SOP-QA-21 V6

Title: DSURs

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Document History

Version	Description of update	Date Effective
5	Reformatted Title updated and removal of text associated with APRs – 1.1, 2, 3, 4 Sections 3.6 and 3.7 added Updated wording to follow latest guidance – 3.8, 3.13, 3.16 and 3.19	16-10-25
6	Updated process for preparation and submission 3.1 – 3.17	28-04-26

1. Scope

1.1 This SOP applies to all researchers involved in Clinical Trials of Investigational Medicinal Products (CTIMPs), and other interventional studies involving a Medicinal Product (MP), which are sponsored or co-sponsored by University of Aberdeen (UoA) and/or NHS Grampian (NHSG) and which have obtained Clinical Trials Authorisation (CTA). This SOP describes the procedure for preparing and submitting a Development Safety Update Report (DSUR).

2. Responsibilities

Chief Investigator (CI)	Completing and submitting DSURs (delegated by Sponsor).
Sponsor	Review DSURs prior to submission.

3. Procedure

Preparation and submission of a Development Safety Update Report (DSUR) to MHRA

3.1 ⚠ DSURs are required for all studies which require a CTA including notifiable trials. The Sponsor is responsible for submitting DSURs to the Medicines and Healthcare products Regulatory Agency (MHRA). This responsibility, along with the preparation of the DSUR, is delegated to the CI.

3.2 ⚠ DSURs shall be submitted annually. The first DSUR is due 12 months after the date of the CTA and shall be submitted within 60 days of this date.

3.3 ❗ If a study lasts less than one year, a DSUR shall be submitted with a Declaration of the End of Trial Notification Form.

3.4 ❗ In the event of a DSUR submission incorporating more than one research project (same IMP), the earliest CTA date will be used as the annual submission date. For research projects involving MP which have a **Development International Birth Date** (DIBD), this date may be used for the

DSUR submission. The DSUR shall be submitted regardless of whether or not recruitment has started. If recruitment has not started, an explanation shall be included in the DSUR.

3.5 MHRA fees include charges for these annual safety reports (DSURs). MHRA only accept online payment of this fee before submission of an annual safety report. Payment must be made via the dedicated DSUR page in the pay portal GOV.UK Pay. These payments must be made by card, Purchase Orders are not accepted. A receipt generated by the portal following payment will be sent by email to the payee. You must include this in the submission, along with the cover letter and DSUR, in its original format as a standalone document that serves as proof of payment.

3.6 The cover letter shall include:

- A list of all the IRAS IDs (for trials approved through the combined review process or EudraCT numbers (for trials not approved through the combined review process) of trials covered by the DSUR
- an email address for correspondence
- the payment reference number in the format: 'DSUR-[5 digit MHRA company number]-[IMP name]-[Payment date DD/MM/YYYY]' (for a trial-specific DSUR using multiple IMPs, only include one IMP in the payment reference)
- If applicable, a statement that the DSUR covers a period of less than one year, to align the international and development international birth date.

3.7 The DSUR should follow the headings in section 3 of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance on Development Safety Update Report (E2F), clearly indicating if a section is not applicable. ICH E2F can also be referenced for additional detail on the content outlined below.

Per regulations A32 and 35 of the Clinical Trials Regulations, the DSUR must include the following:

- Records of any serious adverse reactions (SARs) and serious adverse events (SAEs) which have occurred in clinical trials during that year, including suspected SUSARs, preferably provided as an aggregate summary tabulation. Where a trial includes a NIMP; Serious adverse events or serious adverse reactions with a suspected causal association with a NIMP should be included in the DSUR for the associated IMP.
- Evaluation of these SARs and SAEs, which should be from a global perspective, including any limitations to the evaluation, and evaluation of any changes in the overall risk-benefit.
- Records of any measures taken to investigate, minimise and prevent the risks presented by SARs and SAEs.
- A detailed description of the assessment and management of any serious or non-serious safety concerns, including (but not limited to) temporary halts, actions taken by another regulatory authority, urgent safety measures, serious breaches, Dear Investigator letters, and specific non-clinical or clinical events.

