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
CRS	Combined Review Service
CTA	Clinical Trials Authorisation
CTC	Clinical Trial Coordinator
CTO	Clinical Trials Officer
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
IRAS	Integrated Research Application System
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

- The submission of the final signed off DSUR to the REC is performed by the trial team
- For CRS trials, the DSUR is submitted via CRS to both the REC and MHRA by a delegated member of the trial team
- The final sign off and submission of the APR to the REC via email is delegated to a member of the trial team

5. Items Required

CCTU/TPL012 Development Safety Update Report Template

CCTU/FRM105 SmPC/IB Review Form

CTIMPs Safety Report Form for the REC

Annual Progress Report Form for CTIMPs

6. Summary of Significant Changes

IB/SmPC and their respective review forms to be provided with the DSUR to the regulatory team

APR and DSUR submission process clarification

Change to DSUR review responsibilities

Update to regulatory team email

CTC will now obtain the DSUR template from Q-Pulse directly

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 current DSUR template must be obtained from Q-Pulse by the Clinical Trial Coordinator for completion
- The CTO will be the point of contact 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

- For trials with a significant number of reported safety events, reconciliation of safety events with the PV team can occur at any point between the data cut off and provision of the draft DSUR to the CTO
- A draft DSUR should be provided to the CTO via email 3 weeks prior to the submission deadline
- The currently approved SmPC/IBs must be provided alongside all new SmPCs / IBs that have been released during the reporting period.
- All completed and signed SmPC/IB review forms from the current reporting period must also be provided to the CTO
- The CTO and PV Team will review DSURs and complete the 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
- The CTO will check the SmPC/IB review forms to ensure they are appropriately completed and signed (and cover all released versions of the SmPC/IB during the period). During the review process, any necessary alterations agreed should be made in the relevant sections, as appropriate
- The final DSUR will be reviewed and signed by the Sponsor's representative and the CI if available

For CTIMPs not submitted via CRS:

- The CTO will submit the signed final 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 CTO will provide the CI/CTC 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
- The CTO 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

For CTIMPs submitted via CRS:

- The CTO will provide the signed final DSUR and the supporting documents i.e. Cover letter, approved reference safety information, publication and abstracts (as applicable) to the CTC for upload and submission via the CRS
- The CTC will submit the final DSUR package via the CRS reporting function. This submits the DSUR to both the MHRA and REC
- The CTC will forward any correspondence from the MHRA and REC to the CTO for the Sponsor file
- It is the CI's responsibility to ensure the DSUR and accompanying documents (including the Safety Report Form), acknowledgements and any correspondence with the MHRA 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

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

- The CTO will be the point of contact 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
- For trials with a significant number of reported safety events, reconciliation of safety events with the PV team can occur at any point between the data cut off and provision of the draft APR to the CTO.
    - Three weeks prior to the submission deadline, the following should be provided to the CTO via e mail:
    - A draft APR
    - The currently approved SmPC/IBs with any new SmPCs/IBs that have been released during the reporting period.
    - All SmPC/IB review forms from the current reporting period
- The CTO and 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
- The CTO will check the SmPC/IB review forms to ensure they are appropriately completed and signed (and cover all released versions of the SmPC/IB during the period)
- During the review process, any necessary alterations agreed should be made by the CI, CTC, CTO or PV team in the relevant sections, as appropriate
- The final APR will be signed by the CI

7.3.1. For CTIMPs NOT submitted via CRS:

NOTE

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

- The CTO will submit the final 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 CTO will provide the CI/trial team with a copy of the final full APR in lieu of DSUR 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
- The CTO will file the APR in lieu of DSUR submission package and a copy of the MHRA upload email, as a confirmation that the DSUR has been submitted to the MHRA, in the Sponsor file

7.3.2. For CTIMPs submitted via CRS:

NOTE

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

- The CTO will provide the final APR and the supporting documents:
  - Cover letter,
  - Approved reference safety information,
  - A list of all serious adverse reactions,
  - Publication and abstracts (as applicable) to the CTC for upload and submission via the CRS
- The CTC will submit the final full APR in lieu of DSUR package via the CRS reporting function. This submits the APR in lieu of DSUR to both the MHRA and REC
- The CTC will forward any correspondence from the MHRA and REC to the CTO for the sponsor file
- It is the CI's responsibility to ensure the APR in lieu of DSUR and accompanying documents (including the Safety Report Form) and acknowledgements are filed in the TMF
- For multi-centre trials the CI is responsible for the distribution of the APR in lieu of DSUR to all participating sites

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 cuh.ccturegulatory@nhs.net email for inclusion in the Sponsor file
- The trial team should circulate the APR form to participating sites as soon as possible but normally 10 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.

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