Development Safety Update Reporting for IMP Clinical Trials

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Author: Ana Arbeloa del Moral, Clinical Trials Monitor

Approved by: Ruth Nicholson

Date: 10 Jan 2019

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<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Reason for Change</th>
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<td>Version 1.0</td>
<td>31 Aug 2011</td>
<td>New SOP due to regulatory change</td>
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<td>Version 2.0</td>
<td>03 Dec 2012</td>
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<td>Version 3.0</td>
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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 the means by which new safety issues are detected.

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 Joint Research Compliance Office (JRCO) 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.

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 Joint Research Compliance Office;

ii. Uploaded to the Medicines and Healthcare Products Regulatory Agency (MHRA) via the CESP online portal (https://cespportal.hma.eu/Account/Login). Please contact the JRCO monitor for CESP 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’);

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) 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


5. APPENDICES

5.1 Appendix 1
Development Safety Update Report

<table>
<thead>
<tr>
<th>Developmental Safety Update Report</th>
<th>Report Number: [sequential number for report]</th>
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Trial Title:

<table>
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<tr>
<th>Reporting Period:</th>
<th>[time period covered by this report]</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Imperial College London/Imperial College London Healthcare NHS Trust* (Delete as appropriate)</td>
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<td>Chief Investigator</td>
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<table>
<thead>
<tr>
<th>Joint Research Compliance Office Address (Sponsor)</th>
<th>Room 221 Level 2, Medical School Building Norfolk Place London W2 1PG</th>
</tr>
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</table>

This report contains confidential/unblinded* information and should not be shared or distributed without the approval of the sponsor.

*delete as appropriate
Executive Summary

This section should provide a concise summary of the important information contained in the report. Together with the title page, it can serve as a “stand-alone” document suitable for submission to ethics committees and other stakeholders, if required by national or regional laws or regulations. The following information should be included in the Executive Summary:

- Introduction – report number and reporting period;
- Investigational drug(s) – mode(s) of action, therapeutic class(es), indication(s), dose(s), route(s) of administration, formulation(s);
- Estimated cumulative exposure of clinical trial subjects;
- Marketing approval(s)? (yes/no) – If yes, number of countries;
- Summary of overall safety assessment (based on section 18 of the DSUR);
- Summary of important risks (based on section 19 of the DSUR);
- Actions taken for safety reasons including significant changes to IB;
- Conclusions.

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20. Conclusions

Appendices to the DSUR

1. Introduction

This section should include:

- DIBD or IBD (as applicable);
- Reporting period and sequential number of the report;
- Investigational drug(s) – mode(s) of action, therapeutic class(es), dose(s), route(s) of administration, formulation(s);
- A brief description of the indication(s) and population(s) being studied;
- A short summary of the scope of the clinical trials covered by the report (e.g., all trials with the investigational drug, indication-specific trials, trials with combination products);
- A brief description and explanation of any information that has not been included in the DSUR (e.g., when written agreements with a partner company do not provide for exchange of all safety data);
- The rationale for submission of multiple DSURs for the investigational drug, if applicable

2. Worldwide Marketing Approval Status

This section should provide a brief narrative overview including: date of first approval, indication(s), approved dose(s), and where approved, if applicable.

3. Actions Taken in Reporting Period for Safety Reasons

This section should include a description of significant actions related to safety that have been taken during the reporting period by the sponsor, regulators, data monitoring committees (DMC) or ethics committees that had an impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme. The reason(s) for each action should be provided if known. Relevant updates to previous actions should also be summarised in this section (e.g., resumption of a clinical trial after suspension).

Changes to the Investigator’s Brochure should be discussed separately in the “Changes to Reference Safety Information”; see section 4.

