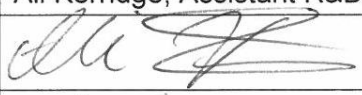
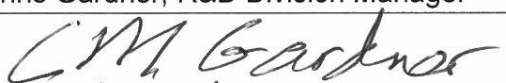
STANDARD OPERATING PROCEDURE

S31 – Reporting required for sponsored CTIMPS

Version	2.0
Effective Date	6th December 2017
Review Date	6th December 2020
Author & Position	Ali Kerridge, Assistant R&D Manager
Signature	
Date	5/12/17
Approver & Position	Chris Gardner, R&D Division Manager
Signature	
Date	6/12/17

Controlled document

This document has been created following the Royal Devon and Exeter NHS Foundation Trust Policy for the Development, Ratification & Management of Procedural Documents. It should not be altered in any way without the express permission of the author or their representative.

It is the responsibility of all users of this SOP to ensure that the correct version is being used. If you are reading this in a paper format please refer to Hub to confirm you have the latest version.

DISCLAIMER

This generic R&D Standard Operating Procedure (SOP) must be followed unless a study specific SOP exists.

Once printed this is an uncontrolled document

Full History			
Version	**Date**	**Author**	**Reason**
1.0			New policy
1.1	03/01/2014	Anoushka Tepielow Assistant R&D Manager	Update to reflect use of new data management system; typographical errors corrected; revision to template
2.0	01/09/2017	Ali Kerridge Assistant R&D Manager	Revision to template

Associated Trust Policies/ Procedural documents:	Research & Development Policy S04 Auditing Processes S22 Safety Reporting S02 Submitting Protocol Amendments S52 Urgent Safety Measures
Key Words:	R&D CTIMP Sponsorship Clinical Trial SOP Reporting

In consultation with:

- Clinical Trials Group (November 2017)
- QA Group (November 2017)

Contents

1 INTRODUCTION

When an organisation agrees to sponsor a clinical trial of an Investigational Medicinal Product (CTIMP) it takes on a major responsibility. The Research & Development Division (R&D) delivers this specific function for the Royal Devon & Exeter NHS Foundation Trust (hereafter referred to as the Trust).

2. PURPOSE

This document describes the procedure(s) required to support preparation and submission of mandatory and locally required reports relating to clinical trials of an investigational medicinal product (CTIMP) for which the Trust has sponsorship responsibilities.

The list of reports includes:

- Annual Safety Reports
- Annual Progress Reports
- Temporarily halting a study
- End of Trial
- Sponsorship oversight

3. SCOPE

This SOP is applicable to all CTIMPs sponsored by the Trust.

The SOP is applicable to Chief Investigators (CI), delegated trial team members involved in Trust-sponsored CTIMPs and R&D team members undertaking sponsor activities on behalf of the Trust.

Where responsibility for reporting (or part of) is delegated to a Clinical Trials Unit (CTU), this SOP is also applicable to the assigned Trial Manager.

4. DEFINITIONS

CESP	Common European Submission Platform
CI	Chief Investigator
CTG	Clinical Trials Group
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DSUR	Development Safety Update Report
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good Clinical Practice
HRA	Health Research Authority
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File
LRM	Local Research Meeting
MHRA	Medicines and Healthcare products Regulatory Agency
R&D	Research & Development
REC	Research Ethics Committee
SOP	Standard Operating Procedure
Sponsor	An individual, company, institution or organisation which takes responsibility for the initiation, management and financing of a clinical trial. Sponsorship activities may be delegated to the Investigator, CTU and/ or other organisations as appropriate
TMF	Trial Master File

5. DUTIES AND RESPONSIBILITIES OF STAFF

It is the responsibility of the **Chief Investigator** to comply with the specific reporting requirements for CTIMPs as outlined in this SOP.

6. PROCEDURES

The CI is required to submit progress reports to regulatory authorities and the Sponsor at regular intervals during the lifetime of the study.

The following procedures should be followed:

6.1 Adverse Event Reporting

6.1.1 Recording and reporting of Adverse Events (AEs), should be managed in line with the reporting procedure as laid out in the S22 Safety Reporting.

6.2 Urgent Safety Reporting

6.2.1 During the course of a Clinical Trial involving an IMP, new safety information may necessitate an immediate change in the study procedures or a temporary halt to the study in order to protect clinical trial subjects from any immediate hazard to their health and safety.

