procedures undertaken by participants
3. 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
4. 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
5. A change of sponsor(s) or sponsor's legal representative
6. Appointment of a new Chief Investigator, or temporary arrangements to cover the absence of a CI
7. In a CTIMP, addition of a new site not listed in the original application or the appointment of a new PI at a trial site
8. A change to the insurance or indemnity arrangements for the study

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9. A change to the payments, benefits or incentives to be received by participants or researchers in connection with taking part in the study, or any other change giving rise to a possible conflict of interest on the part of any investigator/collaborator
10. Temporary halt of a study or temporary halt at a study site to protect participants from harm, and the planned restart of a study following a temporary halt
11. Early closure or withdrawal of a site
12. A change to the definition of the end of the study
13. Any other significant change to the protocol in terms of the REC (Ethics) application

4.1.2 Minor ('non-substantial') amendments defined

A minor amendment is a change that will have no significant implications for participants or for the conduct, management or scientific value of the study.

Examples of minor amendments include:

1. Minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications
2. Changes to the Chief Investigator's research team
3. Changes to the research team at particular trial sites (other than appointment of a new Principal Investigator in a CTIMP)
4. Inclusion of new sites and investigators in studies other than CTIMPs
5. Routine closure of sites at the end of the study
6. Changes in funding arrangements
7. Changes in the documentation used by the research team for recording study data
8. Changes in the logistical arrangements for storing or transporting samples
9. Extension of the study beyond the period specified in the application form
10. Issue of an updated Investigator's Brochure or Summary of Product Characteristics relating to an investigational medicinal product **where the Reference Safety Information (RSI) is unchanged**

4.1.3 Urgent Safety Measures

An Urgent Safety Measure (USM) is an action taken by the sponsor or investigator of a research study in order to protect research participants against any immediate hazard to their health or safety. For obvious reasons action is taken prior to seeking sponsor or regulatory approval – notification is required immediately after the event. For Urgent Safety Measure reporting see the USM SOP referenced in Section 6.

4.2 Obtaining the Sponsor's Approval of an Amendment

Any amendment must be approved by the study Sponsor prior to applying for regulatory approval and/or implementation unless it is an urgent safety measure.

The CI must request permission to make an amendment in writing to the R&D Unit. This request should include:

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- a description of the proposed amendment;
- reason(s) for the proposed amendment;
- revised documentation as a result of the amendment (e.g. updated protocol, consent form, patient information sheet, additional investigator CVs) with tracked changes applied;
- a revised risk assessment (where applicable).

All revised documentation must be subject to strict document control and should be submitted with revised version numbers and dates. Changes should be clearly highlighted using *track changes* to facilitate review.

The R&D Unit will make the following judgements / take decisions on behalf of the Sponsor, obtaining peer review / expert opinion and referring to the R&D Group if this is warranted by the nature of the amendment:

- whether the amendment is such that it might affect the Trust's willingness to continue sponsoring the study;
- whether the proposed amendment will affect the insurance in place for the study (the insurer may be approached and evidence obtained);
- whether the amendment is substantial or non-substantial (minor)

At the end of this process, the R&D Unit will, on behalf of the Sponsoring Trust, confirm in writing whether the proposed amendment is acceptable to the Sponsor.

4.3 Obtaining regulatory approvals for an amendment

Once Sponsor's approval has been given, the CI (or delegated other) should submit the substantial amendment to:

- the Health Research Authority (HRA), and/or
- the REC, and/or
- (for a CTIMP) the Medicines and Healthcare Products Regulatory Agency (MHRA), and/or
- any other regulatory body as necessary (e.g. the Gene Therapy Advisory Committee, ARSAC)

Amendments for studies set up using pre-HRA Approval processes are submitted in exactly the same way as HRA Approval studies. Where the amendment introduces a new site for a pre-HRA Approval study the HRA Assessment Team will ask for the most up to date document set and the template agreements and costing information that will be used when working with the new site.

4.3.1 Substantial Amendments

Substantial amendments that require REC review should be submitted by email to the REC that originally reviewed the study. The appropriate notice of substantial amendment form (accessed through IRAS) with relevant authorisations and supporting documentation should be included in the email. The REC will review the amendment.

For CTIMP studies it is the responsibility of the sponsor to decide whether a substantial amendment requires authorisation by MHRA, or an ethical opinion, or both. Reference should be made to the published Guidance

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available on the HRA website referenced in Section 6 which takes account of the guidance from the European Commission.

For CTIMPs the Substantial Amendments Form must be used for submissions to the MHRA. This is the Notification of amendment form found at: http://ec.europa.eu/health/documents/eudralex/vol-10/
and should be submitted through the Common European Submission Portal (CESP).

It is the responsibility of the CI to ensure that any conditions of approval requested by the Regulatory Authorities are met and that final approval for the amendment from both the REC and (if required) the MHRA is obtained in writing.

