Research Study Amendments

Division: Strategy & Transformation

Specific staff groups to whom this policy directly 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	SOP updated in line with HRA submission guidance – the Notification of Substantial Amendment (NOSA) substituted by the amendment tool. Updated new process for sponsor review of amendments. Changing R&I to R&D. Change format to align with the trust standard template. Change naming convention of R&D SOP's.

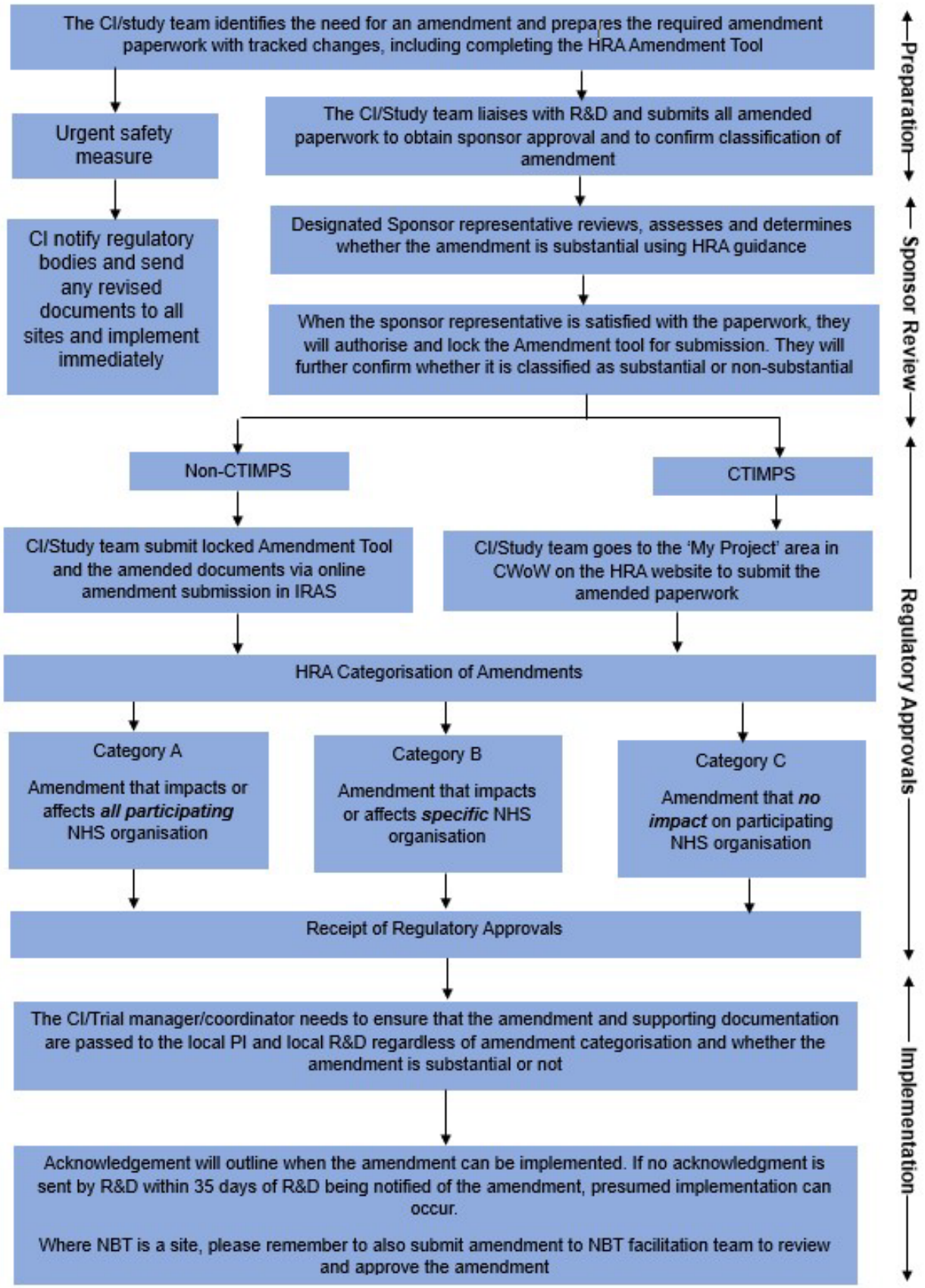
1. Purpose	This SOP describes the process for making amendments, both substantial and non-substantial to NBT sponsored studies; how you obtain sponsor approval of the amendment, the submission to the relevant regulatory body(ies), as applicable and subsequent implementation, and approval by participating sites. Principles in this SOP also apply when amendments are made to studies hosted by NBT.
2. Key Messages	This document sets out the procedures to be followed by all individuals who are responsible for submitting and/or implementing amendments for research studies sponsored, managed, or run at North Bristol NHS Trust. It provides clear guidance on the procedure of classifying and seeking approval for amendments. Any amendments to a study (unless an urgent safety measure) are required to be submitted to the following, before implementation: 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) (all amendments), 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 notifiable amendment requiring review and confirmation of continued capacity and capability. **ABBREVIATIONS/DEFINITIONS** **CI** - Chief Investigator **CTIMP** - Clinical Trial of an Investigational Medicinal product **CIMD** - Clinical Investigation of Medicinal Devices **CWoW** - Combined Ways of Working **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	**Policies and Guidance** • Health Research Authority *Process for handling UK study amendments* www.hra.nhs.uk • UK policy Framework for Health and Social Care Research • The Medicines for Human Use (Clinical Trials) Regulations 2004 • Medicine for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019 • ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 1996 • The following R&D documents are available via LEARN or by contacting the R&D office on Research@nbt.nhs.uk **Associated SOPs** RD/QMS/SOP/013 - Safety Reporting: Clinical Trials of Investigational Medicinal Products (CTIMPS)
4. Operational Areas Included	This SOP is applicable to all research sponsored by the Trust.
5. Operational Areas Excluded	None
6. Who should read this	This SOP should be used by CIs and other members of the research team involved in preparing and submitting amendments to NBT sponsored studies. 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. In the case where NBT are 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 Amendments') for guidance on how to implement amendments at NBT.
7. Roles responsible for carrying out this procedure	The Chief Investigator or delegated Trial Team Members must inform R&D of all planned amendments prior to the submission to the regulatory authorities unless they are related to urgent safety measures. 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 amendments must be filed in the Trial Master File (TMF), superseding any old versions. The **Sponsor** is responsible for the assessment and authorisation of all amendments prior to regulatory submission. The **Sponsor** will determine whether an amendment is substantial or non-substantial and may provide advice/ assistance with the preparation of protocol amendments and related documents to the trial team, as required. The **Trust R&D Facilitation Team** will ensure that once the applicable regulatory approvals have been granted, all documentation and approvals relating to the amendment are complete and correct before R&D issue a notice of continued capacity & capability.

