Standard Operating Procedure CCTU/SOP003

DSUR and Annual progress Reporting

1. Scope

This SOP is for use by the CCTU and Chief Investigators & trial teams working on Cambridge Sponsored CTIMPs

2. Purpose

To ensure that CI's and trial teams are aware of their responsibilities regarding the provision and submission of Safety Reports as required by regulation 35 The Medicines for Human Use (Clinical Trials) Regulations and Annual Progress Reports as a condition for continuous HRA approval.

3. Definitions and Abbreviations

The headings below contain the definitions of terms and meaning of abbreviations used within the document.

3.1. Definitions

Term	Definition
Cambridge Sponsored	Sponsored by: Cambridge University Hospitals NHS Foundation Trust (CUH) or CUH jointly with the University of Cambridge or Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge
Development Safety Update Report (DSUR)	The Development Safety Update Report is the format for annual safety reporting. The focus is specifically on new safety information identified during the reporting period with a view to ongoing risk-benefit analysis.
Adverse Event (AE)	Any untoward medical occurrence that happens to a patient or research participant to whom investigational medicinal Product has been administered in a clinical trial, which may or may not necessarily have causal relationship with the research being undertaken.
Adverse Reaction (AR)	An untoward and unintended reaction that is considered to be related to the administration of the IMP.
Reference Safety Information	A list of medical events that defines which reactions are expected for the IMP within a given trial and thus determining which Serious Adverse Reactions (SARs) require expedited reporting. The RSI is contained in a clearly identified section of the Summary of Product Characteristics (SmPC) (section 4.8) or the Investigator's Brochure (IB). It is not the entire SmPC or IB.
Serious Adverse Event (SAE)	Any AE or effect that at any dose: Results in death Is life threatening

	Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability/incapacity Is a congenital anomaly/birth defect Is an otherwise significant event
Serious Adverse Reaction (SAR)	An SAE that is considered to be possibly, probably or definitely related to the IMP.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction, which is both serious and unexpected, i.e. the nature or severity of which is not consistent with the applicable product information and which fulfils one or more of the criteria listed above for SAE.
Development International Birth Date	The anniversary of the clinical trials authorisation from the MHRA

3.2. Abbreviations

Abbreviation	Meaning
APR	Annual Progress Report
ASR	Annual Safety Report
CI	Chief Investigator
CTA	Clinical Trials Authorisation
CTC	Clinical Trial Coordinator
CTIMP	Clinical Trial of Investigational Medicinal Product
CUH	Cambridge University Hospitals NHS Foundation Trust
DIBD	Development International Birth Date
DSUR	Development Safety Update Report
HRA	Health Research Authority
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare Products Regulatory Agency
PV	Pharmacovigilance
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

4. Undertaken by

The preparation of safety reports is delegated by the Sponsor to Chief Investigators and their trial teams. The collation, final sign off and submission of the DSUR to the MHRA is performed by the CCTU Regulatory Team.

5. Items Required

CCTU/TPL012 Development Safety Update Report Template

CTIMPs Safety Report Form for the REC

Annual Progress Report Form for CTIMPs

6. Summary of Significant Changes

Change to DSUR management responsibilities

APR in lieu of a DSUR process clarification

7. Method

The following sections provide a description of the processes to be followed when implementing this document's procedures.

7.1. Regulations

- The Development Safety Update Report (DSUR) for CTIMPs must be submitted within 60 days of the Development International Birth Date (DIBD), which for the purposes of Cambridge Sponsored CTIMPs will be the anniversary of the clinical trials authorisation from the MHRA
- A copy of the DSUR must also be sent to the REC accompanied by the REC CTIMP Safety Report Form (see 7.6)
- NOTE If the end of trial declaration has been received within a reporting period, or within 60 days following, the data lock point, the corresponding DSUR will not be required

7.2. The Development Safety Update Report (DSUR): For Type B, C & Full Submission Type A trials

- The PV team will send a copy of the current DSUR template, containing guidance for completion to the CI and trial team, and confirmation of the submission timelines
- The PV team will be the point of contact going forward for all questions/queries related to the completion and submission of the DSUR
- The CI or trial team designee should complete those sections marked for their attention in the DSUR template
- A draft DSUR should be provided to the PV team via email3 weeks prior to the submission deadline
- The PV team will review DSUR and complete those sections that are for the Sponsor's attention:
    - Check that the current approved Reference Safety Information (RSI has been used
    - Reconcile safety data in the DSUR line listings and summary tabulations with the CCTU PV database to make sure they correlate
- During the review process, any necessary alterations agreed should be made by the CI, CTC or PV team in the relevant sections, as appropriate
- The final DSUR will be reviewed and signed by the Sponsor's representative and the CI if available

