Plymouth Research and Development

University Hospitals Plymouth NHS Trust

Standard Operating Procedure

Please refer to https://www.plymouthhospitals.nhs.uk/research-sops to ensure the latest version of this document is in use. Printed copies are uncontrolled.

Title:	Periodic Reporting to the Research Ethics Committee and Medicines and Healthcare products Regulatory Agency		
Approver		Document No:	T9
Name:	Chris Rollinson	Version No:	4.0
Signature:		Effective Date:	May 2021
Date:	11th May 2021	Review Date:	May 2023

1. Purpose

The purpose of this SOP is to outline the periodic progress and safety reporting requirements for research studies sponsored by University Hospitals Plymouth NHS Trust (UHP).

After a research study has received all necessary approvals for it to proceed, various bodies and organisations will be interested in its progress. This is particularly the case for CTIMPS which are regarded as high-risk. Annual Progress Reports (APR) must be reported to REC for all studies, and for CTIMPS an annual DSUR must be submitted to MHRA.

The Sponsor is accountable for ensuring periodic reports are submitted within appropriate timelines. Where UHP is the Sponsor, responsibility for compiling and submitting these reports may be delegated to the CI.

2. Scope

Research sponsored by UHP.

3. Responsibilities

The CI or their delegate are responsible for compiling and submitting periodic reports to both the NHS REC and the MHRA (if applicable, CTIMP only). The RD&I Dept. Office when acting as sponsor should have oversight of the process. Individuals who should read this SOP include but not limited to the CI, Trail Manager / Co-ordinator, Senior RD&I Managers and the RD&I Research Facilitators.

4. Documents needed for this SOP

- List any documents here which are needed for this SOP such as templates.

5. Related documents

National Research Ethics Service (NRES)
Annual Progress Reports
www.nres.npsa.nhs.uk/applications/after-ethical-review/annual-progress-reports/#progressReview

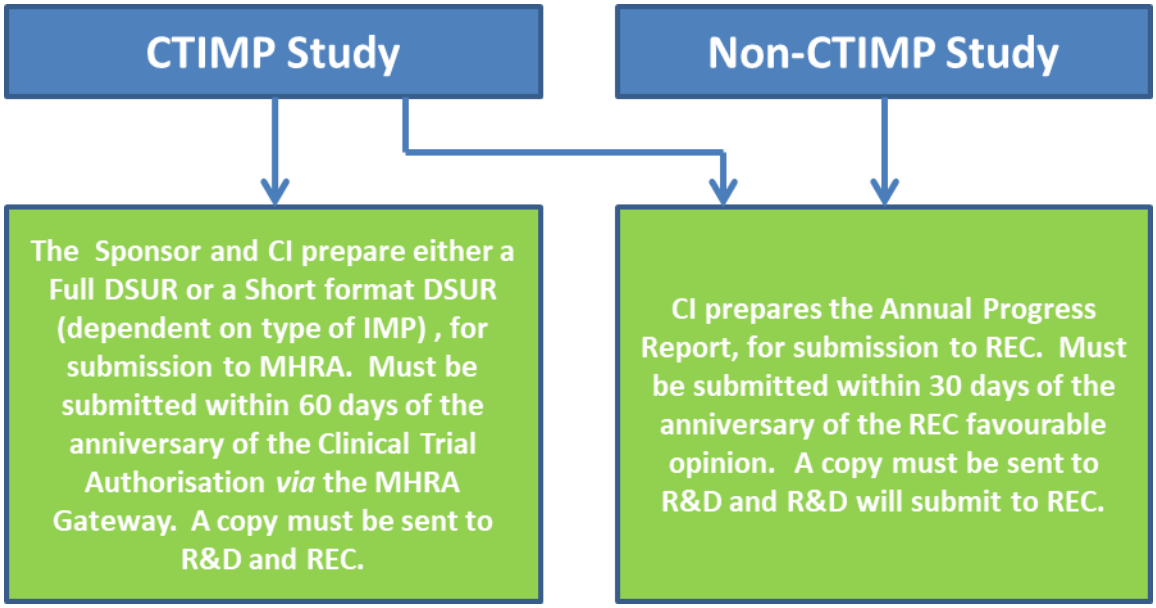
Medicines & Healthcare products Regulatory Agency (MHRA)
Safety Reporting: SUSARs & ASRs
www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm

Note for Guidance on Development Safety Update Report (EMEA/CHMP/ICH/309348/2008)
European Medicines Agency ICH Topic E2F
www.ich.org/products/guidelines/efficacy/efficacy-single/article/development-safety-update-report.html

6. Definitions

APR	Annual Progress Report
CESP	Common European Submission Portal
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
DIBD	Development International Birth Date
DLP	data lock point
DSUR	Development Safety Update Report
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
HCA	Health Care Assistants
HRA	Health Research Authority
IND	Investigational New Drug
MHRA	Medicines and Healthcare products Regulatory Agency
UHP	University Hospitals Plymouth NHS Trust
PI	Principal Investigators
RD&I	Research Development & Innovation
REC	Research Ethics Committee
RO	Research Office
SOP	Standard Operating Procedure
US	United States (America)

7. Process map(s)/ flow chart(s)



8. Procedure

Step	Action	Responsibility
1	**Where UHP acts as Sponsor** For CTIMPs, R&D will issue reminders at least 4 weeks before reports are due. For CTIMPS, where R&D has not received a copy of the report by the due date, an additional reminder will be sent. In the event that the CI fails to provide a copy of the reports submitted within the regulatory timeframes, this will constitute a breach of Good Clinical Practice and the Non-compliance procedure will be followed accordingly, see SOP on Non-compliance Reporting T6. Guidance regarding preparation and submission of reports is outlined below.	R&D & CI
2	**Periodic Progress Reporting to REC** REC has a duty to monitor research that has been granted a favourable ethical opinion by it. In order to do so, periodic progress reports are required to be submitted. Progress reports must be submitted to the REC which granted the favourable opinion. The due date for reports is 12 months after the date on which the favourable opinion was given and each year thereafter until the end of the trial. Where a REC regards a trial as particularly high-risk, they may require quarterly or even monthly reports to be submitted. This will be detailed in the approval letter and must be adhered to.	R&D & CI

	The HRA has produced templates which must be used, available *via* the HRA website: www.hra.nhs.uk/resources/during-and-after-your-study/nhs-rec-annual-progress-report-forms/. Separate forms are available for CTIMP, non-CTIMP studies, Research Tissue Banks and Research Databases. Forms should be completed in typescript and signed by the CI. A paper copy should be sent to the REC within 30 days of the due date, and a copy sent to the R&D Office. Once the first progress report has been received by the REC, the chair has discretion to waive the requirement for further reports upon request. This must be agreed in writing by REC and forwarded to R&D. This may be appropriate where a study has completed recruitment and intervention but has a long period of follow-up with minimal participant involvement.	
3	**Development Safety Update Report (DSURs) (CTIMPs only)** The DSUR is intended to be a common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions. US and EU regulators consider that the DSUR, submitted annually, would meet national and regional requirements currently met by the US IND Annual Report and the EU Annual Safety Report, respectively, and will therefore take the place of existing safety reporting requirements reports.	Information only
4	**Short format DSUR**. MHRA recognises that not all trials are the same in terms of risk and many trials are conducted on already marketed and well-known drugs, with minimal intervention, and closely align with normal clinical practice. Therefore, low-risk trials the production of a full Development Safety Update Reports (DSURs) is not required, as many of the required fields are not relevant to these types of trials. MHRA has made available a short format DSUR form for sponsors of individual clinical trials authorised under the Notification Scheme (Type A trials: No higher than the risk of standard medical care). The short format DSUR form is substantially simpler and shorter form may be submitted *in lieu* of a full DSUR giving a significant time saving. This is not suitable for trials which are part of a multi-study development program and the full DSUR will still be required for these. The shorter form which you may use is the Health Research Authority Annual Progress Report form which can be found here: https://www.hra.nhs.uk/documents/1013/annual-report-form-for-ctimps.docx When submitting your annual report (short format DSUR), please indicate in your cover letter that this is an	R&D & CI

