North Bristol NHS Trust

Standard Operating Procedure

Research Study Amendments

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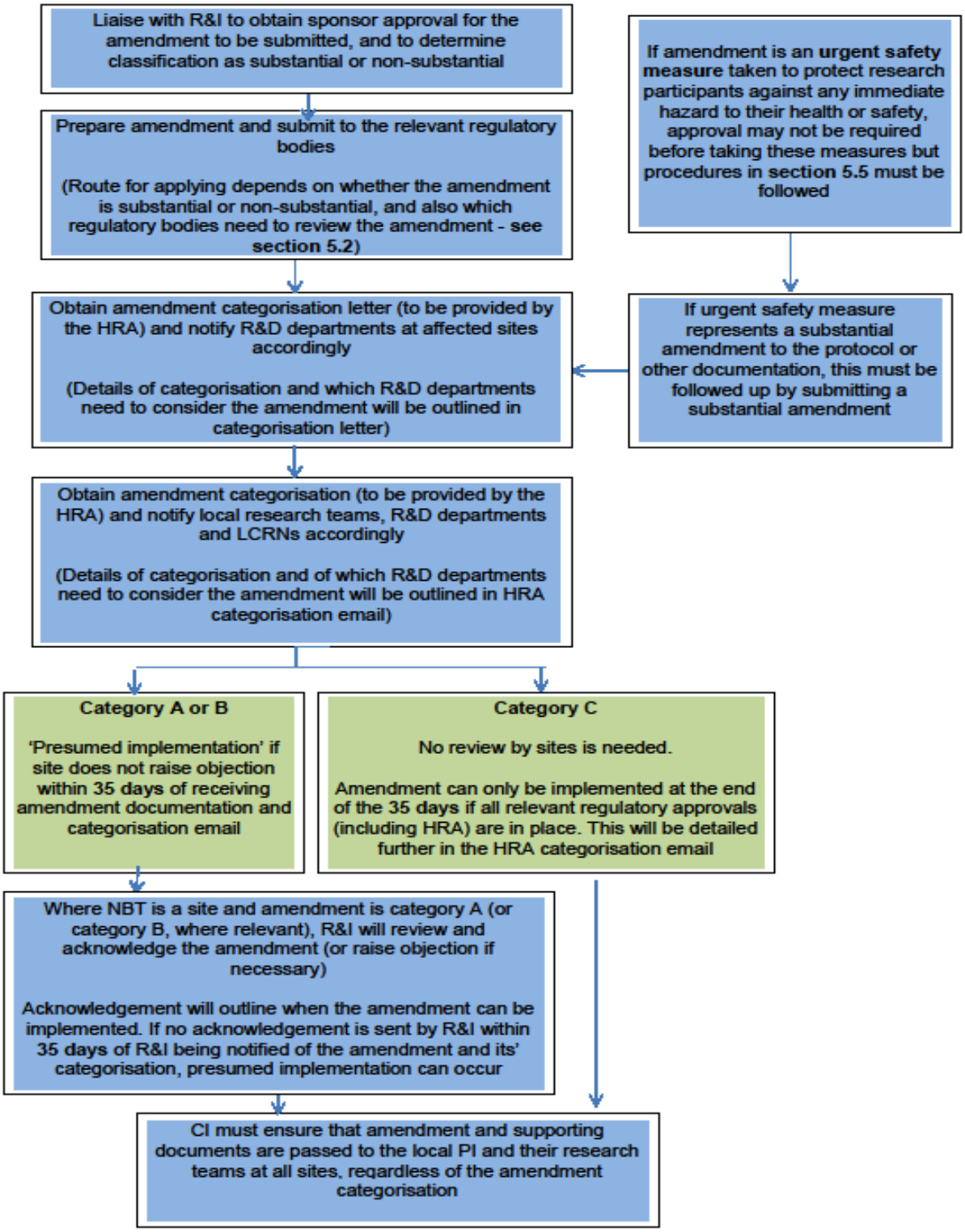
Document Version History

