Standard Operating Procedure – Trust-wide

North Bristol NHS Trust

Periodic Reporting to Regulatory Authorities

Reference	RI/QMS/SOP/009
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Version	5.0
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Purpose

The purpose of this Standard Operating Procedure (SOP) is to outline the periodic progress and safety reporting requirements for research studies sponsored by North Bristol NHS Trust (NBT).

Key messages

After a research study has received all necessary approvals for it to proceed, various bodies and organisations will be interested in its progress. In many (but not all) cases, progress reports must be submitted to regulatory bodies including REC, MHRA and HRA.

You may also need to refer to the following policies and guidance

RI/QMS/SOP/009a	DSUR Template
RI/QMS/SOP/012	Managing Breaches of Good Clinical Practice or the Protocol
RI/QMS/SOP/013	Safety Reporting: Clinical Trials of Investigational Medicinal Products (CTIMPs)

Operational areas included

Research studies sponsored by NBT.

Operational areas excluded

Research studies that are not sponsored by NBT.

Who should read this?

Investigators and research team members involved in research studies sponsored by NBT.

Roles responsible for carrying out this procedure

The Chief Investigator is delegated the responsibility for compiling progress reports to REC, MHRA, and HRA.

The Chief Investigator is delegated responsibility for submitting the reports to REC and HRA.

For CTIMPs, R&I will submit DSUR reports to MHRA.

For device trials, responsibility for submitting summary reports to the MHRA will be agreed contractually and will usually be that of the device manufacturer.

Core accountabilities:

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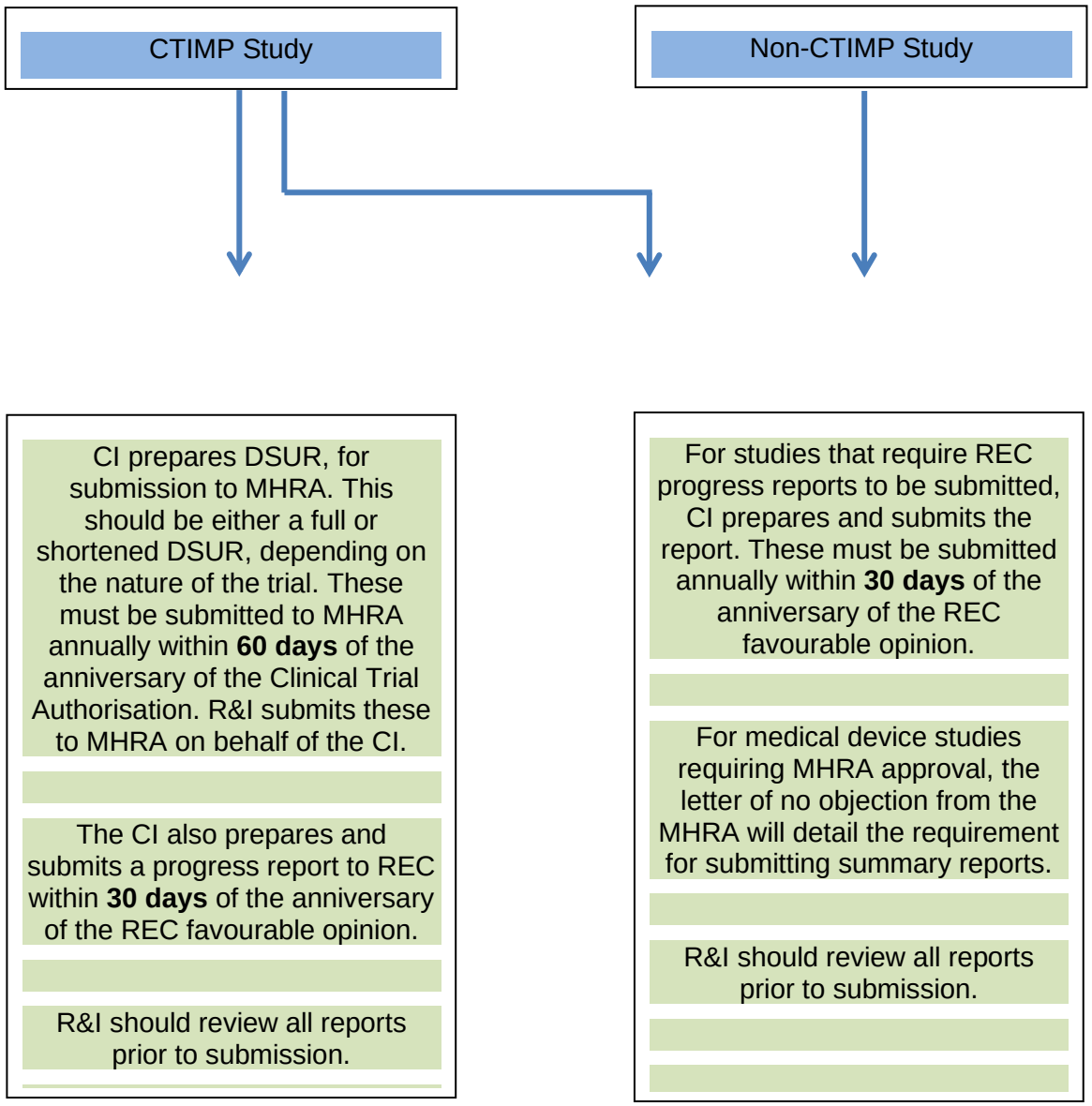
Executive Sponsor	Dr Rebecca Smith, Deputy Director of Research
Approving Committee	Research & Innovation Group