The above relates to not only trials conducted in the UK but also non-UK trials of the same IMP by the same Sponsor.

There are additional sections that are strongly recommended to be included in the DSUR (where relevant) and these include:

- Line listing of SARs from the reporting period or justification if not included.
- Description of the overall safety profile of the IMP and processes implemented to monitor the overall safety profile.
- A list of deaths and associated narrative evaluating the deaths.
- As a region specific appendix, a discussion of the safety review and safety signal review processes (or a justification of why signal evaluation is not appropriate or possible and has not been included).

Further details on the additional section can be found on the MHRA website.

3.10 In preparing the DSUR an annual check shall be made on the Summary of Product Characteristics (SmPC/SPC) and/or the Investigator Brochure (IB) to ensure that the safety profile does not require updating (see SOP-QA-14 – SmPC, IB and IMP Dossier). The date of SmPC/SPC check shall be recorded in the DSUR (section 7.1 of DSUR template (TMP-QA-15)). Any update to the IB should also be recorded in this section. The Reference Safety Information (RSI) used shall be that which was in place at the start of the reporting period.

3.11 The CI shall forward the draft DSUR to the Sponsor for review at least two weeks prior to the required submission date. The Sponsor shall review the draft DSUR and either confirm that the DSUR may be submitted or request changes and further review. For blinded studies, Sponsor may add unblinded information at this stage; ensuring that the CI remains blinded.

Clinical trials approved prior to implementation of the combined review process

3.13 The DSUR must be submitted through the MHRA submission portal, via the Human Medicines option. Select 'Development Safety Update Report' as the Regulatory Activity and 'Original Submission' from the Regulatory sub activity dropdown list.

Clinical trials approved through the combined review process

3.14 If the trial has gone through the combined review process, the DSUR must be submitted via the IRAS combined review platform.

All DSUR submissions

3.15 After Submission the DSUR will be validated. The person that submitted the DSUR will receive acknowledgement of their submission by email. If the submission is invalidated, the person that submitted the DSUR will be informed by email and will be required to resubmit the DSUR with the deficiencies corrected.

3.16 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 set timelines for response. If the DSUR is accepted by the MHRA the person that submitted the DSUR will be informed by email (and through IRAS, if this route of submission was used).

3.17 All correspondence between the MHRA and CI should be forwarded to Sponsor (researchgovernance@abdn.ac.uk)

3.18 The CI shall ensure that a copy of the DSUR and any communication with the MHRA, REC, Sponsor or R&D are filed within the Trial Master File (TMF) (see SOP-QA-7 – Trial Master File).

3.19 In the event of more than one sponsored or co-sponsored trial involving the same MP, the Research Governance Manager shall liaise with the CIs involved to ensure production of a single DSUR and submission via the appropriate pathway.

3.20 For research projects which involve combination/multi-drug therapies it is usual for a single DSUR to be prepared and submitted. However, any exceptions to this (see examples in Appendix 1) shall be discussed with the Research Governance Manager in advance of preparing the first DSUR.

4. Abbreviations and definitions

CESP	Common European Submission Platform
CI	Chief Investigator
CTA	Clinical Trial Authorisation (from MHRA)
CTIMP	Clinical Trial of an Investigational Medicinal Product
DIBD	Development International Birth Date
DSUR	Development Safety Update Report
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
HRA	Health Research Authority
IB	Investigator Brochure
MDCI	Medical Device Clinical Investigation
MHRA	Medicines and Healthcare products Regulatory Agency
MP	Medicinal Product
R&D	Research and Development (NHS)
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SmPC/SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

5. Related documentation and references

SOP-QA-7	Trial Master File
SOP-QA-14	SmPC, IB and IMP Dossier
SOP-QA-19	Modifications
TMP-QA-15	DSUR template

Frequently asked questions regarding the Development Safety Update Report (DSUR)

6. SOP-QA-21 Appendix 1

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).