- The PV team will submit the DSUR and the supporting documents i.e. Cover letter, approved reference safety information, publication and abstracts (as applicable) via the online portal for MHRA submissions
- The PV team will provide the CI/trial team with a copy of the full DSUR package for submission to the REC and for filing in the TMF
- It is the CI's responsibility to ensure the DSUR and accompanying documents (including the Safety Report Form) are provided to the REC and acknowledgements are filed in the TMF
- For multi-centre trials the CI/trial team are responsible for the distribution of the DSUR to all participating sites
- The PV team will file the original DSUR submission package and a copy of the MHRA upload e-mail, as confirmation that the DSUR has been submitted to the MHRA, in the Sponsor file

7.3. APR in lieu of the DSUR: For Type A Notification Trials only

- The PV team will send confirmation of the submission timelines
- The PV team will be the point of contact going forward for all questions/queries related to the completion and submission of the APR in lieu of a DSUR
- The CI or trial team designee should complete the APR:
    - List all serious adverse reactions for the reporting period in section 6 of the APR or as a separate document in the Appendix 3 format of CCTU/TPL012 DSUR
- A draft APR should be provided to the PV team via email 3 weeks prior to the submission deadline
- The PV team will review the APR :
    - Check that the current approved Reference Safety Information (RSI) has been used
    - Reconcile safety data in the SARs line listings and summary tabulations with the CCTU PV database to make sure they correlate
- During the review process, any necessary alterations agreed should be made by the CI, CTC or PV team in the relevant sections, as appropriate
- The final APR will be signed by the CI
- The PV team will submit the APR and the supporting documents: *Cover letter, approved reference safety information, a list of all serious adverse reactions, publication and abstracts (as applicable) via the online portal for MHRA submissions
- The PV team will provide the CI/trial team with a copy of the full APR package for submission to the REC and for filing in the TMF
- It is the CI's responsibility to ensure the APR and accompanying documents (including the Safety Report Form) are provided to the REC and acknowledgements are filed in the TMF
- For multi-centre trials the CI is responsible for the distribution of the APR to all participating sites
- The PV coordinator will file the APR in lieu of a DSUR submission package and a copy of the MHRA upload e-mail, as confirmation that the APR has been submitted to the MHRA, in the Sponsor file

NOTE *The MHRA cover letter should include the EudraCT number, and CTA reference number and indicate that this is an Annual Progress Report (APR) in lieu of a full DSUR

7.4. Short Term Trials

For trials lasting less than 1 year* from CTA approval there is no requirement to submit a DSUR All safety information should be included in the trial report submitted within 1 year of end of trial declaration.

For trials lasting less than 1 year* from REC approval there is no requirement to submit an APR.

* End of trial declaration submitted to the relevant authority

7.5. The Annual Progress Report

For continued favourable opinion from the REC an Annual Progress Report (APR) must be submitted annually, i.e. within 30 days of the anniversary date that favourable opinion for the trial was received from the REC.

The Annual Progress Report Form for CTIMPs published on the HRA website must be used:

- Chief Investigator / trial team are responsible for the completion and submission of the trial APR
- A final signed copy of the APR and submission email must be submitted to the CCTUregualtory@addenbrookes.nhs.uk email for inclusion in the Sponsor file
- The trial team should circulate the APR form to participating sites as soon as possible but normally10 working days after submission
- A copy of the APR and acknowledgement of receipt from the REC should be filed in the TMF

7.6. Waiver of Requirement to Submit an APR

When a trial has closed to recruitment and all patients have completed their intervention phase but continue to be followed up for a long period of time with minimal involvement, a waiver for the requirement to send an APR can be requested

- This must be requested in writing to the chairman of the REC
- The response should be sought in writing and filed in the Trial Master File and provided to the Sponsor for their records

8. Monitoring Compliance with and the Effectiveness of this Document

a. Process for Monitoring Compliance and Effectiveness

As part of routine monitoring visits, audit and inspection

b. Standards/Key Performance Indicators

This process forms part of a quality management system and is reviewed according to CCTU procedures. Standard Operating Procedures are reviewed every two years.

9. References

The Institute of Clinical Research, Abbreviations used in Clinical Trials.

MHRA, Good Clinical Practice "Grey Guide"

The UK Clinical Trial Regulations SI 2004/1031

www.legislation.gov.uk/uksi/2004/1031/contents/made

ICH Pharmacovigilance guidance E2F for Development Safety Update

Clinical trials for medicines: manage your authorisation, report safety issues. MHRA updated 18 March 2021

https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#development-safety-update-reports-dsurs

10. Associated Documents

CCTU/SOP061 RSI in CTIMPS

CCTU/SOP014 Amendment Management of CTIMPs by Trial Teams

11. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

12. Disclaimer

It is the user's responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

Review date	2 years (or earlier in light of new evidence) from approval date
Owning department:	CCTU QA
Supersedes:	CCTU/SOP003 v10
Local reference:	CCTU/SOP003 version 11