Safety Reporting- CTIMPS

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
Trust Wide: All staff involved in the conduct of research	Daily	External Stakeholders including Clinical Trials Units

Main Author(s):	Deborah Warbrick
Consultation:	Research Sponsorship Team
Approval Authority (Committee/ Group/ Lead Clinician):	Research and Development Senior Team Trust Research Group
Executive Lead (Trust-Wide only):	Tim Whittlestone
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KEYWORDS:	CTIMP, Adverse Events, Adverse Reaction, Serious Adverse Event, Serious Adverse Reaction, Suspected Unexpected Serious Adverse reaction, Investigational Medicinal Product, Unblinding, Urgent Safety Measures
Summary of changes since the previous version	This is a substantial update incorporating multiple updates throughout the body of the SOP, which includes: Department name change from Research and Innovation (R&I) to Research and Development (R&D) Updated SOP template to align with NBT SOP template Updated reporting requirements in line with regulatory changes taking effect from 1st January 2021 after the end of the EU transition period. inclusion of acceptability for a variation to the process for low-risk trials

	Clarification and expansion on processes for blinded trials, updates around urgent safety measures. Updates on SUSAR reporting requirements and links to MHRA ICSR Submissions. Inclusion of previous appendix into the main body of the SOP to enhance assessment of Safety Events. Inclusion of more information on Reference Safety Information. Expansion of information and requirements of Data Monitoring Committees. Reference made to the responsibilities of Clinical Trials Units in the management of safety events. Updated in line with the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 (SI 2025/538).

1. Purpose	The purpose of this SOP is to provide a framework by which safety events arising in CTIMPs are recorded, assessed and reported. The SOP aligns with the UK Policy Framework for Health and Social Care Research (2025) and the Medicine for Human Use (clinical Trials) (Amendment) Regulations 2025, which introduce a strengthen risk proportional approach and updated safety reporting pathways. The SOP applies to all CTIMPs sponsored by NBT.
2. Key Messages	Safeguarding the dignity, rights, safety, and wellbeing of research participants must be the primary consideration in any research project, prevailing over the interests of science and society. The reporting of safety events is one of the most important aspects of clinical trial management and quality control. In accordance with the UK policy Framework for Health & Social Care Research (2025), NBT must have systems in place to record, investigate and report adverse incidents arising from any research undertaken within the Trust The Medicines for Human Use (Clinical Trials) Regulations 2025, as amended, govern the conduct of CTIMPs in the UK and have been incorporated into this SOP. These regulations require that all adverse events be reported accurately and within strict timeframes. Specifically, the Sponsor must ensure that all relevant information concerning a Suspected Unexpected Serious Adverse Reaction (SUSAR) is documented and reported to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Health Research

Authority (HRA). Failure to comply with these requirements constitutes a breach of criminal law and may result in the withdrawal of regulatory approval for the trial, as well as for all research conducted by the Chief Investigator (CI) or Principal Investigator (PI).

The Regulations require that the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH GCP) are adhered to strictly and provide the source for the procedures in this SOP.

This SOP does not describe the requirements for externally sponsored CTIMP studies that are hosted by NBT. In these circumstances, the sponsor's reporting procedure should be followed, although there is a requirement to notify the R&D in the event of a Suspected Unexpected Serious Adverse Reaction (SUSAR) occurring.

For guidance on safety reporting in research studies other than CTIMPS (non-CTIMPs), please refer to the respective SOP.

Adverse incidents—including clinical, non-clinical, and near misses involving staff or visitors during routine care or research activities should be reported in accordance with NBT's "Responding to Patients Incidents policy", found on LINK. Please note, that an adverse incident may also qualify as an adverse event; if this is the case, the event must be reported through both the incident reporting process and the adverse event reporting route.

Non-NBT sites should follow their own local policy for reporting Incidents to Risk Leads/Departments.

Abbreviations

AE	Adverse Event
AR	Adverse Incident
CI	Chief Investigator
CTA	Clinical Trials Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
GCP	Good Clinical Practice
DMC	Data Monitoring Committee
DMP	Data Management Plan
DSUR	Development Safety Update Report
EMA	European Medicine Agency
EMEA	European Medicine Evaluation Agency
EU	European Union

