

Research Study Amendments

Division: Strategy & Transformation

Specific staff groups to whom this policy <u>directly</u> applies	Likely frequency of use	Other staff who may need to be familiar with policy
Staff employed by North Bristol Trust who directly or indirectly work on Clinical Research within the Trust	Role dependant	Staff not employed by North Bristol NHS Trust who are working on Research studies sponsored or hosted by NBT

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Summary of changes since the previous version	Major changes to reflect the transition to the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, which introduce updated terminology and processes for the management of modifications (formerly Amendments) to clinical trials of investigational medicinal products (CTIMPs).

1. Purpose	<p>This SOP describes the process for managing modifications to research studies sponsored by NBT. It sets out the requirements for classification of modifications, sponsor review and approval, submission to or notification of the relevant regulatory body(ies) where applicable, and subsequent implementation, including approval by participating sites, in accordance with current UK clinical trial regulations.</p> <p>The principles outlined in this SOP also apply to modifications to studies hosted by NBT.</p>
2. Key Messages	<p>This document sets out the procedures to be followed by all individuals who are responsible for submitting and/or implementing modifications for research studies sponsored, managed, or run at North Bristol NHS Trust.</p> <p>It provides clear guidance on the procedure of classifying and seeking approval for modifications.</p> <p>Modifications must be appropriately classified prior to implementation as:</p> <ul style="list-style-type: none"> • Substantial modification • Modification of an Important Detail • Minor modification <p>The classification determines whether the modification requires:</p> <ul style="list-style-type: none"> • Regulatory approval • Regulatory notification • Internal documentation only <p>Modifications must not be implemented until the appropriate regulatory and/or sponsor requirements have been met.</p> <p>Any modifications (unless an urgent safety measure) to a study are required to be submitted to the following before implementation,</p> <ol style="list-style-type: none"> 1) The Sponsor, North Bristol NHS Trust for review and confirmation of continued Sponsorship. 2) The required regulatory bodies e.g. Health Research Authority (HRA), the Research Ethics Committee (REC) (if substantial) AND the Medicines and Healthcare products Regulatory Agency (MHRA) if a clinical trial of an investigational medicinal product (CTIMP) or clinical investigation of a medical device (CIMD) for review and approval.

3) Participating sites for any Substantial modification or modification of important detail, requiring review and confirmation of continued capacity and capability.

Terminology notes:

For the purposes of this SOP, the term “participating site” is used throughout and should be read interchangeably with “trial location” where applicable for clinical trials of investigational medicinal products, in line with the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025.

The amended regulations use the term “modification” (including categories such as substantial modification). Where legacy documentation refers to “substantial amendments”, this should be interpreted as the equivalent change control concept for the purpose of local documentation and filing.

