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### Development Safety Update Reporting for IMP Clinical Trials

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**Author:** Nabila Youssouf, Clinical Trials Manager  
**Approved by:** Gary Roper  
**Date:** 18/02/15

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Reason for Change</th>
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<tbody>
<tr>
<td>Final 1.0</td>
<td>31/08/11</td>
<td>New SOP due to regulatory change</td>
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<tr>
<td>Final 2.0</td>
<td>03/12/12</td>
<td>Annual Review</td>
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<tr>
<td>Final 3.0</td>
<td>18 Feb 2015</td>
<td>Scheduled Review</td>
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<td>Table of Contents</td>
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<td>-------------------------------------------------------</td>
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<tr>
<td>1 PURPOSE</td>
<td>Page 3</td>
<td></td>
</tr>
<tr>
<td>2. INTRODUCTION</td>
<td>Page 3</td>
<td></td>
</tr>
<tr>
<td>3. PROCEDURE</td>
<td>Page 3</td>
<td></td>
</tr>
<tr>
<td>3.1 Timeline</td>
<td>Page 3</td>
<td></td>
</tr>
<tr>
<td>3.2 DSUR Completion</td>
<td>Page 4</td>
<td></td>
</tr>
<tr>
<td>3.3 DSURs for Combination Therapies</td>
<td>Page 4</td>
<td></td>
</tr>
<tr>
<td>3.4 Reference Safety Information</td>
<td>Page 5</td>
<td></td>
</tr>
<tr>
<td>4. REFERENCES</td>
<td>Page 5</td>
<td></td>
</tr>
<tr>
<td>5. APPENDICES</td>
<td>Page 5</td>
<td></td>
</tr>
<tr>
<td>1. Development Safety Update Report Template</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 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 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 Joint Research Compliance Office (JRCO).

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.

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.

<table>
<thead>
<tr>
<th>Multi-drug therapy used in clinical trial(s)</th>
<th>DSUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational drug (A) + marketed drug(s) (X, Y, Z)</td>
<td>Either a single DSUR focusing on (A+X+Y+Z) or A single DSUR focusing on (A) including data on the multi-drug therapy</td>
</tr>
<tr>
<td>Two investigational drugs (A) + (B)</td>
<td>Either a single DSUR focusing on (A + B) or Two separate DSURs (A) and (B), each including data on the multi-drug therapy</td>
</tr>
<tr>
<td>Two (or more) marketed drugs as an investigational drug combination (X, Y, Z)</td>
<td>A single DSUR focusing on the multi-drug therapy (X + Y + Z)</td>
</tr>
</tbody>
</table>
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 – Please see next page.

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

**Trial Title:**

**Reporting Period:** [time period covered by this report]

<table>
<thead>
<tr>
<th>Name of IMP</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td></td>
<td>Imperial College London/Imperial College London Healthcare NHS Trust* (Delete as appropriate)</td>
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<table>
<thead>
<tr>
<th>Chief Investigator</th>
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<table>
<thead>
<tr>
<th>Address</th>
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<table>
<thead>
<tr>
<th>Joint Research Office Address (Sponsor)</th>
<th>510 Lab Block</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Imperial College London</td>
</tr>
<tr>
<td></td>
<td>Charing Cross Hospital</td>
</tr>
<tr>
<td></td>
<td>Fulham Palace Road</td>
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<tr>
<td></td>
<td>London</td>
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<td>W6 8RF</td>
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</table>

Date

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

*delete as appropriate
**Executive Summary**

Concise summary of the important information contained in the report. Together with the title page, it should serve as a “stand-alone” document suitable for submission to ethics committees.

Information on the following should be included in the Executive Summary:

- Introduction – report version and reporting period;
- Investigational drug – mode of action, class, indications, dose, route of administration;
- Estimated cumulative clinical trial exposure;
- Marketing authorisation(s) (yes/no) – If yes, number of countries;
- Summary of overall safety assessment;
- Summary of important risks (based on section 15 of the DSUR);
- Actions taken for safety reasons including significant changes to IB;
- Conclusion.

All sections must be completed. When no information is available, this should be stated.
TABLE OF CONTENTS

Title page

Executive Summary

Table of Contents:

1. Introduction
2. Worldwide Marketing Authorisation Status
3. Update on Actions Taken in the Reporting Period for Safety Reasons
4. Changes to Reference Safety Information
5. Status of Clinical Trials Ongoing and Completed During the Reporting Period
6. Estimated Exposure
   6.1 Cumulative subject exposure in clinical trials (Phase I-IV)
   6.2 Patient exposure from marketed setting
7. Presentation of Safety Data from Clinical Trials
   7.1 General considerations
   7.2 Interval line listings of Serious Adverse Reactions (SARs)
   7.3 Cumulative summary tabulations
   7.4 Deaths in the reporting period
7.5 Subjects who dropped out in association with any adverse event in the reporting period
8. Significant Findings from Clinical Trials during the reporting period
   8.1 Completed trials and any interim analyses
   8.2 Ongoing clinical trials
   8.3 Other therapeutic use of investigational drug
   8.4 New safety data related to combination therapies
9. Relevant Findings from Non-Interventional Studies
10 Relevant Findings from Other Studies
11. Safety findings from marketing experience
12. Other Information
12.1 Non-clinical data
12.2 Long-term follow-up
12.3 Literature
12.4. Other DSURs
12.5 Significant manufacturing changes
12.6 Lack of efficacy
12.7 Phase I protocol modifications
13. Late-Breaking Information
14. Overall Safety Assessment
14.1. Evaluation of the risks
14.2 Benefit-risk considerations
14.3 Conclusions
15. Summary of important risks

Appendices to the DSUR
1. Introduction

This section should include:

- Reporting period and sequential number of the report;
- Brief description of the drug, e.g., therapeutic class, mode of action, route of administration, formulation;
- Whether the report covers a development programme or a single clinical trial.

This section should also note the scope of the trials covered by the report (e.g., all trials with the investigational drug, or indication-specific trials);
- A brief description of the indications and populations being studied;
- A brief description and explanation of any information that has been excluded (e.g., when written agreements with a partner company do not provide for exchange of all safety data).

2. Worldwide Marketing Approval Status

If information is unavailable please state.

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 by the sponsor, regulators, Data and Safety Monitoring Boards or independent ethics committees that could have an impact on the conduct of a specific trial or the whole clinical development programme. Any relevant updates to previous actions should also be summarised in this section. Changes to the Investigator's Brochure should be discussed separately in the “Changes to Reference Safety Information”.

Examples of significant actions relating to safety issues include:

- Refusal of authorisation of a clinical trial for ethical or safety reasons;
- Partial or complete clinical trial suspension or early termination of a clinical trial due to lack of efficacy or safety issues;
- Resumption of a clinical trial after suspension;
- Failure to obtain marketing approval for a tested indication;
- Risk management activities, including:
  - Protocol modifications due to safety or efficacy concerns (e.g., dosage changes, changes in study inclusion criteria, intensification of monitoring);
  - Restrictions in study population or indications;
- Changes to the informed consent document relating to safety issues;
- Formulation changes for safety reasons;
- Addition of a special reporting requirement;
- Issuance of a communication to investigators or healthcare professionals;
- Plans for new safety trials.
- Important specific advice for safety reasons from a regulatory authority that involves a constraint on development (e.g., requirement to conduct long-term animal studies before initiating a long-term clinical trial; need for thorough QT/QTc study prior to Phase III clinical trials).

In addition a cumulative listing of advice from regulatory authorities should be provided as a table in an appendix.

In addition to the above, for drugs with a marketing approval, examples of significant actions due to safety reasons include:
- Failure to obtain a marketing approval renewal;
- Marketing approval withdrawal or suspension for safety reasons;
- Risk management activities including:
  - Significant restrictions on distribution or introduction of risk minimisation
  - measures;
  - Significant changes in labelling documents that could affect the development
  - programme, e.g., restrictions to indication or population or a new warning;
  - Communications to health care professionals as a result of the above actions;
  - New post-marketing study requirement(s) imposed by regional authorities.

### 4. Changes to Reference Safety Information

Any significant safety-related changes to the IB within the reporting period. This includes information relating to contraindications, warnings, precautions, serious adverse drug reactions, and adverse reactions 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. Status of clinical trials ongoing and completed during the reporting period

This section should refer to an appendix that presents a listing of each clinical trial in progress and each clinical trial completed during the reporting period. Separate tables can be provided by indication, formulation, and study population if appropriate. In addition, where required by local authorities, similar information should be provided for other therapeutic use of an investigational drug in the reporting period e.g., compassionate use or expanded access. The table(s) should include the following information for each trial:
- Protocol number or other trial identifier;
• Clinical trial phase (I, II, III, or IV);
• Status:
  ▪ Ongoing (study has begun; study has begun but is currently on hold; study is completed, but final clinical study report is not yet available);
  ▪ Completed (final clinical study report is available);
• Countries/regions where there is at least one investigational site for the protocol;
• Abbreviated study title;
• Study design (uncontrolled, controlled, open, single blind, double blind, parallel, cross-over, etc., including treatment arms);
• Dose and regimen of study drug and any comparators;
• Subject 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 first visit for first patient;
• Planned enrolment for study as a whole;
• Estimates of cumulative numbers of exposed subjects where available for each treatment arm. The actual enrolment numbers for open or completed trials, and/or an estimate based on the randomisation scheme for blinded trials should also be provided.