	HRA Health Research Authority **IMP** Investigational Medicinal Product **MedDRA** Medical Dictionary for Regulatory Activities **MHRA** Medicine and Healthcare Products Regulatory Agency **NBT** North Bristol NHS Trust **PI** Principal Investigator **REC** Research Ethics Committee **R&D** NBT Research and Development Office **RSI** Reference Safety Information **SAE** Serious Adverse Event **SAR** Serious Adverse Reaction **SUSAR** Suspected Unexpected Serous Adverse Reaction **TMF** Trial Master File Further expansion on some of the abbreviations can be found in the appendix
3. Relevant Policies & Guidance	**Related R&D Templates** RD QMS TMPL 013a - SAE/SAR/SUSAR Initial Reporting Form for CTIMPS RD QMS TMPL 013b - SAE/SAR/SUSAR Follow Up Report Form for CTIMPS **Related R&D SOPs:** RD QMS SOP 003 - Research Study Modifications RD QMS SOP 007- Applying for NBT Sponsorship RD QMS SOP 009 - Periodic Reporting to REC and MHRA RI QMS SOP 013c - Safety Reporting non CTIMP **NBT SOPs** CG- 70 - Responding to Patient Safety Incidents
4. Operational Areas Included	This SOP is applicable for anyone involved in CTIMPS that are sponsored by NBT

5. Operational Areas Excluded	NA
6. Who should read this	This SOP should be used by investigators and research team members involved in CTIMPs sponsored by NBT.
7. Roles responsible for carrying out this procedure	**Chief Investigator (CI) and Delegated Individuals** The CI has overall responsibility for the conduct of a CTIMP and is directly accountable to the sponsor and care organisations where the CTIMP takes place. The CI must ensure that the research team gives priority at all times to the dignity, rights, safety and wellbeing of participants and has a responsibility for coordinating the reporting of safety events to the relevant bodies. The CI is responsible for ensuring the safety of trial participants by overseeing the identification, documentation, and assessment of adverse events, including serious and unexpected reactions. The CI must ensure that Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to the MHRA within strict timelines, as outlined this in this SOP. They must implement urgent safety measures when necessary and maintain clear communication with the sponsor and regulatory bodies. The CI must ensure that any safety reporting tasks that are delegated by the sponsor are carried out in compliance with Good Clinical Practice and regulatory requirements. **Principal Investigator(s)** The PI, who may also be the CI in the case of a single-site CTIMP, has responsibility for the conduct of research at the site at which they are PI and assessing and reporting any safety events. For multi-centre projects, the PI is required to inform the CI, or organising research team, of all safety events that occur at his/her site; following the guidelines and timescales set out in this SOP or as agreed in the protocol. The PI will also be required to provide any supplementary information requested by the sponsor and relevant authorities. **Other Investigators/ Research Nurses** The clinical assessment and classification of any safety event should be undertaken by the CI/PI or, if undertaken by another Investigator or Research Nurse, be verified and countersigned by the PI.