ABBREVIATIONS/DEFINITIONS

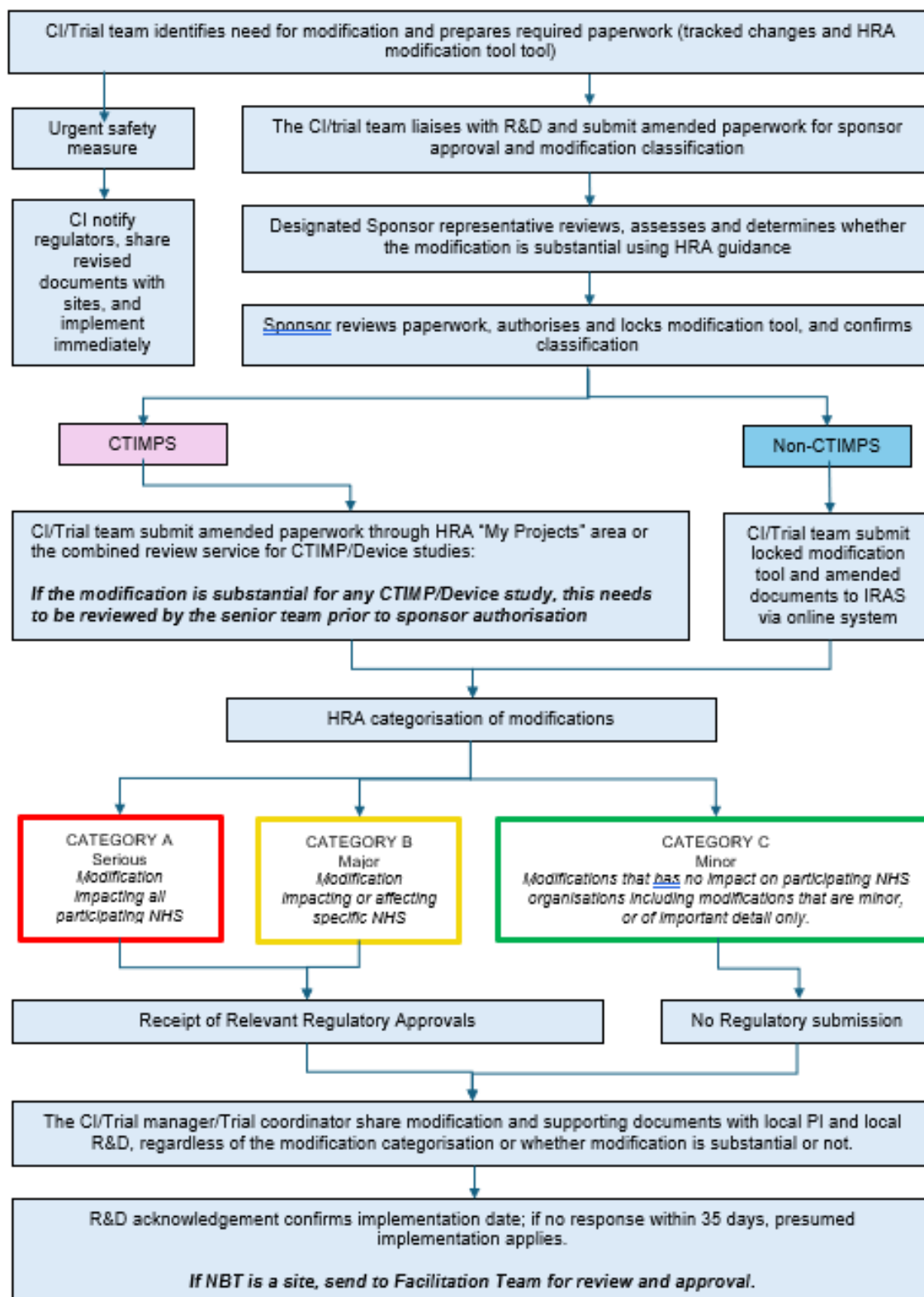
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal product
CIMD	Clinical Investigation of Medicinal Devices
EDGE Database	The research database used by NBT for managing set up and delivery of studies.
HRA	Health Research Authority
IRAS	Integrated Research Application System
MHRA	Medicines and Healthcare Products Regulatory Agency
NBT	North Bristol NHS Trust
PI	Principal Investigator
REC	Research Ethics Committee
R&D	Research and Development
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. Relevant Policies & Guidance	<p>Policies and Guidance</p> <ul style="list-style-type: none"> • Health Research Authority Process for handling UK study modifications www.hra.nhs.uk • UK policy Framework for Health and Social Care Research (2017) • The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended by the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 (SI 2025/538). • ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 (R3) <p>The following R&D documents are available via LEARN or by contacting the R&D office on Research@nbt.nhs.uk</p> <p>Associated SOP's RD/QMS/SOP/013 - Safety Reporting: Clinical Trials of Investigational Medicinal Products (CTIMPS)</p>
4. Operational Areas Included	<p>This SOP is applicable to all research sponsored by the Trust.</p>
5. Operational Areas Excluded	<p>None</p>
6. Who should read this	<p>This SOP should be used by CIs and other members of the research team involved in preparing and submitting modifications to NBT sponsored studies.</p> <p>When collaborating with external stakeholders, such as Clinical Trials Units, on NBT-sponsored projects, it may be appropriate to utilise external SOPs to ensure proper project governance and the fulfillment of delegated roles and responsibilities. In such instances, both the external stakeholder and the NBT sponsorship team must ensure that the external SOP aligns with the procedures outlined in this SOP. If there is a conflict between the external SOP and NBT's procedures, the NBT SOP will take precedence, except in exceptional cases where approval is obtained from the Research Operations Manager or the Deputy Director of Research.</p>

