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Development Safety Update Reporting for Clinical Trials of Investigational Medicinal Products

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Version	Date	Reason for Change
Version 1.0	31 Aug 2011	New SOP due to regulatory change
Version 2.0	03 Dec 2012	Annual Review
Version 3.0	18 Feb 2015	Scheduled Review
Version 4.0	25 Oct 2017	Scheduled Review
Version 5.0	10 Jan 2019	New version for minor updates
Version 6.0	19 Oct 2020	Scheduled Review Templates removed & administrative changes. RGIT name change to RGIT
Version 7.0	07 Jan 2021	DSUR submission through MHRA portal in place of CESP Amendments due to leaving the European Union from 1 st January 2021
Version 8.0	02 Nov 2021	Inclusion of submission via CWOW IRAS
Version 9.0	14 Jun 2024	Updated REC Reporting for CTIMPS not submitted via Combined Review. Minor Updates to the SOP.
Version 10.0	27 Feb 2025	Clarifications that Type A trials require DSUR instead of APR. Adding reference of SmPC within RSI section.
Version 11.0	27 Apr 2026	Updated following legislative changes.

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1. PURPOSE

This SOP describes the process for completing and submitting Development Safety Update Reports (DSURs) to the MHRA in relation to clinical trials of Investigational Medicinal Products (CTIMPs).

2. INTRODUCTION

The DSUR is intended to be a common standard for periodic safety reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions. Under regulation 35 of the Clinical Trials Regulations, for each IMP tested in a clinical trial in the UK, the sponsor must provide the licensing authority with an annual report on the safety of the participants receiving the product. This requirement includes IMPs tested in clinical trials approved via automatic authorisation (notifiable trials) or where the DSUR includes a combination of both notified and non-notified trials.

The main objective of a DSUR is to present a comprehensive, thoughtful 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 provide how new safety issues are detected.

3. PROCEDURE

3.1. Timeline

The DSUR must be compiled annually for the duration of the trial until the regulator has been notified of the end of the trial. This process must commence on the anniversary of:

- **The international birth date:** For products with a marketing authorisation, the anniversary of the date on which the marketing authorisation was issued.
- **The development international birth date (DIBD):** For IMPs without a marketing authorisation, the anniversary of the earliest date on which a clinical trial using the same IMP and that has the same sponsor was authorised in any country.

The data lock point of the DSUR should be the last day of the one-year reporting period. For administrative convenience, or if desired by the sponsor, the data lock point of the DSUR can be designated as the last day of the month prior to the month of the DIBD. Reporting must occur within 60 days of the defined DIBD. The only exception to the above is when the

trial has a duration of less than one year and concludes before the end of the reporting year and the regulator has been informed.

The RGIT Monitors will ensure all active CTIMP trial DSUR due dates are tracked. Teams will be reminded of the requirement to submit their annual safety report one month before the DIBD date. Study teams will then be followed up during the 60-day submission period to ensure reports are submitted on time (please see escalation procedure below).

3.2. DSUR Completion

For Imperial College Academic Health Science Centre (AHSC) sponsored clinical trials it is the responsibility of the Chief Investigator to complete the DSUR and submit to the MHRA and designated Research Governance and Integrity Team (RGIT) monitor.

The DSUR template has a standard format and requires all sections to be completed to be a valid report. 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. No section of the DSUR should be blank at the time of submission. A template DSUR report with question specific guidance is provided as **Appendix 1 – RGIT_TEMP_047** on the RGIT SOP Page ([SOPs and Associated Documents-Templates | Research | Imperial College London](#)).

The DSUR must be sent to the following:

- i. Emailed to the Sponsor for review – for Imperial College Academic Health Science Centre (AHSC) studies, this is the RGIT Team. Each DSUR must first be sent to the RGIT representative overseeing the DSUR prior to MHRA submission to ensure all key details have been captured.
- ii. For studies not submitted through Combined Review (formerly Combined Ways of Working (CWOW)): The DSUR should be uploaded via the [MHRA Portal](#) (*Cited on 29 Oct 2025*). Please contact the RGIT monitor for MHRA submission account registration.
- iii. For studies submitted through Combined Review, the DSUR should be submitted via the reporting section in IRAS (further guidance on this can be found at the following link: [Step by step guide to using IRAS for combined review - Health Research Authority](#)) (*Cited on 29 Oct 2025*). The submission **must** include a cover letter (please see the following link for what details should be included in the cover letter: [Clinical trials for medicines: collection, verification, & reporting of safety events - GOV.UK](#)) (*Cited on 29 Oct 2025*).

There is now a fee associated with the submission/review of DSURs by the MHRA ([User reference guide Paying online before submitting an annual safety report.pdf](#)) (*Cited on 29 Oct 2025*). Please see the following webpage for an accurate review of the cost ([Current MHRA fees - GOV.UK](#), *Cited 29 Oct 2025*). Following payment, a receipt will be sent by email to the payee which must be included in the submission in its original format as a standalone document that serves as proof of payment. Failure to provide this evidence of payment will result in the submission being invalidated.

The MHRA will issue confirmation once a DSUR has been successfully submitted via email. Study teams must send a copy of this to the RGIT Monitor along with filing this in the TMF/ISF as evidence of GCP compliance. If the submission is invalidated, the sponsor will be informed by email and will need to resubmit the DSUR with the deficiencies corrected.

