The University of Nottingham	**Sponsor Standard Operating Procedure**

Title: **PROTOCOL AMENDMENTS**

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Document history:	**Modification to previous version:**
1. V1.0 22nd January 2009 2. V2.0 27th April 2009 3. V2.5 3rd January 2012	1. Change to web links of the Health Research Authority throughout. New links to MHRA guidance replacing links to the EMEA throughout. 2. NRES changed to HRA throughout. 3. Addition of Sponsor responsibility and removal to seek advice from the REC or MHRA in 2.4. 4. Removal of 'in that year' from 4.2.1 5. Clarification of route to process amendments in 4.8, 4.18 and 4.27. 6. Update to flow chart

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1. PURPOSE and SCOPE

PURPOSE:
To provide instructions for the documentation of amendments to trial conduct and documents;
and
to provide instruction for the application for approval of substantial amendments from the ethics committee and, where applicable, the competent authority.

SCOPE:
Applicable to all clinical trials or studies where approval was given by a Health Research Authority REC (formerly the National Research Ethics Service). This includes clinical trials of investigational medicinal products (CTIMPs)

2. NOTES

2.1 All proposed changes to a protocol, after it has received final approval from the ethics committee and competent authority to open as a trial, constitute an amendment. Amendments that occur as part of the initial approvals process shall be dealt with according to SOPs TA006, Ethics Application, and TA007, Regulatory Application. Protocols at this stage are still deemed 'draft' so amended versions shall be numbered accordingly as per SOP QA004, Document Control.

2.2 The Chief Investigator has overall responsibility for ensuring that the correct approvals are sought and that the amendment is implemented.

2.3 Amendments may be minor – requiring issue of revised texts only or may be substantial – requiring formal application for approval to the ethics committee and competent authority before the amendment can be implemented.

2.3.1 A distinction should be made between minor and substantial amendments for tracking purposes. See sections 4.1 and 4.2.

2.4 The decision as to whether an amendment is minor or substantial is the responsibility of the Chief Investigator in conjunction with the Sponsor. Guidance can be found at:

http://www.hra.nhs.uk/research-community/during-your-research-project/

and (CTIMPs only):

http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/ManagingyourCTA/Amendments/index.htm

If in any doubt seek advice directly from the Research Governance Team at RGS.

2.5 Minor amendments are an in-house management issue only, requiring no notification to outside authorities. Substantial amendments must be approved and notified to the relevant authorities according to section 4.5 onwards.

2.6 An amendment is classed as minor if the proposed change does not alter the trial design; objectives; the safety, physical or mental integrity of the trial subjects; the scientific value of the trial; the conduct or management of the trial; or the quality or safety of any investigational medicinal product used in the trial. Examples include changes to the text of trial documents for administrative purposes or changes to the research team where the above criteria aren't altered.

2.7 An amendment is classed as substantial if the proposed change alters the trial design; objectives; the safety, physical or mental integrity of the trial subjects; the scientific value of the trial; the conduct or management of the trial (including temporary suspensions); or the quality or safety of any investigational medicinal product used in the trial.

2.8 All substantial amendments require approval from the ethics committee and where applicable the competent authority (MHRA). For participating NHS sites the local R&D will also require informing of the substantial amendment according to local procedure.

2.8.1 The Chief Investigator may immediately implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior permission(s) but must as soon as possible submit the applications for approval(s).

2.8.2 Where the amendment involves a change to the treatment regime consideration should be given to the feasibility for implementation of the substantial amendment in all participating sites before the amendment is submitted for approvals. If in doubt consult the relevant NHS R&D Departments before the amendment is finalised.

2.9 A change of Principal Investigator at a trial site or the addition of a new site not included in the original application to the REC each constitute a substantial amendment but the process of approval is different to other substantial amendments. Please see section 4.24.

3. CROSS REFERENCES

3.1	Ethics Application	SOP TA006
3.2	Regulatory Application	SOP TA007
3.3	Document Control	SOP QA004
3.4	Trial Amendment Log	RF1 TA013
3.5	Ethics Application	SOP TA006
3.6	Trial Initiation	SOP TA008
3.7	Trial Closure	SOP TA015

4. PROCEDURE

Identification of the Amendment and Decision

4.1 The Chief Investigator in conjunction with any relevant trial committees shall review the proposed amendment and decide on the changes necessary to the trial documents and management. Following the guidance on the HRA and MHRA web pages (links given above in 2.4) shall decide whether the amendment is substantial or not. Advice may be sought from the Research Governance Team.

4.2 Each separate amendment shall be uniquely identified and documented to provide an audit trail recording the amendment itself, the changes to any trial documentation, the dates of the approvals and the implementation date.

