University of Hertfordshire

ANNUAL PROGRESS REPORTS AND DSURS

Clinical Trials Support Network (CTSN)

Standard Operating Procedure for the Generation and Submission of Development Safety Update Reports and Annual Progress Reports for UH Sponsored/Co-Sponsored and UH CTSN adopted Clinical Trials

SOP Number : gSOP-16-02	**Effective Date:** 28th June 2022
Version Number: 2.0	**Review Date:** 3 years (or as required)

1.0 BACKGROUND

This is a University of Hertfordshire (UH) standard operating procedure (SOP).

This document sets out the procedures to be followed by all UH 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 MHRA) for UH sponsored/co-sponsored studies and those studies for which the CTSN has delegated responsibility for preparing progress reports. These progress reports include Annual Progress Reports (APRs) 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 and APRs as a condition for continuous Health Research Authority (HRA) approval.

2.0 PURPOSE

This document defines the research procedures for the preparation and submission of periodic safety reporting and annual reports including DSURs for research studies and clinical trials sponsored/co-sponsored by UH and/or adopted by the UH CTSN.

The document clarifies the requirements for safety reporting to the regulatory authorities 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 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 UH sponsored/co-sponsored clinical trials. The CTSN may take on this responsibility if agreed in the division of responsibilities.

This applies to, but is not limited to, all staff involved in clinical research that is UH sponsored/co-sponsored or adopted by the UH CTSN, including: CIs, Principal Investigators, Research Fellows, Consultants, Statisticians, Clinical Trial Pharmacists, Research Managers, Research Nurses, Clinical Trial Practitioners, Allied Health Professionals, Trial Coordinators, Clinical Studies Officers, Data Managers and Students.

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 or CTSN. This delegation must be on the Sponsor/CI Division of Responsibilities.

5.0 PROCEDURE

For CTIMPS – Preparation of the DSUR:

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.

5.1.2 The start of the Annual Reporting Period will be the month and date of the DIBD.

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

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. the CTSN or a contract research organisation).

5.3.2 The Sponsor representative or delegate will compile all the relevant information then forward the DSUR to the CI for approval and then to the Sponsor representative for submission.

5.3.3 The Sponsor representative will submit the DSUR using MHRA Submissions via the Human Medicines Tile. The CTSN will submit a copy to the REC with a final copy sent to the research teams.

5.3.4 The final documents, including accompanying cover letter and confirmation of MHRA submission are to be stored in the Trial Master File.

5.4 Completion of the DSUR

5.4.1 Guidance for completion of the DSUR isavailable on the MHRA web site. https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues. For report template, please see Appendix 2.

5.4.2 The CTSN will be the point of contact going forward for all questions/queries related to the completion of the DSUR.

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

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

5.4.5 The CTSN will work with the Sponsor representative to 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.

5.4.6 Any necessary alterations agreed are made by the CI or the CTSN in the relevant sections as appropriate.

5.4.7 The final DSUR will then be reviewed and signed by the CI.

The Sponsor representative will submit the DSUR and the supporting documents i.e. cover letter, publications and abstracts (as applicable) using MHRA submissions via the Human Medicines option. "Development Safety Update Report" should be selected as the Regulatory Activity and "Original submission" from the Regulatory sub activity dropdown list. Acknowledgement of receipt for DSUR submissions are generated by MHRA Submissions and confirmation is emailed to the reporter.

5.4.8 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. If defined in

the division of responsibilities the CTSN will take on this responsibility.

5.4.9 When received, a copy of the acknowledgement of receipt email 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, the Sponsor representative in conjunction with the PI or CI, will arrange to prepare a DSUR for the multi-drug therapy.

5.6 DSURs for trials using the Combined Review process

5.6.1 If at least one of the trials covered by the DSUR has gone through the Combined Review process, then the report should be submitted via the Integrated Research Application System (IRAS). Guidance can be found on the Health Research Authority (HRA) website.

5.7 Shortened DSUR

A shortened DSUR is available for trials approved under the Notification Scheme.
This is suitable for:

5.7.1 Individual trials authorised under the Notification Scheme which are not part of a multi-study development programme.

5.7.2 Phase 4 national (UK only) trials of licensed products that commanded a low fee from the MHRA and where all participants have completed treatment and are only in follow-up.