	<p>In the case where NBT is a participating site only, the NBT PI and delivery team can refer to section 8.7 of this SOP (Receipt of Regulatory Approval and Implementation of Modifications) for guidance on how to implement amendments at NBT.</p>
<p>7. Roles responsible for carrying out this procedure</p>	<p>The Chief Investigator or delegated Trial Team Members must inform R&D of all planned modifications prior to the submission to the regulatory authorities unless they are related to urgent safety measures.</p> <p>The Chief Investigator or delegated Trial Team Member shall be responsible for preparing an amended protocol and any related documentation that will be needed, for submission to gain the necessary regulatory approvals (e.g. HRA, REC, and MHRA) and subsequent confirmation of capacity and capability from all participating sites, before implementation. All relevant documentation relating to modifications must be filed in the Trial Master File (TMF), superseding any old versions.</p> <p>The Sponsor is responsible for the assessment and authorisation of all modifications prior to regulatory submission.</p> <p>The Sponsor will determine whether a modification is substantial, minor, or of important detail and may provide advice/ assistance with the preparation of protocol modifications and related documents to the trial team, as required.</p> <p>The Trust R&D Facilitation Team will ensure that once the applicable regulatory approvals have been granted, all documentation and approvals relating to the modification are complete and correct before R&D issue a notice of continued capacity & capability.</p>

8. Procedure:

Flowchart illustrating the submission process of Modifications for non-CTIMP and CTIMP Studies



8.1 Modifications and their Classification

Modifications refer to any change made to a research study after initial regulatory approval.

All proposed modifications must be classified into one of the following categories:

Substantial Modification

A modification is likely to have a significant impact on:

- Participant safety or rights
- Scientific value
- Study conduct or management
- Data quality or reliability

Substantial modifications require regulatory approval prior to implementation (unless implemented as an Urgent Safety Measure).

Substantial modifications can be categorised as Route A or Route B:

Route A substantial modifications are likely to have a substantial impact on the safety or rights of the participants or on the reliability or robustness of the data generated in the trial.

Route B substantial modification are those where there are no new significant safety concerns with any of the investigational medicinal products, as far as the sponsor is aware having made reasonable enquiries.

If the sponsor is aware of such safety concerns, the modification is not a Route B substantial modification and must be submitted as a Route A substantial modification.

Note that where Route B substantial modification involves a change to any quality documentation (i.e. the IMP dossier, the Good Manufacturing Practice (GMP) documentation or the labelling documents), applicants should make this clear in the cover letter. The licensing authority will use this information to determine whether to exercise its right to undertake a full review of a Route B Substantial Modification before issuing a decision.

Modification of an Important Detail

A modification of important detail is one that:

- Does **NOT** significantly impact participant safety or data integrity
- **BUT** requires notification to regulatory authorities

These modifications must be notified via the appropriate regulatory system but do not require approval before implementation.

Minor Modification

A minor modification is one that:

- Has minimal or no impact on participant safety, study conduct, or data integrity
- Does not require regulatory notification
- This includes submitting the date that the first UK trial participant is recruited (CTIMPs)

These modifications may be implemented immediately but must be documented internally.

8.2 Preparation of the modification documents and completion of the Modification Tool

After the CI/Trial Manager/Trial team has determined the need for a modification and consulted with the relevant trial personnel (e.g., support departments, Trial Management Group (TMG), Trial Steering Committee (TSC), Data Monitoring Committee (DMC), Statistician, as appropriate, they must ensure that all study documents impacted by the proposed modification are updated with clear tracked changes and version control. In addition to the updated documentation all modifications require a modification tool on the online IRAS submission system to be completed and submitted; the tool can be found here:

<https://www.myresearchproject.org.uk/help/hlpamendments.aspx>

The process for completing the modification Tool is as follows:

Download the modification Tool from IRAS and fill in information about your modification on the 'Modification Tool' tab, referring to the on-screen guidance notes. You must clearly describe the modification and the rationale for the modification in the summary box. You should then separate out each type of change you are making as part of the modification, entering details using the drop-down menus. The Tool contains a 'glossary of options' tab which details and provides guidance on all types of change available. Referring to this will help you select the correct type/s of change. You can enter up to 10 separate types of change on the same Modification Tool document. If the modification involves more than 10 types of change, please contact amendments@hra.nhs.uk for support.