Version history

Version Number	Effective Date	Summary of changes since previous version
1.0	01-04-11	N/A
2.0	01-03-12	To clarify annual safety and progress report responsibilities
3.0	08-02-16	SOP renamed, updated in line with new template and recoded from ISOP-H11
4.0	28-03-18	To clarify that reference safety information must be reviewed at least once a year
5.0	06-09-21	Updated changes to the reporting requirements to all regulatory bodies

SOP Flowchart



1. PURPOSE AND SCOPE

The purpose of this SOP is to outline the periodic progress and safety reporting requirements for research studies sponsored by NBT.

After a research study has received all necessary approvals for it to proceed, various bodies and organisations will be interested in its progress. In many (but not all) cases, progress reports must be submitted to REC, and DSURs must be submitted to the MHRA for CTIMPs. The requirement for submitting summary reports to the MHRA for device trials varies and is defined in the MHRA notice of no objection letter. There are also situations where the HRA need to receive reports.

2. DEFINITION Of TERMS

CAG	Confidentiality Advisory Group
CI	Chief Investigator
CTIMP	Clinical trial of an Investigational Medicinal Product
DSUR	Development Safety Update Report
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
HRA	Health Research Authority
NBT	North Bristol NHS Trust
R&I	NBT Research & Innovation Office
REC	Research Ethics Committee
RSI	Reference Safety Information
MHRA	Medicines and Healthcare Products Regulatory Agency
NBT	North Bristol NHS Trust
PSUR	Periodic Safety Update Report
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
Sponsor	The sponsor is the individual, organisation or partnership that takes on overall responsibility for proportionate, effective arrangements being in place to set up, run and report a research project. All health and social care research has a sponsor. The sponsor is normally expected to be the employer of the Chief Investigator in the case of non-commercial research, as described in the UK Policy Framework for Health and Social Care Research.
SUSAR	Suspected Unexpected Serious Adverse Reaction

3. ROLES AND RESPONSIBILITIES

The Sponsor is accountable for ensuring periodic reports for research studies are submitted within appropriate timelines[1]. Where NBT is the Sponsor, responsibility for compiling all reports has

[1] Periodic safety update reports (PSURs) must be submitted to MHRA for approved medicinal products in the UK, irrespective of whether it is placed on the market or not. The PSUR is a periodic assessment of the risk-benefit balance of the product, providing an analysis of the safety, efficacy, and effectiveness of the product over its lifecycle. The Marketing Authorisation holder (usually the manufacturer) is responsible for submitting these reports. NBT sponsoring a study that involves the use of an approved medicinal product does not alter this responsibility.

been delegated to the CI. Once a report has been prepared, R&I should review and approve this prior to submission to the relevant regulatory authority.

Responsibility for report submission is as follows:

- The CI is responsible for submitting reports to REC and HRA, and CAG.
- For CTIMPs, R&I will submit reports to the MHRA.
- For device trials, responsibility for submitting summary reports to the MHRA will be agreed contractually and will usually be that of the device manufacturer.

For CTIMPs and device trials, R&I will review annual report due dates with trial managers and/or CIs at regular intervals.

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 procedure will be followed accordingly, see SOP on Managing Breaches of Good Clinical Practice or the Protocol (RI/QMS/SOP/012). Detailed guidance regarding how to prepare and submit reports is outlined in the remainder of this SOP.

4. WHO SHOULD USE THIS SOP

This SOP applies to all investigators and research team members involved in research studies that are sponsored by NBT.

