Research & Innovation

North Bristol NHS
NHS Trust

Standard Operating Procedure

Safety Reporting: Clinical Trials of Investigational Medicinal Products (CTIMPs)

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Document Version History

VERSION NUMBER	EFFECTIVE DATE	REASON FOR CHANGE
1.0	01-04-11	Addition of revised SAE form Appendix D
2.0	13-06-11	Clarification of responsibilities and reporting timelines
3.0	01-03-12	SOP renamed, updated in line with new template and recoded from ISOP-H06
4.0	18-02-16	Updated reference to *Research Study Amendments* SOP
4.1	28-11-16	Updated flowchart

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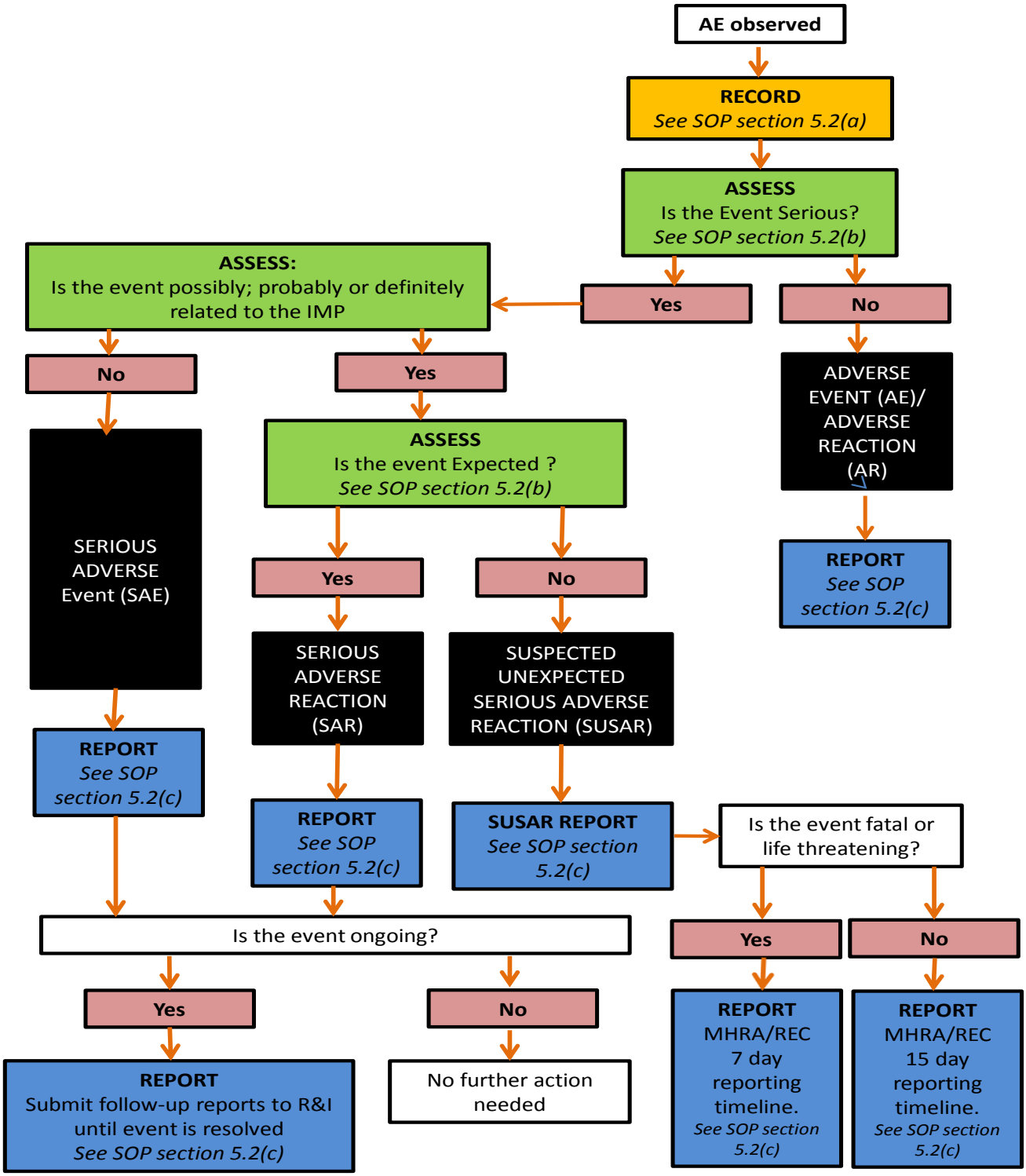
i. SOP Flowchart



1. PURPOSE AND SCOPE

The purpose of this SOP is to provide a framework by which safety events arising in CTIMPs are recorded, assessed and reported according to applicable legal requirements and GCP. The SOP applies to all CTIMPs sponsored by NBT.

