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.

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
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
IMP	Investigational Medicinal Product
IQM	Ideagen Quality Management formally Q Pulse software
MHRA	Medicines and Healthcare Products Regulatory Agency
PV	Pharmacovigilance
REC	Research Ethics Committee
RSI	Reference Safety Information
SAR	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 for CTIMPs NOT submitted via CRS, 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 CTIMPs NOT submitted via CRS)
- For CRS trials, the DSUR is submitted via CRS to the MHRA by a delegated 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

6. Summary of Significant Changes

The MHRA are no longer accepting annual progress reports (APRs) as shortened DSURs for Type A Notification trials. Instead a DSUR will need to be submitted with relevant sections of the report that are applicable to the trial completed.

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 (For CTIMPs not submitted via CRS)
- Payment for DSUR submissionto the MHRA must be completed prior to online submission
- The proof of payment must be included with the DSUR submission package
- 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 A, B, C Trials

- The current DSUR template must be obtained from IQM by the Clinical Trial Coordinator for completion. Details on what to include in each section and whether the section is applicable to all trials are included in the template.
- 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
- The CTC is responsible for ensuring that payment for the DSUR submission has been completed via MHRA Pay
    - A submission number must be entered into the portal. The format for the submission number is DSUR-[First 5 Digits of CTA Number]-[IMP Name]-[Payment Date (DD/MM/YYY)]. E.g. DSUR-24551- APIXABAN-10/08/2024

  - The email receipt must be included in all DSUR submissions and should be emailed to the CTO as part of the DSUR submission package
  - The regulatory team will not make any payments on behalf of trial teams
- 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), receipt of payment, 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), receipt of payment 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 the MHRA *
- ** A separate notification to the REC is not required; the MHRA will liaise with the REC if deemed appropriate.*
- It is the CI's responsibility to ensure the DSUR and accompanying documents 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. (Note: if the DSUR contains potentially un-blinding information, it must not be shared with participating sites)

7.3. 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.

** End of trial declaration submitted to the relevant authority*

7.4. The Annual Progress Report

From 1st June 2024, Trial teams are no longer required to submit Annual Progress Reports; however, they are still required to report anything that materially affects the ethics of a trial application.

There is no change to the expectation that the Chief Investigator should submit this as an amendment.

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

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 26 March 2024

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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