1. Introduction

This Standard Operating Procedure (SOP) describes the procedures for the preparation and timely reporting of the Development Safety Update Report (DSUR) or Short Format Development Safety Update Report (Type A studies only) in order to discharge Sponsor responsibility appropriately in line with regulatory requirements.

The DSUR is an annual review and evaluation of safety information to assure regulators that a Sponsor is adequately monitoring and evaluating the safety profile of an Investigational Medicinal Product (IMP).

The DSUR should be a vehicle to provide safety information from all ongoing clinical trials that are being conducted or completed during the review period.

The DSUR guidance describes in detail the requirements for reporting to both the Competent Authority (CA) and the Central Ethics Committees (CEC) in each member state.

All UHL Sponsor reviews for studies using IMPs include a requirement to detail the responsibility for completion of the DSUR as part of the review and contract.

2. Scope

This SOP applies to all staff, and any external individual who approach the UHL to request that the organisation act as Sponsor for research activity.

3. Procedure

3.1 Development Safety Update Report (DSUR)

The purpose of a DSUR (Appendix 1) is to present a single, comprehensive, scientific annual review and evaluation of pertinent safety information collected during the reporting period relating to a drug under investigation, whether or not it is marketed. The guidance suggests that the document should include:

- Safety information obtained during the current review period
- Analysis of the new information provided based on previous knowledge of the product safety
- New safety issues that may impact the overall programme or specific clinical trial
- Current understanding and management of known and potential safety risks to patients
- Changes in the product's safety profile
- Providing an update on the status of the clinical investigation/development programme and study results

One DSUR is produced for each Investigational Medicinal Product

3.2 Short Format Development Safety Update Report

The purpose of a Short Format DSUR is to provide annual safety information on Type A studies only. Type A studies are those studies submitted under the notification scheme for certain lower risk trials. In these cases the risk to the patient from the IMP is considered to be no greater than that of standard care. This is not suitable for trials which are part of a multi-study development programme and a full DSUR will still be required for these studies.

The document should include:

- Safety information obtained during the current review period
- One DSUR is produced for each Investigational Medicinal Product.
- A copy of the completed DSUR must be retained in the Trial Master File (TMF).
- The appropriate Summary of Product Characteristics (SmPC) in effect at the start of the reporting period must be used as the Reference Safety Information for the DSUR

3.2.1 Development Safety Update Report – Reporting Period for UHL

Every attempt should be made to delegate responsibility for inclusion of all safety information from UHL trials to manufacturer/supplier of the IMP.

Where this is not possible, a DSUR must be completed by the Chief Investigator (CI) for each IMP. Clearly, there will be a great deal of information unavailable to the CI or to UHL when acting as Sponsor. Where information is not available, it must be clearly noted 'information unavailable to author'.

Where it has not been possible to link with the holder of the International Birth Date, for the sake of clarity, the Data Lock Point (DLP) will be taken as the anniversary of the Clinical Trials Authorisation.

One DSUR must be completed for each IMP. Where this involves several CIs, collaboration will be encouraged.

A copy of the completed DSUR must be retained in the TMF.

The appropriate Investigator Brochure (IB) or Summary of Product Characteristics (SmPC) in effect at the start of the reporting period must be used as the Reference Safety Information (RSI) for the DSUR. The version and/or date of this document must be stated in section 7.1 of the DSUR. However, if it has been necessary to update the RSI and the IB or SmPC have been revised during the reporting period and not previously submitted to the relevant Competent Authority, a copy of the revised RSI must be provided as an attachment to the DSUR in addition to submission of a Substantial Amendment to update the documents.

It is recommended that the IB/SmPC review is undertaken at the same time as the DSUR submission.

The appropriate SmPC in effect at the start of the reporting period must be used as the RSI for the DSUR.

Short Format Development Safety Update Report

The process for the submission of a short format DSUR differs from that of a full DSUR. The short format DSUR form is the Health Research Authority Annual Progress Report form which can be found here: https://www.hra.nhs.uk/documents/1013/annual-report-form-for-ctimps.docx

When submitting your annual report, please indicate in your cover letter that this is an Annual Progress Report (APR) in lieu of a full DSUR and include the EudraCT number and CTA reference number. You should include a list of all Serious Adverse Reactions in section 6 of the APR.

The DLP will be taken as the anniversary of the Clinical Trials Authorisation.

One short format DSUR must be completed for each IMP. A copy of the completed DSUR must be retained in the TMF. The appropriate SmPC in effect at the start of the reporting period must be used as the RSI for the DSUR.

3.3 Review and Approval of Development Safety Update Reports

The Sponsor and CI will review the DSUR prior to final submission to the MHRA & REC / HRA via the Common European Submission Portal (CESP). Once the DSUR has been completed it will undergo a quality control review.

In the case of blinded ongoing studies, 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.

The final DSUR must be signed by the C I and Sponsor prior to upload to the MHRA using MHRA portal
You must submit your Development Safety Update Report (DSUR) via IRAS (Integrated Research Application System) if the associated trial was approved via the Combined Review service, formerly CWoW.

Prior to submission to the REC / HRA the NRES CTIMP Safety Report to Research Ethics Committee form must also be completed by the CI / PI and returned to the Sponsor. The Sponsor will then submit this to the REC / HRA with the DSUR documentation.