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.

The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, apply to the conduct of CTIMPs in the UK and have been incorporated into this SOP. A breach of these requirements constitutes a breach of criminal law and may lead to the withdrawal of regulatory approval for the trial and for all research carried out by a CI/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 procedure 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&I in the event of a Suspected Unexpected Serious Adverse Reaction occurring.

For guidance on safety reporting in research studies other that CTIMPS (non-CTIMPs), please refer to the Guidance Document*:* Safety Reporting: Studies other than clinical trials of Investigational Medicinal Products (non-CTIMPs) (RI/QMS/SOP/013c).

2. DEFINITIONS/ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CRF	Case Report Form
CI	Chief Investigator
CTIMP	Clinical trials of Investigational Medicinal Products
GCP	Good Clinical Practice
NBT	North Bristol NHS Trust
PI	Principal Investigator
R&I	NBT Research & Innovation Office
REC	Research Ethics Committee
MHRA	Medicines and Healthcare Products Regulatory Agency
NBT	North Bristol NHS Trust
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
Sponsor	The individual, company, institution or organisation, which takes on ultimate responsibility for the initiation, management (or arranging the initiation and management) of and/or financing (or arranging the financing) for that research
SUSAR	Suspected Unexpected Serious Adverse Reaction

A list of additional definitions is available at **Appendix A** of this SOP.

3. WHO SHOULD USE THIS SOP

This SOP should be used by investigators and research team members involved in CTIMPs sponsored by NBT.

4. WHEN SHOULD THIS SOP BE USED

This SOP is applicable for all CTIMPs that are sponsored by NBT. This SOP does not apply when reporting adverse events in non-CTIMP studies. For these studies, please refer to the Guidance Document: *:* Safety Reporting: Studies other than clinical trials of Investigational Medicinal Products (non-CTIMPs) (RI/QMS/SOP/013c).

5. PROCEDURE

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

A summary of the general overarching responsibilities of different parties in relation to management of trial safety are provided in **Appendix B.**

Guidance on adverse event assessment is available in **Appendix C** of this SOP.

5.1. Pre-trial Planning

Clinical trial protocols should list known side effects and safety events contained within the manufacturer's product information, such as the Summary of Product Characteristics (SmPC) or investigational brochure (IB). 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 clinicians judgement, this should be recorded in the protocol and drawn to the attention of the research team.

Rare events may or may not be included, depending on individual trial requirements. Similarly non-serious events may be regarded as 'notable' by the Sponsor and require recording and reporting.

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.

For large national or international multi-centre trials, 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.

5.2. Safety Reporting Procedure

Upon identifying a safety event, the following procedure should be followed (see **SOP Flowchart** on page 2):

(a) RECORD

Unless the protocol states otherwise, all safety events including non-serious AEs should be recorded, consistent with the purpose of the trial and any toxicity and efficacy endpoints.
The safety event should be recorded on the subjects' medical notes / supplementary source data record, and either worksheets or a CRF. All available information should be recorded for analysis at a later stage and for inclusion in any reports.

In some cases, safety events may also be recorded on an NBT AIMS form (where NBT is a research site) and sent to the Directorate Clinical Risk Lead who will assess whether the event was related to the research. Non-NBT sites should follow their own local policy for reporting to Risk Leads/Departments.

The CI should establish study-specific coding conventions for AEs and SAEs and this should also be recorded.

(b) 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).

The safety event should then be assessed following the assessment guidance in **Appendix C** to enable classification. This involves assessment of seriousness, relatedness, and expectedness. This assessment must be made by the PI or a medically qualified designee who is delegated authority by the PI to undertake this assessment on the study delegation log.

In blinded trials involving a placebo and active drug, the factor in **Appendix C** should be evaluated on the basis that the patient was on the active drug. 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.

(c) REPORT

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

	SPONSOR*	CI**	MHRA	REC
AE/AR	✓♦			
SAE/SAR	✓	✓		
SUSAR	✓	✓	✓♦♦	✓♦♦

* R&I is the representative of NBT where NBT is acting as Sponsor. Where the AE/AR is identified in the protocol as critical to the evaluation of trial safety

****** Subject to contrary agreement in the trial protocol or Investigator's Brochure (IB). R&I will coordinate the submission of these reports

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

Where an AE/AR is identified in the protocol as critical to the evaluation of the safety of the trial, then they must be reported to the Sponsor using the SAE/SAR/SUSAR Initial Report Form for CTIMPs (RI/QMS/SOP/013a), available on the NBT website. This may be reported via fax at the earliest opportunity.