6. Cumulative Exposure

Explain the method used to estimate subject exposure and the overall number of subjects exposed, if available

7. Presentation of Safety Data

Explain your process for coding safety data

8. Significant Findings during 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 trials for this IMP and any interim analyses
The DSUR should provide a brief summary of the clinically important safety findings included in the final study reports from all clinical trials completed and any interim analyses conducted during the reporting period. This information can be in narrative format, or in the study synopsis format

8.2 Ongoing clinical trials
The DSUR should provide a concise summary of any preliminary safety findings from ongoing trials of the IMP, including safety issues that are the same or similar to those previously identified, as well as evidence of new clinically significant safety signals.

8.3 Other Therapeutic use of Investigational Drug
The DSUR should include safety information from expanded access programmes,
8.4 New Safety Data Related to Combination Therapies
If there is a separate DSUR for a multidrug regimen or fixed combination product containing the single investigational drug that is the subject of this DSUR, relevant findings from that DSUR should be summarised in this section.
If this DSUR is for a multidrug regimen or fixed combination product, important safety information arising from trials on the individual components should be briefly summarised here. 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.

<table>
<thead>
<tr>
<th>9. Relevant Findings from Non-interventional studies</th>
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<tbody>
<tr>
<td>If applicable/available/known</td>
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<tr>
<th>10. Relevant Findings from other Sources</th>
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<tr>
<td>Not applicable</td>
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<tr>
<th>11. Safety Findings from Marketing Experience</th>
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<tbody>
<tr>
<td>Not applicable</td>
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<tr>
<th>12. Other Information</th>
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<tr>
<td>e.g. new literature or published findings from other researchers</td>
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<tr>
<th>13. Late-Breaking Information</th>
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<tr>
<td>Information on potentially important safety findings that present while the DSUR is in preparation after the data lock point should be included in this section. Examples include clinically significant new case reports, important follow-up data, and clinically relevant toxicological findings. Any action that the sponsor, a Data and Safety Monitoring Board, or regulatory authority has taken for safety reasons should also be included.</td>
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<tr>
<th>14. Overall Safety Assessment</th>
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<td>The overall safety assessment should be a concise, integrated assessment of all new relevant clinical, non-clinical, and epidemiologic information obtained during the reporting period relative to previous knowledge of the investigational drug. 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. If appropriate, separate assessments can be</td>
</tr>
</tbody>
</table>
14.1 Evaluation of the risks
When relevant, the following points should be considered:

• meaningful changes in previously identified reactions (e.g., increased frequency or severity, outcome, specific at-risk populations);
• newly identified safety issues (detailed description of adverse reaction; 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);
• particular emphasis should be placed on symptoms, signs, and laboratory evidence of newly and previously identified, clinically significant:
  ▪ hepatotoxicity;
  ▪ cardiovascular effects, including QT interval prolongation and results from thorough QT/QTc studies;
  ▪ bone marrow toxicity;
  ▪ renal toxicity;
  ▪ central nervous system toxicity;
  ▪ immunogenicity and hypersensitivity;
  ▪ reactive metabolites;
• deaths that are an outcome of an adverse reaction;
• withdrawals due to safety reasons;
• 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);
• positive and negative experiences during pregnancy or lactation;
• overdose and its treatment;
• drug misuse and abuse;
• experience with long-term treatment;
• risks associated with protocol procedures, including administration of the investigational drug and diagnostic procedures;
• evidence of clinically significant medication errors;
• potential impact of significant new safety issues identified with another drug in the same class; and
• drug–drug and other interactions.

The overall safety assessment should also discuss other relevant findings such as: nonclinical research, manufacturing issues, lack of efficacy and lack of patient compliance, when available.

14.2 Benefit-risk considerations
This section is not meant to be a full benefit-risk assessment but should be a succinct statement on the balance between the theoretical benefits and the identified risks, focusing particularly on whether there have been any changes in this balance since the previous DSUR. If there has been a change, the sponsor should provide an assessment of the impact on the clinical development programme.

14.3 Conclusions
The section should present a brief conclusion, addressing any changes to the previous knowledge of safety and risks resulting from information gained since the last DSUR. Finally, the conclusion should describe how risks have been managed in the trials and any additional actions that should be taken to address emerging safety issues.

**15. Summary of Important Risks**

This section should provide a concise cumulative list of important identified and potential risks (e.g., those that might lead to warnings, precautions, or contraindications in labelling). The information in this section could provide the basis for the Safety Specification of a risk management plan (ICH E2E). The list should be continuously evaluated and updated from DSUR to DSUR and include risks that require further evaluation, as well as safety concerns that have been fully addressed or resolved.

Appendices:

1. IB or SmPC
2. Cumulative Table of Important Regulatory Advice
3. Status of ongoing/completed trials
4. Cumulative Summary Tabulations of Demographic Data
5. Line Listings of Serious Adverse Reactions (SARs)
6. Cumulative Summary Tabulation of Serious Adverse Events (SAEs)
7. Scientific Abstracts (if relevant)