JOINT RESEARCH AND DEVELOPMENT OFFICE

Somers Clinical Research Facility

Submission of the Development Safety Update Report to the MHRA and the Annual Safety and Annual Progress Report to the Research Ethics Committee

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Revision History			
Previous version	Comments	Reviewed by	Date archived
GOSH ICH/05/12- V06 15/01/2014	New SOP Template Addition of submission via CESP and removed submission of	Emma Pendleton	09/08/2016

	studies prior to 2004 as it's not applicable now.		
GOSH ICH/05/12-V05 07/02/2012	Change in R&D department structure and staff, requirement of submitting DSUR and minor changes to the format and content of SOP	Dr Lorna Gibson	15/01/2014
GOSH ICH/05/12-V04 09/06/2010	Annual Review	Dr Sabine Klager	07/02/2012
GOSH ICH/05/12-V03 25/06/2008	Major change SOP to include also annual reporting requirements to the RECs; New SOP title; inclusion of ethics reporting section;	Dr Sabine Kläger	09/06/2010
GOSH ICH/05/S12-V02 27/04/2006	Changed to remove the need for MedDRA codes (section 10.2) after email from EMEA Old logos changed for new ones. Procedure is all described in section 10. Section 10.7: part of this section has been removed. In version 3, the PI only needs to send the ASR to the R&D office and the REC. The R&D office will send the ASR to the MHRA as instructed	Miss E. Pendleton	25/06/2008

	on the Sponsor's OP.		
GOSH ICH/05/S12-V01 03/05/2005	First Version	Prof D. Goldblatt	27/04/2006

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/EC[1] (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 1031[2]. The UK Regulations took effect on 1 May 2004 and then further amendments.

Article 17 paragraph 2 of the Directive states 'Once a year throughout the clinical trial, the Sponsor shall provide the Member States in whose territory the clinical trial is being conducted and the Ethics Committee with a listing of **all** suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety'. In the UK, Article 17 paragraph 2 of the Directive is transposed into national law by Regulation 35, one of the 4 Pharmacovigilance Regulations which make up Part 5 of Statutory Instrument 2004 No. 1031: 'The Medicines for Human Use (Clinical Trials) Regulations 2004' for the UK.

3. Purpose

The purpose of this SOP is to provide guidance on how to prepare, complete and when to submit a Development Safety Update Report (DSUR) to the MHRA, Development Safety Update Report (DSUR) and Annual Progress Reports (APR) to the NHS REC for trials that fall under the scope of Directive 2001/20/EC.

4. Definitions

4.1 Development Safety Update Report (DSUR)

The Development Safety Update Report is the format for annual safety reporting. The focus is specifically on new safety information identified during the reporting period with a view to ongoing risk-benefit analysis.

4.2 Adverse Event (AE); any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

4.3 Adverse Reaction (AR): all untoward and unintended responses to an investigational medicinal product (IMP) related to any dose administered.

Comment: All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as an adverse reaction.

4.4 Unexpected Adverse Reaction (UAR)': an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

Comment: Reports are also considered to be unexpected if they add significant information on the specificity or severity of an expected adverse reaction.

4.5 Serious Adverse Event or Serious Adverse Reaction (SAE/R)': any untoward medical occurrence or effect that at any dose results in:

- death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- a congenital anomaly or birth defect;
- other important medical events.

Other important medical events are the adverse events/reactions that may jeopardise the subjects or may require medical or surgical intervention to prevent one of the

above 5 outcomes defining seriousness (d) from occurring should also be considered serious. Such events could be:

1. Overdose (accidental or intentional)
2. Pregnancy (of subject or partner)
3. An alarming adverse experience
4. Adverse events and/or laboratory abnormalities, which are listed in the trial protocol as critical to safety evaluation and requiring reporting.

4.6 Suspected Unexpected Serious Adverse Reaction (SUSAR): an adverse reaction which is both serious and unexpected.

4.7 Suspected Serious Adverse Reaction' (SSAR): An adverse reaction that is classed as serious and which is **consistent** with the information about the information about the medical product listed in the relevant reference documentation. This is either the 'Summary of Product Characteristics'(SmPC) in the case of a licensed product being used **within** its licensed dosage and indication; or in the 'Investigator's Brochure' (IB) in case of any IMP or a licensed product being used **outside** its licensed dosage and indication.

5. Personnel responsible

The Sponsor is responsible for the preparation, content and submission of the reports. Joint R&D office delegates this duty to the Chief Investigator via the sponsor-CI agreement for GOSH sponsored CTIMPs. The CI or PI may delegate this responsibility to the relevant trial team member. CI, PI and support research staff involved in the conduct and the collection and recording of adverse events/reactions that occur in subjects during the conduct of a clinical trial is also responsible for the collation of data.

Joint R&D office Clinical Trials Coordinator sends a reminder email to the trial team on the anniversary of the trial's Clinical Trials Authorisation with a copy of the DSUR template, containing guidance for completion to the CI and trial team, along with confirmation of the submission timelines. The report should be sent to the Clinical Trials Manager/Coordinator to review before submission.

