Standard Operating Procedure

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Title: Standard Operating Procedure for the Preparation and Submission of Development Safety Update Reports

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DEFINITIONS

AE  Adverse Event (any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product). Each initial AE will be considered for severity, causality or expectedness and may be reclassified as a serious event or reaction based on prevailing circumstances.

AR  Adverse Reaction (any untoward and unintended response in a subject to an IMP which is related to any dose administered to that subject).

CESP  Common European Submission Platform

CRF  Case Report Form or the participant-specific data collection sheet

CTIMP  Clinical Trial of an Investigational Medicinal Product

DIBD  Development International Birth Date (DIBD)

DSUR  Drug Safety Update Report

GCP  Good Clinical Practice in clinical trials (in accordance with the Medicines for Human Use (Clinical Trials) Regulations (2004 and subsequent amendments)

IMP  Investigational Medicinal Product

Regulations  The Medicines for Human Use (Clinical Trials) Regulations (2004 and subsequent amendments)

MHRA  Medicines and Healthcare Products Regulatory Agency

RSI  Reference Safety Information

SAE  Serious Adverse Event (an AE that fits the criteria defined as serious in the Regulations)

SAR  Serious Adverse Reaction (AR that fits the criteria defined as serious in the Regulations)

Serious  Serious, in relation to an SAE, SAR or SUSAR is an event which either:
   a) results in death
   b) is life-threatening
   c) requires hospitalisation or prolongation of existing hospitalisation
   d) results in persistent or significant disability or incapacity, or
   e) consists of a congenital anomaly or birth defect.

SUSAR  Suspected Unexpected Serious Adverse Reaction (is a SAR that is thought to be 'unexpected' i.e. not consistent with the information about the medical product in question set out in the summary of product characteristics (SmPC) or the investigator’s brochure ).

UAR  Unexpected Adverse Reaction (an adverse reaction the nature and severity of which is not consistent with the information about the medical product in question set out in the summary of product characteristics or the investigator’s brochure.

UoM  University of Manchester
1.0 Background
In order to be compliant with the European Directive on Good Clinical Practice in Clinical Trials (2001/20/EC) and The Medicines for Human Use (Clinical Trials) Regulations (2004 and subsequent amendments) organisations conducting Clinical Trials of Investigational Medicinal Products must have clearly documented Standard Operating Procedures covering all aspects of conducting Clinical Trials.

As required by the MHRA, in addition to the expedited reporting required for a SUSAR, Sponsors are required to submit a safety report to the MHRA and the Ethics Committee, once a year throughout the clinical trial or on request. The DSUR will replace the current regulatory requirement for the Annual Safety Report (ASR) format and content (Regulation 35 of SI 2004/1031, p34) but will not affect reporting timelines.

To comply with UK regulations, Sponsors need to provide procedures and systems to support the production and submission of this safety document. The Development Safety Update Report (DSUR) Guidance (ICH E2F), published in the European Union in September 2010 has been implemented in the UK since September 2011. **As of 1st September 2011 only DSUR submissions are being accepted by the MHRA.**

2.0 Purpose
This SOP applies to all clinical trials that come under the regulations where the University of Manchester has Sponsor responsibility for pharmacovigilance. The primary objective of the DSUR is to compile an annual review and evaluation of the safety information.

A DSUR report must be submitted to the MHRA and the Ethics committee, once a year, on the anniversary date of the first CTA approval. The DSUR must include information on all new safety information received during the reporting period for each IMP, including where the IMP has been used in other in other University of Manchester sponsored CTIMPs where separate applications are made.

In accordance with the MHRA guidance on DSURs, information on the analysis of the subjects’ safety in the concerned clinical trial(s) with an appraisal of its ongoing risk: benefit; a line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the concerned trial(s), including all serious adverse reactions from third countries and an aggregate summary tabulation of suspected serious adverse reactions that occurred in the concerned trial(s) should all be included in the report. The DSUR provides assurance to the MHRA that the Sponsor is adequately monitoring safety information for all IMPs used within Sponsored trials. At the end of the DSUR reporting period the Sponsor may assess the new safety information that has been generated and submit any proposed safety changes to the investigator's brochure as a substantial amendment. This amendment should be supported by the DSUR and approved before the reference safety information (RSI) is changed. The RSI for any investigational medicinal product involved in a clinical trial must stay consistent during each reporting period. In trials where The University of Manchester has entered into a co-sponsorship agreement with a
NHS Trust, and the delegation log specifies that the NHS Trust has responsibility for annual safety reports, the Trust will be responsible for the DSUR returns, with copies supplied to the University of Manchester before onwards submission to the MHRA. This also applies to Clinical Trial Units (CTUs) or other third parties that have been contractually delegated this duty.

This SOP is designed to be used in conjunction with trial-specific procedures.

3.0 Procedure

3.1 Responsibility
The University of Manchester and, where appropriate, the co-sponsor require the CI, trial team or CTU that have been delegated responsibility for pharmacovigilance of the CTIMP to complete the DSUR and submit to the MHRA and ethics committee.