Full guidance on its use can be found at:

<https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx>

Completion of the Modification Tool supports classification of the modification and indicates the appropriate regulatory pathway (approval, notification, or internal documentation). The declaration section must be completed by a member of the R&D sponsorship team. Modifications must not be submitted without prior authorisation from the sponsor.

Once the documentation has been completed, all amended study documentation with clear tracked changes and the modification tool, must be forwarded to R&D for Sponsor

(researchsponsor@nbt.nhs.uk) approval prior to regulatory submission. The Sponsor has the responsibility to check the content of the tool and amended documents.

For studies involving Research Tissue Banks or Research Databases, substantial changes must be notified to the Research Ethics Committee (REC) using the “Notice of Substantial Amendment” form generated in IRAS, rather than the Modification Tool. Further guidance on submission requirements is available via the IRAS

<https://www.myresearchproject.org.uk/help/hlpamendments.aspx>

8.3 Sponsor Assessment of Amendments

It is the responsibility of the Sponsor to determine whether an amendment is

- Substantial
- A modification of an important detail
- Minor (as per definitions outlined in section 8 and as per examples provided in Appendix 1).

For NBT sponsored studies, you must liaise with R&D. Please email researchsponsor@nbt.nhs.uk with details of the proposed modification so that this assessment can be made. The Sponsor will ensure the classification is justified and documented based on risk to participants and study integrity.

The R&D Sponsor team will review, and risk assess the modification, identifying any implications it has for the management and delivery of the study, including:

- ✓ Ensuring the participants safety and rights continue to be protected.
- ✓ Ensure the changes are in line with applicable guidelines and legislation.
- ✓ Check whether the changes would affect the Sponsor’s agreement for continued sponsorship.
- ✓ Review ongoing deliverability and feasibility of the project.
- ✓ Check if any changes have an impact on support departments.
- ✓ Check if any changes to the study contract are required.
- ✓ Assess any financial implications of the proposed change.
- ✓ Review changes to participant documents, where required.
- ✓ Ensure all updated documentation is version controlled.

R&D will document this review by completing the modification workflow on the EDGE Database. Where the changes to a study are deemed to increase risk, the study specific risk assessment shall be reviewed and updated. Applicants will be informed of any comments or changes required.

In the case of NBT-sponsored CTIMPs, devices and other interventional trials, it is expected that any potential modifications will be discussed at the meetings between the Sponsor and the Trial Manager, which are held approximately every two months. All substantial modifications for CTIMPs and Device studies must be submitted to senior team for their review and approval at the subsequent senior team meeting. These modifications must not be submitted prior to senior team approval.

Where a modification relates to the addition of a sub-study, R&D will require additional actions/approvals by the study management team before approving such modification.

When the sponsor review of the modification is complete, a sponsor representative will authorise and lock the modification for submission. The 'Lock for submission' button will turn green when this is completed. Locking the Tool will create a PDF version which will be returned to the applicant for online submission.

When you have final copies of all supporting documentation in place, and have saved the pdf of the modification Tool, you should proceed to online submission.

For further guidance about procedures for notifying substantial amendments to the MHRA, please see: <https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues>

8.4 Submission of Amendments for Regulatory Review

Submission process of Amendments for NBT sponsored non-CTIMPS

For all types of NBT non-CTIMP research, the locked tool for substantial modifications and modifications of important detail along with the supporting documentation should be uploaded for online submission via IRAS. Minor modifications do not require submission and must be documented internally. The online modification submission functionality requires a separate login to the main IRAS account the applicant will already have. Any applicant that has not used it before may need to set up a new account. Any issues with account set up should be directed to the IRAS Technical Helpdesk for support on: helpdesk@myresearchproject.org.uk

Once logged in, the applicant should refer to the on-screen step-by-step instructions which will provide guidance through the process. The applicant will be asked to enter the IRAS ID and answer some simple questions about the amendment. The applicant can then upload all documentation relating to the modification and proceed to submit after which the applicant will receive an automated email to confirm submission of the modification.

