Standard Operating Procedure (SOP)

Investigator Preparation of Annual Developmental Safety and Update Report (DSUR) and its review and submission by the Sponsor

SOP ID number:	JREOSOP0008	**Effective Date:**	26/04/2016
Version number and date:	Final Version 4.0 25/04/16	**Review Date:**	25/04/18
Author:	Debbie Rolfe	**Title:**	Regulatory Assurance Manager
Approved by:	Lucy Parker	**Date:**	
Signature of Authorisor			

This is a controlled document.
The master document is posted on the JREO website and any print-off will be classed as uncontrolled.

Researchers and their teams are responsible for checking the JREO website for the most recent version.
They may print off this document for training and reference purposes.

SOP Chronology		
SOP Version Number:	**Reason for Change:**	**Author:**
V1.0	Original Version	Subhir Bedi
V2.0	Updated to new JREO SOP template and DSUR reports replacing ASRs	Debbie Rolfe
V3.0	Updated Trust status & logo, updated emails and external links	Debs Rolfe
V4.0	Updated with electronic submission format via CESP	Debs Rolfe

1. Background

The European Clinical Trials Directive (EUCTD) 2001/20/EC was transposed into UK Regulations by The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) on the 1st May 2004. 'UK Regulations' will be the term used to cover the UK legislation and the EUCTD in this document.

The Development Safety Update Report (DSUR) was developed, by the Committee for Medicinal Products for Human use (CHMP) of the European Medicines Agency (EMA), to ensure a standard format for periodic reporting of drugs under development (inclusive of marketed drugs under further study) among the International Conference for Harmonisation (ICH) regions. The ICH regions are those which have agreed to comply and follow common recommendations with the aim of achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration. The main aim is to reduce or remove the need to duplicate testing carried out during the research and development of new human medicines. The regions comprise Europe, the United States of America and Japan.

US and EU regulators consider that the annually submitted DSUR would satisfy the requirements previously met by the US IND Annual report and the EU Annual Safety report (ASR). The DSUR reporting format replaced the ASR format in September 2011.

To breach these requirements constitutes a breach in criminal law. The requirements have been incorporated into this Standard Operating Procedure (SOP) to define procedure undertaken by the Sponsor (St George's University of London (SGUL) and/or St George's University Hospitals NHS Foundation Trust (SGHT)) to comply with the UK Regulations.

2. Joint Research and Enterprise Office (JREO) Policy

All JREO SOPs will be produced and approved in accordance with the JREO SOP on SOPs and must be used in conjunction with local NHS Trust and St George's policies and procedures.

The JREO acts as the representative of both St George's University of London (SGUL) and St George's University Hospitals NHS Foundation Trust (SGHT). St George's will be the official name used on all SOPs to represent either institution acting as Sponsor.

3. Scope

This SOP describes the process to be used by all Investigators for the preparation of the DSUR and its subsequent approval for submission by the JREO to both the MHRA and the relevant ethics committee throughout the lifetime of the trial.

In addition to the expedited reporting required for SUSARs detailed in JREOSOP0006, Sponsors are required to submit a DSUR report to the MHRA and the Ethics Committee, once a year throughout the clinical trial or on request. The DSUR should take into account all new available safety information received during the reporting period.

The aim of the DSUR is to describe concisely all new relevant safety information for one or several clinical trial(s) and to assess the safety of subjects included in these studies.

Where there may be trial related responsibilities delegated by the JREO to a third party (*i.e.* Clinical Research Organization (CRO) or an external Clinical Trials Unit (CTU)) this SOP must be followed. The same must apply to international trials.

4. Definitions

4.1 Investigational Medicinal Product (IMP)

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use

4.2 Sponsor

An individual, company, institution or organisation, which takes on the responsibility for the initiation, management, and/or, the financing, of a clinical trial.

4.3 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of hospitalisation, results in persistent or significant disability/incapacity or is a congenital anomaly or birth defect.