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

Reports of SAEs/SARs must be notified to the relevant bodies 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 fax or email to R&I using the SAE/SAR/SUSAR Initial Report Form for CTIMPs (RI/QMS/SOP/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&I and logged on the R&I database. The report may be reviewed by a meeting of members of R&I and a clinical trial pharmacist may be consulting along with the CI, if deemed necessary.

If the event is ongoing, additional information should be submitted to R&I by fax using the SAE/SAR/SUSAR Follow Up Report Form for CTIMPs (RI/QMS/SOP/013b), available on the NBT website. There is no mandatory requirement regarding the frequency which follow-up reports should be submitted. As a minimum, a report should be submitted when the event resolves/ends.

iii. Suspected Unexpected Serious Adverse Reactions (SUSARs):

SUSARs must be reported to R&I immediately using the SAE/SAR/SUSAR Initial Report Form for CTIMPs (RI/QMS/SOP/013a), available on the NBT website. All SUSARs must be reported in an unblinded state (see section 5.3 of this SOP regarding unblinding), R&I can support this process if required.

There are several reporting requirements for SUSARs. R&I will coordinate the submission of these reports:

- The main REC (which granted approval for the trial to proceed) should be sent a report using the Safety Report Form available via: http://www.hra.nhs.uk/resources/during-and-after-your-study/nhs-research-ethics-committee-rec-CTIMP-safety-report-form/.
- The MHRA should be sent a report via the eSUSAR electronic reporting system, available via: https://esusar.mhra.gov.uk/.
- The following expedited reporting procedure 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: Relevant bodies must be notified **as soon as possible** but no later than **15 calendar days** after the CI first has knowledge of a reaction which requires expedited reporting. Any further information should be sought and a full report submitted **as soon as possible.**

If the event is ongoing, additional information should be submitted to R&I using the SAE/SAR/SUSAR Follow Up Report Form for CTIMPs (RI/QMS/SOP/013b), available on the NBT website. There is no mandatory requirement regarding the frequency which follow-up reports should be submitted. As a minimum, a report should be submitted when the event resolves/ends.

5.3. 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.

The holder of the code break envelope or list should provide the information upon request. Depending on the severity of any occurrence, R&I should be consulted before unblinding. The breaking of the code should be recorded along with reasons on the CRF and any other documentation.

(a) 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).

(b) Unblinding SUSARs

All SUSARS must be unblinded prior to reporting in accordance with section 5.2 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&I'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.

5.4 Pregnancy in Research Participants

Where pregnancy is an exclusion criterion, the participant should be withdrawn from the trial. Unexpected pregnancies must be reported to the R&I who will retain a separate record of the event on their pharmacovigilance database.

Should a 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 to verify whether there are any congenital anomalies or birth defects which would amount to an SAE/SAR/SUSAR.

5.5 Urgent Safety Measures

Urgent safety measures (USM) may need to be taken as a response to a safety event, in order to safeguard other research participants' health and safety. Details of any USMs taken should be recorded in the patient documentation. Urgent Safety Measures may also require an amendment to be made to trial protocol or other trial documentation. Further information can be found in the SOP on Research Study Amendments (RI/QMS/SOP/003).

5.6 Periodic Progress and Safety Reporting

The MHRA, REC and R&I office require safety and progress reports to be sent periodically, sometimes monthly or quarterly, and annually. Periodic reporting is important to identify any emerging trends in patient safety. Further information can be found in the SOP on Periodic Reporting to the REC and MHRA (RI/QMS/SOP/009).

6 DISSEMINATION AND TRAINING

SOPS will be distributed in accordance with the SOP on Preparation of R&I Research SOPs (RI/QMS/SOP/001). This SOP and any associated templates and forms will be uploaded to the NBT website (www.nbt.nhs.uk/research) 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.