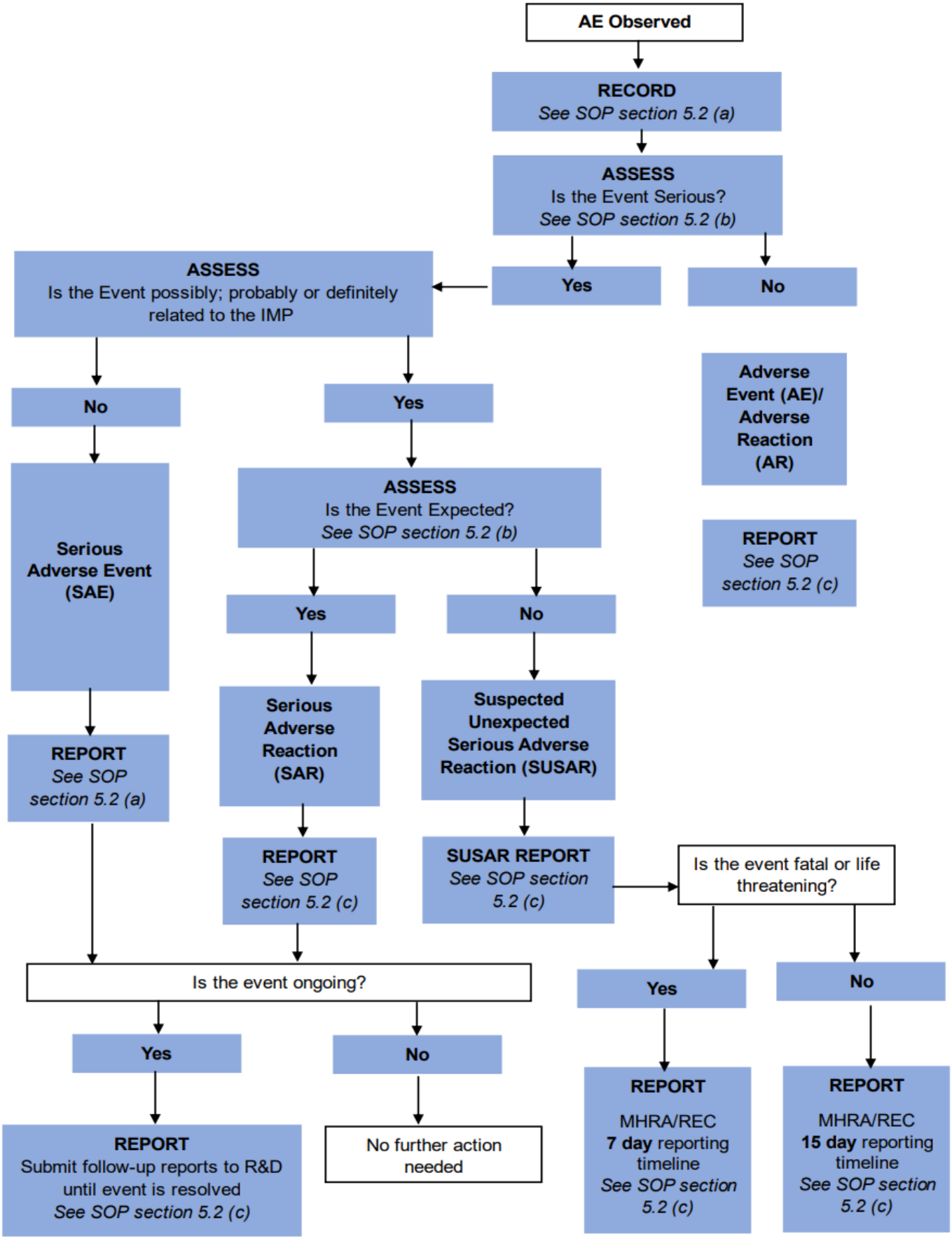
	Tasks relating to the management of safety events may be delegated to a Research Nurse. These must be recorded in a 'Delegation of Responsibilities Log' (see SOP on Applying for NBT Sponsorship (RI/QMS/SOP/007). **Sponsor** Sponsors are responsible for ensuring that before a project begins, there are arrangements in place to allocate responsibilities for the management, monitoring and reporting of the research as well as reviewing significant developments, particularly those which put the safety of participants at risk. The R&D department at NBT as sponsor representative is responsible for maintaining oversight of safety reporting and is responsible for: Performing ongoing safety evaluations of any Investigational Medicinal Products (IMPs), including trend analysis. Keeping detailed written records of all safety events reported by the CI/PI and performing an assessment with respect to seriousness, causality and expectedness. Promptly notifying the NHS Research Ethics Committee (REC), Medicines and Healthcare products Regulatory Agency (MHRA) and other investigators of findings that may affect the health and safety of subjects Reporting safety events to the REC and the MHRA within defined timescales Reporting all SUSARs to the relevant bodies associated with comparator product(s) and Marketing Authorisation holders within given timelines, including the REC and MHRA. If the IMP is an on-license medication with Marketing Authorisation, report the safety event via the MHRA Yellow Card system. Liaising with NHS Research & Development Departments. Breaking treatment codes, if necessary, before submitting expedited reports to the relevant bodies. Submitting Annual Safety and Progress Reports (see SOP on Periodic Reporting. (RD/QMS/SOP/009). Encouraging the setup of Data Monitoring Committees (DMCs) for Phase II and III CTMPs that have high morbidity/mortality. Regularly reviewing safety events to ensure compliance with this SOP.

	Clinical Trials Units When NBT delegates trial management to a Clinical Trials Unit (CTU), the CTU may also take on some responsibilities for safety reporting management. This delegation will be clearly specified in both the trial protocol and the collaboration agreement to ensure transparency and accountability. When safety reporting is managed by a CTU, copies of SAEs for NBT sponsored studies need to be provided to the R&D office (researchsponsor@nbt.nhs.uk) to ensure review by sponsor representative for the study and ongoing oversight. NBT will conduct regular Trial Management Meetings (TMM) to support the review and oversight of Safety reporting, where a CTU has been delegated safety reporting responsibilities It is expected that all CTU personnel involved in the study must receive training on the protocol-specific safety reporting procedures and GCP requirements.

8. Procedure:

A list of definitions for this section is available in Appendix A of this SOP

The below flowchart illustrated the process involved in the assessment of and management of Safety Reporting in CTIMPs



8.1 Pre-trial Planning

Prior to the trial commencing the CI will identify what will be used as the Reference Safety Information (RSI) to determine causality of any adverse events occurring. For CTIMPS, the RSI will be submitted to the MHRA as part of the Clinical Trial Authorisation (CTA) application. The RSI can constitute:

- Summary of product characteristics (SmPC) In the case of products with a marketing authorisation
- Investigator Brochure
- Study Protocol

The RSI will be required for both the active IMP and for any comparator IMPS.

The Clinical trial protocol should list known side effects and safety events contained within the RSI. This should be written in agreement with the relevant drug manufacturer, where applicable. Where those involved in the design of the trial have reason to believe a particular safety event may occur, whether a belief originating from the manufacturer or the clinician's judgement, this should be recorded in the protocol and drawn to the attention of the research team.