Note: hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Therefore subjects do not need to be hospitalised overnight to meet the hospitalisation

criteria. Hospitalisation for an elective procedure or for a pre-existing (prior to study entry) condition which has not worsened is not defined as an SAE.

5. Responsibilities

5.1 Investigator Responsibilities

a) It is the responsibility of the CI and the individual investigators within the research team to follow this SOP and the published guidance listed in section 7.

b) The statutory requirement to provide DSURs starts when the first participant is recruited at a UK trial site and ends when the conclusion or early termination of the trial has been notified in the UK (even if the trial is continuing in other countries). For trials of marketed products, the DSUR should be provided at yearly intervals on the anniversary of the first marketing authorisation granted in the European Union (EU) (the International Birth Date (IBD)). For trials of other products, or where the IBD is not known, the DSUR should be provided at yearly intervals on the anniversary of the Clinical Trial Authorisation (CTA) until the end of the trial.

c) The DSUR will be prepared in the approved format as set out in the ICH guideline E2F and includes the following:

Part 1: Analysis of the subjects' safety in the concerned clinical trial(s) with an appraisal of its on-going risk: benefit

Part 2: A line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the concerned trial(s), including all serious adverse reactions from third countries where relevant

Part 3: An aggregate summary tabulation of suspected serious adverse reactions that occurred in the concerned trial(s).

d) Full details of what to include in a DSUR can be found in Section 5.2 of Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use - April 2006 (external link)

5.2 The JREO (Sponsor) Responsibilities

a) It is the responsibility of the HRG to ensure that this SOP is updated and audited where necessary

6. Procedure

6.1 Investigator Procedure

The Investigator should:

a) Complete all required information for the DSUR in the approved template format www.ich.org/products/guidelines/efficacy/efficacy-single/article/development-safety-update-report.html (Appendix 2) or request the template from the JREO

b) Review previously submitted Annual Safety Reports or DSURs to ensure relevant information in prepared DSUR is updated and included.

c) Ensure all reported safety information during the reporting period is tabulated as illustrated in the approved DSUR template format.

d) Send to the JREO via researchgovernance@sgul.ac.uk within given timeline

e) Upon receipt of queries, suggestions or requests from the JREO, respond within 2 working days.

f) Upon receipt of Sponsor approved DSUR, return the electronically signed document to the JREO contact.

6.2 JREO Procedure

a) The Clinical Trial Monitor (CTM) or Regulatory Assurance Manager (RAM) will ensure that an email reminder is set up in the ReDA database to be sent to the CI and copied to the researchgovernance@sgul.ac.uk mailbox for DSUR preparation within 60 days of the anniversary date defined in 5b above against the project reference.

b) The RAM will upon alert via the researchgovernance@sgul.ac.uk mailbox, ensure close communication is kept with the Investigator of that trial.

c) The RAM will ensure acknowledgement of receipt of the prepared DSUR is communicated via email to the Chief Investigator within 1 working day.

d) Upon receipt of the DSUR via the investigator, the RAM will review the proposed DSUR and ensure any relevant information from previously submitted ASR or DSUR is included.

e) The RAM will review the pharmacovigilance section of the JREO Sponsor file (paper and electronic) to ensure all relevant safety information is tabulated and included.

f) The RAM will assess the prepared DSUR upon receipt for accuracy and completeness and respond with any queries or points for clarification to the study team within 2 working days.

g) The RAM will upon approval of the DSUR, convert the word document to PDF and request a signature from the CI

h) Upon receipt of the electronically signed PDF, save a copy to the electronic Sponsor file– **Note:** double check the next email alert anniversary is set up and recipient list is up to date.

i) The RAM will submit the approved and signed DSUR electronically to the MHRA. The RAM will submit the approved DSUR together with the required documentation to the relevant ethics committee.

j) The CTM/RAM will upload the DSUR into the electronic Sponsor trial file entitled with year of submission e.g. DSUR2013.

