STU-SOP-TM-007 – Standard Operating Procedure on Annual Progress Reports and Development Safety Update Reports

1. Purpose and Definitions

This Standard Operating Procedure (SOP) describes the procedure of drafting, reviewing and submission of Annual Progress Reports (APRs) to the NHS Research Ethics Committee (REC) and NHS or social care organisation where the research is being conducted i.e. Health and Care Research Wales, Health Research Authority (HRA) or equivalent for other devolved nations. Also, the process for drafting, reviewing and submission of full or short form Development Safety Update Reports (DSURs), for Clinical Trials of Investigational Medicinal Products (CTIMPs) to the Medicines and Healthcare products Regulatory Agency (MHRA), or other regulatory bodies.

Definitions	
Interventional Clinical Research Projects	Involve humans as participants and an invasive experimental element that may or may not allocate the treatment by randomisation. Such projects involve a single person or groups of people, using material or behaviours (previously collected or not) from those people. They include surgical and imaging trials, trials providing food supplements or herbal remedies, cosmetics, microorganisms or medicines (whether licensed or not), device trials (whether CE marked or not), used in usual or non-usual clinical practice.
Non-interventional Clinical Research	Involve humans as participants but does not involve an invasive experimental element and may or may not allocate the treatment by randomisation. Such projects involve a single person or groups of people, using material or behaviours (previously collected or not) from those people. They include questionnaire or qualitative studies, observation or cohort studies and retrospective data analysis.

2. Background

An APR should be submitted annually to the NHS REC that provided the favourable ethical opinion until the end of the project. A copy must also be sent to the relevant NHS or social care organisation where the research is being conducted.

The NHS REC may authorise one APR to be submitted for closely linked projects.

A DSUR must be submitted annually to the MHRA (or equivalent regulator) for CTIMPs. For certain Type A projects authorised under the Clinical Trial Notification Scheme a shortened DSUR may be used in lieu of the detailed full DSUR required for Type B and C projects.

A Sponsor can submit a single DSUR for multiple research projects involving one medicinal product (MP).

A DSUR should be used as the annual submission to regulatory bodies outside of the UK. The short format DSUR would not be acceptable.

Annual APRs and DSURs should be submitted whether or not recruitment has commenced.

3. Roles and Responsibilities

The Sponsor is responsible for ensuring that the APR and appropriate DSUR (when required) are completed for all research projects.

The Chief Investigator (CI) is responsible for overseeing the completion of the APR and DSUR and confirming the accuracy of content while ensuring that the blind is maintained for ongoing projects. The CI also has responsibility for checking that the Reference Safety Information (RSI), for MP research projects, remains applicable.

The Trial Manager (TM) or delegate is responsible for coordinating the completion of the APR and DSUR, liaising with the Sponsor and ensuring that only unblinded personnel review the final DSUR while blinded personnel review only initial drafts. The TM will also be responsible for coordinating the review of the RSI documents.

External use of SOP: this SOP and Associated Documents (AD) may be used for research projects not adopted by STU where Swansea University (SU) staff and associated NHS organisations require guidance. In such instances, oversight responsibility for any associated tasks will not be the responsibility of STU.

4. Procedure

4.1 Annual Progress Reports – Draft and Submission

The first APR is due 12 months after the date of the favourable opinion for any research project and must be submitted within 30 days of this date.

There are separate forms to use for submitting APRs depending on the type of research project. The latest versions are available via www.hra.nhs.uk. Drafted reports should be sent to Sponsor or delegate for review when required.

Usually an APR covers one project only. However, the REC may permit submission of an APR to cover projects which are closely connected.

For Type A CTIMPs, it may be possible to submit an APR in lieu of a full DSUR.

Copies of all reports should be submitted to the relevant NHS or social care organisation.