When any amendment is being made to the protocol (e.g. to eligibility criteria) or an updated SmPC is being adopted, care should be taken to ensure that the study will still be using the product strictly within the terms of its marketing authorisation.

4.3.2 Non-substantial amendments

Non-substantial amendments or any amendments that do not require REC review should be submitted by email to hra.amendments@nhs.net using the non-substantial amendment form (located through IRAS or on the HRA website).

4.4 Notifying R&D Offices

All amendments (substantial and non-substantial) should be notified to the R&D office at each site as they may have an impact on the financial or operational arrangements at that site. NOTE that this is separate from the Sponsor approval decision also administered by the R&D Unit; financial and operational considerations may be different in non-sponsoring Trusts.

Once the categorisation email has been received from the HRA, then an amendment package of revised documentation, together with a summary of the amendment and a copy of the HRA email should be shared with all sites. Sites can then make their own arrangements to review the proposed amendment to determine their ability to implement it.

When final outcome communication is received from HRA (and other required regulatory bodies where applicable) then final documentation should be shared with each site so that the amendment can be implemented locally.

Where a Site is unable to accommodate the requirements of an approved amendment, the research may have to be terminated at that Site.

For Category A and B amendments NHS organisations have a maximum of 35 days to raise an objection otherwise the amendment can be implemented after the 35 day period. NHS organisations are however encouraged to complete the review earlier where possible. Category C amendments may be implemented immediately.

It is advised that no amendment should be implemented in a Trust until written confirmation is received that there is no objection to the amendment being implemented at that Site.

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4.5 Notifying others about Amendments you have made

The CI or delegated other, for the Trust sponsored study is responsible for ensuring all involved departments at the CI site and all PIs at other sites are promptly notified that amendments of any kind are being made. The PI (or delegated individual) at a participating site is then responsible for notifying all relevant departments at that site.

The CI's notification to PIs at other sites should specifically delegate to them responsibility for notifying their local departments and provide guidance as to a suitable implementation date of the amendment The Amendment Checklist referenced in Section 6 may be adapted by the CI to assist with this process if wished.

It is important to:

1. Ensure that the following (copy unless otherwise stated) documents are obtained and filed in each Investigator Site File (ISF):
    a. The amended document(s);
    b. REC (and MHRA) approvals (for a substantial amendment);
    c. Site R&D Office notice of no objection where issued.
2. Set and make formal note in the ISF of the local implementation date (having regard to any instructions from the Sponsor and sufficiently in advance to allow for all involved staff in the organisation to be informed);
3. Inform local involved departments (e.g. pharmacy, radiology) of the amendment. Receipt of any revised information should be acknowledged by involved departments and the acknowledgement filed in the ISF. All staff should act upon the information, observing the stipulated local implementation date, and ensure that any elements of the ISF held in that department have the new information properly entered;
4. Check whether extracts of eligibility criteria or other information about the study are used to inform the wider clinical team and assist recruitment. If so, and the amendment has affected this, withdraw all existing copies with effect from the local implementation date. Replace with new information EXTRACTED AS DIRECT COPIES FROM THE AMENDED PROTOCOL OR OTHER MATERIAL and version controlled / dated;
5. Remove, destroy multiple copies and re-file all replaced paperwork in the 'superseded' section of the ISF, writing on it 'replaced by version …..';
6. Check that document control is in place on all documents to enable subsequent reconstruction of exactly what was being used on what date;
7. Check whether study protocol is loaded on local intranet and update if necessary.

5 Reviewing the Investigator Brochure (IB) / SmPC for a CTIMP

The Clinical Trial Regulations provide that: *The Sponsor of a clinical trial shall:*

(a) ensure that the investigator's brochure for that trial, and any update of that brochure, presents the information it contains in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential

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investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial; and

(b) validate and update the investigator's brochure at least once a year.

The IB and SmPC are important documents because they contain the **Reference Safety Information** (RSI) which is a list of medical events that defines which reactions are expected for the Investigational Medicinal Product (IMP). It is one single definitive list or document that determines which Serious Adverse Reactions (SARs) require expedited reporting to the relevant National Competent Authority (in this case the MHRA) and which are exempt.

5.1 Reference Safety Information

The RSI can be used by a number of different trial personnel depending on who is responsible for conducting the expectedness assessment of a Serious Adverse Reaction (SAR). Expectedness can have a lot of different meanings in the medical world, but from a regulatory perspective, in relation to safety reports and Suspected Unexpected Serious Adverse Reactions (SUSARs), it means whether or not the reaction is an expected side effect of the IMP, thus determining whether it does or does not need reporting in an expedited fashion. To be categorised as expected the reaction must be clearly listed in the RSI.