6.3 Submission of Development Update Safety Report (DSUR) to the MHRA

Annual safety reports should be uploaded electronically via CESP.

a) MHRA will acknowledge receipt of the DSUR via email. Ensure a copy of this email is saved in the electronic trial master file and forward to CI for filing in the TMF

6.4 Submission of DSUR to Ethics

a) Visit the HRA website to double check the address of the ethics committee that approved the study.

b) Email the covering letter, a completed Safety report form (a above) and the DSUR to the email contact indicated on the HRA ethics contact page

c) The Research Ethics Committee (REC) will acknowledge receipt by returning a signed copy of the submitted 'Safety Report form': ensure this is filed in the JREO Sponsor file and that a copy is forwarded to the CI for the Trial Master File (TMF)

7. References

Section 5.2 of Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use - April 2006 (external link)

8. Appendices

Appendix 1: Safety report form (CTIMP), version 5.0, September 2011

Appendix 2: JREODOC0046 : DSUR template

.

Appendix 1 REC Safety Report Form

CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS

SAFETY REPORT TO RESEARCH ETHICS COMMITTEE

Please indicate which type(s) of safety report you wish to notify with this cover sheet (tick all that apply). Use a separate sheet for notifications relating to different trials. Please send by email to the main REC for the trial concerned together with enclosures. For further guidance see: http://www.hra.nhs.uk/resources/during-and-after-your-study/nhs-research-ethics-committee-rec-ctimp-safety-report-form

1. **Expedited report(s) of SUSAR in the UK** ☐
   Notify only Suspected Unexpected Serious Adverse Reactions occurring in the concerned trial at a UK site. SUSAR reports must follow the ICH E2B format.

2. **Annual safety report / DSUR** ☐
   ASRs must follow the ICH E2F format for Development Safety Update Reports (DSUR). Include a global list of all SSARs (Suspected Serious Adverse Reactions) related the IMP and occurring in the reporting period.

3. **Other** ☐
   For example, report of Data Monitoring Committee or other safety review.

Full title of study:	
EudraCT number:	
Research Sponsor:	
Name of Chief Investigator:	
Name of main REC:	
Main REC reference number:	

Contact details for person making this notification

Name:	
Address:	
Telephone:	
Fax:	
Email:	
Date of this notification:	

List of enclosed documents

Please list each report submitted with this notification (insert extra rows in table as required).

1. Expedited SUSARs (UK only)

Sponsor's report no. / reference	Trial site	Date SUSAR first reported to Sponsor	Is this a 7 or 15 day report?

2. Other reports

Type of report	Date of report

Acknowledgement of receipt by main REC (please insert name):

The [ ] Research Ethics Committee acknowledges receipt of the above.

Signed:	
Name:	
Position on REC:	
Date:	

Signed original to be sent back only to the Sponsor (or other person submitting the report).

Appendix 2

DELETE TEXT IN GREEN WHEN READY FOR FINAL SUBMISSION

ICH E2F

Development Safety Update Report – Non-Commercial Sponsor

Insert Study Title

Insert Study Acronym

DSUR number	Reports should be numbered sequentially
Investigational drug(s)	
Reporting period	dd/mm/yyyy – dd/mm/yyyy
Date of the Report	dd/mm/yyyy
Sponsor(s) name(s) and address(es)	
EudraCT Number	EudraCT numbers of all trials reported

Chief Investigator responsible for DSUR submission:

Name: _____

Signature: _____

The cautionary statement below should be amended as appropriate

Note: This Development Safety Update Report contains confidential information. This report includes unblinded adverse event data.

Executive Summary

This section should provide a concise summary of the important information contained in the report. Together with the title page, it can serve as a 'stand-alone' document suitable for the submission to ethics committees and other stakeholders. The following information should be included in the Executive Summary:

Introduction – report number and reporting period;

Investigational drug(s) – mode(s) of action, therapeutic class (es), indication(s), dose(s), route(s) of administration, formulation(s);

Estimated cumulative exposure of clinical trial subjects;

Marketing approval(s)? (yes/no) – If yes, number of countries;

Summary of overall safety assessment (based on section 18 of the DSUR);

Summary of important risks (based on Section 19 of the DUSR);

Actions taken for safety reasons including significant changes to the IB;

Conclusions.