6. Procedure

6.1 DEVELOPMENT SAFETY UPDATE REPORT OF A CLINICAL TRIAL TO MHRA AND REC

DSUR is a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period of Investigational Medicinal Product (IMP) of clinical trials. DSUR has to be compiled for each IMP in a trial.

The **Development International Birth Date** (DIBD) is used to determine the start of the annual period for the DSUR. This date is the sponsor's first authorisation to conduct a clinical trial in any country worldwide. The start of the annual period for the DSUR is the month and date of the DIBD. The data lock point of the DSUR should be the last day of the one-year reporting period. The European Commission CT guidelines on the collection, verification and presentation of adverse reaction reports arising from clinical trials of medicinal products for human use (section 5.2.2) states that the Sponsor should submit the DSUR within 60 days of the data lock point.

6.2 Report on the subjects' safety of a clinical trial

This is a concise **safety and risk-benefit analysis** for the clinical trial concerned, including a trend analysis of non-serious adverse events - if appropriate; for example increased frequency or severity in expected Adverse Events observed should be considered. It should describe in a concise way, all new findings related to the safety of the Investigational Medicinal Product (IMP) treatments in the concerned trial and provide critical analysis of them with respect to their impact for the subjects of the concerned trial. The concept of new findings refers to information **not already present** in the Investigator's Brochure or Summary of Product Characteristics.

It should be complemented with an analysis of the implications for the population of the clinical trial and should also analyse the safety profile of the tested IMP and its implication to subjects' exposure, taking into account all available safety data. When relevant, the following points should be considered:

a) relation with dose, duration, time course of the treatment
b) reversibility
c) evidence of previously unidentified toxicity in the trial subjects
d) increased frequency of toxicity
e) overdose and its treatment
f) interactions or other associated risks factors
g) any specific safety issues related to special populations, such as the children, the elderly or any other at risk groups

h) positive and negative experiences during pregnancy or lactation
i) abuse
j) risks which might be associated with the investigation or diagnostic procedures of the clinical trial

The report should also consider supporting results of non-clinical studies or other experience with the IMP that is likely to affect the subjects' safety. It should detail the measures previously or currently proposed to minimise the risks found where appropriate.

Finally, a detailed rationale must be given on whether or not it is necessary to amend the protocol, to change or update the consent form, patient information leaflet and the Investigator's brochure. In the case of a substantial protocol amendment, authorisation must be requested following the procedure outlined in the standard operating procedure GOSH/ICH/11/CT10 for amendments to GOSH sponsored CTIMPs available from the Joint R&D Office.

6.3 Line-listings of all SARs

The line listing provides key information but not necessarily all the details usually collected on individual cases.

It should include each subject only once regardless of how many adverse reaction terms are reported for the case, on one occasion. If there is more than one reaction, they should all be mentioned but the case should be listed under the most Serious Adverse Reaction (sign, symptom or diagnosis) as judged by the researcher or medical adviser to the trial.

It is possible that the same subject may experience **different** adverse reactions on **different** occasions. Such experiences should be treated as separate reports. Under such circumstances, the same subject might then be included in a line listing more than once and the line-listings should be cross-referenced when possible.

The EU Commission has recommended tabulating cases by body system (standard system organ classification scheme).

Listings must also be provided for active comparator or placebo or when appropriate and relevant for other reasons, e.g. in the case that in the same trial for different formulations, indications or routes of administration are studied.

6.3.1 Line listings should consist of the following data:

- Clinical trial identification:
  (DDX exemption certificate number or CTA number, if known, or EUDRACT number)
- Study subjects identification number in the trial
- Case identification number (Refer to section 10(c) of Document GOSH ICH/05/S05)
- Country in which case occurred
- Age and sex of trial subject
- Daily dose of Investigational Medicinal Product, (and, when relevant, dosage form and route of administration)
- Date of onset of the adverse reaction.
  (If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible).
- Dates of treatment.
- Description of adverse reaction as recorded; where medically appropriate, signs and symptoms can be lumped into diagnoses.
- Patient's outcome (e.g. resolved, fatal, improved, sequelae, unknown). This field should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions.
- Comments, if relevant: (e.g. causality assessment and concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge/ rechallenge results if available)
- Unblinding results in the case of unblinded SUSARs: expectedness at the time of the occurrence of the suspected SARs, assessed with the reference document (i.e. Investigator's Brochure) in force at the beginning of the period covered by the report.

A template form has been produced for your guidance for the DSUR. Please refer to the form identified as GOSH/ICH/F54.

6.3.2 Line Listings for trials where there have been no suspected SARs

If there have been no suspected SARs during the trial, you are still required to write an DSUR stating that no SSARs have occurred. For these reports you only need to include a summary of the safety of the trial subjects including the cumulative summary tabulation of Serious Adverse Events (SAEs).

6.3.3 For several trials with the same IMP

DSURs are IMP specific. If the sponsor is also conducting clinical trials with the same IMPs, then data from all the clinical trials using the same IMP can be submitted in the single DSUR.

