The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University

Standard Operating Procedure

SOP number:	SOP-JRO-38-002
SOP full title:	Amendments to Sponsored CTIMP, ATMP or Device Trials.
SOP effective: 16 October 2017	Review date: 16 October 2019

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SOP HISTORY

Version	Date	Reason for change
001	11/09/2017	Requested wet ink signed copies (rather than electronically signed)

1. BACKGROUND/INTRODUCTION

During the lifespan of a clinical trial, the Chief Investigator (CI) and/or associated trial team may wish to amend certain aspects of the protocol. This will involve submitting amendment requests to the appropriate regulatory organisations:

- Research Ethics Committee (REC),
- Health Research Authority (HRA)
- Medicines and Healthcare products Regulatory Agency (MHRA).

For all studies, it is the responsibility of the Sponsor to determine whether an amendment is substantial or non-substantial. It is also a Sponsor responsibility to decide if a substantial amendment requires MHRA authorisation, REC opinion or both. For the purpose of this SOP the Regulatory Compliance team will undertake the amendment review process on behalf of the Sponsor.

1.1 Categories of Amendment

An amendment can be defined as either substantial or non-substantial, and broadly impacts on the following:

- The terms of the request for clinical trial authorisation from the MHRA
- The terms of the REC application
- The protocol
- Any other particulars or documents submitted with the applications to the MHRA or the REC

1.1.1 Substantial amendment definition:

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) or medical device used in the trial.

Depending on the type, the substantial amendment will either require MHRA authorisation, REC opinion or both. Examples, by no means exhaustive, of such are outlined below:

The following amendments would normally require MHRA authorisation only:

- New toxicological or pharmacological data or new interpretation of toxicological or pharmacological data of relevance for the investigator
- New medical device safety information or quality aspects of relevance for the investigator including changes or modifications to the device (applicable for devices that fall under the Medical Device Regulations, 2002).
- Changes to the reference safety information for the development safety update report (DSUR)
- Changes to the investigational medicinal product or device dossier
- Reduction in the Sponsor's planned level of monitoring for the trial

The following amendments would normally require MHRA & REC authorisation:

- Changes to the investigational medicinal product or medical device, design or methodology of the study, or to background information, likely to have a significant impact on its scientific value and/or risk benefit assessment
- Change to the main objective of the trial
- Change of the primary or secondary end-points likely to have a significant impact on the safety or scientific value of the trial
- Use of a new measurement for the primary end-point

- New toxicological or pharmacological data or new interpretation of toxicological or pharmacological data which is likely to impact on the risk benefit assessment
- Addition of a trial arm or placebo group
- Significant change of inclusion or exclusion criteria (for example, age range) likely to have a significant impact on the safety or scientific value of the trial
- Change of a diagnostic or medical monitoring procedure likely to have significant impact on the safety or scientific value of a trial
- Withdrawal of an independent data monitoring committee
- Change of investigational medicinal product(s) or medical device(s)
- Change of dosing/mode of administration of investigational medicinal product(s)
- Any other change to trial design likely to have a significant impact on primary or major secondary statistical analysis or on the risk-benefit assessment
- Change of the Sponsor or Sponsor's legal representative
- Temporary halt of the trial or temporary halt at a trial site, and re-start of the trial following a temporary halt
- Change of the definition of the end of the trial

The following amendments would normally require REC authorisation only:

- Significant changes to information provided to subjects – for example, subject information sheets, consent forms, diaries, letters to GPs or other clinicians, letters to relatives/carers (whether generic to the whole trial or specific to particular trial site)
- Significant changes to recruitment and consent procedures, including the inclusion of adults lacking capacity in the trial
- Significant increase in the radiation exposures to subjects from the protocol
- Change of insurance or indemnity arrangements for the trial
- Change to the payments, benefits or incentives to be received by subjects or researchers in connection with taking part in the trial, or any other change giving rise to a possible conflict of interest on the part of any investigator/collaborator
- Change of the Chief Investigator
- Change of Principal Investigator at a trial site
- Addition of new trial site not listed with the original request for authorisation and REC
- Application Change to the definition of a trial site
- Any other significant change to the conduct or management of the trial at particular trial sites
- Early closure or withdrawal of a site
- Any other significant changes to the terms of the REC application

1.1.2 Minor ('non-substantial') amendments definition:

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. The following are examples of amendments that do not require notification to REC or MHRA but do still require notification to both the Sponsor and the HRA.

- Changes to the identification of the trial (for example, change of title)
- Increase in duration of the trial, provided that the exposure to treatment is not extended, the definition of the end of trial is unchanged and there is no change to monitoring arrangements

- Changes to the numbers of subjects planned in the UK as a whole or at individual trial sites, provided that there is no change to the total number of subjects in the trial or the increase/decrease is insignificant in relation to the overall sample size
- Change in the documentation used by the research team to record trial data (for example, case report form or data collection form)
- Additional safety monitoring which is not part of an urgent safety measure but is taken on a precautionary basis
- Changes to the research team other than to the Chief or Principal Investigators
- Changes to contact details
- Changes to the internal organisation of the Sponsor or persons to whom tasks have been delegated
- Changes to the logistical arrangements for transporting or storing samples
- Changes to technical equipment
- Inclusion or withdrawal of another Member State or third country
- Minor clarifications to the protocol
- Minor clarifications or updates of subjects' information documentation
- Corrections of typographical errors

1.1.3 Urgent Safety Measures

In exceptional circumstances, the CI/CTU and/or Sponsor may instigate an urgent safety measure; an action taken in order to protect trial participants against any immediate hazard to their health or safety, and temporary suspension of recruitment. This is usually notified to sites and implemented immediately while the CI/CTU and/or Sponsor undertake a substantial REC and MHRA amendment. The MHRA (and REC) have to be notified immediately and in any event within 3 days of the implementation of urgent safety measures.. The notice must set out the reasons for the urgent safety measures and plan for further action.