1. Introduction

This section should include:

Date of Clinical Trial Authorisation approval, Development International Birth Date of drug or International Birth Date of Drug as appropriate;

Reporting period and sequential number of the report;

Investigational drug(s) – mode(s) of action, therapeutic class (es), indication(s), dose(s), route(s) of administration, formulation(s);

A brief description of the indication(s) and population(s) being studied.

A short summary of the scope of the clinical trials covered by the report (e.g. all trials with the investigational drug, indication-specific trials, trials with combination products);

A brief description and explanation of any information that has not been included in the DSUR (e.g. when written agreements with a partner company do not provide for exchange of all safety data);

The rationale for submission of multiple DSURs for the investigational drug, if applicable.

2. Worldwide Marketing Authorisation Status

This section should provide a brief narrative overview including: date of first approval, indication(s), approved dose(s), and where approved, if applicable.

3. Actions Taken in the Reporting Period for Safety Reasons

This section should include a description of significant actions related to safety that have been taken during the reporting period by the Sponsor, regulators, data monitoring committee or ethics committee that had an impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme. The reason(s) for each action should be provided if known. Relevant updates to previous actions should also be summarised in this section (e.g. resumption of a clinical trial after suspension).

This section should also summarise requests from regulatory authority(ies) that place a specific limitation on current or future development (e.g. a request to conduct long term animal studies before initiating a long term clinical trial, specification of a maximum dose to be evaluated, a request for specific safety data before initiating trials in paediatric subjects.) A cumulative listing of such requests from regulatory authorities should be provided, including any updates if applicable. This can be provided as a table, in an appendix, or in this section.

4. Changes to Reference Safety Information

This section should list any significant safety-related changes to the Information Brochure (IB) or other reference safety information within the reporting period. Such changes might include information relating to exclusion criteria, contraindications, warnings, precautions, serious adverse drug reactions, adverse events of special interest, interactions, any important findings from non-clinical studies (e.g. carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the DSUR.

5. Inventory of Clinical Trials Ongoing and Completed during the Reporting Period

This section should provide a brief overview of the clinical trials ongoing and completed by the Sponsor during the reporting period, with detailed information presented in a table as an appendix (see examples in Appendix A, Tables 1 and 2).

6. Estimated Cumulative Exposure

6.1. Cumulative Subject Exposure in the Development Programme

6.2. Patient Exposure from Marketing Experience

Sections 6.1 and 6.2 of the DSUR should provide information on cumulative exposure in clinical trials and the marketed setting, respectively.

An estimation of cumulative subject exposure can help provide context for the cumulative summary tabulations of serious adverse events, and the overall assessment of safety. The accuracy of the estimation of clinical trial exposure might be limited because of a number of factors, including the rapidity of subject enrolment and the number of ongoing trials where treatment assignment remains blinded.

For marketed drugs that are under clinical investigation, it might not be feasible or useful to obtain precise cumulative clinical trial exposure data, e.g. when the drug has been marketed for a number of years and/or has many indications. In these circumstances an explanation should be provided.

7. Data in Line Listings and Summary Tabulations

Sections 7.1 – 7.3 of the DSUR should present important clinical safety information through:

- Interval line listings of the Serious Adverse Reactions that were reported during the period covered by the DSUR; and
- If appropriate, cumulative summary tabulations of serious adverse events that have been reported since the Developmental International Birth Date of the drug.

The line listings and tabulations should include blinded and unblinded clinical trial data. Unblinded data might originate from completed trials and individual cases that have been unblended for safety reasons (e.g. expedited reporting), if applicable. Data should not be unblinded for the specific purpose of preparing the DSUR.

