Document Title: Preparation of Regulatory Progress Reports including Periodic Safety Reporting and Annual Reports

Document Number: PTUC SOP062

Staff involved in development: *Job titles only*	Senior R&D Manager, R&D Administration Manager, Clinical Project Managers
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Directorate:	Research and Development
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Summary of Significant Change(s) (for this version only)

Section(s):	Modification:
All	Up-dated links due to the introduction of the Health Research Authority
Section 4	Split up the sections to make them easier to read – no new content

Key Points of this Document

- This document sets out the procedures to be followed by all Papworth Staff who are involved in the preparation, review or dissemination of progress reports for ethics committees and regulatory bodies (including but not limited to the MHRA) for studies managed by Papworth Trials Unit Collaboration (PTUC) or sponsored by Papworth Hospital NHS Foundation Trust. These progress reports include annual reports and Development Safety Update Reports (DSUR).

- It is a requirement of ethical and regulatory approval that annual reports are submitted.
- It provides guidance on the timing and content of DSURs to ensure compliance with the Regulatory Bodies.

1 Purpose and Content

a. This document defines the Trust's research procedures for preparation and submission of periodic safety reporting and annual reports including Development Safety Update Reports (DSURs) for research studies and Clinical Trials managed by Papworth Trials Unit Collaboration (PTUC) or sponsored by Papworth Hospital NHS Foundation Trust.

b. The document describes the requirements for safety reporting to the regulatory authorities so as to aid compliance with Good Clinical Practice (GCP: 'a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected').

c. The document provides guidance on when and how to prepare annual reports and DSURs so as to comply with the regulatory requirements. The DSUR is a standard document for the periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions (Europe, Japan, United States). Annual submission of DSURs meets the requirements of the EU regulators and so takes the place of the EU Annual Safety Report.

d. The objective of the DSUR is to provide a comprehensive review and evaluation of the pertinent safety information collected during the reporting period. This will:

1. Examine whether the information obtained by the sponsor during the reporting period is in accordance with previous knowledge of the drug's safety
2. Describe any new safety issues
3. Summarise the current understanding and management of the known and potential risks
4. Provide an update on the status of the clinical investigation / development programme and study results

e. The reporting of adverse events (pharmacovigilence) is outside the scope of this SOP and is described in PTUC SOP012: Adverse Event Reporting.

2 Roles & Responsibilities

a. This Policy applies to all personnel that are conducting research at the Trust.

b. The trial sponsor is responsible for the preparation, content and submission of the annual reports / DSUR although they may delegate the actual task to a competent member of the study team. This delegation must be on the sponsor / chief investigator delegation log.

3 Policy

a. This SOP is mandatory and, as per the Trust's Information Governance and Records Management framework, non-compliance with this SOP may result in disciplinary procedures.

4 Procedure

4.1 Procedure

a. Table 1 details the reporting requirements for all research studies and highlights the specific requirement for Papworth Sponsored Clinical Trials of Investigational Medicinal Products (CTIMPs). Copies of all annual and end of study reports must be provided to Papworth R&D at the time of submission to the REC and MHRA (if applicable).

b. In order to ensure that progress and safety reports are submitted on time it is recommended that the sponsor (or their delegated representative) makes use of the following tools:

- Reminders in calendars
- Manual spreadsheets
- Electronic trackers with electronic alerts