Valid DSURs are reviewed and requests for additional information may be made by email (and through IRAS, if this route of submission was used), with a timeline for response set by the licensing authority. Once the licensing authority has sufficient information, the sponsor will be informed by email (and through IRAS, if this route of submission was used) that the DSUR has been accepted. Study teams must send a copy of this to the RGIT Monitor along with filing this in the TMF/ISF as evidence of GCP compliance.

3.3. DSURs for Combination 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).

For trials involving multi-drug therapy (i.e. combinations of drugs that are not fixed), the sponsor 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 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 (X + Y + Z)

3.4. Reference Safety Information

The Investigator's Brochure (IB) or Summary of Products Characteristics (SmPC) in effect at the start of the reporting period should serve as the reference safety information (RSI) to determine whether the information received during the reporting period remains consistent with previous knowledge of the safety profile of the investigational drug. The "RSI in effect at the start of the annual reporting period" should be the version of the RSI approved in the UK at a timepoint closest to the data lock point at the start of the DSUR reporting period

(Please see the following link for an example: [PowerPoint Presentation](#)) (Cited on 29 Oct 2025). Section 7.1 of the DSUR should clearly indicate the version and date of the IB/SmPC used for this purpose. The RSI used should be submitted with the DSUR, as well as the proposed new RSI, and any changes to the RSI should be detailed in the 'Changes to the Reference Safety Information' section of the DSUR. If the IB has been updated and there are no proposed changes to the RSI, the new IB should still be submitted with the DSUR.

When an IB is not required by national or regional laws or regulations, the applicable national or regional product label should serve as the reference safety information.

Usually, a single document should serve as the reference safety information. However, in certain circumstances, it might be appropriate to use more than one reference document to support the DSUR (e.g., for a DSUR providing information on an investigational drug used in combination and as monotherapy).

It is highly recommended to update the RSI section of the IB once a year in alignment with the annual reporting period for a DSUR as per regulation 3A of the Clinical Trials Regulations. It is expected that cumulative safety data are reviewed during the preparation of a DSUR and used to support the RSI update. If the RSI is located in an SmPC then periodic review for updates (at minimum annually), using a risk-based approach, is expected.

It is best practice to submit an updated version of the IB (as a substantial modification) and a new DSUR in parallel, or alternatively to submit the application of substantial modification for the authorisation of the updated RSI within one month after the submission of the new DSUR at the latest. Updates to the RSI are generally considered to be substantial modifications. If the change to the RSI involves an increase in frequencies with no new expected adverse reactions or if the change is an update to section 4.8 of the SmPC, the modification should be submitted as a Route B substantial modification. Other updates to the content of the RSI should be considered Route A substantial modifications (however, changes to the format of the RSI that do not involve a change in the content may be considered a minor modification). For further guidance on Route A and Route B substantial modifications, refer to the guidance on Modifying a clinical trial approval ([Clinical trials for medicines: modifying a clinical trial approval - GOV.UK](#)) (Cited on 29 Oct 2025).

If the RSI is within an IB which is not prepared and updated by the sponsor itself (e.g. for non-commercial sponsors using a company's IB), the (non-commercial) sponsor should have a written agreement in place with the company in which the updated authorised IB is sent to the (non-commercial) sponsor using the same IMP immediately. The (non-commercial) sponsor is also encouraged to put in place a process to check on at least an annual basis whether there are any updates to the IB. The (non-commercial) sponsor should submit the approved IB, together with any of the necessary modifications to the protocol as a substantial modification for their own clinical trial.

4. RESPONSIBILITIES AND ESCALATIONS AFTER APPROVAL

It is the responsibility of the CI to ensure once approvals are in place, the study is run in line with the appropriate regulations and as per sponsorship requirements. If the CI does not respond to requests from the regulatory authority, or the sponsor, within required timeframes

(for the sponsor, this would be after two chasing emails have been sent in regards to the creation/submission of the annual safety report for Clinical Trials of Investigational Medicinal Products post the date of the anniversary of Clinical Trial Authority Approval), then the following escalations shall occur for College sponsored studies.

1. Director of Department Operations is notified.
2. Head of Department is notified (if the CI in question is a HoD, then the Dean should be notified instead).
3. Faculty Operating Officer is notified.
4. If there is still no response and there is a reputational risk to the College, then the vice-provost for research will be notified.

5. REFERENCES

- [Clinical trials for medicines: collection, verification, & reporting of safety events - GOV.UK](#)
- [The Medicines for Human Use \(Clinical Trials\) \(Amendment\) Regulations 2025](#)
- [The Medicines for Human Use \(Clinical Trials\) Regulations 2004](#)
- [Clinical trials for medicines: manage your authorisation, report safety issues - GOV.UK \(www.gov.uk\)](#)
- [Current MHRA fees - GOV.UK](#)
- [ICH E6\(R3\) Step4 FinalGuideline 2025_0106.pdf](#)

6. APPENDICES

The following Appendices list the following Templates associated to this SOP which can be found on the [SOP, Associated Documents & Templates page](#) (Cited on 29 Oct 2025).

Appendix 1 – Development Safety Update Report Template – RGIT_TEMP_047