# GD\_006 Guidance on content of Development Safety Update Reports

*For Development Safety Update Report**(DSUR) use TMPL\_028.*

A DSUR is IMP specific. If a Chief Investigator is carrying out more than one trial using the same IMP, one DSUR should be submitted for the IMP. This should occur on the first anniversary of the first regulatory approval in the world, and annually thereafter. For CTIMPS which have more than one IMP, the sponsor and the CI should agree the most appropriate approach to DSUR, and whether a single DSUR should be submitted for each IMP, or whether a combined DSUR should be submitted. Factors which will influence this decision are the dosing regime, form and the method(s) of administration.

The DSUR should have three parts:

**Part 1:** Analysis of the subjects’ safety in the concerned clinical trial(s) with an appraisal of its ongoing risk benefit.

**Part 2**: A line listing of all suspected SARs (including all SUSARs) occurred in the concerned trial, including all serious adverse reactions from third countries

**Part 3:** An aggregate summary tabulation of suspected SARs that occurred in the concerned trial

A full DSUR is not required for trials submitted under the MHRA’s Notification Scheme. Instead, the MHRA will accept a copy of the Annual Progress Report.

1. **Report on the subjects’ safety of a clinical trial** based on the information provided by investigators and the sponsor’s own assessments, the sponsor will report all new findings related to the safety of the IMP treatments in the concerned trial. Where UHBW is the sponsor, this will be delegated to the relevant research team to report. The concept of new findings refers to information not already present in the investigator’s brochure or, for licensed drugs, the summary of product characteristics. When relevant, the following points should be considered:
2. relation with dose, duration, time course of the treatment
3. reversibility
4. evidence of previously unidentified toxicity in the trial subjects
5. increased frequency of toxicity
6. overdose and its treatment
7. interactions or other associated risks factors
8. any specific safety issues related to special populations, such as the elderly, the children or any other at risk groups.
9. positive and negative experiences during pregnancy or lactation
10. abuse
11. risks which might be associated with the investigation or diagnostic procedures of the clinical trial

The report should also consider other experiences with the investigational medicinal product that are likely to affect the subjects' safety. It should detail the measures previously or currently proposed to minimise the risks found where appropriate. Finally, a rationale must be given on whether or not it is necessary to amend the protocol, to change or update the consent form, patient information leaflet and the Investigator’s Brochure. This report will not replace the request for protocol amendments, which will follow its own specific procedure.

1. **Line-listings**

The annual report should contain a trial-specific line-listing of all reports of suspected SARs that were reported during this trial. The line listing provides key information but not necessarily all the details usually collected on individual cases. It should include each subject only once regardless of how many adverse reaction terms are reported for the case. If there is more than one reaction, they should all be mentioned but the case should be listed under the most serious adverse reaction (sign, symptom or diagnosis) as judged by the sponsor. It is possible that the same subject may experience different adverse reactions on different occasions. Such experiences should be treated as separate reports. In such circumstances, the same subject might then be included in a line listing more than once and the line-listings should be cross-referenced when possible. Cases should be tabulated by body system (standard system organ classification scheme). The line listing identifiable by the sponsor listing reference number or date and time of printing should include the information per case as described in 2.1. Usually there should be one listing for each trial, but separate listings might be provided for active comparator or placebo or when appropriate and relevant for other reasons, e.g. in the case that in the same trial for different formulations, indications or routes of administration are studied.

* 1. **Content of line listing**

The line listing identifiable by the sponsor listing reference number or date and time of printing should include the following information per case:

1. clinical trial identification
2. Study subjects identification number in the trial
3. case reference number (Case-ID-Number) in the sponsor’s safety database for medicinal products
4. country in which case occurred
5. age and sex of trial subject
6. daily dose of investigational medicinal product, (and, when relevant, dosage form and route of administration)
7. date of onset of the adverse reaction. If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible.
8. dates of treatment (if not available, best estimate of treatment duration.)
9. adverse reaction: description of reaction as reported, and when necessary as interpreted by the sponsor, where medically appropriate, signs and symptoms can be grouped into diagnoses. MedDRA should be used.
10. patient’s outcome (e.g. resolved, fatal, improved, sequelae, unknown). This field should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions
11. comments, if relevant (e.g. causality assessment if the sponsor disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge/rechallenge results if available)
12. unblinding results in the case of unblinded SUSARs expectedness at the time of the occurrence of the suspected SARs, assessed with the reference document (i.e. Investigator’s Brochure) in force at the beginning of the period covered by the report.
13. **Aggregate summary tabulations**

In addition to individual cases line listings, summary tabulations of SAR terms for signs, symptoms and/or diagnoses across all patients should usually be presented to provide an overview for each trial. These tabulations ordinarily contain more terms than subjects. When the number of cases is very small, a narrative description would be more suitable.

The aggregate summary tabulation should specify the number of reports:

1. for each body system
2. for each ADR term
3. for each treatment arm, if applicable (IMP, comparator or placebo, blinded treatment)

The unexpected ADR terms should be clearly identified in the tabulation. As an example, the table shown in section 3.1 can be used.

* 1. **Example for an Aggregate Summary Tabulation**

Number of reports by terms (signs, symptoms and diagnoses) for the trial number ………

*(An \* indicates an example of a SUSAR)*

|  |  |  |  |
| --- | --- | --- | --- |
| **Body system /ADR term** | **Verum** | **Placebo** | **Blinded** |
| ***CNS***Hallucinations\*Confusion\*  | 21 | 21 | 00 |
| Sub-total | 3 | 3 | 0 |
| ***CV*** |  |  |  |
| Sub-total |  |  |  |