Table 1: Regulatory Progress reporting requirements

Type of Report	Reporting requirements	Useful links
Development Safety Update Reports (DSURs) for CTIMPs	Development Safety Update Reports (DSURs) must be provided to: • The MHRA • The REC that granted approval • The Sponsor (where Papworth R&D is the sponsor or cosponsor this will be the R&D department) Reports must be provided at yearly intervals from the date of the MHRA Clinical Trial Authorisation or original CTX/DDX exemption (for trials ongoing on / before 1 May 2004). The final signed DSUR must be submitted to the MHRA as a pdf document within 60 days of the data lock point	Each submission of a DSUR to the MHRA for Papworth Sponsored studies should use the template provided on the ***intranet (FRMxxy):*** http://www.papworthhospital.nhs.uk/research/index/template-documents/ See Section 4.1 for what the DSUR should contain.
Annual Progress Reports for all research studies	All studies submit an annual progress report to: • The REC that granted the original approval • The Sponsor (where Papworth R&D is the sponsor or cosponsor this will be the R&D department)	For CTIMPs, Chief Investigators submit the Annual Progress Report in addition to the Annual Safety Report, using the specific CTIMP Annual Progress Report Form http://www.hra.nhs.uk/resources/during-and-after-your-study/nhs-rec-annual-progress-report-forms/ Non CTIMPs include any safety information and SAE line listing within the Annual Progress Report using the specific Annual

		Progress Report form for all other research http://www.hra.nhs.uk/resources/during-and-after-your-study/nhs-rec-annual-progress-report-forms/
End of Study Report non CTIMP and other research	Chief Investigator will submit an end of study report to: • Sponsor (where Papworth R&D is the Sponsor or Cosponsor this will be the R&D department) • REC that granted approval	The report should include information on whether the study achieved its objectives, the main findings, and arrangements for publication or dissemination, including feedback to participants. http://www.hra.nhs.uk/resources/during-and-after-your-study/end-of-study-notification-studies-other-than-clinical-trials-of-investigational-medicinal-products/
End of Study Report CTIMP	Within 90 days from conclusion (or 15 days in case of early termination) the Chief Investigator will submit an end of study report to: • The Sponsor (where Papworth R&D is the sponsor or cosponsor this will be the R&D department) • The MHRA • The REC that granted the original approval • Papworth R&D department	Chief Investigator submits the End of Trial Declaration from EudraCT website: http://www.hra.nhs.uk/resources/during-and-after-your-study/end-of-study-notification-clinical-trials-of-investigational-medicinal-products-ctimps-eudract-form/

4.2 Development Safety Update Report (DSUR) content

a. The purpose of the DSUR is to be IMP specific. In general, a single DSUR will be prepared for each IMP under investigation in clinical trials. If a single IMP is being investigated within the same disease area in multiple trials, one DSUR will cover all trials and the Development International Birth Date (DIBD) will be the first Clinical Trials Authorisation

(CTA) of these trials. The DIBD is the date of the MHRA Clinical Trial Authorisation and this is used to determine the start of the annual reporting period for the DSUR.

b. **However, non-commercial organisations who are not developing the drug, may submit separate reports. The rationale for separate DSURs should be provided in each report. A DSUR for a comparator, placebo or Non Investigational Medicinal Product is not required.**

c. One DSUR for an IMP that is being investigated in multiple trials with different patient populations and in different therapeutic areas, may be produced and submitted, or an individual DSUR may be submitted each time.

d. In general, a single DSUR should be prepared for clinical trials involving a fixed combination product (i.e. a product consisting of at least two active ingredients in a fixed dose that is administered in a single dosage form). If the sponsor is also conducting clinical trials with individual components of the fixed combination product, separate DSURs should be submitted for each component.

1. For trials involving multi-drug therapy (i.e. combinations of drugs that are not fixed), the sponsor can either prepare:
   i) A DSUR for the multi-drug therapy
   ii) DSURs for one or more of the individual components. In this case, information on the multi-drug therapy trials can be included in the DSURs of one or all of the components

The following table provides examples of how to prepare DSURs for multi-drug therapies:

Multi-drug therapy used in clinical trial(s)	DSUR
Investigational Drug (A) + marketed drug(s) (X, Y, Z)	Either a single DSUR focusing on (A + X + Y + Z) or a single DSUR focusing on (A) including data on the multi-drug therapy
Two Investigational Drugs (A) + (B)	Either a single DSUR focusing on (A + B) or Two Separate DSURs (A) and (B), each including data on the multi-drug therapy
Two (or more) Marketed Drugs as an Investigational Drug Combination (X, Y, Z)	A single DSUR focusing on the multi-drug therapy

e. Where an unlicensed IMP is being developed by one or more Partner Organisations, one DSUR will be submitted annually for the IMP. This DSUR will cover IMP and safety data from all trials being conducted within the reporting period.

