Standard Operating Procedure for the Preparation and Submission of Development Safety Update Reports

SOP ID Number: JRO/SPON/S31/05	**Effective Date:** 27/10/22
Version Number & Date of Authorisation: V05, 27/09/22	**Review Date:** 27/10/25
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Revision Chronology:			
SOP ID Number:	**Effective Date:**	**Reason for Change:**	**Author:**
JRO/SPON/S31/01	19/07/11	New SOP	Farhat Gilani
JRO/SPON/S31/02	08/11/13	Deletion of Safety Committee Research Fellow from the review process and DSUR template. Update to DSUR workflow, inclusion of RSI process and for process to be used when trial has not opened to recruitment.	Farhat Gilani
JRO/SPON/S31/03	07/07/16	Administration, formatting and clarification changes only	Farhat Gilani
JRO/SPON/S31/04	17/07/19	Additional information regarding management of RSI in line with CTFG guidance, inclusion of recent MHRA acceptance of Short Format DSURs for some trial types, formatting and minor clarification.	Catherine Maidens
JRO/SPON/S31/05	27/10/22	Updated submission processes, formatting and clarifications.	Catherine Maidens

ACRONYMS:	
APR	Annual Progress Report
ASR	Annual Safety Report
CI	Chief Investigator
CESP	Common European Submission Platform
CTA	Clinical Trial Authorisation
CTFG	Clinical Trial Facilitation Group
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTIS	Clinical Trial Information System
CTR	Clinical Trial Regulation
DIBD	Development International Birth Date
DLP	Data Lock Point
DSUR	Development Safety Update Report
EEA	European Economic Area
EU	European Union
GCP	Good Clinical Practice
HRA	Health Research Authority
IB	Investigator's Brochure
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
JRO	Joint Research Office https://www.ucl.ac.uk/joint-research-office
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
PVG	Pharmacovigilance
REC	Research Ethics Committee
PT	Preferred Term
QA	Quality Assurance
RSI	Reference Safety Information
RM (ATMP)	Regulatory Manager for Advanced Therapy Medicinal Products
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SRA	Sponsor Regulatory Advisor
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse
TMF	Trial Master File
UCL	University College London

Standard Operating Procedure for the Preparation and Submission of Development Safety Update Reports

1. PURPOSE

This Standard Operating Procedure (SOP) has been written to describe the procedure for the production and submission of the Development Safety Update Report (DSUR) to the MHRA and REC in the UK, and to other Regulatory Authorities in the EEA. For other international trials, reference on DSUR production and submission will be detailed in contractual agreements and/or specific protocol documents.

2. JOINT RESEARCH OFFICE POLICY

All SOPs produced from the JRO must be used in conjunction with local NHS Trust and UCL policies and procedures.

The JRO acts as the representative of the sponsor and will be the official name used on all SOPs.

3. BACKGROUND

All SOPs are written in accordance with applicable GCP requirements as outlined in Directives 2001/20/EC and 2005/28/EC (in the UK, these Directives were transposed into UK law by SI 2004/1031, SI 2006/1928) and subsequent amendments. Where applicable incorporates elements of ICH GCP tripartite guidelines (E6).

In addition, as UCL sponsors trials with EU and Northern Ireland sites, the SOPs are written to comply with EU Clinical Trials Regulation No. 536/2014 (CTR). In the CTR the DSUR is now referred to as the ASR (Annual Safety Report).

For further guidance refer to:

ICH guideline E2F on development safety update reports published by the European Medicines Agency

European Commission's *Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')*

Clinical Trial Facilitation Group (CTFG) guidance - *Q&A Document: Reference Safety Information, Nov 2017*

Guideline on how to increase transparency when presenting safety information in the Development Safety Update Report (DSUR): region-specific requirements for Canada and the United Kingdom – published by the MHRA

Sponsors are required to submit a DSUR report to the Regulatory Authority and the Ethics Committee, once a year, throughout the life of a clinical trial. This DSUR should present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period for investigational drug(s) in the concerned trial(s) with an appraisal of its ongoing risk/benefit.