Where applicable to the study the CI should establish study-specific coding conventions for AEs and SAEs, such as MedDRA, and this should also be recorded in study documentation,

The sponsor and all other PIs will be provided with the approved RSI prior to the trial commencing. If the CI and/or sponsor is informed of any updates to the document being used as the RSI (for example, if the summary of product characteristics is updated by the manufacturer), the sponsor and CI must agree whether this should replace the existing RSI. If it is agreed, a modification will be submitted to the MHRA and only once approved will the updated RSI be used, except in the case of Urgent Safety Measures.

A robust process must be in place for checking for any applicable updates to the SmPC if it is being used as the RSI. Where changes are required, the process described above should be followed to implement. NBT as sponsor delegates this responsibility to the CI and trial management team.

The RSI used to assess causality and expectedness must be the one which was MHRA approved at the time of onset of the event.

A detailed explanation of safety reporting procedures should be included in the protocol and all members of the research team trained on the procedures. Code-breaking procedures should be agreed beforehand and agreed with pharmacy at each participating site.

It is recommended that a Data Monitoring Committee (DMC) is appointed to review safety data regularly throughout the trial and, when necessary, recommend to the Sponsor whether to continue, modify or terminate the trial.

Safety reporting should also be reflected within the Data Management Plan (DMP). The safety reporting and DMP should ensure the trial is able to efficiently and proactively collect data required for reporting purposes.

8.2 Safety Reporting Procedure

Upon identifying a safety event, the following procedure should be followed (see Flowchart on page 7)

1. **RECORD**

The trial protocol should be consulted and unless the protocol states otherwise, all safety events including non-serious AEs should be recorded.

The safety event should be recorded in the subjects' medical notes / supplementary source data record, and either worksheets or a CRF. AEs should be recorded and reported within a follow-up period for safety as defined in the protocol. In some trials AEs may not be recorded, or only particular AEs will be collated. This will be detailed in the protocol. All available information should be recorded for analysis at a later stage and for inclusion in any reports.

Failure to record an AE/AR as required by the protocol constitutes a protocol deviation and must be documented and reported per the guidance.

In some cases, safety events may also need to be recorded on an NBT Incident Management system (where NBT is a research site) and reviewed by the Trusts Risk Team, in line with NBT trust policy on "Responding to Patient safety Incident", a copy of this policy can be found on the intranet. Non-NBT sites should follow their own local policy for reporting to Risk Leads/Departments.

2. ASSESS

The CI/PI or delegated medically qualified member of the research team must review all documentation including CRFs and source documents (hospital notes, laboratory and diagnostic reports) relevant to the safety event. The trial protocol should also be consulted to see whether the safety event is disease-related (and thus expected).

All AEs will need to be assessed as follows to enable classification of the event, the assessment must be made by the PI or a medically qualified designee who is delegated authority by the PI to undertake this assessment, reflected on the study delegation log.

Intensity Assessment

The assessment of intensity will be based on the Investigators clinical judgement using the following definitions

Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities

To note, the term 'severe' used to describe the intensity of an event or reaction should not be confused with the term 'serious' which is a regulatory term used for trial participant/event outcome. For example, a headache may be severe but not serious, while a minor stroke may be serious but not severe.

Seriousness

The adverse event will be assessed by the investigator for seriousness.
An adverse event, adverse reaction or unexpected adverse reaction is defined as serious if it:
(a) results in death,
(b) is life-threatening*,
(c) requires hospitalisation (any inpatient admission regardless of length of stay) or prolongation of existing hospitalisation,
(d) results in persistent or significant disability or incapacity, or
(e) consists of a congenital anomaly or birth defect.

*Life threatening in the definition of an SAE or SAR refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Medical judgement by the PI/CI or medical delegate should be exercised in deciding whether an AE/AR is serious. SAE/SARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one or the other outcomes listed in the definition above, should also be considered serious.

Causality

The relationship between the drug and the occurrence of each adverse event will be assessed and categorised in terms of Relatedness and Expectedness. The investigator will use the agreed RSI in conjunction with their clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors etc. will be considered.

Relatedness

Not related: Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.

Unlikely: Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.

***Possibly related**: Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.

***Probably related**: Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and the event is more likely explained by the product than any other cause.

***Definitely related**: Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

*Where an event is assessed as possibly related, probably related, or definitely related the event is an adverse reaction
Note: Neither CI nor Sponsor can downgrade a PI causality assessment, however, upgrading of an event is possible. In the event of differing opinions during assessment, BOTH must be provided on the reports.

Expectedness

If an adverse event has been deemed as possibly related, probably related or definitely related then the expectedness of an adverse reaction will need to be recorded. This is a sponsor responsibility although this assessment is usually delegated to the PI, unless otherwise stated. Whether an adverse reaction is considered expected should be established by referring to the RSI and the study protocol.