Examples of significant actions taken for safety reasons include:
Actions related to investigational drugs:
• Refusal to authorise a clinical trial for ethical or safety reasons;
• Partial or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy (see section 15);
• Recall of investigational drug or comparator;
• Failure to obtain marketing approval for a tested indication including voluntary withdrawal of a marketing application;
• Risk management activities, including:
  o Protocol modifications due to safety or efficacy concerns (e.g., dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);
  o Restrictions in study population or indications;
  o Changes to the informed consent document relating to safety issues;
  o Formulation changes;
  o Addition by regulators of a special safety-related reporting requirement;
  o Issuance of a communication to investigators or healthcare professionals;
  o Plans for new studies to address safety issues;

Actions related to marketed drugs:
• Failure to obtain a marketing approval renewal;
• Withdrawal or suspension of a marketing approval;
• Risk management activities including:
  o Significant restrictions on distribution or introduction of other risk minimisation measures;
  o Significant safety-related changes in labelling documents that could affect the development programme, including restrictions on use or population treated;
  o Communications to health care professionals;
  o New post-marketing study requirement(s) imposed by regulators

This section should also summarise requests from regulatory authority(ies) that place a specific limitation on current or future development (e.g., a request to conduct long-term animal studies before initiating a long-term clinical trial, specification of a maximum dose to be evaluated, a request for specific safety data before initiating trials in paediatric subjects). A cumulative listing of such requests from regulatory authorities should be provided, including any updates if applicable. This can be provided as a table, in an appendix, or in this section.

4. Changes to Reference Safety Information

This section should list any significant safety-related changes to the IB or other reference safety information within the reporting period. Such changes might include information relating to exclusion criteria, contraindications, warnings, precautions, serious adverse drug reactions, adverse events of special interest, interactions, and any important findings from non-clinical studies (e.g., carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the DSUR.
5. Inventory of Clinical Trials Ongoing and Completed during the Reporting Period

This section should provide a brief overview of the clinical trials ongoing and completed by the sponsor in the reporting period, with detailed information presented in a table as an appendix (see examples in Appendix B, Table 1 of the guideline E2F on Development Safety Update Report at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf). Separate tables can be provided by indication, formulation, and study population, if appropriate. In addition, where required by national or regional laws or regulations, similar information should be provided for other therapeutic use of an investigational drug in the reporting period. The table(s) should include the following information for each clinical trial:

- **Study ID** (e.g., protocol number or other identifier);
- **Phase** (I, II, III, or IV);
- **Status**:
  - Ongoing (clinical trial has begun; has begun but is currently on hold; has concluded but clinical study report has not been finalised);
  - Completed (clinical study report is finalised);
- **Countries/regions where there is at least one investigational site for the protocol**;
- **Abbreviated study title**;
- **Design** (uncontrolled, controlled, open, single blind, double blind, parallel, crossover, etc., including treatment arms);
- **Dose and regimen of investigational drug and any comparators**;
- **Study population as appropriate** (age; sex; indication(s); specific patient groups, e.g., trial subjects with impaired renal function or trial subjects resistant to treatment);
- **Date of clinical trial start** (as defined by the sponsor, e.g., first visit of first patient (FVFP));
- **Planned enrolment for study as a whole**;
- **Estimates of cumulative numbers of exposed subjects for each treatment arm, where available. The actual enrolment numbers for open or completed trials, and/or an estimate based on the randomisation scheme for blinded trials, should be provided.**


6. Estimated Cumulative Exposure

Sections 6.1 and 6.2 of the DSUR should provide information on cumulative exposure in clinical trials and the marketed setting, respectively.

An estimation of cumulative subject exposure can help provide context for the cumulative summary tabulations of serious adverse events (SAEs), and the
overall assessment of safety. The accuracy of the estimation of clinical trial exposure might be limited because of a number of factors, including the rapidity of subject enrolment and the number of ongoing trials where treatment assignment remains blinded.

The optimal method of data presentation will depend on a number of factors, and the following general points should be considered in the preparation of the estimated exposure for the DSUR:

• Data should be presented in tabular format;
• When there are important differences among trials in dose, route of administration, or patient population, these differences can be noted in the tables, or separate tables can be considered;
• If the summary tabulations of SAEs are presented by indication, the exposure data should also be presented by indication, when available;
• When there are substantial differences in time of exposure between subjects randomised to the investigational drug and comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure data in subject-time (subject-days, -months, or -years);
• Investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, particularly when volunteers are exposed to only a single dose. Such data can be presented separately with explanation, when appropriate;
• For marketed drugs that are under clinical investigation, it might not be feasible or useful to obtain precise cumulative clinical trial exposure data, e.g., when the drug has been marketed for a number of years and/or has many indications. In these circumstances the sponsor should provide an explanation.