	Annual Progress Report (APR) *in lieu* of a full DSUR and include the EudraCT number and CTA reference number. You should include a list of all Serious Adverse Reactions in section 6 of the APR.	
5	**Full DSUR**. The main objective of a DSUR is to present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, by: (1) examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety; (2) describing new safety issues that could have an impact on the protection of clinical trial subjects; (3) summarising the current understanding and management of identified and potential risks; and (4) providing an update on the status of the clinical investigation/development programme and study results. A DSUR should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug. All safety issues discovered during the reporting period should be discussed in the text of the DSUR; however, it should not be used to provide the initial notification of significant new safety information or provide the means by which new safety issues are detected. The DSUR must be compiled annually for the duration of the clinical trial until the regulator has been notified of the end of the trial. This process must commence on the anniversary of the first international regulatory approval regardless of the approval status in the UK. The annual time point is referred to as the Development International Birth Date (DIBD) in EMA guidance. Reporting must occur within 60 days of the defined DIBD. For Trust studies if this is not known use the date of the MHRA approval of the study. If a Chief Investigator is conducting more than one trial using the same investigational medicinal product (IMP) one DSUR may be submitted for the IMP rather than submitting individual reports for each trial including that IMP. This should occur on the anniversary of the first regulatory approval anywhere in the world and this date is classed as single data lock point (DLP). Again, for Trust studies if this is not known use the date of the MHRA approval of the study. If there is a valid reason for submitting separate reports this should be clearly explained on the DSUR.	R&D & CI

DSUR Completion

R&D & CI

It is the responsibility of the Chief Investigator to complete the DSUR by reviewing the document and signing off the report if they are happy with it.

The DSUR template has a standard format and requires all sections to be completed to be a valid report. If a section is not applicable to the clinical trial (e.g., manufacturing issues, non-clinical data, and marketing status), or the information is not currently available this should be stated and explained where applicable. No section of the DSUR should be blank at the time of submission.

A template DSUR report with question specific guidance can be located on the RD&I Shared drive (G:\RandD\Shared\ Templates & Forms or research\Safety reports_DSUR).

DSURs for Combination Therapies

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 component(s) of the fixed combination product, separate DSUR(s) should be submitted for each component.

For trials involving multi-drug therapy, i.e., combinations of drugs that are not fixed, the sponsor can prepare either:

(1) A DSUR for the multi-drug therapy, or

(2) DSUR(s) 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 strategies for preparation of 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 (X + Y + Z)

	Reference Safety Information The Investigator's Brochure (IB) in effect at the start of the reporting period should serve as the reference safety information to determine whether the information received during the reporting period remains consistent with previous knowledge of the safety profile of the investigational drug. Section 7.1 of the DSUR should clearly indicate the version number and date of the IB used for this purpose. When an IB is not required by national or regional laws or regulations, the applicable national or regional product label should serve as the reference safety information. Usually, a single document should serve as the reference safety information. However, in certain circumstances, it might be appropriate to use more than one reference document to support the DSUR (e.g., for a DSUR providing information on an investigational drug used in combination and as monotherapy). If the IB has been revised during the reporting period and not previously submitted to the relevant regulatory authority, the sponsor should provide a copy of the current version of the IB as an attachment to the DSUR. Additional guidance is available via: www.ich.org/products/guidelines/efficacy/efficacy-single/article/development-safety-update-report.html The DSUR must be submitted to both the MHRA and REC and a copy must be sent to RD&I. Submissions to the MHRA must be made via CESP. RD&I are the account holder for CESP thus the CI should liaise with RD&I. Submissions to REC should be made by e-mail, accompanied by the CTIMP safety report form available from the HRA website: www.hra.nhs.uk/resources/during-and-after-your-study/nhs-research-ethics-committee-rec-CTIMP-safety-report-form/	
	The CI must ensure that a copy of the DSUR and Annual Progress Report (APR), acknowledgement and any other communication with the REC, Sponsor / RD&I are filed in the Trial Master File (TMF).	CI

9. Changes from last revision

Version Number:	4.0
Date Of Amendment:	May 2021
Details Of Amendment:	Updated SOP to include the use of a Short Format DSUR. SOP updated to the R&Ds latest SOP template.
Version Number:	3.2
Date Of Amendment:	29th Apr 2021
Details Of Amendment:	Addition of details of the Short format DSUR
	3.1
	Jan 2019
	Updated Trust and Dept. name. Reduce signature requirement to single senior RD&I Manager.
Version Number:	3.0
Date Of Amendment:	Aug 2017
Details Of Amendment:	Re-combined APR and DSUR SOPs. Updated SOP template and numbering system. Reviewed and updated SOP.
Version Number:	2.0
Date Of Amendment:	Apr 2014
Details Of Amendment:	Split SOP to cover only DSUR reporting
Version Number:	1.1 (minor amendment)
Date Of Amendment:	Mar 2012
Details Of Amendment:	Cover page - Change of SOP location address.