Expected: Reaction previously identified and described in the RSI and/or protocol

Unexpected: Reaction not previously described in the RSI and/or protocol.

An Adverse reaction must be considered as unexpected if they add significant information on the specificity, severity or frequency of an expected adverse reaction

Note:

- The protocol must identify the RSI used.
- SARs due to lack of efficacy or due to disease progression should not be considered as expected events unless explicitly stated in the RSI.

In blinded trials involving a placebo and active drug, the assessments should be made assuming that the subject received the active IMP. In blinded trials involving two active drugs, the person responsible for assessment may be able to state that if the patient were on drug 'A', the event would be causal and/or unexpected, but if on drug 'B' it would be expected. Where the event is believed to be a SUSAR, then the trial may need to be unblinded depending in the circumstances. Please refer to section 5.3 of this SOP for the additional procedures to follow for blinded trials.

3. REPORT

Reports will need to be sent to the 'relevant bodies' depending on the nature of the safety event. These are as follows: (7 days)

	Sponsor* (or Delegate)	CI**	MHRA	REC
AE/AR	✓	-	-	-
SAE/SAR	✓ (within 24 hours)	✓	-	-
SUSAR (fatal/Life-threatening)	✓	✓	✓ (7 days)	-
SUSAR (non-fatal)	✓	✓	✓ (15 days)	-

*R&D are the representatives of NBT where NBT are acting as the sponsor.
** Subject to contrary agreement as listed in the trial protocol R&D will coordinate submission of these reports

i. Adverse Events (AEs) & Adverse Reactions (ARs)

In the event of an AE/AR, the investigator (or delegated member of research team) must review all documentation (e.g. hospital notes, laboratory and diagnostic reports) relevant to the event. The event and relevant comments must then be recorded in the subject's medical notes (or source data where this is not the medical notes). Except where the protocol states otherwise, all AE/AR should be recorded in detail on a case record form or equivalent to allow analysis at a later stage.

For all AE/AR's the investigator must make an assessment of intensity, causality, expectedness and seriousness as described in 8.2 (b). It is important to record intensity because in some expected events the intensity could become greater than expected, resulting in the event being defined as unexpected, and this may change the reporting requirements.

AEs and/or laboratory abnormalities identified in the protocol as critical to the evaluations of the safety of the study must be reported to the sponsor in accordance with the reporting requirements documented in the protocol

The Chief Investigator will review all AEs/ARs reported to identify any trends which may require urgent action

The Chief Investigator will keep the Sponsor, the main REC and the MHRA informed of any significant findings and recommendations by an independent Data Monitoring Committee or equivalent body where one has been established for the trial.

At the conclusion of the study all AEs/ARs recorded during a study must be subject to statistical analysis as determined by the protocol and that analysis and subsequent conclusions included in the final study report

ii. Serious Adverse Events (SAEs) & Serious Adverse Reactions (SARs):

Reports of SAEs/SARs must be notified to the relevant parties (as per table above) within **24 hours** from the point a safety event has been assessed as an SAE/SAR (other than those identified in the protocol as not requiring immediate reporting). An initial report may be made orally but must be followed up within 48 hours of the event with a written report, including an assessment of seriousness. Information not available at the time (such as test results) must be forwarded once available.

In all circumstances this report should be submitted by email to R&D at researchsponsor@nbt.nhs.uk using the SAE/SAR/SUSAR Initial Report Form for CTIMPs (RD/QMS/TMPL/013a), available on the NBT website. All forms must be signed by the PI (submission of the form by email from the PIs professional address will act as PI signature). Receipt of the form will be reviewed by a delegated member of R&D and logged on the R&D database. The report may be reviewed by members of R&D, and a clinical trial pharmacist may be consulted along with the CI, if deemed necessary. The only exception to this is where the protocol or other relevant RSI (e.g. investigator brochure) identifies the event as not requiring immediate reporting.

If the event is ongoing, additional information should be submitted to R&D by email Researchsponsor@nbt.nhs.uk using the SAE/SAR/SUSAR Follow Up Report Form for CTIMPs (RI/QMS/TMPL/013b), available on the NBT website; this must be submitted within 10 days of the initial report . After the first follow up report, further Follow up Report Forms do not need to be completed within a specified timeframe unless the R&D department informs you that this is

a requirement. They should only be submitted if there has been a significant change/update of the SAE including where the event is now resolved or a decision for no further follow up has been taken.

The CI will review all serious adverse events/reactions reported to identify any trends which may require urgent action.

The CI will provide the main REC with copies of all reports and recommendations of any independent DMC established for a trial as applicable.

On request of the MHRA the CI will submit detailed records of all adverse events that have been reported.