Upon submission the modification will be shared with the relevant regulatory bodies including HRA if it is minor and REC and HRA if it is substantial. For further details regarding the online submission refer to [IRAS Help - Maintaining your approvals - Amendments](#)

Submission process of modifications for NBT sponsored CTIMPS

Submitting an application for approval of a substantial modification

To request approval for a Route A or Route B substantial modification to a clinical trial approval:

For trials approved through the **combined review process**, submit a single application (including all documentation) through the 'My Projects' area of the combined review service. Detailed guidance on using IRAS to submit an application for clinical trial approval can be found on [Step by step guide to using IRAS for combined review - Health Research Authority \(hra.nhs.uk\)](https://www.hra.nhs.uk/step-by-step-guide-to-using-iras-for-combined-review)

- if the clinical trial to be modified was not originally approved through the combined review process, submit applications to both the licensing authority (via [MHRA Submissions](#)) and the ethics committee (via the [online portal on IRAS](#))

There are fees applicable to submission of an application to modify a clinical trial approval. To pay these fees, refer to the guidance on [making a payment to MHRA](#).

- For some types of substantial modification, submitting multiple applications for approval in parallel may be possible. Refer to [the HRA website](#) for further guidance.

Documents that should accompany an application to make a substantial modification

The cover letter should include the following:

- all relevant trial identifiers, including the full trial title (and abbreviated title where appropriate), protocol number, IRAS ID (for trials approved through combined review) or EudraCT number (for trials not approved through combined review), and any global identifiers such as an EU CT number
- a statement explaining why the applicant considers the modification to be a Route A or Route B substantial modification
- an outline of the substantial modification, with clear justification for changes
- an outline of any minor changes to the clinical trial approval to be made alongside the proposed substantial changes
- an outline of minor changes that have already been implemented, even if unrelated to the proposed substantial modification
- for resubmissions, highlight the changes made compared to the previous submission
- a table of all submitted documents, including version numbers and dates
- a purchase order number for invoicing for fees applicable to submission of an application to modify a clinical trial approval
- Not all modifications in a CTIMP are required to be reported to the MHRA, this will be indicated by the modification tool.

Notifying the authorities about a modification of an important detail

If the sponsor makes a modification of an important detail, they must subsequently notify the authorities of this change. Instructions for notifying the authorities about a modification of an

important detail are provided on completion of the [modification tool](#). No fees are associated with this process.

Note that all sponsors will need to notify the authorities of the date on which the first participant was recruited to a clinical trial through the modification of an important detail process, in order to demonstrate that the trial has been registered in a public registry within the applicable deadline and to [support the licensing authority in monitoring the trial's approval status](#).

8.5 HRA Categorisation of Amendments

When amendments (both substantial and non-substantial) are completed using the amendment tool, the tool will categorise the amendment as either category A, B, or C.

- **Category A:** *Modifications that impacts or affects all participating NHS organisations.*
All participating NHS organisations are expected to consider the modification to determine whether they are able to continue to support the study.
- **Category B:** *Modifications that impacts or affects specific participating NHS organisations.*
Only those participating NHS organisations affected by the modification are expected to consider the modification to determine whether they are able to continue to support the study.
- **Category C:** *Modification that has no delivery impact on NHS organisations. However participating sites should be notified of all modifications.*

8.6 What happens after submission?

Once a sponsor submits a modification, it undergoes a validation check, which is typically completed within one working day. If no issues are found, the submission is confirmed as valid; however, if there are validation issues, these are communicated to the sponsor, who then has seven calendar days from the submission date to resolve them. If the issues are addressed within this timeframe, the modification is considered valid; if not, it is deemed invalid and must be resubmitted with the necessary corrections.

Once a modification is validated, it is reviewed by the relevant regulatory body, either the MHRA and/or REC. If no concerns arise during this review, a final decision is issued within 35 calendar days of validation. If issues are identified, the sponsor may be asked to provide further information and will have up to 60 calendar days to respond. After a response is submitted, the reviewing body will assess it and provide a final decision within 10 calendar days.

After the modification has been submitted, it is the responsibility of the CI/Trials team to inform participating sites of the pending modification, including NBT, where we are also a participating site. The completed modification tool with confirmation of the modification categorisation should be shared with participating sites, as applicable. When sharing you need to ensure that the local PI, NHS R&D office and Local research team are included. This will enable all participating sites to start assessing the modification for continued local capacity and capability.