6.2.2 If time does not allow for an amendment to be authorised by the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC) and Sponsor, this change in procedure can be implemented as an Urgent Safety Measure (USM), by the CI or Sponsor. For further guidance on USMs and the reporting requirements please see the S52 Urgent Safety Measures.

6.3 Temporary halt to a trial

6.3.1 When a trial is halted temporarily for a reason that does not pose a risk to participants' health or safety (in which case the halt must be reported as an Urgent Safety Measure), the CI must notify the Sponsor as soon as practicably possible, and both MHRA and REC within 15 days from when the trial is temporarily halted.

6.3.2 The notification must be made as a substantial amendment and clearly explain exactly what aspect(s) of the trial has been halted (e.g. stopping recruitment and/ or interrupting treatment of subjects already included) and the reasons for the temporary halt. For further details please refer to the S02 Submitting Protocol Amendments and MHRA website.

6.3.3 There may be occasion when the trial Sponsor may be required to halt a trial temporarily (e.g. in light of issues highlighted in a monitoring report). In this eventuality, the Sponsor may either notify the MHRA and ethics committee or may delegate this responsibility to the CI. This will be clearly laid out in a delegation of responsibilities drawn up before the trial begins.

6.3.4 Submission and correspondence from the MHRA and/or REC must be copied to the Sponsor.

6.3.5 A copy of the complete application and any correspondence with MHRA, REC and/ or sponsor must be retained in full in the Trial Master File (TMF)/ Investigator Site File (ISF).

6.4 Restarting a halted trial

6.4.1 To restart the trial the CI should request permission to make an amendment in writing to the R&D Department. The request must include:

- a description of the proposed amendment
- reason(s) for the proposed amendment
- Revised documentation as a result of the amendment (e.g. updated version controlled protocol, consent form, patient information sheet, additional investigator Curriculum Vitaes [CVs])

The Local Research Meeting (LRM) will decide whether the amendment might affect Trust Sponsorship of the study and refer it to the R&D Clinical Trials Group (CTG) if this is considered necessary.

6.4.2 Once Sponsor's approval has been given, the CI must submit the substantial amendment (request to restart the trial) to the main REC and the MHRA (see S02 Submitting Protocol Amendments for further detail) and provide evidence that it is safe to restart the trial.

The trial must **not** be restarted until the MHRA and REC have confirmed that this is acceptable in writing and written approval has been received from R&D.

6.4.3 If the CI makes a decision not to recommence a temporarily halted trial, then this decision must be notified to the R&D Department in writing giving a clear explanation as to why the decision not to recommence has been taken. It is the responsibility of the CI to notify the MHRA and Ethics Committee within 15 days of this decision, using the End of Trial Declaration form, including a brief explanation of the reasons for ending the trial. This form should be submitted using the Common European Submission Portal (CESP).

6.5 Annual Development Safety Update Report (DSUR) for MHRA

6.5.1 In addition to the expedited reporting required for SUSARs, Sponsors are required to submit a safety report to the MHRA and the Ethics Committee, once a year throughout the life of the clinical trial or on request. The DSUR must take into account all new available safety information received during the reporting period. For CTIMP studies sponsored by the Trust, the preparation and submission of the DSUR within the specified timescales is delegated to the CI. A template is available from R&D to facilitate this reporting requirement.

6.5.2 The first DSUR is due one year from the date of the MHRA Clinical Trial Authorisation for the study. DSURs are then due on the same date each consecutive year for the duration of the study. The DSUR must be submitted to the MHRA within 60 days from the date it was due. Details for how to submit to MHRA via CESP may be found at the MHRA website. A copy of the signed DSUR should be sent to the Research Ethics Committee responsible for your study at the same time as submitting to the MHRA.

6.5.3 The aim of the DSUR is to describe concisely all new safety information relevant for the clinical trial and to assess the safety of subjects included in these studies.

6.5.4 The DSUR should include the following:

- A cover letter
- An analysis of the subjects' safety in the clinical trial with an appraisal of its ongoing
- Risk benefit
- A line-listing of all suspected serious adverse reactions (including all SUSARs) that
- occurred in the trial (if any)
- An aggregate summary tabulation of suspected serious adverse reactions that have occurred in the trial (if any)

6.5.5 A copy of the signed DSUR must be submitted to R&D as Sponsor representative, for inclusion in the Study R&D File/ Sponsor File and the original signed DSUR retained in the TMF/ISF.

