Periodic Reporting to Regulatory Authorities

Division: Trust-Wide

Specific staff groups to whom this policy directly applies	Likely frequency of use	Other staff who may need to be familiar with policy
Staff employed by North Bristol Trust who directly or indirectly work on Clinical Research within the Trust	Role Dependant	Staff not employed by North Bristol NHS Trust who are working on Research studies sponsored or hosted by NBT

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Approval Authority (Committee/ Group/ Lead Clinician):	R&D Senior Team
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KEYWORDS:	Development Safety Update Report (DSUR), Regulatory authorities, REC and HRA Reporting, CTIMPS, Reporting timelines, Submission Responsibilities.
Summary of changes since the previous version	Changed format to align with NBT SOP template Changed R&I to R&D Updates to reporting requirements to HRA and REC Added information in relation to responsibilities when working with Clinical Trials Units. Change the naming convention of R&D SOP's

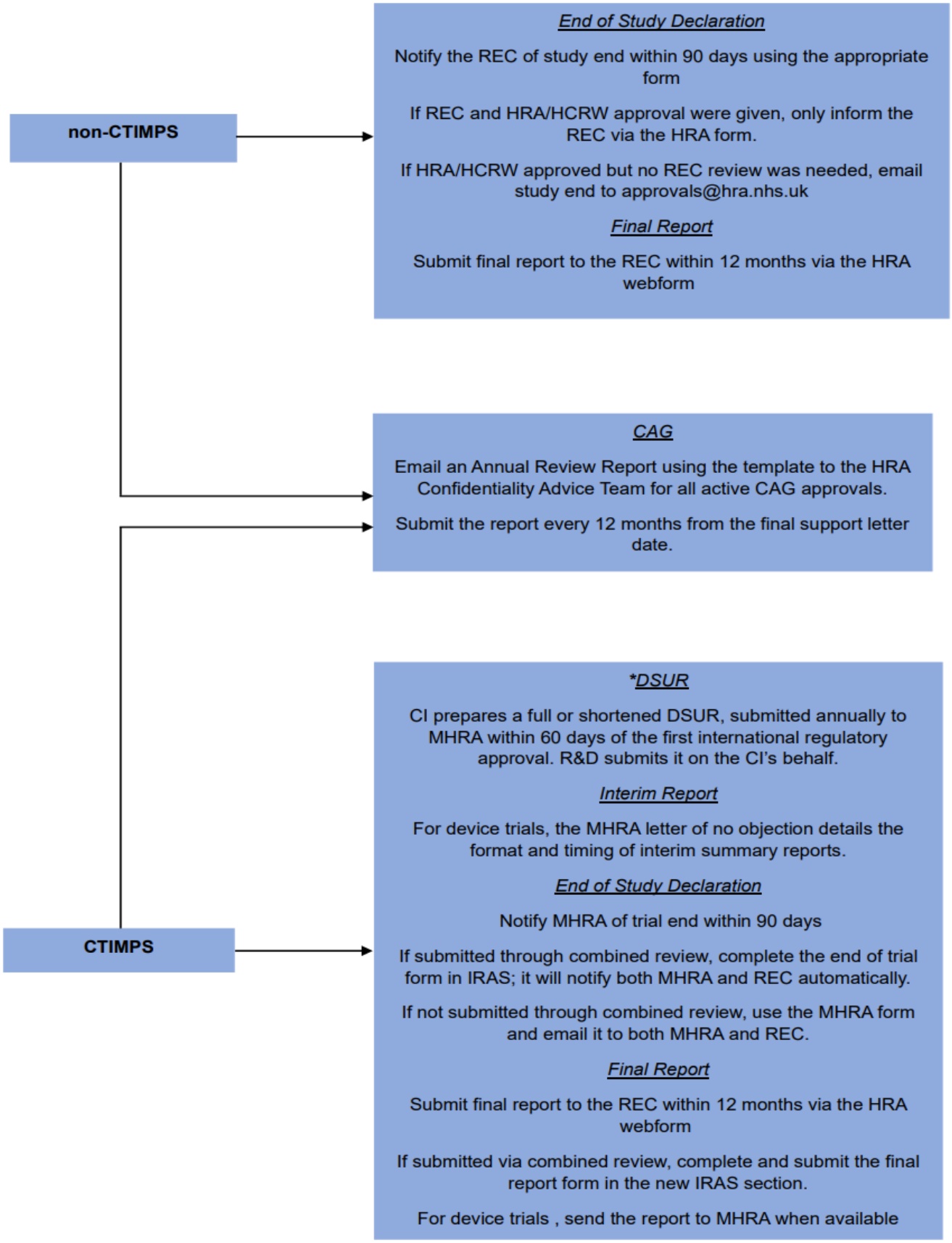
1. Purpose	The purpose of this Standard Operating Procedure (SOP) is to outline the periodic progress and safety reporting requirements for research studies sponsored by North Bristol NHS Trust (NBT).
2. Key Messages	After a research study has received all necessary approvals for it to proceed, various bodies and organisations will be interested in its progress. Progress reports, in the form of a Development Safety Update Report (DSUR) must be submitted to the Medicine Healthcare Regulatory Agency (MHRA) for Clinical Trial of an Investigational Medicinal Product (CTIMP) studies on an annual basis. This DSUR should present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period for the investigational drug(s) with an appraisal of its ongoing risk/benefit. Studies that have Confidentiality Advisory Group (CAG) approval require annual review reports to assess ongoing approval and compliance; these must be submitted at least 4 weeks before approval expiry. **Abbreviations** **CAG** Confidentiality Advisory Group **CI** Chief Investigator **CTIMP** Clinical Trial of an Investigational Medicinal Product **CTU** Clinical Trials Unit **DSUR** Development Safety Update Report **HRA** Health Research Authority **R&D** Research and Development **REC** Research Ethics Committee **RSI** Reference Safety Information **MHRA** Medicine Healthcare Regulatory Agency **SOP** Standard Operating Procedure **SUSAR** Suspected Unexpected Serious Adverse Event
3. Relevant Policies & Guidance	**Policies and Guidance:** • HRA End of Study Declaration and Final study Report to the REC Ending your project - Health Research Authority • MHRA Safety reporting SUSARs

