DSURs

Research & Development

Standard Operating Procedure for the Generation and Submission of Development Safety Update Reports and Annual Progress Reports for WHHT Sponsored CTIMPs

SOP Number : SOP-16-07	**Effective Date:October 2021**
Version Number: v07	**Review Date:** 2-3 Years

1.0 BACKGROUND

This document sets out the procedures to be followed by all West Hertfordshire Hospitals Trust (WHHT) staff who are involved in the preparation, review or dissemination of progress reports for ethics committees and regulatory bodies (including but not limited to the Medicines and Healthcare products Regulatory Agency (MHRA)) for WHHT sponsored studies. These progress reports include annual reports and Development Safety Update Reports (DSURs).

It is a requirement of ethical and regulatory approval that annual reports are submitted.

It aims to provide clear guidance on the timing and content of DSURs to ensure compliance with the regulatory bodies.

2.0 PURPOSE

This document defines the Trust's research procedures for the preparation and submission of periodic safety reporting and annual reports including DSURs for research studies and clinical trials sponsored by WHHT.

The document clarifies the requirements for safety reporting to the regulatory authorities so as to aid compliance with Good Clinical Practice (GCP).

The document aims to provide clear guidance on when and how to prepare annual reports and DSURs so as to comply with the regulatory requirements. The DSUR is a standard document for the periodic reporting on drugs under development (included marketed drugs that are under further study).

The objective of the DSUR is to provide a comprehensive review and evaluation of the pertinent safety information collected during the reporting period. This will:

- Examine whether the information obtained by the Sponsor during the reporting period is in accordance with previous knowledge of the drug's safety
- Describe any new safety issues
- Summarise the current understanding and management of the known and potential risks
- Provide and update on the status of the clinical investigation/development programme and study results

3.0 APPLICABLE TO

The submission of safety reports is delegated by the Sponsor to the Chief Investigator (CI) or Delegated Individual (DI) and their study team involved in the managements of WHHT sponsored Clinical Trials for an Investigational Medicinal Product (CTIMPs).

The study team can include, but is not limited to, Unit Heads, Chief Investigators (CI), Principal Investigators (PI), Co-Investigators, Consultants, Clinical Trial Pharmacists, Research Managers, Statisticians, Research Nurses, Allied Health Professionals, Trial Coordinators & Data Managers.

4.0 RESPONSIBILITIES

The trial Sponsor is responsible for the preparation, content and submission of the annual reports/DSUR although they may delegate the actual task to a competent member of the study team. This delegation must be on the Sponsor/CI delegation log.

5.0 PROCEDURE

5.1 Annual Reporting period and Development International Birth Date (DIBD)

5.1.1 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. The start of the annual period for the DSUR is the month and date of the DIBD.

5.1.2 The start of the Annual Reporting Period will be the month and date of the DIBD. For clinical trials that commenced before 1 May 2004, the reporting period starts with the issue date of the Clinical Trial Exemption (CTX) letter or first Doctors and Dentists Exemption (DDX) letter by the MHRA.

5.1.3. Where the same Investigational Medicinal Product (IMP) is used in different trials, the data will be provided by indication.

5.2 Data-Lock date

5.2.1 The data lock point of the DSUR should be the last day of the one-year reporting period. For administrative convenience, if desired by the Sponsor, the data lock point of the DSUR can be designated as the last day of the month prior to the month of the DIBD.

5.2.2 The DSUR should be submitted to all concerned regulatory authorities no later than 60 calendar days after the DSUR data lock point.

5.3 Preparation of the DSUR and co-ordinated responsibilities

5.3.1 The Sponsor of a clinical trial is considered responsible for the preparation, content and submission of a DSUR. The Sponsor can delegate the preparation of the DSUR to a third party (e.g. a contract research organisation).

5.3.2 The CI/DI will complete their relevant sections and return to the R&D Department. The delegated member of the research team will also send all appendices to the R&D Department.

5.3.3 The R&D Department will compile all the relevant information then forward the DSUR to the MHRA and the Research Ethics Committee (REC) with a final copy sent to the research teams.

5.3.4 The final documents are to be stored in the Trial Master File (TMF).

5.4 Completion of the DSUR

5.4.1 The CI will receive a reminder email from the R&D Department on the anniversary of the trial's Clinical Trials Authorisation (CTA).

5.4.2 Guidance for completion of the DSUR is available on the MHRA web site. DSUR completion guidelines. For the report template, please see Appendix 2.

5.4.3 The R&D Department will be the point of contact going forward for all questions/queries related to the completion and submission of the DSUR.