VERSION NUMBER	EFFECTIVE DATE	REASON FOR CHANGE
1.0	01-04-11	SOP renamed, updated in line with new template and recoded from ISOP-H05
2.0	08-02-16	Updated in line with HRA requirements
3.0	28-11-16	Clarification that substantial amendments to CTIMPs require electronic authorisation by the Sponsor
3.1	17-08-17	Updated in line with HRA requirements and to include a specific reference to the approval for sub-studies in NBT-sponsored CTIMPs

DO NOT USE THIS SOP IN PRINTED FORM WITHOUT CHECKING IT IS THE LATEST VERSION

Current versions of all Research & Innovation SOPs and accompanying documents are available online. If you are reading this document in printed form, please check that the version number and date match the most recent version on the Research & Innovation website: www.nbt.nhs.uk/research

i. SOP Flowchart



1. PURPOSE AND SCOPE

This SOP describes the process for submitting and implementing both substantial and non-substantial amendments for NBT sponsored studies. Principles in this SOP also apply when amendments are made to studies hosted by NBT.

Amendments are changes to research after a REC favourable opinion has been granted and/or in the case of a CTIMP, MHRA Clinical Trial Authorisation has been granted. They can be 'substantial' or 'non-substantial.'

2. DEFINITIONS/ABBREVIATIONS

CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
EDGE Database	The research database used by NBT for managing set up and delivery of studies
EudraCT	(European Union Drug Regulating Authorities Clinical Trials) is the European Clinical Trials Database of all clinical trials commencing in the European Union after 1 May 2004
HRA	Health Research Authority
IRAS	Integrated Research Application System
LCRN	Local Clinical Research Network
MHRA	Medicines and Healthcare Products Regulatory Agency
NBT	North Bristol NHS Trust
PI	Principal Investigator
REC	Research Ethics Committee
R&D	Research & Development
R&I	NBT Research & Innovation Office
NIHR CRN Portfolio	National Institute for Health Research Clinical Research Network Portfolio
SOP	Standard Operating Procedure
Sponsor	The individual, company, institution or organisation, which takes on ultimate responsibility for the initiation, management (or arranging the initiation and management) of and/or financing (or arranging the financing) for that research
USM	Urgent Safety Measure

3. WHO SHOULD USE THIS SOP

This SOP should be used by CIs and other members of the research team involved in preparing and submitting amendments to NBT sponsored studies.

In the case of NBT hosted studies, the NBT PI can refer to section 5.4 of this SOP (*'Implementation of Amendments*') for guidance on how to implement amendments at NBT.

4. WHEN SHOULD THIS SOP BE USED

This SOP should be used when an amendment to a research study needs to be made.

5. PROCEDURE

5.1 Sponsor Assessment of Amendments

It is necessary to identify if an amendment is **substantial** or **non-substantial** (please see **Appendix A** for definitions of substantial and non-substantial amendments).

It is the responsibility of the Sponsor to determine whether an amendment is substantial or non-substantial. For NBT sponsored studies, you must liaise with R&I when determining this classification. Please email researchsponsor@nbt.nhs.uk with details of the proposed amendment so that this assessment can be made.

R&I will review the amendment and any implications it has for the management and delivery of the study, including any contractual implications. R&I will document this review by completing the amendment workflow on the EDGE Database. R&I will also update the sponsorship risk assessment for the study, where necessary.

In the case of NBT-sponsored CTIMPs, any potential amendments will be discussed at the meetings between the Sponsor and the Trial Manager, which are held approximately every two months. Where an amendment relates to the addition of a sub-study on a CTIMP, R&I will require additional actions/ approvals within the study management team before approving such amendment.

5.2. Preparation and Submission of Amendments

Where a project has HRA approval, the HRA must be notified of both substantial and/or non-substantial amendments.