6.1. Cumulative subject exposure in the development programme
This section should include the following information; in tabular format (see Appendix B, Tables 2-4 of the ICH guideline E2F on Development Safety Update Report for examples; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf)

• The cumulative number of subjects from ongoing and completed clinical trials; the number exposed to the investigational drug, placebo, and/or active comparator(s) since the DIBD (Note: When treatment assignment is blinded, numbers of subjects can be estimated based on the randomisation scheme.);
• Cumulative number of subjects exposed to the investigational drug from ongoing and completed clinical trials, subgrouped by age range, sex, and racial group for the development programme when the data are available;
• Demographic characteristics for a single trial if the trial is of particular importance (e.g., a pivotal Phase III trial).

The specific categorisation of age might be dependent on the subject population and indication.

This section should also include an explanation of the sponsor’s rationale for selecting the method to estimate subject exposure, and the limitations of that method, based on the points above.

6.2. Patient exposure from marketing experience
If the investigational drug is marketed by the sponsor, the DSUR should include an estimate of the cumulative patient exposure in the marketed setting, based on the information provided in the most recent PSUR or other suitable data source, with an explanation of the method(s) used to determine the estimate.
7. Data in Line Listings and Summary Tabulations

Sections 7.1-7.3 of the DSUR should present important clinical safety information through:
• Interval line listings of the SARs that were reported to the sponsor during the period covered by the DSUR; and
• Cumulative summary tabulations of serious adverse events that have been reported to the sponsor since the DIBD.

Although causality assessment is generally useful for the evaluation of individual rare adverse drug reactions (ADRs) and for making decisions regarding expedited reporting, individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations in a DSUR should include all SAEs and not just SARs for the investigational drug and comparators.

The line listings and tabulations should include blinded and unblinded clinical trial data. Unblinded data might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g., expedited reporting), if applicable. Sponsors should not unblind data for the specific purpose of preparing the DSUR.

At the sponsor’s discretion, graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

If the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the Preferred Term level should be presented in the line listings and summary tabulations.

In general, the tabulation(s) of SAEs should include only those terms that were used in defining the case as serious; they should not include non-serious events.

Certain adverse events can be excluded from the line listings and summary tabulations, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as “exempt” from special collection and entry into the safety database, and those that are integral to efficacy endpoints, can be excluded (e.g., deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).

7.1. Reference information
This section of the DSUR should specify the version(s) of the coding dictionary used. If applicable, it should also specify the document and version used as Reference Safety Information for determining expectedness for the tabulations, where required by national or regional laws or regulations.

7.2. Line listings of serious adverse reactions during the reporting period
This section of the DSUR should summarise how case reports were selected for
inclusion in the line listings. This section should not serve to provide analyses or conclusions based on the SARs. The line listings should be provided in an appendix (see Appendix B, Table 5 of the ICH guideline E2F on Development Safety Update Report at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf)

The line listings should provide key information on all SARs (blinded and unblinded) reported from the sponsor’s clinical trials during the reporting period. The data should be organised by trial and then by System Organ Class (SOC).

Where possible the line listing(s) should include each subject only once regardless of how many SAR 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 could experience different SARs on different occasions (e.g., weeks apart during a clinical trial). Under such circumstances, the SARs can be listed separately, and a single subject can be included in a line listing more than once.