5.4.4 The DSUR contains sections for completion by the CI/trial team and sections for completion by the Sponsor.

5.4.5 The CI/DI should complete those sections marked for their attention in the template.

5.4.6 The R&D Department will then complete those sections that are for the Sponsor's attention, check that the instructions in the template have been appropriately followed and the current approved Reference Safety Information (RSI) has been used.

5.4.7 The draft DSUR must be provided to the R&D Office 2 weeks prior to the submission deadline.

5.4.8 Any necessary alterations agreed are made by the CI or the R&D Department in the relevant sections.

5.4.9 The final DSUR will then be reviewed and signed by the Sponsor's representative in the R&D Department and the CI.

5.4.10 The R&D Department will submit the DSUR and the supporting documents i.e. cover letter, approved RIS, publications and abstracts (as applicable) via the Common European Submission Portal (CESP), the online portal for MHRA submissions.

5.4.11 The R&D Department will provide the CI/trial team with a copy of the full DSUR submission for submission to the REC and for filing in the TMF. (see SOP-06)

5.4.12 It is the responsibility of the CI to provide the DSUR and accompanying documents (including the Safety Report Form) to the REC which gave favourable opinion for the trial, via email

5.4.13 The R&D Department will file a copy of the CESP upload email as confirmation that the DSUR has been submitted to the MHRA.

5.4.14 When received, a copy will be filed in the Sponsor file and the original confirmation forwarded to the trial team for filing in the TMF.

5.5 DSURs for combination therapy

5.5.1 DSURs are IMP-specific and it is the Sponsor's responsibility to ensure a single DSUR is submitted for individual IMPs.

5.5.2 In cases of multi-drug therapy trials, where it is not possible to submit DSURs for individual IMPs, a delegated member of the R&D Department in conjunction with the PI or CI, will arrange to prepare a DSUR for the multi-drug therapy.

5.6 Submission of the final DSUR

Ensure that all the original reports are signed and dated appropriately.

DSUR Submission	**Annual Progress Report Submission**
Submit DSUR using MHRA Submissions via the Human Medicines Tile. Please select 'Development Safety Update Report' as the Regulatory Activity and 'Original Submission' from the Regulatory sub activity dropdown list.	Send completed and signed APR form to the REC via email
Include: ● covering letter listing all EudraCT numbers of trials covered by the DSUR. Please include an email address for correspondence ● an 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 trial(s), including all SUSARs from third countries ● an aggregate summary tabulation of SUSARs that occurred in the concerned trial(s)	No covering letter
Please follow the link to the current submission guidance - Guidance on submitting clinical trial safety reports	
Make two copies of all the signed documents, one set for filing in the TMF and send the second set to Research and Development for inclusion in the Sponsor files	

5.7 Annual Progress Reports Submitted to the REC Only

It is a requirement for continued favourable opinion from the REC that an Annual Progress Report (APR) be submitted annually, i.e. within 30 days of the anniversary date of favourable opinion for the study which was received from the REC.

The APR Form for CTIMPs published on the HRA website must be used:

- The CI will receive a reminder email from the R&D Department on the anniversary of the 'favourable opinion' from the REC for their trial
- If any extension to the duration of the trial is required, this must be included in the APR as notification of the extension to the REC
- A final signed copy of the APR and submission email must be submitted to the R&D Department for review and inclusion in the Sponsor file

The trial team should notify participating sites of any changes in the duration of the trial as stated in the APR as soon as possible by normally 10 working days after submission.

The trial team should request participating sites to acknowledge the receipt of the APR form. A copy of the APR and acknowledgement of receipt from the REC should be filed in the Sponsor file and in the Trial Master File (TMF). (see SOP-06)

6.0 RELATED DOCUMENTS

- SOP-02- SAEs (Sponsored)
- SOP-06- TMF
- ICH E2F Development safety update report | European Medicines Agency (europa.eu)
- For information on submission to the MHRA please refer to the MHRA website
- For information on submission to the HRA (REC) please refer to the HRA website

7.0 APPENDICES

Appendix 1 - Definitions
Appendix 2 - Example DSUR

8.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**
SOP-16-07	**October 2021**	1. Change from general Standard Operating Procedures (gSOP) to SOP 2. Removal of the '10.0 Agreement' from the template - all agreement signatures will be collated on a new 'SOP Signature Sheet Document' 3. Updates in line with the new guidance 4. Other minor amendments and clarification of terms following review
gSOP-16-06	**10/2017**	Minor amendments following review

gSOP-16-05	**01/10/2015**	Minor amendments following dissolution of R&D consortium
gSOP-16-04	**07/05/2014**	Minor amendments following review
gSOP-16-03		1, SOP modified for implementation at ENHT/WHHT. gSOP-16-03 replaces 2011-158
gSOP-16-02 (MVCC)		1. SOP modified for implementation at MVCC