4. SCOPE OF THIS SOP

This SOP relates to the process to facilitate the production and submission of the DSUR for Clinical Trials Sponsored by UCL. It will outline the key responsibilities of all personnel involved and detail the interactions required to ensure the report is produced adequately and submitted to meet regulatory timelines. Where the JRO has been delegated responsibility for DSUR production in a non-UCL sponsored trial this SOP may be used.

5. RESPONSIBLE PERSONNEL

- Chief Investigator (CI) or trial team members with delegated duties regarding the production of the DSUR.
- JRO Pharmacovigilance (PVG) Manager or in their absence Sponsor Regulatory Advisor (SRA) or Regulatory Manager (Advanced Therapy Medicinal Products) (RM(ATMP))

6. PROCEDURE

6.1 Duration of DSUR Submission

The **Development International Birth Date (DIBD)** is used to determine the start of the annual period for the DSUR. This is the date of the sponsor's first clinical trial authorisation (CTA) 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 (DLP) of the DSUR should be the last day of the one-year reporting period. The DSUR should be submitted to all concerned regulatory agencies no later than **60 calendar days** after the DSUR data lock point.

If a trial has received a Clinical Trial Authorisation (CTA) approval and has not yet opened to recruitment at the DLP then a letter in lieu of a DSUR (associated template - Letter in lieu of DSUR template) detailing any safety updates that have occurred may be submitted to the Regulatory Authority and REC instead of a full DSUR (see section 6.5 for submission procedure).

DSURs should continue to be submitted until the End of Trial notification has been submitted for UK trials. For International trials this will be dependent on their applicable laws and regulations. When submission of an annual report is no longer required, the sponsor should state that the final DSUR serves as the last annual report of the Investigational Medicinal Product (IMP) (if this is known at the time of preparation of the report). The Sponsor should also indicate whether or not clinical trials using the same IMP which are sponsored by UCL are continuing elsewhere.

When the CTA for a trial is received the PVG Manager will add the trial details including the DIBD onto the 'DSUR/RSI/PVG Tasks Tracker' saved in the PVG section of the S-Drive.

Where the same IMP is used in multiple UCL sponsored JRO managed trials a single DSUR should be written, with DIBD as the date of the CTA for the first trial authorised.

6.2 DSURs for combinations therapies

In general, a single DSUR should be prepared for clinical trials involving a fixed combination product (i.e., a product consisting of at least two active ingredients in a fixed dose that is administered in a single dosage form). If the sponsor is also conducting clinical trials with individual

components of the fixed combination product, separate DSURs should be submitted for each component. Relevant findings from each DSUR should be summarised in Section 8.5 of the DSUR template (New Safety Data Related to Combination Therapies) of the other DSUR(s).

For clinical trials involving multi-drug therapy, (i.e., combinations of drugs that are not fixed) the Sponsor, in conjunction with the CI will decide to 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 following table provides examples of strategies for preparation of DSURs for multi-drug therapies:

Multi-drug therapy used in clinical trial(s)	DSUR
Investigational drug (A) + marketed drug(s) (X, Y, Z)	Either a single DSUR focusing on (A+X+Y+Z) or A single DSUR focusing on (A) including data on the multi-drug therapy
Two investigational drugs (A) + (B)	Either a single DSUR focusing on (A + B) or Two separate DSURs (A) and (B), each including data on the multi-drug therapy
Two (or more) marketed drugs as an investigational drug combination (X, Y, Z)	A single DSUR focusing on the multi-drug therapy

For UK trials however, where the sponsor is not the Marketing Authorisation Holder, the MHRA recognise that it may be more appropriate to submit trial specific DSURs.

The Sponsor will endeavor to inform the trial team of the DSUR format at trial initiation or at the DLP.

6.3 Responsibilities for the Preparation of a DSUR

All DSURs must meet the standard that adheres to the UK trials regulations SI 2004/1031 and the EU CTR for trials with sites in Northern Ireland or the EEA. The UCL JRO DSUR template (associated template) meets these requirements and should be used for all UCL sponsored trials (unless stated otherwise in contractual agreements).

