



**University of Leicester Research Governance Office
Standard Operating Procedures**

SOP S-1014 UoL

**Development Safety Update Report for Clinical Trials of
Investigational Medicinal Product for Studies Sponsored by
University of Leicester**

Version 5.0 January 2024

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Effective Date: January 2024

This SOP will be implemented in line with this document's effective date for all UoL Sponsored research still in set up. For active clinical research that is already in the recruitment phase (or further) at the time of implementation, this SOP must be implemented within 3 months of the effective date.

Please note the appendices associated with this SOP may be subject to interim changes. Please ensure that appendices are downloaded from the RGO webpages prior to use to ensure the latest version of the document is being used.

1.0 Introduction

The sponsor must provide the competent authority (CA) and Research Ethics Committee (REC) with an annual review on the safety of subjects in all clinical trials of a product for which the Sponsor is responsible, whether in the UK or elsewhere. All annual safety reports should be in the format of developmental safety update reports (DSURs).

This Standard Operating Procedure (SOP) describes the procedures for the preparation, reporting and submission of a DSUR. For UoL Sponsored Clinical Trials, the responsibility for writing and submitting the DSUR is delegated to the Chief Investigator (CI).

The main objective of a DSUR is to present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, by: (1) examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety; (2) describing new safety issues that could have an impact on the protection of clinical trial subjects; (3) summarising the current understanding and management of identified and potential risks; and (4) providing an update on the status of the clinical investigation/development programme and study results.

A DSUR should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug. All safety issues discovered during the reporting period should be discussed in the text of the DSUR; however, it should not be used to provide the initial notification of significant new safety information or be the mechanism through which new safety issues are detected.

2.0 Scope

This SOP applies to all researchers conducting Clinical Trials of Investigational Medicinal Products (CTIMPs) sponsored by University of Leicester (UoL).

3.0 Procedure

3.1 Timelines and Important Definitions

A DSUR must be submitted annually for the duration of the clinical trial, until the regulator has been notified of the end of the trial. This process must commence on the anniversary of the first international regulatory approval, regardless of the approval status in the UK. The annual time point is referred to as the Development International Birth Date (DIBD) in European Medicines Agency (EMA) guidance. However, where it has not been possible to link with the holder of the Developmental International Birth Date (DIBD), a single Data Lock Point (DLP) will be used.

For UoL Sponsored CTIMPs, the DLP is defined as the first anniversary of the Clinical Trials Application (CTA) authorisation date (i.e., the anniversary of MHRA/CA approval). Thus, the first DSUR will be produced on the first anniversary of MHRA/CA approval, taking into account the data generated in the preceding year.

Subsequent DSURs will then be produced annually thereafter on the anniversary of MHRA/CA approval taking into account the data generated in the preceding year. The reporting period is therefore the time between two anniversaries.

Reporting (i.e., submission to the regulators) must occur within 60 days of the defined DIBD/DLP.

4.0 General Considerations

For Type A studies approved under the notification scheme a short form DSUR can be submitted using the HRA CTIMP Annual Progress Report form which can be found on the [HRA Progress reports website](#).

For all other CTIMPs, the DSUR template (Appendix 1) must be used (unless stated otherwise in contractual agreements).

As a general rule, one DSUR must be provided for each IMP under investigation – therefore, if a CI is conducting more than one trial using the same IMP, only one DSUR should be submitted for the IMP rather than submitting individual reports for each trial including that IMP. Where separate DSURs are submitted, a clear justification for doing so should be included in the covering letter.

For trials involving multi-drug therapy (i.e., combinations of drugs that are not fixed), the CI can prepare either: (1) A DSUR for the multi-drug therapy, or (2) DSUR(s) for one or more of the individual components; in this case information on the multi-drug therapy trials can be included in the DSURs of one or all of the components. The MHRA must be contacted for advice on the most appropriate format prior to the submission of the first DSUR.

No section of the DSUR should be left blank, nor should they be deleted. If a section is not applicable to the clinical trial (e.g., manufacturing issues, non-clinical data, and marketing status), or the information is not currently available this should be stated and explained where applicable (i.e., ‘not applicable and therefore will not be completed’ or ‘information unavailable to author’).

In the case of blinded trials and if individual SUSARs have been unblinded for the purposes of expedited reporting, these cases should be included in the DSUR in the unblinded format. Therefore, the line listings in the DSUR may contain both blinded and unblinded data. However, please note that you are not required to unblind data specifically for the purpose of the DSUR. A robust process must be put in place to protect the integrity of the blind. For example, blinded personnel may only review an initial draft of the DSUR, prior to the addition of any unblinded information. The final review of the DSUR, with unblinded information included, must only be made by unblinded personnel. Extra care should also be given to the storage of the final DSUR within the TMF; an alternative location may be more appropriate.

The [MHRA website](#) can be accessed for further details on the purpose, content and submission of DSURs.

Where DSURs need to be submitted to a CA outside the UK, the CI or their delegate is responsible for understanding and following the different submission requirements.