The following information should be included in the line listings:

a) Study identification number and EudraCT number as applicable;
b) Subject clinical trial identification number;
c) Sponsor’s adverse reaction case reference number;
d) Country in which case occurred;
e) Age and sex of trial subject;
f) Treatment group; identified as “blinded” if the blind has not been broken;
g) Dose and dosing interval of investigational drug (and, when relevant, dosage form and route of administration);
h) Date of onset and/or time to onset of the most serious adverse reaction;
i) Dates of treatment and/or best estimate of treatment duration;
j) Serious adverse reaction(s); when MedDRA is used, the Preferred Term should be presented;
k) 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.
l) 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). Appendix B, Table 5 of ICH the guideline E2F on Development Safety Update Report provides an example of the headings for a line listing. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf

7.3. Cumulative summary tabulations of serious adverse events

This section should refer to an appendix that provides a cumulative summary tabulation of SAEs reported in the sponsor’s clinical trials, from the DIBD to the data lock point of the current DSUR. The sponsor should explain any omission of data (e.g., clinical trial data might not be available for products marketed for many years or for products acquired through a business merger). The tabulation(s) should be organised by SOC, for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo, and treatment unknown due to
8. Significant Findings from Clinical Trials during the Reporting Period

The information in this section can be provided by indication, when appropriate, and should address the following topics, when applicable:

8.1. Completed clinical trials
This section of the DSUR should provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting period. This information can be presented in narrative format or as a synopsis. It could include information that supports or refutes previously identified safety issues, as well as evidence of new safety signals.

8.2. Ongoing clinical trials
If the sponsor is aware of clinically important information that has arisen from ongoing clinical trials (e.g., learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this section should briefly summarise the issue(s). It could include information that supports or refutes previously identified safety issues, as well as evidence of new safety signals.

8.3. Long-term follow-up
Where applicable, this section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products (e.g., gene therapy, cell therapy products and tissue engineered products). When the development programme is completed and long-term follow-up is the only ongoing activity generating data for the DSUR, this could be the only section where new information is presented.

8.4. Other therapeutic use of investigational drug
This section of the DSUR should include clinically important safety information from other programmes conducted by the sponsor that follow a specific protocol, with solicited reporting as per ICH E2D (e.g., expanded access programmes, compassionate use programmes, particular patient use, single patient INDs and treatment INDs).

8.5. New safety data related to combination therapies
If the DSUR is for an investigational drug that is also under development as a component of a fixed combination product or a multi-drug regimen, this section
should summarise important safety findings from the combination therapy DSUR. Conversely, if this DSUR is for a multi-drug therapy or fixed combination product, this section should summarise important safety information arising from trials on the individual components.

Alternatively, the information specific to the combination can be incorporated into a separate section(s) of the DSUR for one or all of the individual components of the combination.

Procedure, section 3.3, provides additional guidance on preparation of DSURs for combination products.

**9. Safety Findings from Non-interventional studies**

This section should summarise relevant safety information from non-interventional studies that became available to the sponsor during the reporting period (e.g., observational studies, epidemiological studies, registries and active surveillance programmes).

**10. Other Clinical Trial/Study Safety Information**

This section should summarise relevant safety information from any other clinical trial/study sources that became available to the sponsor during the reporting period (e.g., results from pooled analyses or meta-analyses of randomised clinical trials, safety information provided by co-development partners or from investigator-initiated trials).

**11. Safety Findings from Marketing Experience**

If the investigational drug has been approved for marketing in any country, this section should include a concise summary of key safety findings that have arisen from marketing experience and that became available to the sponsor during the reporting period, particularly if the findings resulted in changes to the product labelling. Investigator’s Brochure, informed consent document or amendments to the product’s risk management plan. This includes not only safety findings relating to approved use but also off-label use, administration to special populations (e.g., pregnant women), medication errors, overdose and abuse.

**12. Non-clinical Data**

This section should summarise major safety findings from non-clinical in vivo and in vitro studies (e.g., carcinogenicity, reproduction, or immunotoxicity studies)
ongoing or completed during the reporting period. Implications of these findings should be discussed in the Overall Safety Assessment (see section 18 of this template).

### 13. Literature

This section should summarise new and significant safety findings, either published in the scientific literature or available as unpublished manuscripts, relevant to the investigational drug that the sponsor became aware of during the reporting period. This section should include information from non-clinical and clinical studies and, if relevant and applicable, information on drugs of the same class. It should also summarise significant new safety information presented at a scientific meeting and published as an abstract; the sponsor should provide a copy of the abstract, if possible.