f. Either the Investigators brochure (IB) or Summary of Product Characteristics (SmPC) that is in effect at the start of the DSUR reporting period should serve as the reference safety information. This will be used to determine whether the information received during the reporting period remains consistent with previous knowledge of the safety profile of the investigational drug.

g. The IB or SmPC in place at the beginning of the reporting period should be appended to the DSUR, regardless of whether the IB or SmPC was altered during the period of the DSUR. The Reference Safety Information (RSI) in place at the beginning of the period should be the reference for the expectedness assessments in the DSUR line listings, regardless of whether the RSI was updated during that reporting period.

h. If the IB or SmPC has been revised during the DSUR reporting period, the sponsor should also submit the correct version and list any significant safety-related changes in the relevant section of the DSUR.

4.3 DSUR Preparation

a. The DSUR should indicate the version number and date of the IB used for this purpose.

b. The start of the annual period for the DSUR is the month and date of the Development International Birth Date (DIBD). The data lock point (date at which no further data can be added) of the DSUR will be the last day of this one-year reporting period.

c. The Papworth DSUR Template should be used when preparing a DSUR for a Clinical Trial managed by PTUC or sponsored by Papworth Hospital NHS Foundation Trust. A copy is available on the R&D website (http://www.papworthhospital.nhs.uk/research/index/template-documents/).

d. Where there is no information available or the section is not applicable, this should be clearly stated.

e. The DSUR MUST be signed and dated by the Chief Investigator and Sponsors representative.

f. The final signed DSUR must be submitted to the MHRA as a pdf document within 60 days of the data lock point. The document, cover letter and any accompanying information will be submitted via the Common European Submission Portal (CESP). The Trial Manager for each CTIMP will be registered on CESP.

g. A paper copy of the report must be submitted to the approving REC(s).

h. A paper copy of the report must be filed in the Sponsor File

i. For multi-centre trials, a copy of the DSUR submission should be sent to all participating sites for inclusion in their site files.

j. A DSUR must be submitted during every 12 months until the End of Trial notification has been submitted to the Competent Authority within the Member State.

5 Risk Management / Liability / Monitoring & Audit

a. The R&D department will ensure that this SOP, and any future changes to it, are adequately disseminated.

b. The R&D department will monitor adherence to this SOP via the routine audit and monitoring of individual clinical trials and the Trust's auditors will monitor this SOP as part of their audit of Research Governance. From time to time, the SOP may also be inspected by external regulator agencies (e.g. Care Quality Commission, Medicines and Healthcare Regulatory Agency).

c. In exceptional circumstances it might be necessary to deviate from this SOP for which the written approval of the Senior R&D Manager should be gained before any action is taken. SOP deviations should be recorded including details of alternative procedures followed and filed in the Investigator and Sponsor Master File.

d. The Research and Development Directorate is responsible for the ratification of this procedure.

Further Document Information

Approved by: *Managment/Clinical Directorate Group*	Research and Development Directorate
Approval date: *(this version)*	[Current active version approved date]
Ratified by Board of Directors/ Committee of the Board of Directors:	STET
Date:	N/A
This document supports: *Standards and legislation*	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. Research Governance Framework for Health and Social Care (2005)
Key related documents:	Trust Research Policy [Insert list of linked or relevant documents to this SOP]

Equality Impact Assessment: Does this document impact on any of the following groups? If YES, state positive or negative, complete Equality Impact Assessment Form available in Disability Equality Scheme document DN192 and attach.

Groups	Disability	Race	Gender	Age	Sexual orientation	Religious & belief	Other
Yes/No	NO	NO	NO	NO	NO	NO	NO
Positive/Negative							

Review date:	

Version Control

Version	Date effective	Valid to	Approved by	Date of approval
1.0				
2.0				
3.0				
4.0				

I certify the contents of this SOP has been reviewed and ratified

..... 18 Aug 2016

Signed by Dr Ian Smith, Clinical Director of R&D Date

SOP release date: 6/9/16