(a) Substantial Amendments

i. If the amendment is **substantial** you will have to generate and complete a 'Notice of Substantial Amendment' (NOSA) form though IRAS. It will be necessary to have all modified documents including tracked versions for upload along with any further supporting documentation required.

ii. For non-CTIMPs NOSA forms must be electronically authorised by **both CI and Sponsor** via IRAS.

iii. For CTIMPs, NOSA forms must be electronically authorised by the **Sponsor only** via IRAS.

(A) (*Please note that although the submission system provides an option for either CI or Sponsor to authorise substantial amendments to CTIMPs, for NBT sponsored CTIMPs, this authority has **NOT** been delegated to the CI, and therefore the option for Sponsor sign off must be selected*).

Sponsor electronic authorisation requests must be requested via researchsponsor@nbt.nhs.uk

iv. The method for submitting the amendment differs depending on the nature of the study:

- Where HRA approval for the study included NHS REC review, substantial amendments should then be submitted to REC via email.
- Where the REC is in England, REC will notify HRA of the amendment, thus no separate submission to HRA is required. However, where the REC is in Scotland, Wales, or Northern Ireland you should also copy hra.amendments@nhs.net.
- Where the project did not require NHS REC review, the substantial amendment should be submitted directly to hra.amendments@nhs.net.

v. Substantial amendments for CTIMPs and/or Medical Devices with Clinical Trial Authorisation will require MHRA review in addition to HRA and REC (although not all substantial amendments that require REC review also require MHRA review; you must consult R&I to determine whether MHRA need to be notified).

vi. Substantial amendments will need to be submitted to MHRA using the European Commission form. This document is available from the EudraCT website or can be downloaded from the Amendment tab in IRAS. The form must be accompanied by an amended EudraCT application. Submission to MHRA is done outside of IRAS. Please liaise with R&I and refer to the MHRA website for the most up to date guidance: www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues.

vii. The applicant will be informed by letter whether the amendment has been accepted by the MHRA. Please forward this MHRA notice on to the HRA assessment team via email (hra.approval@nhs.net) as soon as possible.

(b) Non-substantial Amendments

i. If the amendment is **non-substantial** a 'Notification of Non-Substantial Amendment' form should be completed by the CI. The template form can be found in resources on the HRA website: www.hra.nhs.uk/approvals-amendments/amending-approval.

ii. The notification form should be submitted, with any supporting documentation, by email to hra.amendments@nhs.net. Please include the IRAS ID for your project in the subject line of the email along with the text “Notification of Amendment” and ensure that your email includes your contact details (email and phone number).

5.3. Categorisation of Amendments

(a) When amendments (both substantial and non-substantial) are submitted to REC/HRA, the HRA will categorise the amendment as either category A, B, or C within **5 business days**.

- **Category A:** Amendment that impacts or affects all participating NHS organisations.

  All participating NHS organisations are expected to consider the amendment to

determine whether they are able to continue to support the study.

- **Category B:** Amendment that impacts or affects specific participating NHS organisations.

  Only those participating NHS organisations affected by the amendment are expected to consider the amendment to determine whether they are able to continue to support the study.

- **Category C:** Amendment that has no impact on NHS organisations.

  Participating NHS organisations are NOT expected to consider the amendment.

(b) The applicant will be informed of this categorisation and also whether HRA assessment is required for the amendment. If there are participating NHS/Health and Social Care (HSC) sites in other nations, the HRA will share the amendment and categorisation with the other participating nations.

(c) It is the applicant's responsibility to communicate the categorisation and the amendment to English sites (i.e. the local research team, the R&D office and the LCRN, where appropriate – contact details for R&D offices and LCRNs are available via www.rdforum.nhs.uk/content/contact-details).

(d) The CI must send the amendment and the categorisation information to participating NHS organisations so that, where necessary, arrangements can be put in place to continue the site's capacity and capability to deliver the study. Instructions will be detailed further in the categorisation email from the HRA, thus this letter must be read carefully and the instructions followed.