### 14. Other DSURs

A sponsor should prepare a single DSUR for a single investigational drug. However, if a sponsor prepares multiple DSURs for a single investigational drug (e.g., covering different indications, development programmes, or formulations), this section should summarise significant findings from the other DSURs if they are not presented elsewhere within this report.

When available, the sponsor should summarise significant findings from DSURs provided by other sponsors conducting clinical trials with the same investigational drug during the reporting period.

### 15. Lack of Efficacy

Data indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for investigational drugs intended to treat serious or life-threatening illnesses (e.g., excess cardiovascular adverse events in a trial of a new anti-platelet drug for acute coronary syndromes) could reflect a significant risk to clinical trial subjects and should be summarised in this section.

### 16. Region-Specific Information

The information in this section can be used to comply with national or regional requirements and can be provided in appendices to the DSUR. Sponsors should refer to national or regional requirements to determine which of the following sections should be included, as well as the scope of clinical trials that should be covered by these sections. Examples include:

- Cumulative summary tabulation of serious adverse reactions
This cumulative summary tabulation of all SARs should specify the number of SARs by: a) SOC, b) adverse reaction term and c) treatment arm, if applicable. Unexpected adverse reaction terms should be identified.

- List of subjects who died during the reporting period
  The list of subjects who died during participation in the clinical trials should include the following information at a minimum: case number, assigned treatment (could still be blinded), and cause of death of each subject. Any safety issues identified from a review of these deaths should be addressed in section 18 of the DSUR as appropriate.

- List of subjects who dropped out of clinical trials in association with an adverse event during the reporting period
  This list should include all subjects who dropped out of clinical trials in association with adverse events during the reporting period, whether or not thought to be drug-related. Any safety issues identified from a review of these withdrawals should be addressed in section 18 of the DSUR as appropriate.

- Significant Phase I protocol modifications
  This section should describe significant Phase I protocol modifications made during the reporting period, if not previously submitted as a protocol amendment, as described in the US Code of Federal Regulations.

- Significant manufacturing changes
  This section should include a summary of significant manufacturing or microbiological changes during the reporting period and discuss potential safety issues arising from these changes in Section 18 of the DSUR, if applicable.

- Description of the general investigation plan for the coming year
  This section should outline an investigational plan to replace that submitted for the previous year. US 14 IND holders should refer to the US Code of Federal Regulations.

- Log of outstanding business with respect to the US IND
  If desired by the sponsor, this section can provide a log of any outstanding business with respect to the US IND for which the sponsor requests or expects a reply, comment or meeting.

17. Late-Breaking Information

This section should summarise information on potentially important safety findings that arise after the data lock point but while the DSUR is in preparation. Examples include clinically significant new case reports, important follow-up data, clinically relevant toxicological findings and any action that the sponsor, a DMC, or a regulatory authority has taken for safety reasons. The Overall Safety Assessment (see section 18) should also take these new data into account.

18. Overall Safety Assessment
The overall safety assessment should be a concise, integrated evaluation of all new relevant clinical, non-clinical, and epidemiologic information obtained during the reporting period relative to previous knowledge of the investigational drug. This assessment should consider cumulative experience, new information collected in the period covered by the DSUR and, for investigational drugs with a marketing approval, clinically significant post-marketing data. It should not summarise or repeat information presented in previous sections of the DSUR, but should provide an interpretation of the information and its implications for the clinical trial population and the development programme. If appropriate, separate assessments can be provided by therapeutic area, route of administration, formulation and/or indication.