4.2.1 The applications for approvals require the use of a unique identifier to allow cross referencing for the approvals process. Use a unique identifier such as MA01/yy for minor amendments and SA01/yy for substantial amendments with incremental increases for each subsequent amendment.

4.2.2 Record all amendments on RF1 TA013, Trial Amendment Log, and store in the Trial Master File. Copy to participating sites for inclusion in the local Trial Site File – see section 4.4.6

4.3 It is imperative that all amendments are implemented in a timely fashion and that the conduct of the trial demonstrating that the amendment has been implemented is evident at all sites from the implementation date – see section 4.4

Minor Amendments

4.4 The Chief Investigator shall agree the proposed changes, plan for their implementation and shall record the amendment on RF1 TA013, Trial Amendment Log.

4.4.1 The implementation shall include production of any new documents required and these are to be distributed to participating sites prior to the implementation with instruction to remove previous versions from local circulation and to implement the new ones from the implementation date. All new documents must be version numbered and dated as per SOP QA004, Document Control.

4.4.2 Retain evidence of the instruction (such as email or letter) and evidence that the recipients received the instruction (such as a response email).

4.4.3 Where the amendment requires participating staff to be trained in the implementation of the amendment sufficient time must be allowed for the training to take place before the implementation date.

4.4.4 Update any electronic documents to reflect the minor amendment and the new version numbers. Archive previous versions.

4.4.5 Destroy paper stocks of previous document versions retaining one copy of each for audit trail purposes. Instruct participating sites to do the same.

4.4.6 Copy the Trial Amendment Log, RF1 TA013, and all subsequent updates to each participating site for inclusion in the local Trial Site File.

Substantial Amendments of CTIMPs

Note: In practice virtually all substantial amendments will involve altering the trial documentation in some way so this section is written with this in mind. A SA that involves the appointment of a new Principal Investigator at a site or the inclusion of a new site not included in the original REC and MHRA approvals is dealt with in section 4.24. A temporary halt to a trial is also a substantial amendment and is dealt with in section 4.28.

4.5 Produce the revised text and change the version number of the document. Where there have been previous minor amendments incorporate those changes as part of the substantial amendment.

4.5.1 Uniquely identify the substantial amendment, such as:

SAnn/yy, version xx

where ‘nn’ is the next sequential number for that amendment, and ‘xx’ is the version number of this amendment. The version number allows tracking until

the REC and, where applicable, the MHRA have given approvals. The version number will be dropped for final recording purposes on RF1 TA013.

4.6 Devise a summary table of all of the proposed changes.

4.7 Record the substantial amendment on the Trial Amendment Log, RF1 TA013 and retain in the Trial Master File.

4.8 Complete the Notification of Amendment Form (Annex 2) using the amendments tab in IRAS.

https://www.myresearchproject.org.uk/SignIn.aspx

4.8.1 Information on its completion can be found at:

http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/ManagingyourCTA/Amendments/Whattosend/index.htm

Two copies will be needed – one for the application to the ethics committee (REC) and one for the application to the competent authority (MHRA).

4.8.2 Note that all authorisations of the amendment form are now electronic. Follow the instructions in IRAS to obtain electronic authorisation.

4.9 Collate the substantial amendment applications:

i) Notification of Amendment form, completed and signed by the Chief Investigator
ii) Copy of the revised documents to include:
an updated XML and PDF file of the Clinical Trial Application Form (Annex 1) with changes highlighted, if the amendment affects the information previously submitted
description of the amendment
reasons for the proposed amendment
copy of the proposed changes to the protocol or any other documents (eg IMPD), showing previous and new wording, where applicable
iii) Summary table of the proposed changes
iv) Covering letter, signed by the applicant (the Chief Investigator)
v) Any supporting documentation as required.

4.10 Approval of a substantial amendment from the MHRA may incur a fee depending on what is amended. See the list of fees payable at:

http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Fees/index.htm

Include the appropriate fee in the application to the MHRA. Approvals from the REC are free.

4.11 Post one application package to each of the REC for the trial and to the MHRA .

Note: For the MHRA all documents are to be stored as pdf (not file protected) on a disk and submitted with the paper documents to the address given on the MHRA web page for submission of substantial amendments.

4.12 Respond to any clarifications and requests for further changes, changing the version number of each subsequent draft document. Both the REC and MHRA must approve the same versions of the amendment (so even if one requests no changes the proposed changes of the other must be notified to them)

4.13 Once approval is given, store copies of all signed documents, the summary of amendments table and copies of the supporting documentation in the Trial Master File.