4.2 Development Safety Update Report – Draft and Submission (CTIMPS only)

Following a Clinical Trial Authorisation (CTA) involving a MP, a sponsor/ CI as delegate must submit an annual DSUR:

- Type A CTIMPs – authorised under the Clinical Trial Notification Scheme and not part of a multi-study MP development programme may submit a shortened DSUR in the form of the APR. A cover letter to the MHRA and REC should state that the APR is in lieu of a full DSUR and include the EudraCT and Clinical Trial Authorisation (CTA) reference numbers and a list of all Serious Adverse Reactions.
- Type B or C CTIMPs – must submit a full DSUR containing all required information as detailed in the DSUR template (STU-AD-FRM-023) to the MHRA (or equivalent regulator).

A DSUR is required 12 months after the date of a CTA for NHS and Academic Sponsors. Alternatively, it may be aligned to the Developmental International Birthdate (DIBD) of the MP when the manufacturer is submitting the DSUR.

The European Medicines Agency (EMA) provide detailed guidance of the requirements for reporting to all regulatory authorities and ethics committees in each member state. This guidance document can be found as STU-AD-GDN-008.

Where possible, the responsibility for the completion of the DSUR should be with the manufacturer/supplier of the MP.

Where the research team do not have access to information required for the DSUR (e.g. manufacturing issues, marketing status, non-clinical data) this should be recorded as 'not applicable for this report'. DSUR sections in the template should not be removed or left blank.

For blinded ongoing projects, blinded personnel will only review an initial draft of the DSUR. The final version of the DSUR with unblinded safety data will be reviewed only by unblinded personnel e.g. by the Data Monitoring Committee (DMC). This process shall be coordinated by either the TM or delegate to ensure that the blind is maintained. Sponsor will allocate unblinded personnel to review when appropriate.

The shortened DSUR can only be submitted for individual CTIMPs. A Sponsor can still submit a single full DSUR for multiple research projects involving one MP.

A full DSUR should be used as the annual submission to regulatory bodies outside of the UK. The short form DSUR would not be acceptable.

4.3 Multiple Projects involving one medicinal product

An APR is required for all research projects involving a MP that have received a favourable opinion, regardless of whether recruitment has begun.

Where there is involvement with several CIs, the Sponsor will be responsible for recognising and ensuring collaboration in the completion of one or several DSURs for the MP as the regulations allow.

Where STU are involved in the multiple research projects there will be coordination with relevant TMs over responsibility for completion of the DSUR. Where STU are not involved in all research projects there will be liaison with the Sponsor over STU involvement in the multiple project DSUR or the drafting of separate DSURs.

If a DSUR submission incorporates more than one research project by the same Sponsor, the earliest CTA authorisation date may be used as the basis for the annual completion date

When unblinding of data are required, each DMC will review their own project data. The TM or delegate will compile the data into the final report. Each DMC will be asked to comment on the near final / final document before submission. The blind should be maintained for all projects.

4.4 Review and Approval of Annual Progress Report and Development Safety Update Reports

The Sponsor requirements for review of APRs and DSURs should be followed. Often the requirements are:

- Non-interventional project: potentially no sponsor review, the CI or delegate shall ensure signed APRs are submitted to the NHS REC that provided the favourable opinion.

- Interventional research project: the CI or delegate shall forward the draft APR or DSUR (CTIMPS only) to the Sponsor or delegate at least 2 weeks prior to the submission date. The Sponsor shall review and confirm whether the submission is acceptable or request changes and further review.

When involved, the Sponsor will advise the CI (or delegate) in writing when the review has been completed.

4.5 Submission Timelines, Process and Documentation

The Sponsor timelines for review and submission of APRs or DSURs should be followed. It is usually the responsibility of the CI to submit all reports for review.

APRs for all research projects must be submitted to the NHS REC as electronic copies by email.