5.4. Implementation of Amendments

(a) There can be 'presumed implementation' following regulatory approval, unless an objection to the amendment is raised by an NHS organisation within a reasonable time. Presumed implementation of an amendment can occur after **35 days** of notifying the site of that amendment (subject to other regulatory approvals being in place), unless the NHS organisation raises an objection within this period.

Details will be outlined in the HRA categorisation letter as to which sites need to be given 35 days before presumed implementation, thus this letter must be read carefully. As a rule of thumb, the case will usually be that:

- 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 (Subject to regulatory approvals being in place).
- For **Category C amendments** can be implemented immediately (subject to regulatory approval being in place).

(b) In all cases, the CI must ensure that amendments and any supporting documentation are passed to the local PIs and their research teams at all sites.

(c) Where NBT are a site, R&I will review all category A amendments once the categorisation letter is received, and aim to issue an acknowledgement of the amendment once it has been reviewed (or raise objection where necessary).

(d) Acknowledgement will outline when the amendment can be implemented (e.g. immediately, if HRA approval is already in place, or as soon as Sponsor confirms HRA approval is subsequently in place). If no acknowledgement is sent by R&I within **35 days** of R&I being notified of the amendment and its' categorisation, presumed implementation can occur.

(e) Category B amendments will also be reviewed, where NBT is deemed to be an organisation affected by amendment.

5.5 Urgent Safety Measures (USMs)

The Sponsor, CI or PI may take appropriate USMs in order to protect research participants against any immediate hazard to their health or safety. Approval is not required *before* taking these measures.

(a) The HRA, MHRA (in the case of CTIMPs) and R&I office should be notified within **3 days** of taking the measures, detailing the measures taken and the reasons why.

(b) In the case of CTIMPs, the MHRA's Clinical Trial Unit should be phoned on 020 3080 6456 to discuss the issue with a safety scientist, ideally **within 24 hours.** This should then be submitted to the MHRA in writing within **3 days** (as above) - MHRA will provide guidance for this submission when you phone. In cases where NBT are sponsor, you must ensure you liaise with R&I throughout this process.

(c) Where USMs are taken and the participant suffers harm, safety reporting procedures should be followed. Please refer to Safety Reporting: Clinical Trials of Investigational Medicinal Products (CTIMPs) (RI/QMS/SOP/013) for further guidance.

(d) Where a USM represents a substantial amendment to the protocol or other documentation, a substantial amendment will need to be prepared and submitted following the procedures outlined in this SOP.

6. DISSEMINATION AND TRAINING

SOPs will be distributed in accordance with the SOP on Preparation of Research SOPs (RI/QMS/SOP/001).

This SOP and any associated templates and forms will be uploaded to the Trust website (www.nbt.nhs.uk/research) and the Managed Learning Environment (MLE) system on the Trust intranet shortly after having been released.

All staff whose activities are subject to this SOP should ensure that they read and understand the content of this SOP.

The training log within the Investigator Site File/Trial Master File should be completed to document that members of staff have read and understood the content of this SOP.

7. RELATED SOPS AND DOCUMENTS

- Health Research Authority
  Process for handling UK study amendments
  www.hra.nhs.uk

- The following R&I documents are available on the NBT website: www.nbt.nhs.uk/research

RI/QMS/SOP/013	Safety Reporting: Clinical Trials of Investigational Medicinal Products (CTIMPs)

Appendix A
Definitions of Substantial and Non-substantial Amendments

Term	Definition	Examples (as defined by the HRA)
Substantial Amendment	Amendments to the original REC application, 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 study; • the scientific value of the study; • the conduct or management of the study; • the quality or safety of any investigational medicinal product used in the trial.	• 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) in a CTIMP; • Appointment of a new PI at a trial site in 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 REC application.

Non-substantial Amendment	Minor changes to the original REC application, to the protocol, or any other supporting documentation that will NOT affect to a significant degree: • the safety or physical or mental integrity of the subjects of the study; • the scientific value of the study; • the conduct or management of the study; • the quality or safety of any investigational medicinal product used in the trial.	• 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.