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<b>Development Safety Update Reporting for IMP Clinical Trials</b>	
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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 and administrative changes to SOP. 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 <sup>st</sup> January 2021
Version 8.0	02 Nov 2021	Inclusion of submission via CWOW IRAS

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## 1. PURPOSE

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

## 2. INTRODUCTION

The Development Safety Update Report (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.

For studies approved under the notification scheme (Type A) Short form DSUR can now be used using the HRA CTIMP APR report form which can be found on the [HRA Progress reports](#) website.

The MHRA will issue confirmation of DSUR submission via email. Study teams must send the confirmation of submission email to the RGIT Monitor and to the TMF as evidence of GCP compliance. If you do not already have a 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. 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\_049**.

The DSUR must be sent to the following:

- i. Emailed to the Sponsor - for Imperial College Academic Health Science Centre (AHSC) studies, this is the Research Governance and Integrity Team;
- ii. Upload to the Medicines and Healthcare Products Regulatory Agency (MHRA) via [the MHRA submission online portal](#). Please contact the RGIT monitor for MHRA submission account registration and [submission guidelines](#).
- iii. Email the executive summary to the Research Ethics Committee (REC) which gave a favourable opinion of the research (the 'main REC');
- iv. For studies using the Combined Ways of Working (CWOW) system the DSUR can be submitted via the reporting section in IRAS. This should also include a cover letter. If preferred it is also possible to submit DSURS via the Human Medicines Portal. Please note DSURS should either be submitted for a project in IRAS **or** on the Human Medicines Portal, not both.

### Shortened DSUR available for Notification scheme approved trials

This is suitable for individual trials authorised under the Notification scheme which are not part of a multi-study development programme. Phase 4 national (UK only) trials of licensed products, that commanded a low fee from the MHRA, and where all participants have completed treatment and are only in follow-up will also be suitable for submission of a short format DSUR. As an alternative to producing a full DSUR for these trials you may use the Health Research Authority Annual Progress Report form which can be found here: <https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/> (Checked 14Dec2020)

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.

### 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)
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### 3.4. Reference Safety Information

The Investigator's Brochure (IB) 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 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 has 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](#)

## 5. APPENDICES

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

**Appendix 1 – Development Safety Update Report Template – RGIT\_TEMP\_047**