3.3.1 Short Format Development Update Reports

The Sponsor and CI will review the short format DSUR prior to final submission to the MHRA & REC / HRA via the Common European Submission Portal (CESP). Once the short format DSUR has been completed it will undergo a quality control review.

In the case of blinded ongoing studies, blinded personnel may only review an initial draft of the Short format DSUR, prior to the addition of any unblinded information. The final review of the short format DSUR, with unblinded information included must only be made by unblinded personnel.

The final short format DSUR form must be signed by the C I prior to upload to the MHRA using MHRA Submissions by the Sponsor.

A DSUR must be completed for each IMP.

A copy of the completed short format DSUR must be retained in the TMF.

The appropriate SmPC in effect at the start of the reporting period must be used as the Reference Safety Information for the DSUR

3.4 Distribution and Filing

A signed paper copy of each DSUR/ Short format DSUR must be filed in the TMF. If the TMF is held by personnel involved in the conduct of a blinded study, the signed paper copy of each DSUR/ short format DSUR will be retained by the Sponsor's responsible person for pharmacovigilance until the end of the study when it will be inserted in the TMF.

Copies of the DSUR/ Short format DSUR will be stored electronically by the Sponsor.

3.5 Submission Timeframe Compliance

A DSUR reporting timeframe working illustration gives details of the timeframes for reporting a DSUR (Appendix 2), and a DSUR reporting timeframe working instruction has also been produced to further clarify the requirements (Appendix 3). In the event of the Investigator failing to submit the DSUR/ Short Format DSUR within the specified timeframes, the Non-Compliance SOP S-1016 UHL will be implemented at a minimum of a MAJOR finding.

4. Responsibilities

	Responsibility	Undertaken by	Activity
1	Sponsor	Head of Research Operations or their delegate	Ensures that each DSUR/ Short format DSUR meets the appropriate regulatory requirements and is submitted within the required timeline.
2	Sponsor & Chief Investigator	Head of Research Operations or their delegate & Chief Investigator	Ensures that each study remains blinded to blinded operational and study site personnel
3	Sponsor	Head of Research Operations or their delegate	Ensures that the Sponsor has reviewed and approved all blinded DSURs/ Short Format DSURs before finalisation and submission
4	Sponsor	Head of Research Operations or their delegate	Ensures that all documentation is filed appropriately
5	Sponsor	Head of Research Operations or their delegate	Submits the DSUR/ Short format DSUR to the MHRA & REC / HRA
6	Chief Investigator	Chief Investigator	Completes the DSUR/ Short Format DSUR
7	Chief Investigator	Chief Investigator	Reviews the completed DSUR/ Short Format DSUR with the Sponsor

	Responsibility	Undertaken by	Activity
8	Chief Investigator	Chief Investigator	Ensure the DSUR/ Short Format DSUR has been finalised within the required timeline

5. Legal Liability Statement

Guidelines or Procedures issued and approved by the Trust are considered to represent best practice. Staff may only exceptionally depart from any relevant Trust guidelines or Procedures and always only providing that such departure is confined to the specific needs of individual circumstances. In healthcare delivery such departure shall only be undertaken where, in the judgement of the responsible healthcare professional it is fully appropriate and justifiable – such a decision to be fully recorded in the patient's notes and in the research site file.

6. Monitoring and Audit Criteria

Key Performance Indicator	Method of Assessment	Frequency	Lead
All CTIMP research sponsored by UHL submits DSUR/ Short Format DSUR	Included in the monitoring / audit programme.	Random audits / monitoring conducted on 10% of research activity.	Head of Research Operations / Clinical Trials Monitor & Trainer

7. Supporting Documents and Key References

SOP S-1004 Appendix 1, 2 & 3

8. Key Words

Research, Innovation, Volunteers, Participants, CTIMPS, Trials, DSUR, Safety, Clinical Trials, Investigational Medicinal Product, CA, CEC, TMF, SmPC

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This table is used to track the development and approval and dissemination of the document and any changes made on revised / reviewed versions

DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT		
Author / Lead Officer:	Carolyn Maloney	**Job Title:** Head of Research Operations
Reviewed by:	R&I Governance Meeting	
Approved by:	Professor Nigel Brunskill DocuSigned by: Nigel Brunskill EB83FF9A871E447...	**Date Approved:** 07-10-2021

REVIEW RECORD

Date	Issue Number	Reviewed By	Description Of Changes (If Any)
Dec 2013	2	Carolyn Maloney	Version 1 amended following review of Sponsor processes.
March 2015	3	Carolyn Maloney	Amendments to Logo and name
June 2015	4	Carolyn Maloney	Removal of DSUR template & general review.
July 2016	5	CM, LW, JJ	Consistency Check, addition of HRA
Nov 2016	6	CM	Update to RSI
Feb 2017	7	Carolyn Maloney	Update Logo
Oct 2018	8	CCL, JJ, LW	Updated R&I logo General review, changed wording to reference CESP
Oct 2019	9	CM,JJ	Update to include Short Format DSUR reporting requirements
February 2021	10	JJ LW AM	General review and update to change CESP to MHRA submissions. Reformatted to new template.
August 2021	11	LW JJ	CWoW update

DISTRIBUTION RECORD:

Date	Name	Dept.	Received