The Sponsor is considered responsible for the preparation, content and submission of the report. However, the completion of some sections of the DSUR is delegated to the trial team and the Chief Investigator as described in the table below. The final collation, sign off and submission is performed by members of the JRO (unless stated otherwise in individual contractual agreements).

Timeline*	**Task**	**Responsibility**
15 days before DLP	Begin drafting the DSUR (associated template) with information available to Sponsor from the following sources: • Protocol • Amendments, Urgent Safety Measures • Updates to Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC)	PVG Manager

	• JRO SAE Collection Database For the line listings, the Serious Adverse Events (SAE) and Serious Adverse Reactions (SAR) event terms should be coded as Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA Web-Based Browser can be used for coding event terms (UCL MedDRA ID: 21486, https://tools.meddra.org/wbb/).	
DLP (Day 0)	PVG Manager sends draft DSUR to trial team and CI to review and complete additional information required (including literature searches, recruitment details and overall safety assessment).	CI, Trial Team
Day 45	Updated DSUR received from trial team. Finalise report. ***Blinded Trials:*** Where treatment has been unblinded by the Sponsor for the purposes of expedited 'Suspected Unexpected Serious Adverse Reaction' (SUSAR) reporting this unblinded information should be included in the final DSUR submitted to the MHRA and REC. A blinded version of the DSUR should be prepared for the trial team.	PVG Manager
On or before Day 60	Submit report to all applicable Regulatory Authorities and Ethics Committees (see section 6.5)	PVG Manager

**Timelines are not definitive except for the 60 calendar days submission deadline from the DSUR reporting period data lock point (DLP)*

6.4 Reference Safety Information (RSI)

The **Reference Safety Information (RSI)** is a list of medical events used for the assessment of the expectedness of 'suspected' SARs that occur in clinical trials. An expectedness assessment is required to be conducted by the sponsor on each 'suspected' SAR to determine expedited reporting of SUSARs, and for the identification of SUSARs in the cumulative summary tabulation of 'suspected' SARs in the DSUR.

The RSI is a specific section in the **Investigator's Brochure (IB)** or the list of expected adverse reactions contained in section 4.8 Undesirable Effects of the **Summary of Product Characteristics (SmPC),** and is submitted as part of the CTA application. For more details on RSI management refer to the SOP for Pharmacovigilance Oversight and Management by Sponsor (JRO/SPON/S14).

The RSI for any IMP involved in a clinical trial should **stay consistent during each DSUR reporting period**. For the purposes of the identification of SUSARs in the 'Cumulative summary tabulation of SARs' in the DSUR, the version of the RSI that was **approved at the beginning of the reporting year** by the MHRA should be used.

Note: An RSI can be considered to be approved 'at the beginning of the reporting year' if it was approved by the MHRA within 95 days of the end of the previous reporting period (this allows time for the updated RSI to be submitted to the MHRA as a substantial amendment at the same time as the DSUR (within 60 days of the DLP), and an additional 35 days for the amendment to be assessed by the MHRA).

'Suspected' SARs must be assessed against the RSI in place at time of occurrence of the adverse event, for the purposes of **expedited SUSAR reporting** to the MHRA and REC (for more details on SUSAR reporting refer to the SOP for Pharmacovigilance Oversight and Management by Sponsor (JRO/SPON/S14)).

Where an RSI has been updated during the trial, any impact on the DSUR line listings will need to be assessed. Any SUSARs listed in the DSUR should have an expectedness assessment based on the RSI version approved at the beginning of the reporting period. The RSI used to assess expectedness and any subsequent updates will be described in the DSUR and attached as appendices, this information will act as justification for any RSI update submission to the MHRA.

6.4.1 Process for IB and SmPC updates

If the IB is **prepared by UCL** it is highly recommended that it should be updated annually after the DSUR DLP, so it can be submitted to the MHRA (if needed) in line with, or soon after the DSUR submission.