	Safety reporting - Health Research Authority **Associated SOP's and Templates:** RD/QMS/TMPL/009 - DSUR Template RI/QMS/SOP/012 - Managing Breaches of Good clinical Practice or the Protocol. RD/QMS/SOP/013 - Safety Reporting: Clinical Trials of Investigational Medicinal Products (CTIMPS)
4. Operational Areas Included	This SOP is applicable to all research studies sponsored by NBT
5. Operational Areas Excluded	Research Studies that are not sponsored by NBT
6. Who should read this	This SOP should be used by Investigators and other members of the research team involved in research studies sponsored by NBT. When collaborating with external stakeholders, such as Clinical Trials Units, on NBT- sponsored projects, it may be appropriate to utilise external SOPs to ensure proper project governance and the fulfillment of delegated roles and responsibilities. In such instances, both the external stakeholder and the NBT sponsorship team must ensure that the external SOP aligns with the procedures outlined in this SOP. If there is a conflict between the external SOP and NBT's procedures, the NBT SOP will take precedence, except in exceptional cases where approval is obtained from the Research Operations Manager or the Deputy Director of Research
7. Roles responsible for carrying out this procedure	**Chief Investigator (CI)** The CI is delegated the responsibility for compiling the DSUR or CAG annual review report. If the CI fails to provide a copy of the reports 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). **NBT Sponsorship Team**

	For CTIMPs and device trials, the R&D Sponsorship Team will regularly liaise with Trial Managers and/or CI to review annual report due dates. **For CTIMPs**, R&D sponsorship team will review and submit DSUR reports to the MHRA. For the CAG annual review report, R&D sponsorship team will review the CAG report pre-submission. The CI holds responsibility for submitting the final report to CAG. Please note, for device trials, responsibility for submitting summary reports to the MHRA will be agreed contractually and will usually be that of the device manufacturer.