7.1. Reference Information

This section should specify the version of the medical coding dictionary used. If applicable, it should also specify the document and version used as Reference Safety Information for determining expectedness (e.g. IB, Summary of Product Characteristics, listing version and date used).

7.2. Line Listings of Serious Adverse Reactions during the Reporting Period

This section should summarise how case reports were selected for inclusion in the line listings. This section should not serve to provide analyses or conclusions based on the SARs. The line listings should be provided in an appendix (see Appendix A, Table 3).

Where possible the line listings should include each subject only once regardless of how many SAR items are reported for the case. If there is more than one reaction, they should all be mentioned by the case should be listed under the most serious or primary adverse reaction. It is possible that the same subject could experience different SARs on different occasions (e.g. weeks apart). Under such circumstances, the SARs can be listed separately and a single subject can be included in the line listing more than once.

7.3. Cumulative Summary Tabulations of Serious Adverse Events

See appendix A, Table 3 for an example of the headings for the line listing.

8. Significant Findings from Clinical Trials during the Reporting Period

The information in this section can be provided by indication, when appropriate, and should address the following topics, when applicable:

8.1. Completed Clinical Trials

Should provide a brief summary of clinically important emerging efficacy and safety findings from clinical trials completed during the reporting period.

8.2. Ongoing Clinical Trials

Should provide details of clinically important safety information that has arisen from ongoing clinical trials (e.g. learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this section should briefly summarise the issue(s).

8.3. Long-term Follow-up

Where applicable, this section should provide information from long-term follow up of subjects from clinical trials of investigational drugs.

8.4. Other Therapeutic Use of Investigational Drug

This section should include clinically important information from other programmes conducted by the same Sponsor or co-Sponsor that follows a specific protocol.

8.5. New Safety Data Related to Combination Therapies

If this DSUR is for an investigational drug that is also under development as a component of a fixed combination product or a multi-drug regimen, this section should summarise important safety findings from the combination therapy DSUR.

Conversely, if this DSUR is for a multi-therapy drug or fixed combination product, this section should summarise important safety information arising from trials on the individual components.

9. Safety Findings from Non-interventional Studies

This section should summarise relevant safety information from Sponsored or co-Sponsored non-interventional studies that becomes available during the reporting period (e.g. observational studies, epidemiological studies, active surveillance programmes.

10. Other Clinical Trial/Study Safety Information

This section should summarise relevant safety information from any other Sponsored or co-Sponsored clinical trial/study sources that becomes available during the reporting period (e.g. results from pooled analyses or meta analyses of randomised clinical trials).

11. Safety Findings from Marketing Experience

If the investigational drug has been approved for marketing in any country, this section should include a concise summary of key safety findings that have arisen from marketing experience and that became available to the Sponsor during the reporting period.

12. Non-clinical Data

This section should summarise major safety findings from non-clinical *in vivo* and *in vitro* studies (e.g. carcinogenicity, reproduction or immunotoxicity studies) ongoing or completed during the reporting period. Implications of these findings should be discussed in the Overall Safety Assessment (section 18)

13. Literature

This section should summarise new and significant findings, either published in the scientific literature or available as unpublished manuscripts, relevant to the investigational drug during the reporting period. This section should include information from non-clinical and clinical studies and, if relevant an applicable, information on drugs of the same class. It should also summarise significant new safety information presented at a scientific meeting and published as an abstract; a copy of the abstract should be provided, if possible.

14. Other DSURs

One single DSUR should be prepared for all trials being undertaken on one investigational drug. However, if multiple DSURs are to be prepared for a single investigational drug (e.g. covering different indications, development programmes, or formulations), this section should summarise significant findings from other DSURs if not presented elsewhere in the report.

15. Lack of Efficacy

Data indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for investigational drugs intended to treat serious or life-threatening illnesses (e.g. excess cardiovascular adverse events in a trial of a new anti-platelet drug for acute coronary syndromes) could reflect a significant risk to the clinical trial subjects and should be summarised in this section.