9.0 AUTHORSHIP & APPROVAL

Author

Signature  **Date** 28/10/2021

R & D Steering Group Approval

Signature  **Date** 28/10/2021

Appendix 1: Definitions

Chief Investigator (CI)
The investigator with overall responsibility for the research. In a multi-site study, the CI has coordinating responsibility for research at all sites. All applications for ethical review should be submitted by the CI. For Trust sponsored trials, the CI had been delegated the pharmacovigilance responsibility for identification, recording and reporting of safety events, including submission of Development Safety Update Reports (DSURs) to the MHRA and REC.

Clinical Trial
A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions. A Study Type.

Clinical Trial of Investigational Medicinal Product (CTIMP)
A clinical trial that is within the scope of the UK Medicines for Human Use (Clinical Trials) Regulations 2004. An investigation in human subjects, other than a non-interventional trial, intended: a) to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products, b) to identify any adverse reactions, or c) to study absorption, distribution, metabolism and excretion, with the object of ascertaining the safety and/or efficacy of those products.

Data Lock Point
This should be the last day of the one year reporting period and the Development Update Safety Report (DSUR) should be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC) no later than 60 days after the data lock date.

Delegated Individual (DI)
An individual delegated by a person of responsibility to carry out their task(s).

Good Clinical Practice (GCP)
Good Clinical Practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.

International Conference on Harmonisation (ICH)
International Conference for Harmonisation, a collaboration between regulators and the pharmaceutical industry in Europe, the United States and Japan to establish common standards for clinical trials. ICH GCP is a widely recognised standard for Good Clinical Practice in clinical trials.

Investigational Medicinal Products (IMP)
A pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a Clinical Trial, and includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial - a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation, b) used for an indication not included in the summary of product characteristics under the authorisation for that product, or c) used to gain further information about the form of that product as authorised under the authorisation.

Sponsor's Representative

The Director/Associate Director of R&D will appoint an appropriate staff member to act as the Sponsor's representative.

The Medicines & Healthcare products Regulatory Agency (MHRA)
The MHRA is the competent authority for the UK in relation to the Directive 2001/20/EC and the Clinical Trials Regulations, and for Medical Devices, the competent authority in relation to the Medical Devices Regulations 2002.

The Regulations
Medicines for Human Use (Clinical Trial) Regulations 2004 transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 no 1031. This became effective on the 1st May 2004. An amendment to implement Directive 2005/28/EC was made to the Regulations as Statutory Instrument 2006 no 1928.

Trial Master File
The Trial Master File contains all essential documents held by the sponsor/Chief Investigator which individually and collectively permits the evaluation of the conduct of a trial and the quality of the data produced.

Appendix 2 - Example DSUR
(As found in ICH E2F guidance)

Development Safety Update Report

Report Number:

Trial Title:

Reporting Period:

Name of IMP	
Sponsor	West Hertfordshire Hospitals NHS Trust
Chief Investigator	
Sponsor Address	West Hertfordshire Hospitals NHS Trust Watford General Hospital Vicarage Road Watford Hertfordshire WD18 0HB
Chief Investigator Address	West Hertfordshire Hospitals NHS Trust Watford General Hospital Vicarage Road Watford Hertfordshire WD18 0HB
Date	

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

This report contains unblinded information (delete if not applicable)

Executive Summary

Table of Contents

1. Introduction

2. Worldwide Marketing Approval Status

3. Actions Taken in the Reporting Period for Safety Reasons

4. Changes to Reference Safety Information

5. Inventory of Clinical Trials Ongoing and Completed During the Reporting Period

6. Estimated Cumulative Exposure

6.1 Cumulative Subject Exposure in the Development Programme:

6.2 Patient Exposure from Marketing Experience

7. Data in Line Listings and Summary Tabulations

7.1 Reference Information

7.2 Line Listings of Serious Adverse Reactions during the Reporting Period

7.3 Cumulative Summary Tabulations of Serious Adverse Events

8. Significant Findings from Clinical Trials during the Reporting Period

8.1 Completed Clinical Trials

8.2 Ongoing Clinical Trials

8.3 Long-term Follow-up

8.4 Other Therapeutic Use of Investigational Drug

8.5 New Safety Data Related to Combination Therapies

9. Safety Findings from Non-interventional Studies

10. Other Clinical Trial/Study Safety Information

11. Safety Findings from Marketing Experience

12. Non-clinical Data

13. Literature

14. Other DSURs

15. Lack of Efficacy

16. Region-Specific Information

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