Please note for some NBT sponsored research where the IMP/s or intervention/s are considered low risk it may be agreed within the approved protocol that a slight variation on the process described above is acceptable (including for example, a description of anticipated events within the patient population which if not causally related to the study drug/intervention do not require onward reporting to sponsor). However, any variations will be reviewed by a member of the NBT R&D sponsorship team prior to implementation of the process. The agreement will be based on risk, ensuring patient safety is at the forefront of any decision making.

iii. Suspected Unexpected Serious Adverse Reactions (SUSARs):

SUSARs must be reported to R&D immediately using the SAE/SAR/SUSAR Initial Report Form for CTIMPs (RD/QMS/TMPL/013a), available on the NBT website. All SUSARs must be reported in an unblinded state (see section 8.3 of this SOP regarding unblinding), R&D can support this process if required.

There are several reporting requirements for SUSARs. The R&D sponsorship team will coordinate the submission of these reports:

Reporting SUSARs to the MHRA

The R&D sponsorship team will report the SUSAR to the MHRA using the ICSR Submissions https://icsrsubmissions.mhra.gov.uk/login. The instructions given within the ICSR submission will be followed.

The following expedited reporting will apply:

Fatal or Life-threatening SUSARs

Relevant bodies must be notified as soon as possible but no later than **7 calendar days** after the CI first has knowledge of a reaction which requires expedited reporting. Any further information should be forwarded to these bodies within an additional **8 calendar days**.

Non-fatal or non-life-threatening SUSARs

The Sponsor or delegate must inform the relevant bodies as soon as possible but no later than **15 calendar days** after they first have knowledge of a reaction which requires expedited reporting. Follow up information should be sent within **15 days** of the Sponsor having knowledge of the information. If significant new information on an already reported case is received by the Sponsor, the clock starts again at day zero, i.e. the date of receipt of new information. This information should be reported as a follow-up report within 15 days (or 7 days for fatal/life threatening events).

Reporting SUSARs to the REC

R&D may choose to delegate responsibility of reporting to the REC.

All SUSAR's that are fatal or life threatening need to be submitted to the REC that granted approval within **7 days** of becoming aware of the event.

For CTIMP's not submitted via the combined review: REC should be notified using the REC Safety Report Form (CTIMPS), available on the HRA website: Safety reporting - Health Research Authority
A single form may be used for the submission of several safety reports relating to the same trial. Reports should not normally cover more than one trial. However, the REC may permit this where two trials are very closely connected, for example a main study and an extension study with the same treatment regime

For CTIMPS submitted via the combined review: SUSARs are submitted through the ICSR portal only. Separate REC notifications are no longer required.

8.3 Safety Reporting when using a Clinical Trials Unit

This section applies to all CTIMPs sponsored by NBT where a Clinical Trials Unit (CTU) is responsible for conducting study-related activities, including aspects of safety monitoring.

Sponsor Responsibilities

NBT, as the Sponsor, retains overall responsibility for safety oversight. This includes the timely reporting of SAEs, SUSARSs, and other safety signals to regulatory authorities. The safety reporting principles outlined in this SOP remain applicable regardless of the involvement of a CTU. CTU safety processes are to be reviewed during study set-up.

CTU Responsibilities

The CTU is responsible for:

- Identifying and documenting safety events in accordance with the study protocol.
- Promptly communicating safety events to the Sponsor, as per the roles and responsibilities agreed and contracted during study setup.
- Where safety events are reported directly to the CTU, the unit must comply with this SOP. SAEs must be reported to NBT within **24 hours** of awareness using the designated SAE reporting form.
- CTU's must maintain documentation demonstrating timely triage of safety events.
- Non-serious AEs should be reported according to the timelines specified in the study protocol. Cumulative safety data should be reviewed regularly as part of Trial Management Meetings to ensure ongoing safety oversight.

8.4 Blinded trials

Where possible, blinding should be maintained for all patients prior to final analysis and, in the case of double-blinded trials, for all those involved with the trial on a daily basis and involved in data analysis at the end of the trial. Individual trials, where one or more IMPs are blinded should have a section in the protocol which describes the circumstances in which unblinding is necessary and also the procedure for unblinding. This may also be detailed in a trial specific unblinding procedure, which should be referred to in the protocol. The PI may take advice on individual circumstances, from the CI, CTU or Sponsor or the relevant pharmacy department.

The Sponsor should be consulted before unblinding and the process described in the protocol for unblinding should be followed. The breaking of the code should be recorded along with reasons on the CRF and any other documentation, as required in the protocol

Unblinding SAE/SARs

In the event of an SAE/SAR, for which an assessment of causality or expectedness is proving difficult, the blind should be broken for the specific patient to confirm whether the occurrence is linked to the trial drug(s) (where knowing the outcome of the blind would potentially influence the treatment the patient was receiving).

Unblinding SUSARs

All SUSARS must be unblinded prior to reporting in accordance with section 8.2 of this SOP.

