STANDARD OPERATING PROCEDURE

S31 – Reporting required for sponsored CTIMPS

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DISCLAIMER

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

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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
3	23/02/2021	Assistant R&D Manager	Revision to template, minor changes to wording and updates due to Brexit & updates to R&D governance structure

Associated Trust Policies/ Procedural documents:	Research & Development Policy Safety Reporting SOP Submitting Amendments SOP Urgent Safety Measures SOP
Key Words:	R&D CTIMP Sponsorship Clinical Trial SOP Reporting
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Contents

1 INTRODUCTION

The Royal Devon & Exeter NHS Foundation Trust (hereafter referred to as the Trust) acts as Sponsor to high quality research activity including Clinical Trials of an Investigational Medicinal product (CTIMP). This document has been produced to ensure the Trust runs CTIMPs in accordance with the Clinical Trials Regulations 2004 (Directive 2001/20/EC) as well as the Research Ethics Committee (REC) reporting procedures.

The Medicines for Human Use (Clinical Trials) Regulations 2004 in conjunction with the Amendment Regulations (collectively referred to hereafter as "the Regulations") stipulates the reporting requirements for Clinical Trials of Investigational Medicinal Products (CTIMPS) and these are incorporated into this procedure.

2. PURPOSE

This document describes the procedure(s) required to support preparation and submission of mandatory and locally required reports relating to CTIMPs 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

CI	Chief Investigator
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
GOG	Governance Oversight Group
HRA	Health Research Authority
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File
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
SUSAR	Suspected Unexpected Serious Adverse Reaction
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 Safety Reporting SOP.

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), 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 Urgent Safety Measures SOP.

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. The MHRA should be informed using the MHRA Submissions Portal via the Human Medicines Tile and the REC that gave the original approval via email.

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 Submitting Amendments SOP 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])

6.4.2 R&D will decide whether the amendment might affect Trust Sponsorship of the study and refer it to the Governance Oversight Group (GOG) if this is considered necessary.

6.4.3 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 Submitting Amendments SOP 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.

6.4.4 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 to the MHRA using the Submissions Portal using the Human Medicines Tile and the REC that gave the original approval via email.

6.5 Annual Development Safety Update Report (DSUR) for MHRA

6.5.1 In addition to the expedited reporting required for Suspected Unexpected Serious Adverse Reactions (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 the MHRA Submissions Portal using the Human Medicines Tile 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 defined and 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 to the MHRA via the MHRA Submissions Portal using the Human Medicines Tile and the responsible REC via email.

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 to the MHRA via the MHRA Submissions Portal using the Human Medicines Tile and to the responsible REC via email.

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 RDE Research 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 *If applicable, a 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 EFFECTIVENESS OF THIS SOP

8.1 In order to monitor compliance with this SOP, the auditable standards will be monitored as follows:

No	Minimum Requirements	Evidenced by
1.	Presence of annual report(s) and timely submission (annually, from ethical approval)	Copy(ies) of annual report in TMF & R&D file
2.	Presence of annual Safety report(s) and timely submission (annually + up to 60days, from CTA approval)	Copy(ies) of annual DSUR report in TMF & R&D file
3.	End of Study Reports to the MHRA within 90 days of the global end of the trial	Clinical Trial End of Trial Declaration form in the TMF & R&D File
4.	Sponsor Oversight Meetings	Minutes in TMF & R&D File
5	Posting results via End of trial study summary to EudraCT within one year of end of trial	Email evidence confirming submission in TMF & R&D File in correct time frame

8.2 Outcomes from audit will be presented to the R&D Governance Oversight Group (GOG) 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 GOG.

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 RDE Research website.

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 V3.3 07/11/2017

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)

Medicines and Healthcare products Regulatory Agency (MHRA) website www.mhra.gov.uk

European Clinical Trials website eudract.ema.europa.eu

Health Research Authority (HRA) website www.hra.nhs.uk