5. WHEN SHOULD THIS SOP BE USED

This SOP is applicable for all studies that are sponsored by NBT.

6. PROCEDURE

6.1. Progress Reporting to REC and HRA

6.1.1. Progress reports to REC are required for studies that are:

- more than two years in duration;
- research tissue banks; and
- research databases.

6.1.2. There is no requirement for a progress report for:

- proportionate review studies (of any duration); and
- here the study is two years or less in duration (unless it is a research tissue bank or research database). If an amendment is made to extend a study beyond two years in duration, progress reports are required to be submitted as per section 6.1.1. of this SOP, from the point the study is extended.

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 study. An electronic copy should be emailed to the REC within **30 days** of the end of the reporting period. The report should be submitted

to the Sponsor (ResearchSponsor@nbt.nhs.uk) for review and approval before being submitted to the REC.

The HRA templates must be used for these reports, available via the HRA website (www.hra.nhs.uk). There are different templates for different study types.

For research with HRA Approval which were not required to be reviewed by a REC, progress reports should be sent to approvals@hra.nhs.uk.

6.2. Development Safety Update Report (DSURs)

For CTIMPs, reporting requirements differ depending on the type of trial, as follows:

6.2.1. A shortened DSUR can be submitted for:

- Individual trials authorised under the Notification Scheme which are not part of a multi-study development programme (i.e. Type 'A' trials).
- Phase 4 national (UK only) trials of licensed products, that commanded a low fee from the MHRA, and where all participants have completed treatment and are only in follow up.

These DSURs can be submitted using the HRA Progress Report Template. A covering letter must be included that indicates an Annual Progress Report (APR) is being submitted in lieu of a full DSUR, and must include the EudraCT number and Clinical Trial Application (CTA) reference number. A list of all serious adverse reactions should be included in section 6 of the report.

6.2.2. A full DSUR must be submitted for all other trials[2].

A full DSUR should take into account all new available safety information received during the reporting period. It should include:

- a cover letter listing all EudraCT numbers of trials covered by the DSUR, including an email address for correspondence.
- an analysis of the subjects' safety in the concerned clinical trial(s) 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(s), including all SUSARs from third countries

[2] One DSUR should 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. If there is a valid reason for submitting separate reports this should be clearly explained on the DSUR. DSURs are IMP specific therefore for trials involving multi-drug therapy (ie combinations of drugs that are not fixed) R&I, in conjunction with the CI will need to decide to either prepare a DSUR for the multi-drug therapy, or 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.

- an aggregate summary tabulation of SUSARs that occurred in the concerned trial(s)

Comprehensive details of what to include in a full DSUR can be found in the ICH E2F guidance. R&I provide a template for the report based on this guidance (RI/QMS/SOP/009a), which must be used.

The relevant DSUR must be compiled annually for the duration of the clinical trial until the MHRA has been notified of the end of the trial The DSUR due date is the **anniversary** of the first international regulatory approval regardless of the approval status in the UK. The data lock point of the DSUR should be the last day of the one-year reporting period. The DSUR must be submitted within **60 days** of the due date.

The report should be submitted to the Sponsor for review and submission prior to the due date. DSURs must be submitted using MHRA Submissions. R&I will submit the reports.

The Reference Safety Information (RSI) in the Investigator's Brochure (IB), or Summary of Product Characteristics (SmPC) if used instead, must be reviewed by the CI at least **once a year** (i.e. at the end of the DSUR reporting period). This RSI review should be clearly documented in the Trial Master File. If there are any changes to the RSI, a substantial amendment is required to be submitted to the MHRA and approved before it is implemented in the trial. For further details, see SOP on Safety Reporting: Clinical Trials of Investigational Medicinal Products (CTIMPs) (RI/QMS/SOP/013).

6.3. Device Trial Summary Reports

For device trials, requirements for submitting summary reports to the MHRA are detailed in the letter of no objection from the MHRA. The letter outlines the format these reports should follow, as well as the required frequency for submitting these reports.

7. DISSEMINATION AND TRAINING

SOPs will be distributed in accordance with the SOP on Preparation of Research SOPs (RI/QMS/SOP/001).

This SOP and any associated templates and forms will be uploaded to the Trust website (www.nbt.nhs.uk/research) and the Managed Learning Environment (MLE) system on the Trust intranet shortly after having been released.

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

8. REFERENCES

- Health Research Authority (HRA)
Progress Reports

www.hra.nhs.uk

- Medicines & Healthcare products Regulatory Agency (MHRA)
  Safety Reporting: SUSARs & ASRs
  www.gov.uk