3.2 Timeline
The DSUR should be submitted to all concerned regulatory agencies no later than 60 calendar days after the DSUR data lock point. The data lock point of the DSUR is usually the last day of the one-year reporting period. The Development International Birth Date (DIBD) is used to determine the start of the annual period for the DSUR. This date is the Sponsor’s first authorisation to conduct a clinical trial in any country worldwide. In the UK this is usually the date of the CTA approval date received from the MHRA. Where the DIBD date is different from the CTA date, the Sponsor will inform the CI at the trial initiation or ahead of the DSUR data lock point.

A DSUR report must be submitted to the MHRA and the Ethics committee, once a year, on the anniversary date of the first CTA approval. Where the same IMP is used across different CTIMPs, it is recommended that a single DSUR be submitted for that specific IMP.

3.3 Completing the DSUR
A single DSUR per IMP should be submitted. The University of Manchester, in line with guidance provided by the MHRA, recommends that a trial specific DSUR should be submitted. Included with a DSUR should be a covering letter justifying why this approach has been undertaken. Where a single DSUR is submitted covering multiple trials, the covering letter must list all the relevant trials via their EudraCT number. All sections of the DSUR should be included in the report. Only use ‘Not Applicable’ where there is nothing to comment on or no information. Only relevant and available information should be included in the DSUR. Where a CTIMP has not started by the DSUR reporting date, a covering letter to the MHRA should be sent explaining why a DSUR will not be submitted.

3.4 How to submit the report
The DSUR must be submitted using the CESP portal, selecting the regulatory activity G0042 (DSURs).
3.5 Format and Presentation of DSUR

As described by the ICH Topic E2F Development Safety Update Report June 2008 (http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002827.pdf), the University of Manchester recommends that the DSUR should follow the ICH Topic E2F Development Safety Update Report June 2008 guidance as set out below. The information provided follows the EU Directive and is a standard template. Some sections may not apply and should be marked as not applicable (n/a).

The format and content of the DSUR should follow the table of contents below. For each heading where information is available, the information should be presented concisely. When no information is available, this should be stated. Guidance on the content of each section is provided below. Note that the section numbers below reflect the numbering in the DSUR.

Title page
The title page of the DSUR should include the following information:
• DSUR number (reports should be numbered sequentially);
• Investigational drug(s);
• Reporting period;
• Date of the report;
• Sponsor name and address;
• Confidentiality statement; and
• Note regarding the inclusion of unblinded information in the DSUR.

Executive Summary
This section should provide a 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 and other stakeholders, if required by local regulations. 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

Table of contents
A standard table of contents including all of the sections below:

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Executive Summary
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3. Actions Taken in the Reporting Period for Safety Reasons
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15. Lack of Efficacy
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17. Late-Breaking Information
18. Overall Safety Assessment
   18.1. Evaluation of the risks
   18.2 Benefit-risk considerations
19. Summary of important risks
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;
- Brief description of the investigational drug, e.g., therapeutic class, mode of action, dose, 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, indication-specific trials or combination products);
- 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...
2. Worldwide Marketing Authorisation Status

This section should be completed only if a marketing application for the product has been submitted in one or more countries/regions. Cumulative information should be provided where available, usually in the form of a table that provides the status of each application including the date of first approval, indications, approved dose/s and where approved as applicable.

3. Actions Taken in the 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 Monitoring Committees 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”, see section 4.

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;
- Recall of investigational drug or comparator;
- 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 future 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:
  o Significant restrictions on distribution or introduction of risk minimisation measures;
  o Significant changes in labelling documents that could affect the development programme, e.g., restrictions to indication or population or a new warning;
  o Communications to health care professionals as a result of the above actions; and
  o New post marketing study requirement(s) imposed by regional authorities.

4. Changes to Reference Safety Information
This section should list any significant safety-related changes to the IB within the reporting period. This includes information relating to contraindications, warnings, precautions, serious adverse drug reactions, 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. Inventory of Clinical Trials Ongoing and Completed During the Reporting Period

6. Estimated Cumulative Exposure
This section should clearly explain in the DSUR the method used to estimate subject/patient exposure.

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 (tabulated):
- 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 marketed setting
If the investigational product is marketed, the commercial sponsor should provide the estimated cumulative patient exposure in the marketed setting based on the information provided in the PSUR for that product or other suitable data source.

7. Data in Line Listings and Summary Tabulations
The DSUR should contain both cumulative and interval (periodic) safety information relating to the investigational drug. This section of the report should present important clinical safety information through interval line listings of the serious adverse reactions that arose during the period covered by the DSUR, and cumulative tabulations of serious adverse events that have been reported to the sponsor since the DIBD. If MedDRA 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 serious adverse events should include only those terms that were used in defining the case as serious. Non-serious and incidental findings should not be included.

If important and appropriate, the report should also include adverse reactions of special interest within the line listings and adverse events of special interest in summary tabulations. The basis for selection of such events/reactions should be explained.