The RSI should be clearly identified in the protocol and specified in the Clinical Trial Authorisation application. It is not sufficient to simply state that the IB or SmPC applies, a clearly defined section must be identified (e.g. section 4.8 of the SmPC).

5.2 Updates to the SmPC or IB

The version of the SmPC or IB that was submitted with the application for Clinical Trial Authorisation to MHRA is the version that must be used as the RSI for the trial. If a new SmPC is released or the IB is updated and there is ANY change to the RSI then a substantial amendment must be submitted to the MHRA and approved before the new version can be implemented.

For Trust sponsored CTIMPs any change to the SmPC or IB must be discussed with the R&D Unit before any change to the trial is proposed.

There are three potential scenarios:

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A new version of the SmPC/IB is issued at the same time as the DSUR for the new reporting period and there are new events listed as expected	You must send an amendment to the MHRA and not implement the new SmPC IB until you have obtained approval.
A new version of the SmPC/IB is issued at the same time as the DSUR for the new reporting period and there are **no changes to the RSI** (this means no new events listed as expected and no events removed)	You do not need to send an amendment to the MHRA before you use the new SmPC/IB but you must document the assessment that demonstrates the RSI has not changed in your TMF.
A new version of the SmPC/IB is issued mid DSUR period and **there are new events listed as expected**	You must send an amendment to the MHRA and not implement the new SmPC/IB until you have obtained approval. Any change in RSI is a change in risk benefit. However, you do not have to implement the new SmPC/IB. You can risk assess the new version of the SmPC/IB against the current version and if the RSI changes are minimal or not relevant to your study or patient population, then you can choose to continue with the current RSI in the current SmPC/IB version for the remainder of the period.

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5.3 How to handle updated IBs and SmPCs

For Trust Sponsored CTIMPs it is a requirement to formally review the SmPC/IB 9 months after the date of the CTA and to ensure any substantial amendment is able to be approved by the MHRA prior to the beginning of the next DSUR reporting period.

The proposed 9 month review date must be clearly documented in the ISF. The Sponsor will issue reminders but it is the responsibility of the CI (or delegate) to ensure that this review is undertaken, documented and an appropriate course of action agreed with the Sponsor. This will be determined by an assessment of the changes that have been made to the SmPC/IB and any resulting change in risk/benefit to the trial. This must involve medical input.

5.4 Reviewing current knowledge and producing the IB update

For Trust sponsored CTIMP the CI is responsible for undertaking the annual update of the IB. S/he should arrange appropriate (e.g. pharmacology) input to ensure that required expertise is applied to the process of reviewing current knowledge of the IMP.

The CI should ensure that work begins in good time to meet the one-year deadline, allowing for consideration by the R&D Group. The timing of 'at least once a year' should be calculated from the date of the original Clinical Trial

Authorisation from the MHRA. The R&D Unit will send a reminder to the CI three months before the annual update is due.

The CI should submit to the R&D Unit:

- **Either** a revised IB **or** a statement that full review has been carried out and no updating is necessary;
- **Either** a revised risk assessment for the study **or** a statement that no revision is necessary
- A list of the names and qualifications of all who have been involved in reviewing the IB;
- For anyone involved in the review whose CV was not supplied to the R&D Unit in the course of the sponsorship application, a CV.

The revised IB and risk assessment or statements of 'no change' should be signed by all who have been involved in the review.

The R&D Unit will confirm whether the Sponsor considers that the benefit-risk assessment for the study has changed. Independent advice may be sought if considered necessary and the matter may be referred to the R&D Group. Where the RSI has been updated or when the risk:benefit assessment for he study has been changed (note a change to the RSI is automatically a change to the risk:benefit assessment) then the updated IB must be submitted to the MHRA as a substantial amendment for approval PRIOR to being implemented at the start of the next DSUR reporting period. Refer to previous section for other possible scenarios.

6 Related SOPs and Documents

R&D/S03 Delegation of Roles and Responsibilities

R&D/S06 Reporting Requirements During Studies

R&D/S68 Urgent Safety Measures

R&D/S07 Implementing Amendments for Research Studies not Sponsored by the Trust

R&D/S09 Set Up and Management of Research Studies

R&D/S75 R&D Processing of Amendments

R&D/F11 Trial Master File/Investigator Site File Contents

R&D/F18 Amendment Checklist (Research Teams)

Information on which regulatory approvals are required for CTIMP substantial amendments is available in the *Memorandum of Understanding between MHRA, NRES, GTAC and AAPEC*

https://www.hra.nhs.uk/about-us/partnerships/memorandum-understanding-mhra/

https://webarchive.nationalarchives.gov.uk/20100809102959/http://www.nres.npsa.nhs.uk/news-and-publications/news/memorandum-of-understanding-between-nres-mhra-gtac-and-aapec/

https://www.hra.nhs.uk/approvals-amendments/

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