6.5.6 Full details of what to include in an annual safety report can be found on the European Commission website.

6.6 Annual Progress Report

6.6.1 The first annual progress report is due one year from the date of the REC favourable opinion for the study. Reports are then due on the same date each year for the duration of the study.

6.6.2 The report form for CTIMPS is available from the HRA website.

6.6.3 The CI is responsible for making the submission directly to the REC and to the R&D Department as Sponsor representative, for inclusion in the Study R&D File/ Sponsor File. The original, signed annual progress report should be filed in the TMF/ ISF.

6.7 End of trial

6.7.1 The CI must notify the R&D Department as soon a trial has ended, providing the specific date. The end of trial time point must be clearly stated in the protocol. Any trial activities (i.e. follow-ups, visits) should be completed before the submission of the end of trial declaration form.

6.7.2 The CI must then submit:

- Clinical Trial End of Trial Declaration form to the MHRA within 90 days of the global end of the trial
- Clinical Trial End of Trial Declaration Form to the REC which gave a favourable opinion of the research within 90 days of the global end of the trial

6.7.3 End of trial declarations must be submitted via CESP.

6.7.4 A copy of the End of Trial Form must be submitted to the R&D Department as Sponsor representative. A copy of the signed completed notification must be retained in the TMF/ISF.

6.7.5 Any correspondence relating to the notification of end of trial from the MHRA, REC and/ or Sponsor must also be retained in the TMF/ ISF. For further details please visit HRA web pages 'Notifying the End of Study'.

6.8 Reports within one year of trial end

6.8.1 The Sponsor is required to submit an end of trial study summary to EudraCT as per the Commission Guideline on posting and publication of result-related information on clinical trials. The time frame for posting the summary is within six months of the end of trial for paediatric clinical trials or within one year of the end of trial for non-paediatric clinical trials.

6.8.2 The clinical trial summary report does not need to be submitted to the MHRA as well, however a short confirmatory email must be sent to CT.Submission@mhra.gsi.gov.uk once the result-related information has been uploaded to EudraCT, with 'End of trial : result-related information: EudraCT XXXX-XXXXXX-XX' as the subject line. An acknowledgment email or letter will **not** be sent in return.

6.8.3 Any reports and subsequent correspondence must be retained in the TMF/ISF and copies sent to the R&D Department as Sponsor representative.

6.9 Early termination of a trial

6.9.1 If a trial is terminated before the specified date for its conclusion (as documented in the Protocol) then the CI must notify R&D as Sponsor representative immediately.

6.9.2 The CI is responsible for notifying the MHRA and appropriate REC within 15 days of the date of termination by submitting a Clinical Trial End of Trial Declaration

Form including a brief explanation of the reasons for ending the trial. This form should be submitted via CESP.

6.9.3 A copy of the signed completed notification must be retained in the TMF/ISF and any correspondence relating to the notification of end of trial from the MHRA, REC and/or Sponsor must be retained in the TMF/ISF.

6.10 Periodic Sponsor oversight reporting

6.10.1 For Trust-sponsored CTIMPS, periodic oversight reports and meetings will be requested by the sponsor as laid out in the monitoring plan. R&D will liaise with the CI regarding the frequency and content of reporting.

7. DISSEMINATION AND TRAINING

7.1 This SOP and associated templates and forms will be uploaded to the Trust intranet and external website shortly after having been released.

7.2 All staff whose activities are subject to this SOP should ensure that they take time to read and understand the content of this SOP.

7.3 The training log within the Investigator Site File/ Trial Master File should be completed to document that members of staff have read and understood the contents of this SOP.

8. MONITORING COMPLIANCE AND EFFECTIVESS OF THIS SOP

8.1 This SOP will be audited in line withS04 Auditing Processes.

8.2 Outcomes from audit will be presented to the R&D Quality Assurance Group which will monitor any resulting action plans until all issues have been addressed to satisfaction.

8.3 Issues identified via the audit process which require escalation will be referred to the R&D Divisional Governance Group.

9. ARCHIVING ARRANGEMENTS

9.1 The original of this document will remain with the R&D Quality Assurance Coordinator. An electronic copy will be maintained on the R&D section of the Q-Pulse document management system and a pdf copy on the Trust Intranet.

