JOINT RESEARCH AND DEVELOPMENT OFFICE

Somers Clinical Research Facility

Amendments to a GOSH sponsored Clinical Trial of Investigational Medicinal Product (CTIMP)

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Previous version	Comments	Reviewed by	Date archived
GOSH/ ICH/11/OP01 V2	Review and update	Emma Pendleton	09/08/2016
GOSH/ ICH/11/OP01 V1	First Issue	Dr Lorna Gibson	18/01/2014

1. Scope /Background

This SOP is applicable to all the clinical trials sponsored, co-sponsored by Great Ormond Street Hospital. The SOP is applicable to Chief Investigators (CI), PIs, and delegated trial team members involved in Trust-sponsored CTIMPs and the Joint R&D Office Clinical Trials Team with responsibility for performing sponsor activities on behalf of the Trust.

2. Legal basis

The legal basis for this OP is Council Directive 2001/20/EC1 (Article 15). This Directive (published in 2001) is also known as the Clinical Trials Directive (CTD) and relates to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use. In the UK the CTD was transposed into law by the 'The Medicines for Human use (Clinical Trials) Regulations 2004: SI 2004 No 10312. The UK Regulations took effect on 1 May 2004 and then further amendments.

3. Purpose

The purpose of this SOP is to inform Investigators and trial staff on the process of making amendments to CTIMPS sponsored or managed by GOSH.

4. Definitions

Amendments are changes made to the research after review body approval has been given. Amendments can be referred to as "Substantial" or "Non-Substantial".

"Non-substantial" amendments may be made at any time and have no significant implications to the trial. There is no requirement to notify the main Research Ethics Committee (REC) or MHRA of non-substantial amendments and there are no legal requirements to obtain an ethical opinion before implementation. Examples of such amendments are:

- 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 chief investigator's research team
- changes to the research team at particular trial sites (other than appointment of a new principal investigator 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.

"Substantial amendment" (as defined by the EU Directive and the Clinical Trials Regulations) is changes that are likely to affect to a significant degree, such as:

- 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 used in the trial.

5. Personnel responsible

It is the Sponsor's responsibility to decide whether an amendment is 'substantial' or 'non-substantial' and whether it requires authorisation from the MHRA, or an ethical opinion from the REC, or both. It is the PI or CI's responsibility to notify the Sponsor of all amendments to a GOSH sponsored CTIMP prior to requesting or implementing any amendments.

6. Procedure

Once the details have been received the Sponsor will confirm that the amendment is non-substantial. Should the sponsor deem the amendment to be substantial the procedure for substantial amendments should be followed. Sponsor should review and confirm the documentation prior to the submission to MHRA, REC and HRA.

6.1. Substantial amendments

Information on what constitutes a substantial amendment is available in the European Commission document titled: 'Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of trial'.

Substantial amendments should be notified by using a **substantial amendment notification form** which can be found at EudraLex website - Volume 10 Clinical trials guidelines under Chapter I: Application and Application Form

The form should be completed and sent to the Sponsor with the amended documents prior to requesting authorisation from MHRA and/or REC and HRA. It should be indicated on the form whether the amendment requires competent authority (MHRA), or a favourable opinion

from the REC, or both. In some cases, the amendment may be for information only for one or other agency.

A number of different changes can be listed in one substantial amendment notification form and completed forms should be accompanied by the documents that have been modified, showing both the previous and the new wording, lengthy changes to be listed in a separate document, showing both the previous and the new wording. The Sponsor or CI may also include other supporting information, such as a summary of trial data, scientific review, an updated safety analysis or a report from a trial monitoring committee where applicable.

A completed substantial amendment form and supporting documentation should be sent to sponsor before requesting favourable opinion from the competent authority (MHRA), or REC. Review of the substantial amendment will take place by the Sponsor, should other departments be affected by implementation of the amendment such as pharmacy, radiology or imaging they will be consulted before favourable option is requested. Substantial amendments may be submitted by the Sponsor, the sponsor's legal representative, the CI, or another person or organisation authorised by the Sponsor.

Documents to be included when sending substantial amendments to competent authority (MHRA), or a REC for favourable opinion are:

- cover letter including description of the amendment and reason(s) for the proposed amendment
- the signed substantial amendment notification form
- copy of the proposed changes to the protocol or any other documents (eg IMPD), showing previous and new wording, where applicable
- proof of payment(MHRA only)
- supporting data for the amendment, including as applicable:
- summaries of data
- updated overall risk benefit assessment
- possible consequences for subjects already in the trial
- Possible consequences for the evaluation of results.

Please note to submit the documents to MHRA through the Common European Submission Portal (CESP). R&D Clinical Trials Team will generate an account for the CI or delegate if it is necessary.