DSURs and shortened DSURS must be submitted to the MHRA portal for which you need to register via Register to make submissions to the MHRA - GOV.UK (www.gov.uk) using the Human Medicines Tile
Submissions to other EU regulatory bodies are via the Common European Submission Portal (CESP) via https://cespportal.hma.eu/. Training slides are available on the use of the portal for registered users. When submitting a DSUR, please select “regulatory activity G0042 – Development Safety Update Reports”.

Submission details serve as evidence of DSUR submission in lieu of an acknowledgment.

When DSURs or any other safety reports e.g. expedited adverse reactions, DMC reports are submitted to the REC they should be accompanied by a completed REC CTIMP Safety Report form. The most recent version of the form will be available on the HRA website http://www.hra.nhs.uk/resources/during-and-after-your-study/nhs-research-ethics-committee-rec-ctimp-safety-report-form/.
The REC will authorise and return the completed form. This notification must be filed in the TMF.

In all cases, APRs and DSURs must be submitted regardless of whether recruitment has begun, including an explanation when required of why there has been no recruitment.

4.6 Annual Reference Safety Information Review

The appropriate Investigator Brochure (IB) or Summary of Product Characteristics (SmPC) in effect at the start of the reporting period must be used as the RSI for the DSUR. The IB or SmPC used in MP projects require at least an annual review which is recorded on the DSUR template (STU-AD-FRM-023).

If the IB or SmPC have been revised during the reporting period and not previously submitted to the MHRA or other regulatory authority, a copy of the revised RSI must be provided as an attachment to the DSUR. If there is a substantial change to the RSI there will be a need to submit a substantial amendment (to both the REC and MHRA) to update the RSI in the protocol prior to implementing a change to the RSI.

It is recommended that the IB/SmPC review is undertaken immediately prior to the start of drafting the DSUR submission.

4.7 Distribution and Filing

For CTIMPS a signed paper copy of each APR and DSUR must be filed in the Trial Master File (TMF). For STU adopted research studies, if the TMF is accessible to personnel involved in the conduct of a blinded project and contains unblinded participant data, the signed paper copies will be retained by the STU Manager or delegate until the end of the project when they will be inserted into the TMF.

For all other research, the APR may be stored as an electronic document with appropriate controlled access to maintain the blind where required.

Where a DSUR covers multiple projects, a copy must be held in each TMF.

The MHRA and where relevant CESP submission details must be filed in each TMF to demonstrate DSUR submission.

5. References

- Health Research Authority website (HRA) - http://www.hra.nhs.uk/
- Medicine and Healthcare products Regulatory Agency website (MHRA) - https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/services-information
- UK policy framework for health and social care research (2017) - https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/
- UK Medicine for Human Use (Clinical Trials) Regulations 2004 - http://www.legislation.gov.uk/uksi/2004/1031/contents/made
- Common European Submission Portal (CESP) - https://cespportal.hma.eu/Account/Login?ReturnUrl=%2f

It is assumed that by referencing the principal regulations that all subsequent amendments are included in this citation.

6. Associated Documents

Number	Title	Location
STU-AD-GDN-008	ICH guideline E2F on development safety update report	Q-Pulse
STU-AD-FRM-023	DSUR template	Q-Pulse