For these trials the HRA APR may be used as an alternative. The cover letter should indicate that this is an APR in lieu of a full DSUR and include the EudraCT number and CTA reference number. A list of all serious adverse reactions should also be included in section 6 of the APR.

5.8 Submission of the final DSUR

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

DSUR Submission	Annual Progress Report Submission
Send DSUR to the MHRA via the online portal (refer to the MHRA website for current requirements)	Send completed and signed Annual Progress Report (APR) form to the REC via email
Include covering letter and all appendices	No covering letter
Send a copy of the DSUR to the REC via email accompanied by the REC CTIMP safety report form	

For Sponsored trials copies of all the signed documents should be sent for filing in the TMF, and to the UH Research Office for inclusion in the Sponsor files. For co- sponsored trials a copy should be filed in the Trust R&D files.

For all Clinical Trials:

5.9 Annual Progress Reports Submitted to the REC Only

It is a requirement for continued favourable opinion from the REC that an 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 template (for CTIMPs / for non-CTIMPs) published on the HRA website must be used:

- The CI will receive a reminder email from the Sponsor Representative 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 Sponsor representative for review and inclusion in the Sponsor file.

The trial team should notify participating sites of any change 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).

6.0 RELATED DOCUMENTS

- gSOP-02- Adverse Event reporting (Sponsored/co-sponsored)
- The Development Safety Update Report (DSUR) Guidance – ICH E2F
- 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

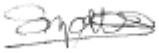
- Appendix 1 – Definitions
- Appendix 2 – Example DSUR

8.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**
02	28th July 2022	Regular review update. Change to submission following Brexit. Inclusion of Shortened DSUR for trials approved under Notification scheme.

9.0 AUTHORSHIP & APPROVAL

Author

Signature  **Date 16 June 2022**

Pro-Vice Chancellor (Research & Enterprise) Approval

Signature  **Date 16 June 2022**

Professor J M Senior

10. AGREEMENT (MOVE ON TO SEPARATE SHEET BEFORE PRINTING)

Please detach and retain within <u>your training files</u>

I have read and understood the contents and requirements of this SOP (ref gSOP-16-01) and accept to follow University policies implementing it.

Recipient

Signature: ……Date: ……..

Name & Position: ……

Please retain copy of the signed form for your reference in your training file

Appendix 1: Definitions

Chief Investigator (CI)
A Registered Physician, Dentist, Pharmacist or Registered Nurse who has overall responsibility for the conduct of the trial.

Clinical Trial
A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or control) to evaluate the effects of those interventions on health outcomes.

Clinical Trial of Investigational Medicinal Product (CTIMP)
A study that looks at the safety or efficacy of a medicine/food stuff/placebo in humans as defined by the Medicines for Human Use Regulations (2004).

Data Lock Point
This should be the last day of the one year reporting period and the DSUR should be submitted to the MHRA and the REC no later than 60 days after the data lock date.

Delegated Individual (DI)
An individual delegated by the PI to carry out their task(s).

Good Clinical Practice (GCP)
As defined in the Regulations.

International Conference on Harmonisation (ICH)
The ICH produced a series of guidelines in 1996, E6 being the guideline on Good Clinical Practice, otherwise known as (ICH-GCP).

Investigational Medicinal Products (IMP)
A pharmaceutical form of an active substance or placebo being tested, or used as a reference in a clinical trial. This 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 / Assistant Director of R&D will appoint an appropriate staff member to act as the Sponsor's Representative.

The Medicines & Healthcare products Regulatory Agency (MHRA)
UK Competent Authority responsible for regulation of clinical trials.

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 (TMF) will be held at the principal site by the sponsor, Chief Investigator or at the co-ordinating Centre. The TMF should contain all essential documents defined as documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. A Trial Master File should be set up at the beginning of a trial and maintained up-to-date throughout the trial until trial conclusion.

For trials currently running, it is recommended that Section 8 of the ICH-GCP Guideline is followed as guidance in order to meet statutory requirements. However, some of the documents listed may not be available or applicable in many non-commercial trials. The appropriate documentation will vary according to the trial and sponsor requirements.

Appendix 2 - Example DSUR

Development Safety Update Report

Report Number:

Trial Title:

Reporting Period:

Name of IMP	
Sponsor	University of Hertfordshire
Chief Investigator	
Sponsor Address	University of Hertfordshire College Lane Hatfield Hertfordshire AL10 9AB
Chief Investigator Address	
Date	

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

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