2 PURPOSE

This document aims to describe the process for the submission and review of amendments by Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH). Mainly:

- Categorisation of amendments i.e. substantial or non-substantial
- Impact on NuTHs agreement to continue Sponsorship of the study
- Proposed amendments are relevant in nature
- Amendments are submitted to the appropriate authorities

3 SCOPE

This SOP applies to all CTIMP, ATMP and device studies sponsored by NuTH, whereby a change is made to the original REC and/or MHRA approved application. This SOP does not apply to Hosted study amendments or low risk NuTH sponsored study amendments.

4 PROCEDURE

All planned amendments whether considered to be substantial or non-substantial must be prepared by the CI with the support of the CTU then sent to the Regulatory Compliance Team (Tnu-tr.sponsormanagement@nhs.net) for review and approval prior to submission to regulatory authorities.

4.1 The CI and/or CTU duties

- Inform the Regulatory Compliance Team of all planned amendments and associated updated documents prior to submission to the regulatory authorities unless related to urgent safety measures.

- Prepare an amended protocol and any related documentation, as required, for submission and gain the necessary regulatory approvals and confirmation of capacity and capability from all participating sites, before implementation.

- Consider whether an amendment will have any impact on the Case Report Form and database (e.g. changes to participant assessments, visits, samples taken or inclusion/exclusion criteria) and to contact the Data Management team accordingly.

- Discuss with the Trial Management Group (TMG) and/or Trial Oversight Committee as appropriate. Consider whether the amendment will have any bearing on the risk assessment. Ensure the necessary support is available i.e. Statistical review to access impact on study endpoints and analysis.

- Supersede any old versions of study documents in the TMF as soon as a new version is implemented.

- Ensure that all relevant documentation and pertinent correspondence relating to amendments are filed in the Trial Master File (TMF).

- Ensure version control of all study documents and update/maintain the study version log following any amendments.

For substantial amendments the following documents should be prepared:

- New or updated trial documents with tracked changes
- A Notice of Substantial Amendment form (NoSA - created in IRAS)
- A covering letter or email summarising changes and a list of the updated documents, version numbers and dates.

4.2 Regulatory Compliance duties

- To provide advice/assistance with the preparation of protocol amendments and related documents to the trial team, as required.

- Determine whether the amendment is substantial or non-substantial as per guidance in section 1.1. If substantial, decide if the amendment requires MHRA authorisation or REC opinion, or both. The rationale for the decision must be documented and stored within the Sponsor Trial Master file. If unclear regarding the appropriate categorisation or route of submission, the matter must be escalated to the Clinical

Director of R&D for further opinion. If uncertainty remains the MHRA (clinical trials helpline) and/or REC should be contacted for further advice and guidance.

- If necessary, a face-to-face meeting with the Chief Investigator and Clinical Trials Unit will be requested to discuss the proposed amendment in detail.

- Review each proposed amendment for compliance with regulatory standards and assesses their impact on the study and participants. If required, the review may involve contacting support departments for expert advice i.e. Pharmacy, Radiology, Cellular Therapies etc.

- Identify any potential risks and hazards associated with the proposed change. Assess impact to risk management and revise the initial Sponsor risk assessment form as necessary. This must be undertaken in association with the CI and trial management team.

- The monitoring plan should be reviewed in relation to the proposed amendment. Any change to the design, methodology, conduct, end points or risk categorisation of the study may result in the need for a revised monitoring plan.

- Any suggested or required changes to the updated documentation will be provided to the CI or Trial Manager using the tracked changes to allow review.

- Classify the amendment as per HRA and MHRA guidance (e.g. substantial /non substantial)

- Once the proposed amendment and all associated documentation has been reviewed, finalised and judged appropriate, the Regulatory Compliance Team will send an email to the CI and/or Trial Manager confirming continued Sponsorship and authorisation for submission to the relevant regulatory bodies.

5 REVIEW AND MONITORING OF THIS DOCUMENT

All SOPs must be reviewed every 2 years unless changes to legislation dictate otherwise. How use of the SOP will be monitored should also be outlined here.

6 REFERENCES

Note any literature that has been quoted in the procedure or that has direct relevance to the procedure.

- http://www.hra.nhs.uk/research-community/during-yourresearchproject/amendments/preparing-amendments/
- http://ec.europa.eu/health//sites/health/files/files/clinicaltrials/docs/pc_rev3_2009-11/list_sa_uk_en.pdf
- *http://eudract.emea.europa.eu/*

- https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues
- MHRA Good Clinical Practice Guide (2012).

7 APPENDICES

N/A