4.13.1 Copy all documents to the Sponsor for inclusion in the Sponsor's Research Database

4.13.2 Instruct participating sites to inform their local R&D Departments of the amendment according to local procedure.

4.14 Implement the substantial amendment as for minor amendments, given in section 4.4

Substantial Amendments of non–IMP Trials

4.15 Produce the revised text and change the version number of the document. Where there have been previous minor amendments incorporate those changes as part of the substantial amendment.

4.15.1 Uniquely identify the substantial amendment, such as:

SAnn/yy, version xx

where 'nn' is the next sequential number for that amendment, and 'xx' is the version number of this amendment. The version number allows tracking until the REC have given approvals. The version number will be dropped for final recording purposes on RF1 TA013.

4.16 Devise a summary table of all of the proposed changes.

4.17 Record the substantial amendment on the Trial Amendment Log, RF1 TA013 and retain in the Trial Master File.

4.18 Complete the Notification of Substantial Amendment form (non-CTIMP) via the amendment tab in IRAS. Information on its completion can be found at:

http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/

One copy only will be needed – for the application to the ethics committee (REC)

4.18.1 Note that all authorisations of the amendment form are now electronic. Follow the instructions in IRAS to obtain electronic authorisation.

4.19 Collate the substantial amendment application:

i) Notice of Substantial Amendment form, completed and signed by the Chief Investigator
ii) Copy of the revised documents
iii) Summary table of the proposed changes
iv) Covering letter, signed by the applicant (the Chief Investigator)
v) Any supporting documentation as required.

4.20 Post the application package to the REC for the trial.

4.21 Respond to any clarifications and requests for further changes, changing the version number of each subsequent draft document.

4.22 Store copies of all signed documents, the summary of amendments table and copies of the supporting documentation in the Trial Master File.

4.22.1 Copy to the Sponsor for inclusion in the Sponsor's Research Database
4.22.2 Instruct participating sites to inform their local R&D Departments of the amendment according to local procedure.

4.23 Implement the substantial amendment as for minor amendments, given in section 4.4

Substantial Amendment: Change of Principal Investigator or inclusion of a new site and Principal Investigator

For CTIMPs:
Note: The addition of a new site not listed in the original application is a substantial amendment which requires the submission of a Notice of Substantial Amendment to the REC and submission of a SSI form to the NHS Trust R&D office concerned.

4.24 Complete the Site Specific Information part of the REC application detailing the new site and the Principal Investigator or the change of PI (as per SOP TA006, Ethics Application). Submit to the NHS Trust R&D department for the new site. Copy to the Sponsor.

4.25 Apply to the REC only (the MHRA no longer need to be notified of additional sites) as for other substantial amendments of CTIMPs as per 4.5-4.13. The front of the form should show that it is being submitted for information only. An updated xml file of the original clinical trial authorization (CTA) form should also be submitted.

4.25.1 A copy of the Notification of Amendment form (annex 2) must be sent to the REC that gave the original favourable opinion for the trial for notification purposes only. The REC will acknowledge receipt of this and confirm that the new site has a favourable opinion on condition that the NHS management permission, including the SSA is obtained.

4.26 Both the site and the Chief Investigator will be notified of the outcome of the SSA by the NHS Trust R&D department. **Copy to the Sponsor.**

4.26.1 The acceptance of the SA from the NHS Trust must be in place before recruitment can commence at that site. For a new site a non-commercial research agreement must also be issued and fully signed before recruitment can commence. See SOP TA008, Trial Initiation, section 4.5.

Non-IMP trials:
4.27 Complete the Site Specific Information part of the REC application detailing the new site and the Principal Investigator or the change of PI (as per SOP TA006, Ethics Application). Submit to the NHS Trust R&D department for the new site.
It is not necessary to submit a Notice of Substantial Amendment form to the REC in these cases. Both the site and the Chief Investigator will be notified of the outcome of the SSA by the NHS Trust R&D department. Copy to the Sponsor.

4.27.1 For a new site a non-commercial research agreement must also be issued and fully signed before recruitment can commence. See SOP TA008, Trial Initiation, section 4.5.

Temporary Suspension of Trials

For CTIMPs:
Note: Temporary suspensions of CTIMPs require notification to the MHRA immediately or at least within 15 days of the suspension

4.28 Notify the MHRA and the REC using the Notification of Amendment form (annex 2) as in sections 4.5-4.13. The reasons for the temporary halt should be given.

4.29 To restart a trial that has been temporarily halted, make the request as a substantial amendment using the Notification of Amendment form and providing evidence that it is safe to restart the trial.

For Non-IMP trials:
4.30 Notify the REC as per sections 4.15-4.231.

All trials:
4.31 If the trial is not to recommence, the MHRA (as appropriate) and Ethics Committee should be notified within 15 days of this decision as per SOP TA015, Trial Closure.

5. FLOW CHART