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 Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.

The definitive versions of all R&D Unit SOPs appear online. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the R&D Unit website: www.research.yorkhospitals.nhs.uk/sops-and-guidance-/ and/or Q-Pulse

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

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	Reviewers	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.
6.0	27th February 2023	Greg Forshaw Deborah Phillips	Thorough revision. All amendment submission processes updated to IRAS & all references to European processes removed.

Contents

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 (IB) or Summary of Product Characteristics (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.

In this SOP 'the Trust' refers to York and Scarborough Teaching Hospitals NHS Foundation Trust.

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.

3 When this SOP Should be Used

This SOP should be used:

- when an amendment to a Trust-Sponsored study is required;
- when an IB or SmPC is being updated for a CTIMP;

For Urgent Safety Measures – refer to SOP R&D/S68.

[1] As defined by ICH-GCP, essential documents are "those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements." (https://ichgcp.net/8-essential-documents-for-the-conduct-of-a-clinical-trial)

4 Procedure(s)

4.1 Amendments and their classification

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

Amendments can be made to the protocol, other essential documentation, or other aspects of a study's arrangements. All research documents must 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 must have a corresponding amendment to the date and version number of that research protocol or study documentation.

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

The current guidance is published on the HRA website https://www.hra.nhs.uk/approvals-amendments/

4.1.1 Substantial amendments defined

The definition of a substantial amendment applies to CTIMP and non-CTIMP studies alike. It 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.

Examples of substantial amendments include:

- Changes to the design or methodology of the study, or to background information, likely to have a significant impact on its scientific value;
- Changes to the procedures undertaken by participants;
- 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;
- 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 temporary arrangements to cover the absence of a CI;
- In a CTIMP, re: non-NHS sites only, the appointment of a new PI or the addition of a new site not listed in the original application;
- A change to the insurance or indemnity arrangements for the study;
- 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 an investigator/collaborator;
- The 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 in terms of the REC (Ethics) application;

4.1.2 Non-substantial ('minor') amendments defined

The definition of a non-substantial amendment applies to CTIMP and non-CTIMP studies alike. It 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:

- Minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications;
- Updates of the IB (unless there is a change to the risk/benefit assessment for the trial);
- Changes to the CI's research team;
- Changes to the research team at particular NHS trial sites;
- Inclusion of new NHS sites and investigators;
- 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;
- The early closure or withdrawal of a site
- Change to the study end date;

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 USM reporting see **SOP R&D/S68**.

4.2 Obtaining the Sponsor's Pre-Approval of an Amendment

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

Permission to make an amendment must be requested from R&D by the CI (or delegated other) in writing. Their email should include:

- a completed Amendment Tool, the latest version of which is available in IRAS. The Amendment Tool can be used for all amendments to all types of studies. It will contain a description of the proposed amendment and the reason(s) for it;
- revised documentation as a result of the amendment (e.g. a revised risk assessment, where applicable; updated protocol; updated consent form; updated patient information sheet; additional investigator CVs) - **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 *tracked changes* to facilitate review**.

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

- 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 pre-approval has been given, the completed Amendment Tool and amended documents should be submitted by the CI (or delegated other) to IRAS as directed on the "Submissions Guidance" tab of the Tool to the appropriate regulatory bodies, which may include:

- the 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)

Detailed submission guidance depending on the amendment categorisation will be provided on the Amendment Tool and should be followed.

For non-substantial amendments requiring a study-wide review, you will receive confirmation of HRA and HCRW Approval via email if the amendment affects NHS sites in England and/or Wales.

For non-substantial amendments requiring no study-wide review, you will not receive anything from the HRA. The automated acknowledgement email you receive when the amendment is submitted **is** your approval, and the amendment can be implemented according to the categorisation information contained in the Amendment Tool.

The Amendment Tool is not currently intended for amendments to research tissue banks and research databases. For these types of research, substantial amendments need to be notified and ethical approval sought before implementing the amendment. A substantial amendment should be generated by accessing the original application form on IRAS.

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 pre-approval decision also administered by our local R&D Unit.

Following the implementation of the Amendment Tool and Online Submission for amendments, sponsors will no longer receive a separate categorisation email post-submission. They will instead receive an automated acknowledgement email confirming the submission has been successful. The Amendment Tool outputs include confirmation of the category of the amendment.

After you have submitted your amendment, you should share your completed Amendment Tool with confirmation of amendment category and, if applicable, amended documents with relevant participating NHS organisations in England and/or Wales. In doing so, you should include the NHS R&D Office, LCRN (where applicable) as well as the local research team. Sites can then make their own arrangements to review the proposed amendment to determine their ability to implement it.

When the final approval email is received from the 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.

IRAS states that “Sponsors should **not** expect to receive a letter or email of confirmation from NHS/HSC organisations before implementing the amendment. If all relevant regulatory approvals are in place and there has been no objection from site, category A and B amendments can be implemented after 35 days.” NHS organisations are however encouraged to complete the review earlier where possible. Category C amendments may be implemented immediately.

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 other 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.

