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 1st 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.

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1. PURPOSE

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

2. INTRODUCTION

The DSUR is intended to be a common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions. US and EU regulators consider that the DSUR, submitted annually, would meet national and regional requirements currently met by the US Investigational New Drug (IND) Annual Report and the EU Annual Safety Report, respectively, and will therefore take the place of existing safety reporting requirements reports.

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.

The MHRA will issue confirmation of DSUR submission via email. Study teams must send the confirmation of submission email to the RGIT Monitor and file within the TMF/ISF as evidence of GCP compliance. If you do not already have an MHRA submissions account, one can be requested from the Clinical Monitor who will request an account on your behalf.

3. PROCEDURE

3.1. Timeline

The DSUR must be compiled 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 EMA guidance. 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.

If a Chief Investigator is conducting more than one trial using the same investigational medicinal product (IMP), only one DSUR should be submitted for the IMP rather than submitting individual reports for each trial including that IMP. This should occur on the anniversary of the first regulatory approval anywhere in the world and this date is classed as single data lock point (DLP).

If there is a valid reason for submitting separate reports this should be clearly explained on the DSUR.

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, Ethics Committee 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.**

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.

ii. For studies not submitted through Combined Ways of Working (CWOW):

- **MHRA**: The DSUR should be uploaded via the MHRA submission online portal (*Cited on 25 Feb 2025*). Please contact the RGIT monitor for MHRA submission account registration.
- **REC**: Should be notified via email with a copy of the report (alongside any appendices) and a CTIMPs Safety Report form attached to the email (CTIMP_Safety_Report_Form_Accessible_Template_v5.2_October_2022_clean_002.odt (live.com) (*Cited on 25 Feb 2025*). 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.

iii. For studies submitted through Combined Ways of Working (CWOW) (now referred to as Combined Review) the DSUR should be submitted via the

reporting section in IRAS. The submission should include a cover letter and will be automatically forwarded on to the MHRA and REC.

Note: As of 2024, there is now a fee associated with the submission/review of the DSUR by the MHRA. Please see the following webpage for an accurate review of the cost. Evidence of payment will need to be provided alongside any DSUR submission or the submission will be rejected (Current MHRA fees - GOV.UK, *Cited 25 Feb 2025*).

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). If the sponsor is also conducting clinical trials with individual component(s) of the fixed combination product, separate DSUR(s) should be submitted for each component.

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 for safety information to determine whether the information received during the reporting period remains consistent with previous knowledge of the safety profile of the investigational drug. Section 7.1 of the DSUR should clearly indicate the version number and date of the IB/SmPC used for this purpose.

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).

If the IB/SmPC have been revised during the reporting period and not previously submitted to the relevant regulatory authority, the sponsor should provide a copy of the current version of the IB as an attachment to the DSUR.

4. REFERENCES

Note for Guidance on Development Safety Update Report (EMEA/CHMP/ICH/309348/2008) European Medicines Agency ICH Topic E2F (*Cited on 25 Feb 2025*)

Clinical trials for medicines: manage your authorisation, report safety issues - GOV.UK (www.gov.uk) (*Cited on 25 Feb 2025*)

Current MHRA fees - GOV.UK (*Cited on 25 Feb 2025*)

Safety reporting - Health Research Authority (hra.nhs.uk) (*Cited on 25 Feb 2025*)

5. 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 25 Feb 2025*).

Appendix 1 – Development Safety Update Report Template – RGIT_TEMP_047