6.3.4 DSURs for combinations therapies

For trials involving multi-drug therapy, i.e., combinations of drugs, the Sponsor in conjunction with the CI will decide to prepare either:
(1) A single DSUR focusing including data on the multi-drug therapy or
(2) Separate DSUR(s) each individual IMP

The sponsor in conjunction with the CI will select the most appropriate option to submit the DSUR. This decision should be based on the considering the patient population, indication, formulation, etc. The justification for this decision should be provided in the report.

6.4 REPORTING TIME FRAME FOR DEVELOPMENT SAFETY UPDATE REPORT

6.4.1 For short term trials

If a clinical trial has been started and ended (CT1 (2.5)) within a time period shorter than 1 year, it will not be subject to annual safety reporting in accordance with current Article 17(2) of CTD 2001/20/EC, even if multiples of such short clinical trials were performed. However, for the latter case of multiple performed short trials for one IMP, in line with the ICH's objective of comprehensive assessed safety information of one IMP it is recommended to consider submitting a DSUR to MHRA

6.4.2 For trials that have not started within 1 year of their authorisation

If your trial has not started within 1 year of its authorisation, there is no need for submitting blank DSUR instead submit a cover letter to MHRA and REC with reasons for delays and any other relevant information available.

6.5 COVERING LETTER TO BE SUBMITTED WITH DSUR

DSUR should be accompanied by a covering letter to the MHRA.

For submission of the DSUR to your main REC, please use the standard cover form that can be found on the NRES website (click on Safety Reports in Applicants Page).

6.6 WHERE TO SUBMIT DSUR

Submit your DSUR and the REC Annual Safety Report cover form as electronic versions via e-mail to the Clinical Trials Manager in the Joint R&D Office for review.

After review, CI or the delegate can submit the DSUR and the covering letter to the MHRA and to the main REC who approved the study with the REC cover form. DSUR should be submitted to MHRA via Common European Submission Portal (CESP). It is important that to sustain the ethical approval for a CTIMP with favourable ethical opinion a Development Safety Update Report (DSUR) must be submitted to the main REC each year of the project's duration.

6.7 ANNUAL PROGRESS REPORT TO REC

For the Annual Progress Report Investigator need to download the CTIMP annual progress report form from the HRA website.

6.7.1 Submission of the Annual Progress Report

The Annual Progress Report Form should be completed in typescript and signed by the Chief Investigator of the CTIMP. A paper copy should be sent to the REC within 30 days of the anniversary date of receiving the first ethical favorable opinion – which marks the end of the reporting period.

Submit your APR and covering letter as electronic versions via e-mail to the Clinical Trials Manager in the Joint R&D Office for review.

After review, the APR will be submitted to the REC together with the covering letter by either the Clinical Trials Manager, or the CI/PI will be advised on how to make the submission.

6.7.2 Duration of the CTIMP and its ethical favourable opinion

First Annual Progress Report should include the commencement date for trial. This is normally assumed to be the date on which first patient has been enrolled. Annual progress reports should be submitted thereafter until the trial is completed.

If trial has not started within 12 months of the favourable opinion, the first progress report should give an explanation for the delay.

In case you plan to extend the duration of your trial beyond the period specified in the original ethics application form, the main REC should be notified for information either in one of the Annual Progress Reports or by letter, giving reasons for the extra time needed to complete the research, .

Remember, that the REC does not need to re-confirm its favourable ethical opinion each time a progress report is received. It is generally assumed that the opinion applies for the duration of the research, although the REC may review its opinion at any time

6.7.3 Multi-site CTIMPs

In case trial has more than one site, CI should include data of all participating sites into their Annual Progress Report. The final report should be sent to the other sites

6.7.4 Waiving requirement for progress reports

In case your trial has been completed recruitment of patients and all patients have completed the intervention phase, but will continue to be followed up for a long period of time with minimal involvement, you could request a waiver for the requirement of an Annual Progress Report. The Chair of the main REC has the discretion to waive the requirement on receipt of a written request from the CI.

7. Associated documents and SOPs*

Document Name	File Path	Author
GOSH ICH/05/S05-Recording and Reporting of AE/Rs that arise during clinical trials of medicinal product for human use – SOP for Investigators	**http://www.gosh.nhs.uk/research-and-innovation/information-researchers/joint-rd-office/clinical-trials/standard-operating-procedures-sops-and-forms**	**Clinical Trials Team**
GOSH ICH/11/F54/01-Development Safety Update Report (template)	**Available upon request from the R&D Clinical trials Team**	**Clinical Trials Team**

8. Recommendations

Please also read the associated documents listed in section 7.

9. References

Detailed guidance on the collection, verification, and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. Revision 1 April 2004. EU Commission, Brussels ENTR/ CT 3.

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

Frequently asked questions regarding the Development Safety Update Report (DSUR) Available on http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARsandASRs/#I9

HRA Website, Available on http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/ , Accessed on 30th June 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