6.2. Validation of notice of amendments

6.2.1. MHRA

The substantial amendment will be validated on receipt (the MHRA will not retain copies of invalid applications and send details of such) and an acknowledgement letter will be sent to the person submitting the application (named in section C of the clinical trial application form). If the application is valid then the assessment period will begin and will be performed within 35 days. Assessment will result in letter informing of the following:

- acceptance of the amendment,
- acceptance of the amendment subject to conditions, or
- grounds for non-acceptance of the amendment

Should the MHRA give ground for non-acceptance of the amendment this will usually require re-submission. Further information regarding substantial amendments can be found on the MHRA website.

Please note: there is no longer a need to notify 'for information only' substantial amendments to the MHRA if the information is to be assessed only by the Ethics Committee.

6.2.2. Research Ethics Committee

The main REC has 35 days from receipt of a valid notice of amendment to give an opinion. The clock does not stop during this period. Amendments may be reviewed in sub-committee or at a full Committee meeting, but not by the Chair acting alone.

If an unfavourable opinion is given, the Sponsor or CI may modify the amendment. The REC should give an opinion on a modified amendment within a further 14 days. Responsibility may be delegated to the Chair. If an unfavourable opinion is then given the amendment may not be re-submitted.

Substantial amendments can only be implemented once all applicable favourable approvals have been granted. In certain circumstances it is possible that the outcome of the amendment is acceptable of the request with conditions applied. Where the conditions are met, no further action is required by the sponsor and it is not necessary to confirm that the conditions are met. Where the conditions are not met, the authorisation is not valid and the Sponsor should submit a further substantial amendment supported by the relevant documentation to make the necessary changes.

6.2.3. Health Research Authority

Amendments will be forwarded to the Health Research Authority by the relevant ethics committee. The HRA will assess the amendment and categorise as A,B and C and sent to the applicant with confirmation of acceptance.

6.4.4 Site R&D Department

In multi-centred trials, it is the CI's responsibility to ensure all participating centres are provided information regarding amendments, disseminating information and ensuring receipt of information. Once they have received the relevant information from the CI, it is the site PI's responsibility to inform their R&D department about the amendment before implementing it at their site.

6.3. Non Substantial amendments

Sponsor should be notified of the non-substantial amendment. However, they do not require an ethical opinion from the Research Ethics Committee or acceptance from MHRA.
However, HRA should be notified of minor amendment so updated documents should be sent to hra.amendments@nhs.net.

6.4. Temporary halt of a trial

When a Sponsor halts a trial temporarily the MHRA and Ethics Committees should be notified immediately and at least within 15 days from when the trial is temporarily halted. The notification should be made as a substantial amendment using a substantial amendment notification form which can be found at EudraLex website - Volume 10 Clinical trials guidelines under Chapter I: Application and Application Form

The form should be completed and sent to the sponsor prior to sending to the MHRA and Ethics Committees clearly explaining what has been halted (eg stopping recruitment and/or interrupting treatment of subjects already included) and the reasons for the temporary halt.

To restart a trial that has been temporarily halted, the Sponsor should make the request as a substantial amendment using the substantial amendment notification form and providing evidence that it is safe to restart the trial. If a Sponsor decides not to recommence a temporarily halted trial, the MHRA and Ethics Committees should be notified within 15 days of his decision, using a Declaration of the End of Trial Form which can be found at EudraLex

website - Volume 10 Clinical trials guidelines under Chapter I: Application and Application Form and including a brief explanation of the reasons for ending the trial.

6.5. Change Control Form

It is the responsibility of the CI/PI to forward the completed change control form to the Clinical Trials Manager before implementing the amendment. This change control form provides the details of training and impact of amendment on the study management. Clinical Trials Manager makes the assessment if the risk assessment or Case Record Form needs to be amended according to the amendment.

6.6. RECORDS

All documents relating to amendments should be filed in the appropriate section of the Trial Master File.

7. Associated documents and SOPs*

Document Name	File Path	Author
Change Control Form Version V1 18/01/2016	http://www.gosh.nhs.uk/research-and-innovation/information-researchers/joint-rd-office/clinical-trials/standard-operating-procedures-sops-and-forms	Praseeda Thaikalloor

8. Recommendations

NA

9. References

Directive 2001/20/EC of the European Parliament and of The Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities; 1st May 2001, L121/34

Communication from the Commission — Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:082:0001:0019:en:PDF

http://www.ct-toolkit.ac.uk/, Accessed on 11 July 2016

http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/ , Accessed on 7 July 2016

https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#apply-to-change-your-trials-protocol-or-documentation, Accessed on 7 July 2016

Statutory Instrument 2004 No. 1031. The Medicines for Human Use (Clinical Trials) Regulations 2004. The Stationery Office Limited. ISBN 0110490487.

10. Appendices

*all these documents are available electronically