There are three possible outcomes that should be considered after unblinding SUSARs:

i. If the product administered to the subject is the **tested IMP**, the case should be reported as a SUSAR.

ii. If the product administered to the subject is the **comparator IMP** with a marketing authorisation, the event should be reassessed for expectedness according to the SmPC and the protocol. If the event is unexpected, the SUSAR should be reported; otherwise, it is an expected SUSAR and is not reportable on an expedited basis.

iii. If the product administered to the subject is the **placebo**, then this will not usually satisfy the criteria for a SUSAR and therefore will not require expedited reporting. If, after unblinding, SUSARs are found to be associated with the placebo, it is R&D's responsibility to report such cases in their discretion. The reaction may be a hypersensitive response to an excipient compound in the formulation of the placebo.

8.5 Urgent Safety Measures

The sponsor and investigator may take appropriate Urgent Safety Measures (USMs) to protect a research participant from an immediate hazard to their health and safety. This measure can be taken before seeking approval from the competent authorities (MHRA in the UK) and ethics committees of all member states concerned.

The first action is to protect patient safety/health.

Where NBT is sponsor, the CI on behalf of the sponsor should discuss the USM by telephone with an MHRA medical assessor, ideally within **24 hours** (**but no later than 7 days**) from the date the measures are taken.

After discussing the USM with the MHRA assessor via phone the MHRA must be provided with written notification of the measures taken and discussed with the medical assessor, within **7 days** from the date the measures were taken. Details of how to make the written notification can be found on the MHRA website Clinical trials for medicines: manage your authorisation, report safety issues - GOV.UK. REC notification is NOT required under the updated guidance.

All communication between the MHRA, the CI/PI and the sponsor should be documented and placed in the ISF and TMF.

Where an USM requires a modification to study documents, (Modification tool plus any updated documents including the changes agreed with the medical assessor), this should be submitted

as a substantial modification as soon as possible. The modification should be marked as being in response to urgent safety measures. Details of how to submit a modification can be found on the MHRA and HRA websites; Aligned to R&D: RD/QMS/SOP/003 Research Study Modifications.

The substantial modification covering the changes made as part of the USM is anticipated within approximately two weeks of notification of the MHRA. Any potential reason for delay to submission of the substantial modification should be discussed and agreed with the MHRA at the time of initial notification or through a follow up call if necessary. Submission of the substantial modification should not be delayed by additional changes outside of those taken and required as an urgent safety measure. Unrelated and unacceptable changes may result in rejection.

8.6 Pregnancy

If a study patient, or the partner of a study patient falls pregnant when participating in a clinical trial, where pregnancy is an exclusion criterion, the participant should be withdrawn from the trial.

Unexpected pregnancies must be reported to NBT R&D who will retain a separate record of the event on their pharmacovigilance database.

Should a participant or the partner of a study participant, become pregnant while taking part in a clinical trial, the participant must be followed up no less than 18 months after completion of the trial. It will be necessary to take informed consent in order to follow up the pregnancy. The trial subjects should be aware of this before they enter the trial, and if consent for pregnancy follow up is not incorporated in the original PIS/ICF, separate informed consent should be gained.

Any congenital anomalies or birth defects, foetal death or spontaneous abortion or any SAE occurring to the mother or neonate should be recorded and reported as an SAE/SAR/SUSAR, as appropriate.

8.7 Data Monitoring Committee

During trial setup, the Sponsor and CI must assess the necessity of establishing a Data Monitoring Committee (DMC) to provide independent oversight of participant safety and trial conduct. If a DMC is deemed necessary, its role and responsibilities must be clearly defined in both the trial protocol and a DMC charter, finalised prior to study initiation.

For trials sponsored by NBT, the DMC is expected to operate under the following principles:

Independence: DMC members must be independent of both the Sponsor and CI to ensure impartial oversight.

Charter Documentation: The frequency of meetings, communication methods, and operational procedures must be detailed in the DMC charter before the trial commences. The Charter must specify unblinding boundaries, communications pathways and handling of emerging safety signals.

Reporting and Action Management: The process for generating DMC reports and addressing any resulting actions must be clearly documented to ensure timely and effective responses.

Liaison and Record-Keeping: A designated member of the DMC or research team must be assigned responsibility for maintaining DMC documentation and serving as the liaison between the DMC, Sponsor, and CI.

Blinded Trials: In blinded studies, the DMC may review unblinded data to maintain safety oversight without compromising trial integrity.

Recommendations: The DMC may provide recommendations to the Sponsor or Trial Steering Committee (if established) regarding trial design, protocol modifications, urgent safety measures, or other safety-related matters.

Where NBT is the Sponsor, DMC requirements will be reviewed and agreed upon during the Study set up process, with expectations and procedures formally documented in the DMC charter.