8. Procedure:

Flowchart illustrating the periodic reporting requirements for NBT sponsored research



* *Refer to Section 8.2 for guidance on the process when working with CTUs*

8.1 Progress Reporting to REC and HRA

Current Requirement:

Annual progress reports are no longer required for studies that have received a final opinion from a UK Research Ethics Committee (REC), regardless of study duration or type (including research tissue banks and research databases).

For research that has HRA and HCRW Approval only (and was not reviewed by a REC), there is also no requirement to submit progress reports.

Exception: Studies with CAG approval must continue to submit annual review reports as per CAG guidance**- see section 8.3 of this SOP.**

Ongoing Obligations:

End of Study Notification: A final report must still be submitted to the REC (or HRA for HRA-only approvals) at the end of the study, using the appropriate HRA template.

Safety and Urgent Updates: Any urgent safety measures, serious breaches, or other reportable events must continue to be reported in line with HRA and REC requirements. See Safety Reporting SOP (as applicable) for CTIMPS (RD/QMS/SOP/013) and non-CTIMPS (RI/QMS/SOP/013d)

Amendments: Substantial and non-substantial amendments must still be submitted for approval as per HRA guidance- See Research Study Amendments (RD/QMS/SOP/003)

8.2 Development Safety Update Report

Requirement:

A DSUR must be submitted annually for all CTIMP studies for the duration of the trial until the MHRA has acknowledged the end-of-trial notification.

The DSUR due date is the anniversary of the first international regulatory approval for the trial, regardless of UK approval status.

The data lock point is the last day of the one-year reporting period.

The DSUR must be submitted within 60 days of the data lock point.

Content:

A full DSUR must comply with ICH E2F guidance and include:

- A cover letter listing all EudraCT numbers and IRAS IDs for trials covered by the DSUR, and an email address for correspondence.
- Proof of payment for the DSUR review fee (mandatory since June 2024), with the payment reference in the format:

- DSUR-[5-digit MHRA company number]-[IMP name]-[Payment date DD/MM/YYYY].
- An analysis of subject safety and an appraisal of the ongoing risk/benefit.
- A line listing of all suspected serious adverse reactions (including SUSARs) that occurred in the trial(s), including those from third countries.
- An aggregate summary tabulation of SUSARs.
- Any other information required by ICH E2F.

Comprehensive details of what to include in a full DSUR can be found in the ICH E2F guidance.

NBT R&D provide a template for the report based on this guidance (RD/QMS/TMPL/009), which must be used.

[1] 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 (i.e. combinations of drugs that are not fixed) R&D, 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.

Shortened DSURs:

A shortened DSUR may be acceptable for:

Type A trials authorised under the Notification Scheme are not part of a multi-study development programme.

Phase 4 UK-only trials of licensed products where all participants have completed treatment and are only in follow-up.

Shortened DSURs must still meet minimum MHRA requirements and should only be used if agreed with the MHRA.

The use of the HRA progress report template for DSURs is no longer recommended

Submission Process:

The Sponsor (ResearchSponsor@nbt.nhs.uk) must review and approve the DSUR. The CI or delegated representative must submit the DSUR to the sponsor with a minimum of 1 week prior to the DSUR submission deadline.

The NBT Sponsorship team will be responsible for submission:

DSURs must be submitted via MHRA Submissions portal (or IRAS for combined review trials).

The submission must Include the cover letter, proof of payment, and the DSUR document.

DSURs are not required to be submitted to the REC for combined review trials.

Reference Safety Information (RSI):

The RSI in the Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC) must be reviewed annually by the CI at the end of the DSUR reporting period.

Any changes to the RSI require a substantial amendment to be submitted to the MHRA and approved before implementation.

Documentation of the RSI review must be maintained in the Trial Master File.