16. Region-Specific Information

The information in this section can be used to comply with national or regional requirements and can be provided in appendices to the DSUR. Should a DSUR be required for a country other than Britain the Chief Investigator should determine the requirements for that country.

Examples of what may be included are:

Cumulative summary tabulation of serious adverse reactions;

List of subjects who died during the reporting period

List of subjects who dropped out of clinical trials in association with an adverse event during the reporting period, whether or not thought to be drug related. Any safety issues should be addressed in Section 18 of the DSUR as appropriate;

Significant manufacturing changes.

17. Late-Breaking Information

This section should summarise information on potentially important safety findings that arise after the data lock point but while the DSUR is in preparation. Examples include clinically significant new case reports, important follow-up data, clinically relevant toxicological findings and any action that the Sponsor or co-Sponsors, data monitoring committee, or a regulatory authority has taken for safety reasons. Section 18 should also take account of this new data as appropriate.

18. Overall Safety Assessment

This section should be a concise, integrated evaluation of all new relevant clinical non-clinical and epidemiological information obtained during the reporting period relative to the previous knowledge of the investigational drug. This assessment should consider cumulative experiences, new information collected in the period covered by the DSUR and, for investigational drugs with a marketing approval, clinically significant post-marketing data. It should not summarise or repeat information presented in previous sections of the DSUR, but should provide an interpretation of the information and its implications for the clinical trial population and the development programme. If appropriate, separate assessments can be provided by therapeutic area, route of administration, formulation and/or indication.

19. Summary of Important Risks

This section should provide a concise, cumulative, issue-by-issue list of important identified and potential risks, e.g. those that might lead to warning, precautions, or contraindications on labelling. Such risks might include, for example, toxicities known to be associated with a particular molecular structure or drug class, or concerns based on accumulating non-clinical or clinical data. Each risk should be re-evaluated annually and re-summarised as appropriate, based on the current state of the knowledge. New information should be highlighted. The appropriate level of detail is likely to be dependent on the stage of the drug development. For example, summaries covering drugs in early development might include information on individual cases, whereas in later development, as more knowledge and perspective are gained the information on each risk might be less detailed.

Risks that have been fully addressed or resolved should remain in the summary and be briefly described, e.g. findings from toxicology studies or early clinical trials that were not borne out by later clinical data.

20. Conclusions

This section should briefly describe any changes to the previous knowledge or efficacy and safety resulting from information gained since the last DSUR. The conclusions should outline the actions that have been or will be taken to address emerging safety issues.

21. Appendices to the DSUR

The DSUR should be accompanied by the following appendices, as appropriate, numbered as follows:

1. Status of Ongoing and Completed Trials;
2. Cumulative Summary Tabulations of Demographic Data;
3. Line Listings of Serious Adverse Reactions;
4. Cumulative Summary Tabulation of Serious Adverse Events;
5. Scientific Abstracts (if relevant).

Appendix A- Tables and Table headings for Clinical Trial Listings

Table 1 – Overview of Ongoing Studies [Study Drug]

Study ID	Phase	Country	Study Title	Study design	Dosing regimen	Study Population	FVFP†	Planned enrolment	Subject exposure‡

†FVFP = first patient first visit

‡ Based upon total numbers of patients recruited as of [date] and applied randomisation schemes.

Table 2 – Overview of Studies Completed During the DSUR period [Study drug]

Study ID	Phase	Country	Study Title	Study design	Dosing regimen	Study Population	Subject exposure per treatment arm (M/F)

Table 3 – Examples of Headings for Interval Line Listings of Serious Adverse Reactions

Study ID EudraCT number	Case ID/Subject number†	Country Gender Age	Serious Adverse Drug Reactions (SARs)	Outcome	Date of onsent Time to onset‡	Suspect drug	Daily dose Route Formulation	Dates of treatment Treatment duration	Comments

† Study/Centre/patient

‡ 'Primary' SAR only