When an IB is prepared by a **drug supplier**, the provisions for supplying updates at least annually will be stated in the relevant agreement with the supplier. If the supplier has submitted a substantial amendment to authorities in EU Member States in relation to the updated IB (for any trial for which it is sponsor), UCL should await the completion of the assessment of the substantial amendment before submitting the IB to the MHRA for approval for their trial.

For trials where a SmPC is used as the RSI, the updates are managed by the IMP Marketing Authorisation Holder (MAH). When the JRO are made aware of an SmPC update it will be reviewed:

- To see if the safety profile of the IMP has been altered and impacts on trial process and patient safety (new contraindicated drugs, dosing levels altered etc.).
- To see if the RSI has been changed (any new events added or removed from the list of adverse reactions in Section 4.8).

The below table describes how updates to the IB and SmPC are managed for trials sponsored by UCL:

IB/SmPC Update Details	DSUR Comments	Approval
A new version of the IB/SmPC is available at the same time as the DSUR for the new reporting period and there are **new events listed** as expected in the RSI section.	The current IB/SmPC will be used for the DSUR reporting period. The new IB with changes to the RSI section will be described in the DSUR. This will be the version used for the next DSUR reporting period (following MHRA approval).	A **substantial amendment** to update the RSI is sent to the MHRA, the new RSI is not implemented until approval has been obtained. (In the HRA amendment tool 'IB, SmPC – Substantial changes (e.g. affecting the risk/benefit assessment)' should be selected.)
A new version of the IB/SmPC is issued at the same time as the DSUR for the new reporting period and there are **no changes to the RSI** (this means no new events listed as	The current IB/SmPC will be used for the DSUR reporting period. The new IB/SmPC with no changes to the RSI section will be described in the DSUR. The current RSI will remain	If there have been no changes to the RSI and no other substantial changes then there is no need to obtain approval from the MHRA before sending the IB/SmPC to sites, but you must document the assessment that demonstrates the RSI has not changed in your TMF.

expected and no events removed).	the same for the next reporting period.	
A new version of the IB/SmPC is issued mid DSUR period and there are **new events listed** as expected in the RSI section.	The current IB/SmPC will be used for the current DSUR reporting period. The new IB/SmPC with changes to the RSI section will be described in the next DSUR. This will be the version used for the next DSUR reporting period (following MHRA approval).	Risk assess the changes and if minimal or not relevant to study population continue to use current RSI for reporting period. Document risk assessment in TMF. Submit a **substantial amendment** to MHRA mid DSUR period, but state in the cover letter it will not be implemented until start of next reporting period, or wait and submit to MHRA in line with next DSUR submission. If updates are important to patient safety, submit a substantial amendment immediately and implement upon MHRA approval.

6.5 Submission Procedures

6.5.1 DSUR Submission in the UK

The final signed DSUR will be submitted to both the MHRA and REC by the Sponsor.

All enclosures should be listed and referenced on the report. A cover letter (associated template) should be included listing all EudraCT/ IRAS numbers of trials covered by the DSUR.

If at least one of the trials covered by the DSUR has gone through the **Combined Review** process, then the report should be submitted using the **Integrated Research Application System (IRAS)**. Select the 'Reporting' button from within the project, then select 'DSUR', the status of the submission can be viewed in the 'Project History' section.

If none of the trials covered by the DSUR have gone through the Combined Review process, then the report must be submitted to the MHRA using the **MHRA Submissions** (select 'Development Safety Update Report' as the Regulatory Activity and 'Other' from the Regulatory Sub-activity dropdown). The acknowledgement of receipt will be sent as an email to the reporter confirming the submission. The report should also be emailed to the **REC**, accompanied by the CTIMP Safety Report Form (available from the HRA website).

If a DSUR is being submitted late to the regulatory agencies, the reason for the late submission should be included in the cover letter.

For trials where the DSUR submission responsibilities are delegated to another organisation, a final signed copy and proof of submission must be sent to the Sponsor.