8.8 Periodic progress and Safety Reporting

The MHRA and R&D office require safety and progress reports to be sent periodically. Periodic reporting is important to identify any emerging trends in patient safety. Further information on reporting requirements including DSURs can be found in the SOP on Periodic Reporting (RD/QMS/SOP/009).

Collated safety reporting data should be reviewed at each trial management meeting. Periodically the trial team and R&D should review data held on their respective databases to ensure the safety data is concordant.

Safety reporting data should be collated to facilitate the regulatory reporting requirements

9. References (if applicable):

UK Policy Framework for Health & Social Care Research 2025
https://www.hra.nhs.uk/planning-and-improving-research/policiesstandards-legislation/uk-policy-framework-health-social-care-research/

The Medicines for Human Use (Clinical Trials) Regulations 2004 Statutory Instrument 2004 No. 1031. www.legislation.gov.uk/uksi/2004/1031/contents/made

The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025.
https://www.legislation.gov.uk/uksi/2025/538/contents

Department of Health (DoH) / Medical Research Council (MRC)
Clinical Trials Toolkit: Safety Reporting
www.ct-toolkit.ac.uk

ICH Secretariat
Guidelines for Good Clinical Practice (GCP) (E6 R3 Step 4, 2025)

https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf

Appendix A

Definitions and Terminology

Term	Abbreviation	Definition
Adverse Event	AE	*Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, medical device or intervention and which does not necessarily have a causal relationship with this treatment.* An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with use of an IMP, whether or not considered related to the IMP. AEs require continuous assessment in relation to the relatedness of AEs to their frequency or severity, which may lead to an escalation from AE to that of SUSAR. Not all adverse events are adverse reactions, but all adverse reactions are adverse events There are occasions when the protocol dictates that some AE events are not to be recorded or logged within the CRF, this is based on a decision by the sponsor to risk adapt the standard requirements and should be fully documented in the protocol and approved by the MHRA and Research Ethics Committee (REC)
Adverse Reaction	AR	*Any untoward and unintended response in a subject to an investigational medicinal product/medical device/intervention which is related to any dose administered to that subject* As such, the distinguishing feature between an AR and AE is whether there is evidence to suggest there is a causal relationship between the event and the IMP. All adverse reactions are adverse events. These events should be recorded in the source data and CRF.
Serious Adverse Event	SAE	*"Any untoward medical occurrence that at any dose:* • *Results in death* • *Is life-threatening** • *Requires hospitalisation or prolongation of existing hospitalisation* • *Results in persistent or significant disability or incapacity; or*

		• *Consists of a congenital abnormality or birth defect."* * Life-threatening refers to an event where the subject was at risk of death at the time of the event; not to an event that hypothetically might have caused death if it was more severe. Medical judgement should be exercised in deciding whether an SAE/SAR is serious in other situations. Those events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one or more of the other outcomes listed, should be considered serious. SAEs should be fully and clearly documented in the source notes, CRF and reported to the sponsor immediately; within 24 hours of the investigator site team's knowledge of the event.
Serious Adverse Reaction	SAR	*"Any SAE that is classed in nature as serious and which is consistent with the information about the IMP set out in the SmPC for that product or the Investigator's Brochure."* *A serious adverse reaction is suspected (possible, probably or definitely) related to the IMP* It is therefore vital that the SmPC and Investigator's Brochure are reviewed at regular intervals throughout the trial to see if the profile of any IMP has changed. A note should be made on the Trial Master File (TMF) to show that this has been undertaken. SARs should be fully and clearly documented in the source notes, CRF and reported to the sponsor immediately.
Suspected Serious Adverse Reaction	SSAR	Any serious adverse reaction that is suspected (possibly or probably or definitely) to be related to the investigational medicinal product/medical device/intervention.
Suspected Unexpected Serious Adverse Reaction	SUSAR	This terminology ius used in relation to CTIMPS only *"Any SAE/SAR that is suspected to be caused by the IMP, but which is not consistent with the information available about the IMP set out in the SmPC for that product or the Investigator's Brochure."* The protocol should list any known side effects for each trial drug, and this should be checked against each SAE/SAR for expectedness. If the event is not listed as expected or has occurred in a more serious form than anticipated, it should be considered a SUSAR.
Investigational Medicinal Product	IMP	An IMP is a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including licensed products that are being used: • Off licence

		• Within license but where the study involves assessing the efficacy and/or safety of the product • Or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation.
Reference Safety Information	RSI	It is important to know what document constitutes the reference Safety Information (RSI) for each study. The RSI document should be submitted to the MHRA and approved as part of the clinical trial authorisation. The types of RSI most commonly used include: SmPC- Summary of Product Characteristics IB- Investigator Brochure Protocol
Summary of Product Characteristics	SmPC	The SmPC is a technical document which profiles a drug and contains information relating to composition, form and strength, known reactions, cautions, shelf-life and storage conditions.