Standard Operating Procedure CCTU/SOP003

DSUR and Annual progress Reporting

1. Scope

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

2. Purpose

This SOP is designed to ensure that investigators 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 ethical favourable opinion.

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 the University of Cambridge (UoC); or jointly by CUH and UoC 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**
CUH	Cambridge University Hospitals NHS Foundation Trust
CTO	Clinical Trials Officer
CTC	Clinical Trial Coordinator
CTA	Clinical Trials Authorisation
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
DSUR	Developmental Safety Update Report
ASR	Annual Safety Report
APR	Annual Progress Report
CTIMP	Clinical Trial of Investigational Medicinal Product
MHRA	Medicines and Healthcare Products Regulatory Agency
REC	Research Ethics Committee
IMP	Investigational Medicinal Product
DIBD	Development International Birth Date
HRA	Health Research Authority
CESP	Common European Submission Platform
RSI	Reference Safety Information
PV	Pharmacovigilance
CI	Chief Investigator
TMF	Trial Master File

4. Undertaken by

The preparation of safety reports is delegated by the Sponsor to Chief Investigators and their study teams involved in the management of Cambridge sponsored CTIMPs. The collation, final sign off and submission of the DSUR is performed by the CCTU Regulatory Team.

5. Items Required

CCTU/TPL012 Development Safety Update Report Template

CTIMPs Safety Report Form for sending DSUR to the REC

Annual Progress Report Form for CTIMPs

Access to the Health Research Authority Website and the MHRA Website

6. Summary of Significant Changes

Addition of a process to notify the HRA of an extension of the trial duration via minor amendment

Change to the requirement for filing REC DSUR and APR acknowledgments in the Sponsor File

7. Method

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

7.1. Regulations

Refer to "ICH guideline E2F: Note for guidance on development safety update reports" available online and from the CCTU.

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).

7.2. The Development Safety Update Report (DSUR)

- Chief Investigators will receive a reminder email from the CCTU on the anniversary of the trial's Clinical Trials Authorisation
- The assigned CTO in the CCTU will send a copy of the current DSUR template, containing guidance for completion to the CI and trial team, along with the current CCTU SOP003 and confirmation of the submission timelines
- The CTO will be the point of contact going forward for all questions/queries related to the completion and submission of the DSUR
- The DSUR contains sections for completion by the CI/trial team and sections for completion by the Sponsor

- The CI or trial team designee should complete those sections marked for their attention in the template
- The CTO will 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
- The CCTU PV coordinator will reconcile safety data in the DSUR line listings and summary tabulations (Appendix 3&4 of CCTU/TPL012 DSUR) with the CCTU PV database to make sure they correlate
- A draft DSUR must be provided to the CTO 3 weeks prior to the submission deadline. Any delay in providing this, without prior agreement of the CCTU will be escalated as a non-compliance to the Sponsor
- Any necessary alterations agreed are made by the CI, CTC or CTO and PV coordinator in the relevant sections as appropriate
- The final DSUR will be reviewed and signed by the Sponsor's representative in the CCTU and the CI if available
- The CTO will submit the DSUR and the supporting documents i.e. Cover letter, approved reference safety information, publication and abstracts (as applicable) via CESP the online portal for MHRA submissions
- The CTO 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 provide the DSUR and accompanying documents (including the Safety Report Form) to the REC which gave favourable opinion for the trial, electronically via email
- For multi-centre trials the CI is responsible for the distribution of the DSUR to all participating sites
- A copy of the Safety Report Form and acknowledgement of receipt from the REC should be filed in the TMF
- In exceptional circumstances, and on the direction of the Sponsor, the CTO may submit the DSUR to the REC on behalf of the CI
- The CTO will file the original DSUR submission package and a copy of the CESP upload e-mail, as confirmation that the DSUR has been submitted to the MHRA, in the Sponsor file

7.3. Short Term Trials

For short term 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.

7.4. 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 study was received from the REC.

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

- Chief Investigators will receive a reminder email from the CCTU 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 and submitted as a minor amendment to the HRA for categorisation and approval
- A final signed copy of the APR and submission email must be submitted to the CTO 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
- 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 TMF

7.5. 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

7.6. Submission of Reports

Ensure that all the original reports are signed and dated appropriately

DSUR Submission	**Annual Progress Report Submission**
CTO to send DSUR to the MHRA via CESP. Include covering letter and all appendices. Refer to the website for current requirements	The CI/CTC to send completed and signed APR form to the REC via email. No covering letter
The CI/CTC to send a copy of the DSUR to the REC via email accompanied by the REC CTIMP safety report form.	

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

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 v9
Local reference:	CCTU/SOP003 version 10