Certain adverse events can be excluded from the summary tabulations and line listings, 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 or disease progression in cancer trials).

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.

7.1 Reference Information
This section of the DSUR should include the version of the coding dictionary used, and the document and version used as Reference Safety Information for determining expectedness for the tabulations, where required by regional authorities.

7.2 Interval line listings of Serious Adverse Reactions (SARs) during the Reporting Period
This section of the DSUR should include general information about the content of the line listings, the criteria for inclusion, and reference to appropriate appendices. The line listings should provide key information on all blinded and unblinded SARs reported during the reporting period, organised by System Organ Class (SOC). They can integrate data from all the trials being conducted with an investigational drug. Alternatively, when useful and feasible, SARs can be listed by protocol, indication, or other variables.

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). Such experiences can be treated as separate reports. Under such circumstances, the same subject can be included in a line listing more than once, and the line listings should be cross-referenced when possible.

The following information should be included in the line listings:

a) Study identification number and EudraCT 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;

The following information should be included in the line listings:

a) Study identification number and EudraCT number11 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;

7.3 Cumulative summary tabulations of Serious Adverse Events
This section of the DSUR should include general information about the content of the	tabulations, the criteria for inclusion, and reference to appropriate appendices. Summary	tabulations should present cumulative safety data 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 summary tabulations in a DSUR should include the number of serious adverse events, organised by SOC, for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo, and treatment unknown due to blinding) used in the programme. Data can be integrated across the programme. Alternatively, when useful and feasible, tabulations of SAEs can be presented by protocol, indication, or other variables. This section should not serve to provide analyses or conclusions based on the SAEs.

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

8.2 On-going clinical trials
The DSUR should provide a concise summary of any clinically important findings from ongoing trials (through interim analysis or a result of unblinding of subjects with adverse events), 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 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
The DSUR should include safety information from other programmes conducted by the Sponsor, compassionate use programmes and treatment investigational new drugs, that follow a specific protocol.

8.5 New safety data related to combination therapies
If the sponsor has prepared 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.

Conversely, 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.

9. Safety Findings from Non-Interventional Studies
This section of the DSUR should summarise relevant safety information that became available in the reporting period from non-interventional studies, e.g., observational studies, registries, active surveillance programmes or epidemiological studies.

10. Relevant Findings from Other Studies
The DSUR should also discuss relevant safety findings from any other available sources that became available to the Sponsor during the reporting period (e.g., results from pooled or meta-analyses of randomised clinical trials, lack of efficacy from trials in high morbidity/mortality disease states and trials with vaccines).
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 during the reporting period, particularly if the findings resulted in changes to the labelling, Investigator 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
Major safety findings from non-clinical in vivo and in vitro studies (e.g. carcinogenicity, reproduction, or immunotoxicity studies) initiated or completed during the reporting period should be summarised, and any impact on the clinical safety of the investigational drug should be discussed in the overall safety assessment.

13. Literature
The sponsor is expected to review the scientific literature, either published or available as unpublished manuscripts, periodically for new safety information. This section should summarise new and significant safety findings from non-clinical studies and clinical trials that have been published during the reporting period. When available, this section should also include relevant new information on drugs of the same class. Significant new safety information published as an abstract for a scientific meeting should be summarised and a copy provided if possible.

14. Other DSURs
When available, a sponsor should summarise significant findings from the DSUR provided by another sponsor conducting clinical trials with the investigational drug during the reporting period.

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.

15. Lack of efficacy
For investigational drugs intended to treat serious or life-threatening illnesses, lack of efficacy could constitute a significant risk to clinical trial subjects. In this setting, data received during the reporting period that indicates lack of efficacy or lack of efficacy relative to alternative therapies should be summarised.

16. Region-Specific Information

17. Late-Breaking Information
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 Committee, or regulatory authority has taken for safety reasons should also be included. The Overall Safety Assessment should also take these new data into account.

18. Overall Safety Assessment
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 provided by therapeutic area 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. 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;
• study drug discontinuations because of adverse events, including abnormal laboratory values or investigations;
• important non-clinical safety findings;
• manufacturing issues that could affect risk;
• lack of efficacy where this would place trial participants at risk;
• evidence of lack of patient compliance;
• 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 • 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;
• 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.

18.2 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.

19. 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.

20. 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.

Appendices to the DSUR
The following are appendices that might accompany the DSUR:
1 Investigator’s Brochure (if required);
2 Cumulative Table of Important Regulatory Advice;
3 Status of Ongoing and Completed Clinical 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).

Regional Appendices (as required by regional regulatory authority):
1 Drop-outs in Association with Adverse Events;
2 Deaths;
3 Cumulative Summary Tabulations of SARs.4. Significant Phase I protocol modifications with respect to a US IND;
5. Significant manufacturing changes;
6. Description of the general investigation plan for the coming year with respect to a US IND;

4.0 References


- MHRA Good Clinical Practice Guide