A copy of the DSUR, and proof of submission to the MHRA and REC will be filed in the JRO Sponsor File and forwarded to the trial team to be filed in the TMF. If an unblinded DSUR is prepared by the sponsor, a separate final blinded copy will be forwarded to the trial team for filing in the TMF. The unblinded version will be filed in the JRO Sponsor file.

6.5.2 DSUR Submission to Regulatory Authorities in EEA countries

For a trial with sites within an EEA country the DSUR should be submitted to all the Regulatory Authorities where clinical trial approvals have been obtained up until the End of trial declaration.

For trials submitted via the **Common European Submission Portal (CESP)** the DSUR should be submitted to all concerned Regulatory Authorities via CESP. Separate submissions should be made to all applicable Ethics Committees as per local regulations.

For trials that have been submitted through (or transitioned to) the **Clinical Trial Information System (CTIS)**, the DSUR should be submitted via CTIS. The report will be accessible to all applicable Regulatory Authorities and Ethics Committees that have approved the trial.

6.6 Shortened Format DSUR

For clinical trials authorised under the MHRA's **Notification Scheme**, a short form DSUR may be submitted in lieu of a full DSUR. The shorter form is the Health Research Authority (HRA) Annual Progress Report (APR) form for CTIMPs available from the HRA website. The report should also include a cumulative list of SARs for the trial.

When submitting this report the cover letter (associated template) must state that it is an APR in lieu of a full DSUR and include the EudraCT/ IRAS/ CTA number.

7. REFERENCES

ICH guideline E2F: Note for guidance on development safety update reports
https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-26.pdf

European Commission - Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'): https://ec.europa.eu/health/documents/eudralex/vol-10_en

Clinical Trial Facilitation Group (CTFG) guidance - Q&A Document: Reference Safety Information, Nov 2017: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf

Guideline on how to increase transparency when presenting safety information in the Development Safety Update Report (DSUR): region-specific requirements for Canada and the United Kingdom:
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/993808/DSUR-Guideline-08June2021.pdf

8. TEMPLATES/LOGS ASSOCIATED TO THIS SOP

1	UCL JRO DSUR Template
2	UCL JRO DSUR Cover Letter Template
3	UCL JRO Letter in lieu of a DSUR Template
4	UCL JRO APR in lieu of DSUR Cover Letter Template

HRA Templates:

APR for CTMIPS: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/progress-reports/

CTIMPs Safety Report form: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

9. SOP DISSEMINATION AND TRAINING

SOPs will be distributed to the concerned staff, by the named author on the front page of the SOP. Staff concerned by the SOP will sign the SOP training log (12. SOP TRAINING LOG) which is part of each SOP.

In some instances, the SOP or the changes to the SOP will be basic. The training will constitute of the person reading the SOP and being provided with the opportunity to ask specific questions to the author of the SOP.

10. SIGNATURE PAGE

Author and Job Title:	Catherine Maidens, Pharmacovigilance Manager
Signature:	DocuSigned by: Catherine Maidens 6A859A9CF4EB497...
Date:	27/09/22
Authorised by: Name and Job Title	Helen Cadiou, Head of Quality Assurance
Signature:	DocuSigned by: Helen Cadiou 9FE319AE9B744D5...
Date:	27/09/22

12. SOP TRAINING LOG

	Name of Staff (Capital letters)	**Job Title:** **Department:**	**Training Date**	*I confirm that I understand & agree to work to this SOP* **SIGNATURE**	**Name of Trainer** (if training required)	**Signature**	**Date**
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	Name of Staff (Capital letters)	**Job Title:** **Department:**	**Training Date**	*I confirm that I understand & agree to work to this SOP* **SIGNATURE**	**Name of Trainer** (if training required)	**Signature**	**Date**
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	Name of Staff (Capital letters)	**Job Title:** **Department:**	**Training Date**	*I confirm that I understand & agree to work to this SOP* **SIGNATURE**	**Name of Trainer** (if training required)	**Signature**	**Date**
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