8. Procedure:

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



8.1 Amendments and their Classification

Amendments refer to changes made to the research after receiving a favorable opinion from the REC, and/or, in the case of a CTIMP, after the MHRA Clinical Trial Authorisation and once HRA Approval has been granted. Amendments can be 'substantial' or 'non-substantial.'

A **substantial amendment** is defined as a change to the original IRAS application, or to the protocol, or any other supporting documentation that is likely to affect to a significant degree:

i. the safety or physical or mental integrity of the subjects of the study;

ii. the scientific value of the study;

iii. the conduct or management of the study; or

iv. the quality or safety of any investigational medicinal product used in the trial.

The substantial amendment will require approval from the relevant bodies before it can be implemented, unless it is an Urgent Safety Measure, which is taken by the Sponsor or Investigator in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety (see section 8.8 for further information)

A **non-substantial amendment** is defined as minor changes to the original IRAS 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, scientific value of the study, conduct or management of the study, or quality and safety of any investigational medicinal product used in the trial.

8.2 Preparation of the amendment documents and completion of the Amendment Tool

After the CI/Trial Manager/Trial team has determined the need for an amendment 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 amendment are updated with clear tracked changes and version control. In addition to the updated documentation all amendments require an amendment 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 Amendment Tool is as follows :

Download the Amendment Tool from IRAS and fill in information about your amendment on the 'Amendment Tool' tab, referring to the on-screen guidance notes. You must clearly describe the amendment and the rationale for the amendment in the summary box. You should then separate out each type of change you are making as part of the amendment, entering details using the drop-down menus. The Tool contains a 'glossary of amendment 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 Amendment Tool document. If the amendment 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 amendment tool will define whether the amendment is substantial or non-substantial and whether the amendment is categorised as A, B or C. Additionally, the amendment will also highlight what regulatory body needs to review the amendment and if participating sites are required to be informed.

The declaration section must be completed by a member of the sponsorship team. Amendments 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 amended 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 tissue banks or research databases, instead of using the Amendment Tool, you must use the "Notice of Substantial Amendment Form" (generated in IRAS) to notify the REC about the changes. For further guidelines regarding the submission please refer to 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 or non-substantial (as per definitions outlined in section 8 and as per example 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 amendment so that this assessment can be made.

The R&D Sponsor team will review, and risk assess the amendment, 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 amendment 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 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, R&D will require additional actions/ approvals by the study management team before approving such amendment.

When the sponsor review of the amendment is complete, a sponsor representative will authorise and lock the amendment 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 Amendment 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, amendments and supporting documentation should be uploaded for online submission via IRAS. The online amendment 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 amendment, and proceed to submit after which the applicant will receive an automated email to confirm submission of the amendment.

Upon submission the amendment 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 Amendments for NBT sponsored CTIMPS

As of January 2022, the combined review service should be used for CTIMP approvals, this offers a single application route and co-ordinated review leading to a single UK decision for CTIMPS. The amendment should be created and submitted using the new part of IRAS instead of submitting through the IRAS online amendment portal.
For guidance on this process, you will need to follow the instructions for amendment submission at the following link:

Step by step guide to using IRAS for combined review - Health Research Authority (hra.nhs.uk)

Any substantial amendment to a CTIMP must be notified to the MHRA before it is implemented unless it is an urgent safety measure. Not all amendments in a CTIMP are required to be reported to the MHRA, this will be indicated by the amendment tool. Note, notification to the MHRA is not required for amendments not meeting the criteria for a substantial amendment.

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:** 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 delivery impact on NHS organisations. *However, participating sites should be notified of all amendments*.

8.6 What happens after submission?

After submission the REC and MHRA have 35 days from valid receipt to review an amendment. The REC/HRA letter will confirm the documents received, including dates and versions numbers. It is expected that the Chief Investigator/Trial teams will check these for accuracy

purposes as the approval will be based on the information contained in this letter.

After the amendment has been submitted, it is the responsibility of the CI/Trials team to inform participating sites of the pending amendment, including NBT, where we are also a participating site.

The completed Amendment tool with confirmation of the amendment 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 amendment for continued local capacity and capability.

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

8.7 Receipt of Regulatory approval and Implementation of Amendments

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

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.

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

(c) 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&D within **35 days** of R&D being notified of the amendment and its' categorisation, presumed implementation can occur.

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

(e) Category C amendments 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 amendment to the protocol or other documentation, a substantial amendment 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

Definitions of Substantial and Non-substantial Amendments

A **substantial amendment** is defined as a change to the original IRAS application, or to the protocol, or any other supporting documentation that is likely to affect to a significant degree:

i. the safety or physical or mental integrity of the subjects of the study;

ii. the scientific value of the study;

iii. the conduct or management of the study; or

iv. the quality or safety of any investigational medicinal product used in the trial.

Examples (as defined by the HRA)

- 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.

A **non-substantial amendment** is defined as minor changes to the original IRAS 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, scientific value of the study, conduct or management of the study, or quality and safety of any investigational medicinal product used in the trial.

Examples (as defined by the HRA)

- 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;
- Early Closure or Withdrawal of research sites.