It is important to:

- Ensure that the following documents (copy unless otherwise stated) are obtained and filed in each Investigator Site File (ISF):
    a. The amended document(s);
    b. HRA (and for substantial amendments) REC and MHRA approvals;
    c. Site R&D Office email of no objection to the amendment and issue of Continuing Capacity & Capability.
- Set a local implementation date and make a formal note of it in the ISF (having regard to any instructions from the Sponsor and being sufficiently in advance to allow for all involved staff in the organisation to be informed);
- 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 ensuring that any elements of the ISF held in that department have the new information properly entered;
- Check whether extracts of eligibility criteria or other study information are used to assist in recruitment. If so, and if the amendment has affected this, withdraw all existing copies with effect from the local implementation date. Replace with new information EXTRACTED DIRECTLY FROM THE AMENDED PROTOCOL OR OTHER MATERIAL and version controlled and dated;
- Remove, destroy multiple copies, and re-file all replaced paperwork in the 'superseded' section of the ISF, writing on it 'replaced by version …..';
- Check that document control is in place on all documents to enable subsequent reconstruction of exactly what was being used on what date;
- Check whether study protocol is uploaded on the local intranet and update it if necessary.

5 Reviewing the IB / SmPC for a CTIMP

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

(a) ensure that the IB 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 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 IB 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 the 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 RSI

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), 'expectedness' means whether or not the reaction is a known 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 as listing the RSI (e.g. section 4.8 of the SmPC).

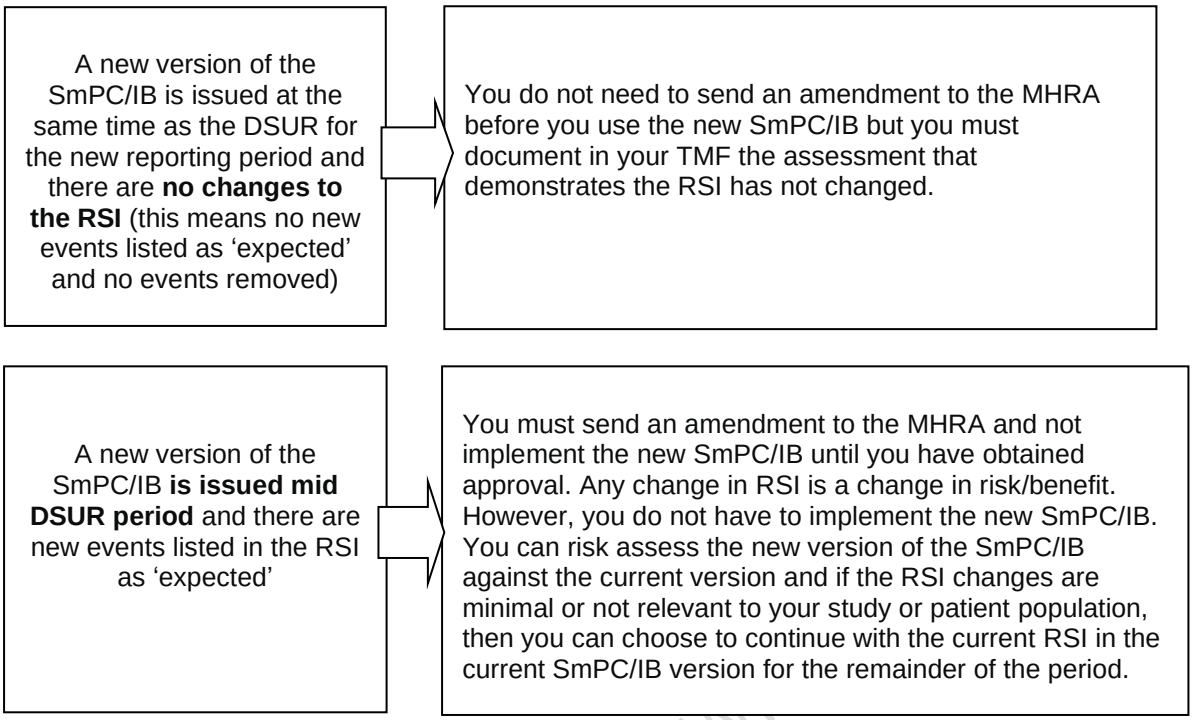
5.2 Updates to the SmPC or IB

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 amendment to the trial is submitted, taking into account the Development Safety Update Report (DSUR). This is used by the Sponsor to present a comprehensive annual review of pertinent safety information collected during the reporting period and to evaluate whether it is consistent with the previous knowledge of the safety profile of the IMP.

There are three potential scenarios:

A new version of the SmPC/IB is issued at the same time as the DSUR for the new reporting period & there are new events listed as 'expected' in the RSI	You must send an amendment to the MHRA and not implement the new SmPC/IB until you have obtained approval.



5.3 How to handle updated IBs and SmPCs

For Trust-Sponsored CTIMPs it is a requirement to begin to formally review the SmPC/IB **9 months** after the date of the CTA (annually thereafter) and to ensure that any substantial amendment is submitted in sufficient time 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 TMF. The Sponsor will issue reminders but it is the responsibility of the CI (or delegated other) to ensure that this review is undertaken and documented, and that an appropriate course of action is then 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** be discussed with the responsible clinicians.

5.4 Reviewing current knowledge and producing the IB update

For Trust-Sponsored CTIMPs 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;
- A CV for anyone involved in the review whose CV was not originally supplied to the R&D Unit in the course of the sponsorship application.

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 risk/benefit 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 the 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)