Delegation of DSUR Preparation and Submission to Clinical Trials Units

As Sponsor, we retain overall responsibility for the safety reporting obligations associated with Clinical Trials of Investigational Medicinal Products (CTIMPs), including the annual Development Safety Update Report (DSUR). However, where a Clinical Trials Unit (CTU) is involved in the management of a trial, NBT may formally delegate the preparation and submission of the DSUR to the CTU, in accordance with applicable regulatory requirements and internal agreements.

Responsibilities of the CTU (when delegated):

- **Preparation of DSUR** in line with ICH E2F and MHRA guidance, including collation of safety data, narrative summaries, and trial progress updates.
- **Coordination with CI** to ensure accuracy and completeness of safety information.
- **Submission of DSUR** via the MHRA Submissions Portal or IRAS, ensuring timely delivery by the Data Lock Point (DLP).
- **Maintenance of documentation** to evidence DSUR preparation, review, and submission.
- **Notification to Sponsor** upon successful submission, including provision of final DSUR and confirmation of receipt.

Sponsor Oversight when working with CTU:

- NBT as sponsor will retain oversight of the DSUR process and ensure that delegation is documented in the trial oversight records or equivalent.
- NBT R&D will review and approve the DSUR prior to submission, unless otherwise agreed and documented.
- NBT R&D will ensure that the CTU has appropriate SOPs, training, and systems in place to fulfil this responsibility.

8.3 Confidentiality Advisory Group

This section applies to all research projects operating under CAG support for the use of confidential patient information without consent under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002.

An Annual Review Report must be submitted to the HRA Confidentiality Advice Team for all active CAG approvals.

The report must be submitted every 12 months from the date of the final support letter.

The report must be submitted at least 4 weeks before the approval expiry date (no later than 11 months after approval).

The content of the report includes:

- Progress against conditions of the approval
- Any changes to data flows, purpose or security arrangement
- Evidence that the amount of confidential patient information processed remains appropriate

The Annual Review Template available on the HRA website must be used: IRAS Help - Maintaining your approvals - Confidentiality Advisory Group (CAG)

Prior to submission the completed document must be reviewed and approved by the sponsor (Researchsponsor@nbt.nhs.uk)

The completed form will then be submitted by the CI or delegated representative to cag@hra.nhs.uk

Delegation of Annual CAG Preparation and Submission to CTUs

When working with CTUs the responsibility for drafting and compiling the report may be delegated.

- Preparation of the CAG report.
- Coordination with CI to ensure accuracy and completeness of information.
- Sponsor Engagement: A copy of the draft report will be shared with NBT R&D for approval prior to submission
- Submission of CAG report
- Maintenance of documentation to evidence CAG preparation, review, and submission.
- Notification to Sponsor upon successful submission

Sponsor Oversight when working with CTUs

NBT R&D retain ultimate accountability for the content, quality and timely submission for the annual CAG report. As such NBT R&D will ensure:

- This delegation will be clearly documented within the trial oversight records and communicated to all relevant stakeholders.
- NBT R&D will review and approve the DSUR prior to submission, unless otherwise agreed and documented.
- NBT R&D will ensure that the CTU has appropriate SOPs, training, and systems in place to fulfil this responsibility.
- Any issues or discrepancies identified during the review are resolved collaboratively with the CTU.

8.4 Device Trial Summary Reports

For device clinical investigations, the MHRA letter of no objection specifies the required format and frequency of interim summary reports. Sponsors must comply with these instructions and submit reports via the route indicated (usually IRAS).

All reports should be reviewed by the sponsor before submission and filed in the Trial Master File.

9. Dissemination and Training

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

This SOP and any associated templates and forms will be uploaded to the Managed Learning Environment “LEARN” system on the Trust intranet shortly after having been released, The trust website (www.nbt.nhs.uk/research) will be updated to capture the list of current SOP’s in place.

All staff whose activities are subject to this SOP should ensure that they read and understand the content of this SOP, this is monitored and audited via LEARN.

10. References (if applicable):