7. Abbreviations

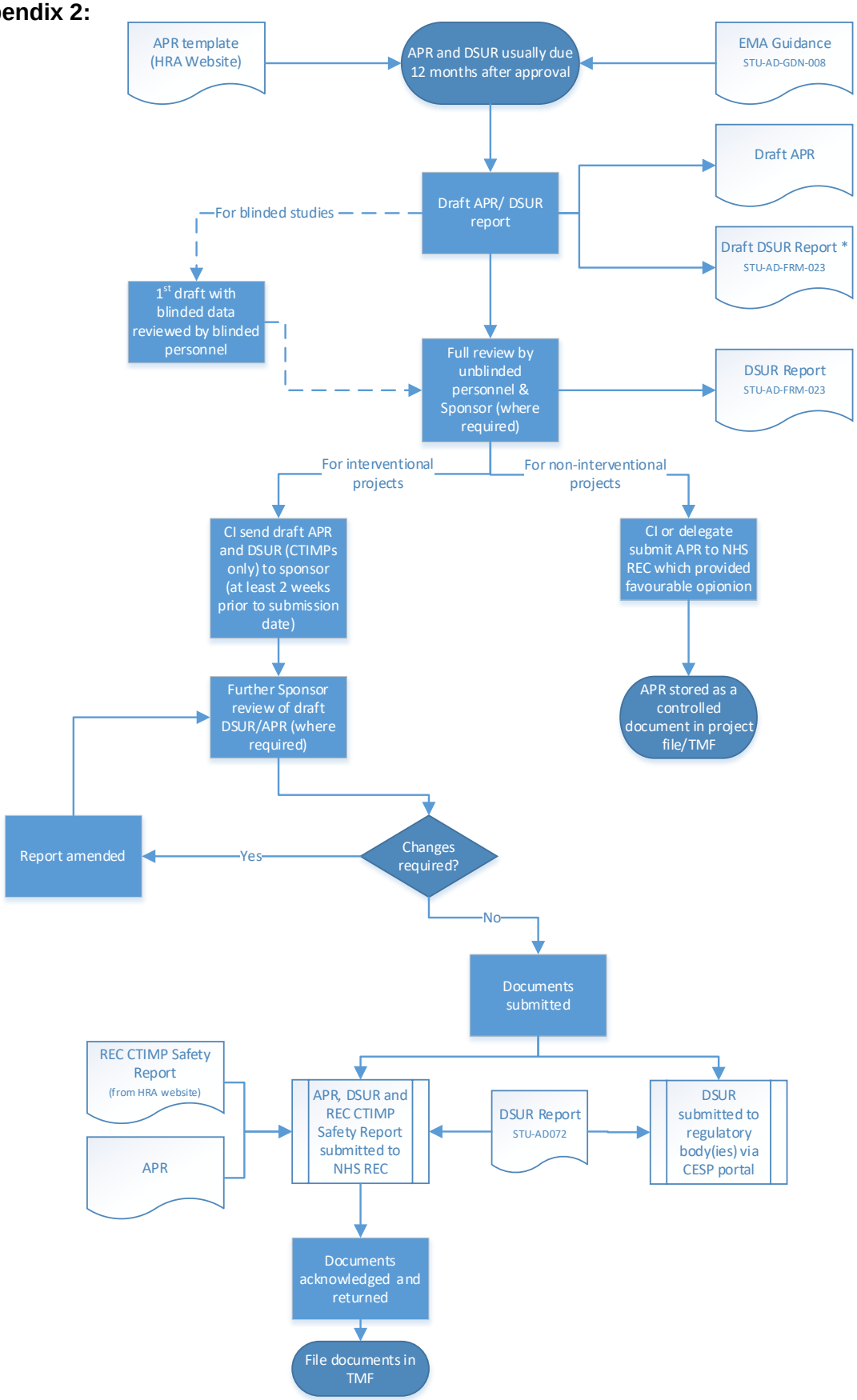
List of Abbreviations	
AD	Associated Document
APR	Annual Progress Reports
CESP	Common European Submission Portal
CI	Chief Investigator
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DIBD	Development International Birth Date
DMC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
EMA	European Medicines Agency
HRA	Health Research Authority
IB	Investigator Brochure
MHRA	Medicines and Healthcare products Regulatory Agency
MP	Medicinal Product
REC	Research Ethics Committee
RSI	Reference Safety Information
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
STU	Swansea Trials Unit
SU	Swansea University
TM	Trial Manager
TMF	Trial/Project Master File

8. Appendices

Appendix 1: Document History

Version No:	4	**Effective Date:**	22-Apr-2024
Description of changes:	Updated to SOP Template v5		

Appendix 2:



* APR may be used as a shortened DSUR for some Type A CTIMPs.