18.1. Evaluation of the risks
In evaluating the risks, particular emphasis should be placed on interpretation of data related to newly identified safety concerns or providing significant new information relative to previously identified safety concerns. Relevant points to consider include (where applicable):
• newly identified safety issues (detailed description of adverse events or reactions; associated laboratory values; risk factors; relationship to dose, duration, time course of the treatment; reversibility; factors that could be useful in predicting or preventing reactions);
• meaningful changes in previously identified adverse reactions (e.g., increased frequency or severity, outcome, specific at-risk populations);
• symptoms, signs, and laboratory evidence of newly and previously identified clinically significant toxicities, for example:
  o hepatotoxicity;
  o cardiovascular effects, including QT interval prolongation and results from thorough QT/QTc studies; o bone marrow toxicity;
  o pulmonary toxicity;
  o renal toxicity;
  o central nervous system toxicity;
  o immunogenicity and hypersensitivity;
• deaths that are an outcome of an adverse event;
• study drug discontinuations because of adverse events, including abnormal laboratory values or investigations;
• drug–drug and other interactions;
• important non-clinical safety findings;
• manufacturing issues that could affect risk;
• lack of efficacy where this would place trial participants at risk;
• any specific safety issues related to special populations, such as the elderly, children, patients with hepatic or renal impairment, or any other at-risk groups (e.g., slow or fast metabolisers);
• pregnancy and lactation exposure and outcomes;
• safety findings arising from experience with long-term treatment;
• evidence of clinically significant medication errors;
• evidence of lack of patient compliance;
• experience with overdose and its treatment;
• occurrences of drug misuse and abuse;
• any safety issues resulting from procedures required by the protocol (e.g., bronchoscopy, biopsy, central line insertion) or associated with the conduct or design of a particular study (e.g., inadequate subject monitoring schedule, excessive period without active treatment); and
18.2. Benefit-risk considerations

This section should provide a succinct statement on the perceived balance between risks that have been identified from cumulative safety data and anticipated efficacy/benefits and should note whether there have been any changes in this balance since the previous DSUR. This section is not intended to be a full benefit-risk assessment of the investigational drug.

19. Summary of Important Risks

This section should provide a concise, cumulative, issue-by-issue list of important identified and potential risks, e.g., those that might lead to warnings, precautions, or contraindications in labelling. Such risks might include, for example, toxicities known to be associated with a particular molecular structure or drug class, or concerns based on accumulating non-clinical or clinical data. Each risk should be re-evaluated annually and re-summarised as appropriate, based on the current state of knowledge. New information should be highlighted. The appropriate level of detail is likely to be dependent on the stage of drug development. For example, summaries covering drugs in early development might include information on individual cases, whereas in later development, as more knowledge and perspective are gained, the information on each risk might be less detailed. The information in this section could provide the basis for the safety specification of a risk management plan (ICH E2E).

Risks that have been fully addressed or resolved should remain in the summary and be briefly described, e.g., findings from toxicology studies or early clinical trials that were not borne out by later clinical data.

The information can be provided in either narrative or tabular format (see examples of both in Appendix C of the guideline E2F on Development Safety Update Report http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf)

20. Conclusions

The conclusion should briefly describe any changes to the previous knowledge of efficacy and safety resulting from information gained since the last DSUR. The conclusion should outline actions that have been or will be taken to address emerging safety issues in the clinical development programme.

Appendices to the DSUR

The DSUR should be accompanied by the following appendices, as appropriate, numbered as follows:

- potential impact of significant new safety issues identified with another drug in the same class
1. Investigator’s Brochure (if required by national or regional laws or requirements);
2. Cumulative Table of Important Regulatory Requests;
3. Status of Ongoing and Completed Clinical Trials;
4. Cumulative Summary Tabulations of Demographic Data;
5. Line Listings of Serious Adverse Reactions;
6. Cumulative Summary Tabulation of Serious Adverse Events;
7. Scientific abstracts (if relevant)

The DSUR should also be accompanied by the following Regional Appendices, as appropriate (see section 16):
  o Cumulative summary tabulation of serious adverse reactions; o List of subjects who died during the reporting period;
  o List of subjects who dropped out of studies during the reporting period;
  o Significant Phase I protocol modifications with respect to a US IND;
  o Significant manufacturing changes;
  o Description of the general investigation plan for the coming year with respect to a US IND;
  o Log of outstanding business with respect to a US IND