Written confirmation to approve or reject a modification will be provided by each applicable regulatory body following their review.

8.7 Receipt of Regulatory approval and Implementation of Modifications

On receipt of regulatory approvals, the CI/Trials team must provide a copy of all approval letters where relevant and final approved documents to R&D sponsor.

Substantial modifications can only be implemented once the relevant approvals have been obtained. Modifications of important detail can be implemented once the notification has been submitted and minor modifications can be implemented immediately.

In all cases, the CI or Trial Manager must ensure that amendments and any supporting documentation are passed to the local PIs, NHS R&D Offices and their research teams at all sites.

There can be 'presumed implementation' following regulatory approval, unless an objection to the modification 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 modifications**, 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 modifications** can be implemented immediately (subject to regulatory approval being in place).

(a) Where NBT are a site, R&D will review all category A modifications once the documents are received and aim to issue an acknowledgement of the modification once it has been reviewed (or raise objection where necessary).

(b) Acknowledgement will outline when the modification 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&D within **35 days** of R&D being notified of the modification and its' categorisation, presumed implementation can occur.

(c) Category B modifications will also be reviewed, where NBT is deemed to be an organisation affected by modification.

(d) Category C modifications are processed by R&D without a formal review.

8.8 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&D 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) – the MHRA will provide guidance for this submission when you phone. In cases where NBT are sponsor, you must ensure you liaise with R&D 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 \(CTIMPs\) \(RD/QMS/SOP/013\)](#) for further guidance.
- (d) Where a USM represents a substantial modification or modification of important detail to the protocol or other documentation, a subsequent modification will need to be prepared and submitted following the procedures outlined in this SOP.

9. Dissemination and Training

SOPs will be distributed in accordance with the SOP on [Preparation of Research SOPs \(RD/QMS/SOP/001\)](#).

This SOP and any associated templates and forms will be uploaded to the Managed Learning Environment “LEARN” system on the Trust intranet shortly after having been released, The trust website (www.nbt.nhs.uk/research) will be updated to capture the list of current SOP's in place.

All staff whose activities are subject to this SOP should ensure that they read and understand the content of this SOP, this is monitored and audited via LEARN.

Appendix A

Substantial Modifications

Examples (as defined by the HRA)

- temporary halt of the project or temporary halt at a site within the UK
- re-start of the project following a temporary halt
- significant changes to participant information sheets, consent forms, letters to GPs or other clinicians, letters to relatives/carers, and other similar documents (whether generic to the whole study or specific to a particular site)
- significant changes to recruitment and consent procedures, including the inclusion of adults lacking capacity in the project
- significant increase or decrease to the radiation exposures to participants from the protocol
- change of insurance or indemnity arrangements for the project
- 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 or collaborator
- change of the chief investigator
- any other significant change to the conduct or management of the project at particular sites
- any other significant change to the terms of the original REC application
- change of the main objective of the project
- change of primary or secondary endpoints likely to have a significant impact on the safety or scientific value of the project
- addition of a project 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 project
- change of a diagnostic or medical monitoring procedure likely to have a significant impact on the safety or scientific value of the project
- withdrawal of an independent data monitoring committee
- any other change of study design likely to have a significant impact on primary or major secondary statistical analysis or on the risk and benefit assessment

Modifications of important detail

Examples (as defined by the HRA)

- changes to the trial identification (for example the trial title)
- submitting the date that the first UK trial participant is recruited
- 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
- change to contact details for named contacts for the trial, for example the sponsor, sponsor representative or chief investigator
- change of investigator (other than the chief investigator) at a trial location in a multi-centre trial

- addition of new trial locations not listed with the original request for authorisation and REC application where there are no additional documents for submission
- change of the sponsor's legal representative

Minor modification

Examples (as defined by the HRA)

- changes in the number of participants per trial site, if any change is insignificant in view of the absolute number of participants
- changes in the processes associated with recording keeping used by the research team for recording trial data
- internal changes to the sponsor's organisation
- changes in the logistical arrangements for storing or transporting samples
- changes in technical equipment
- minor changes to the protocol or other study documentation, for example correcting errors, updating contact points, minor clarifications