5.0 Expectedness Assessments and Reference Safety Information (RSI)

The Investigator Brochure (IB)/Summary of Product Characteristics (SmPC) contains the Reference Safety Information (RSI). It is important that the correct RSI is used to determine whether information received during the reporting period remains consistent with previous knowledge of the safety profile of the IMP. For expectedness assessments within the DSUR, you must use the RSI that was in place at the beginning of the reporting period. Note that this may not be the same RSI that is/was approved for expectedness assessments at the date of onset of a safety event(s) (please refer to SOP S-1009 Processing and reporting of serious adverse events, serious adverse reactions and suspected unexpected serious adverse reactions for all research sponsored by University of Leicester). Therefore, you may need to re-assess the expectedness of an event(s) for the purpose of the DSUR report if there has been a change to the approved RSI during the reporting period. Please note that you are not required to update individual SAE reports, the expectedness change relates to the DSUR only.

- A copy of the IB/SmPC in place at the beginning of the reporting period should be appended to the DSUR as evidence of the RSI that has been used for the report; the version and date should be listed within the DSUR.
- If the IB/SmPC has been revised during the reporting period, the current version should be appended to the DSUR and any significant safety-related changes should be listed in the relevant section of the DSUR; the version and date should be listed within the DSUR.

The Sponsor recommends a review of the current IB/SmPC and RSI is undertaken at the same time as the DSUR submission. Where possible and where there is no safety risk to participants, updating the approved RSI should be aligned with the start of a new reporting period to avoid having multiple versions of the documents in place across a single reporting period and/or being used for single case reports. To aid with decision making about updating the approved RSI, please review Appendix 2 to SOP S-1023 - Investigator's Brochure (IB)/Summary of Product Characteristics (SmPC) Preparation, Review, Approval and Amendment. Please liaise with the Sponsor if you think a change to the RSI is required.

6.0 DSUR Completion and Submission

1. The Research Governance Office (RGO) will notify the Chief Investigator (CI) and Trial Manager/their delegate (as applicable) by email that the DSUR is due. Timelines for (1) the DLP, (2) submission to the RGO for Sponsor review, and (3) submission to the regulators will be clearly stated.
2. Draft reports must be sent by the CI (or their delegate) to the RGO for Sponsor review.
3. Confirmation of Sponsor review and approval of the DSUR for submission to the regulators will be sent by email to the appropriate parties. A copy must be retained in the Trial Master File (TMF).
4. The CI (or their delegate) must then submit the DSUR. Evidence of submission should be retained in the TMF and a copy sent to rgosponsor@le.ac.uk

a. For CTIMPs not submitted via combined review:

Upload the DSUR(s) to the MHRA via the [MHRA submission online portal](#). Please contact the RGO for MHRA submission account registration. Guidelines for the submission portal can be accessed via the [MHRA website](#).

The REC should be notified by using the [CTIMPs Safety Report form](#), which is a standard cover sheet. A single CTIMP Safety Report form may be used for the submission of multiple safety reports for the same trial. The CTIMP Safety Report form should not normally cover more than one trial, though this may be permitted by the REC where two trials are very closely connected, for example a main study and an extension study with the same treatment regime.

Acknowledgment of receipt of all safety reports, including a signed copy of the covering letter, should be received within 30 days. Reports sent without the CTIMP safety report form cover sheet will not be acknowledged.

b. For CTIMPs submitted via combined review:

Upload the DSUR(s) via the reporting section in Combined Review IRAS. This should also include a cover letter. You do not need to submit the DSUR(s) through the MHRA's Medicines Portal nor do you need to report them separately to the REC.


Further guidance on the submission of DSURs for CTIMPs submitted via combined review can be found on the [HRA website](#).

5. A copy of all completed documentation, and where applicable/available, evidence of submission/acknowledgement, and relevant correspondence must be retained in the (TMF).
- 6.

7.0 Responsibilities

Responsibility	Undertaken by	Activity
Sponsor	Chief Investigator (CI)/their delegate	Ensures that each DSUR meets the appropriate regulatory requirements and is submitted within the required timeline to the MHRA and REC/HRA
Sponsor	Chief Investigator (CI)/their delegate	Maintaining the integrity of the blind Ensuring that unblinded data is not exposed to blinded personnel
Sponsor	Head of Research Governance/their delegate	Ensures that the Sponsor has reviewed and approved all DSURs before finalisation and submission
Sponsor	Head of Research Governance/their delegate Chief Investigator (CI)/their delegate	Ensures that all documentation is filed appropriately
Sponsor	Chief Investigator (CI)/their delegate	Complete the DSUR

8.0 Development and approval Record for this document

Author	Job title	Reviewed by	Approved by	Date approved
Cat Taylor	Head of Research Governance	UoL Research Management and Operations Group (RSMOG)	Professor Nigel Brunskill 	19/01/2024

9.0 Review Record

Date	Issue Number	Reviewed By	Description Of Changes (If any)
Oct 2013	2	Wendy Gamble	Version 1 amended following review of Sponsor processes.
Jun 2015	3	Wendy Gamble	Version 2 amended to bring in line with UHL text.

Date	Issue Number	Reviewed By	Description Of Changes (If any)
Nov 2016	4	Diane Delahooke	Reference to HRA and RSI added. Logo changed.
Sept 2021	4.1	Cat Taylor	Administrative changes
January 2024	5.0	Cat Taylor	Administrative changes Significant edits to wording including the addition of instructions around Combined Review trials, clarification around the RSI to be used, updates to the table of responsibilities and the delegation for the submission of reports to the CI/their delegate Removal of distribution record table and several sections have been combined to improve accessibility and understanding Appendix 1 – Guidance and example tables added alongside administrative changes Removal of Appendix 2 – DSUR reporting timeframe illustration. Removal of Appendix 3 - DSUR reporting timeframe working instructions.