9.2 Archive copies must be maintained for any documents which have been superseded. Archive copies in electronic format should be retained indefinitely.

10. REFERENCES

UK Policy Framework for Health and Social Care Research

The World Medical Association Declaration of Helsinki (2000)

Medicines for Human Use (Clinical Trials) Regulations (2004)

ICH Guidelines for Good Clinical Practice (E6 (R2) Step 5. Dec 2016)

SSAR = Suspected Serious Adverse Reaction **SUSAR** = Suspected Unexpected Serious Adverse Reaction

A ***serious adverse reaction*** is an untoward and unintended response to an IMP at any dose, that:

(a) results in death
(b) is life-threatening
(c) requires hospitalisation or prolongation of existing hospitalisation
(d) results in persistent or significant disability or incapacity; or
(e) consists of a congenital anomaly or birth defect

An **adverse reaction** is unexpected if its nature and severity are not consistent with the information about the medicinal product in question set out:

- In the case of a product with marketing authorisation, in the Summary of Product Characteristics for that product
- In the case of any other IMP, in the Investigator's Brochure relating to the trial in question

For more detailed guidance, see the European Commission guidance on adverse reaction reporting (ENTR/CT3)

	Who	When	To whom and how	
			MHRA	**REC**
Reporting of individual SUSARs (see also SOP 22)	Sponsor, Sponsor's legal representative or CI.	(a) or (b) must be reported within 7 days of the sponsor becoming aware of the event. Any additional information must be reported within 8 days of sending the first report. (c) (d) or (e) must be reported within 15 days of the sponsor becoming aware of the event.	**YES** Submit 'e-SUSAR form' via e-SUSAR website	**YES** Email PDF of e-SUSAR form accompanied by a 'Safety Report to REC form' to the REC which issued the favourable ethical opinion. REC will acknowledge within 30 days.
Annual safety reporting by Development Safety Update Reports (DSUR) (see also SOP 22)	Sponsor, Sponsor's legal representative or CI.	Annually – within 60 days of reporting date. Reporting date defined as either : (1) The International Birth Date for the product (IMP with a marketing authorisation (MA) in any EU member state) *OR* (2) The date on which any trial of the IMP being conducted by the sponsor was first authorised by a competent authority in any EU member state (IMP without a MA)	**YES** Submit annual report (R&D have a template) via MHRA's CESP system	**YES** Email DSUR report accompanied by a 'Safety Report to REC form' to the REC which issued the favourable ethical opinion.

	Who	When	To whom and how	
			MHRA	**REC**
Urgent safety measures (see also SOP 52)	Sponsor, Sponsor's legal representative or CI. Or exceptionally by local PI.	(i) Immediately (by telephone) (ii) Within 3 days (in writing).	**YES** Phone the MHRA's Clinical Trial Unit ideally within 24 hrs. Inform MHRA in writing within 3 days of the incident including a completed 'Notification of Urgent Safety Measure Report Form'. Written notification in the form of a substantial amendment (annex 2) is also required.	**YES** Initially phone and then provide notice in writing of the urgent measure to the REC which issued the favourable ethical opinion.
Progress reports	To be submitted by Sponsor, Sponsor's legal representative or CI. Must always be signed by CI.	Annually (starting 12 months after the date of the favourable opinion). The REC may exceptionally request more frequent reports.	**NO**	**YES** Email 'Annual progress report form (CTIMPs)', available from the HRA website to the REC which issued the favourable ethical opinion.
Declaration of the conclusion or early termination of the research (CTIMPs)	Sponsor, Sponsor's legal representative or CI.	Within 90 days (conclusion). Within 15 days (early termination). NB The end of the trial should be defined in the protocol.	**YES** Submit via MHRA's CESP system the 'EudraCT Declaration of End of Trial Form' on available from EudraCT website.	**YES** Email 'EudraCT Declaration of End of Trial Form' to the REC which issued the favourable ethical opinion.

	Who	When	To whom and how	
			MHRA	**REC**
Summary of final report	Sponsor, Sponsor's legal representative or CI.	Within one year of the conclusion of the research	**NO** No summary is expected, however EudraCT require a summary report and MHRA should be informed via email that the upload to EudraCT has been done.	**YES** Summary should be emailed to the REC which issued the favourable ethical opinion. No standard format required but the summary should include information on whether study achieved its objectives, main findings and arrangements for publication or dissemination including feedback to participants.