7 RELATED SOPS AND DOCUMENTS

- Department of Health
  Research Governance Framework for Health & Social Care, 2nd Edition, April 2005
  www.dh.gov.uk/en/publicationsandstatistics/publications/publicationspolicyandguidance/dh_4108962

- 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 R1 Step 4, 1996)
  www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

- Medicines & Healthcare products Regulatory Agency (MHRA)
  Maintaining Clinical Trial Authorisations: Safety Reporting
  www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm

- Health Research Authority (HRA)
  Progress and Safety Reporting
  www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting

- UK Government
  Medicines for Human Use (Clinical Trials) Regulations 2004
  www.legislation.gov.uk/uksi/2004/1031/contents/made

- North Bristol NHS Trust *Incident Reporting Policy (CG01a)* available on the policy pages of the staff intranet

- The following NBT documents are available on the R&I website: www.nbt.nhs.uk/research

RI/QMS/SOP/013a	SAE/SAR/SUSAR Initial Report Form for CTIMPs
RI/QMS/SOP/013b	SAE/SAR/SUSAR Follow Up Report Form for CTIMPs
RI/QMS/SOP/013c	Safety Reporting: Studies other than clinical trials of Investigational Medicinal Products (non-CTIMPs)
RI/QMS/SOP/003	Research Study Amendments
RI/QMS/SOP/007	Applying for NBT Sponsorship
RI/QMS/SOP/009	Periodic Reporting to the REC and MHRA

Appendix A
Abbreviations & Definitions

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.
Adverse Reaction	AR	*"Any noxious or unintended response to an Investigational Medicinal Product (IMP) related to any dose which, in the pre-approval clinical experience with an IMP or its new usages, may not be established."* 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.
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.
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."* 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.
Suspected Unexpected Serious Adverse Reaction	SUSAR	*"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.
Accidents Incidents or near Misses	AIMS	The AIMS system is common in many NHS Trusts and implements and NHS Trust's policy on Incident Reporting – including relevant AEs that occur in relation to research and during normal clinical practice.
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 licence 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.
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.

Appendix B

Responsibilities

Party	Responsibilities
PI / CI	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 or through which the team has access to participants, their organs, tissue or data. 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 co-ordinating the reporting of safety events to the relevant bodies and undertaking other duties as delegated by the sponsor. 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 Sponsor 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-licence medication with Marketing Authorisation, report the safety event via the MHRA Yellow Card system • Liaising with NHS Research & Development Departments (such as the North Bristol NHS Trust (NBT) Research & Innovation Office)*; • Breaking treatment codes, if necessary, before submitting expedited reports to the relevant bodies, even if the Investigator has not broken the code (see guidance on maintaining blinding below)*; • Submitting Annual Safety and Progress Reports (see SOP on Periodic Reporting to the REC and MHRA (RI/QMS/SOP/009). • Encouraging the set up of Data Monitoring Committees (DMCs) for Phase II and III CTMPs that have high morbidity/mortality; • Register users for pharmacovigilance data entry with the European Medicines Evaluation Agency (EMEA); • Regularly review safety events to ensure compliance with this SOP; * Where NBT is Sponsor, these responsibilities are delegated to the Chief Investigator.
Organisations providing care	Organisations providing care to participants or providing access to participants, their organs, tissue or data, remain liable for the quality of care and for their duty towards anyone who might be harmed by research. They are also required to report any safety events through their internal systems and to report safety events to the National Patient Safety Agency (NPSA) and Strategic Health Authority (SHA), where necessary.
Clinical Risk Leads and Clinical Risk Department	Where NBT is a research site, Clinical Risk Leads are responsible for ensuring that all Serious Adverse Events (SAEs) occurring at NBT are reported on a NBT Accidents, Incidents and near Misses (eAIMS) Form and submitted to the Clinical Risk Department on the 'Safeguard' database system within the timescales specified in the NBT Incident Reporting Policy. Upon receipt of an AIMs Form, the Clinical Risk Department will assess whether the event is research-related and, if so, pass the information to the NBT R&I office to be dealt with accordingly. For Non-NBT sites participating in NBT sponsored trials, it is recommended that local policies regarding reporting of events to Clinical Risk Leads/Departments are followed.

Appendix C
Adverse Event Assessment Guide

SERIOUSNESS

An event is considered serious if it meets one or more of the following criteria:

- Results in death;
- Is life-threatening;
- Requires hospitalisation or prolongation of existing hospitalisation (it is not an SAE if the prolongation of hospitalisation relates to non-medical fitness for discharge);
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect.

CAUSALITY

The relationship between the drug/device/procedure and the occurrence of each adverse event will be assessed and categorised as below. The Investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural historical of the underlying diseases, concomitant therapy, other risk facts etc, will also be considered. The Investigator will also consult the Investigator Brochure or other product information.

NOT RELATED	Temporal relationship of the onset of the AE, relative to the administration of the product, is not reasonable or another cause can explain the occurrence
UNLIKELY	Temporal relationship of the onset of the AE, relative to the administration of the product, is likely to have another cause which can by itself explain the occurrence
POSSIBLY RELATED*	Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the even 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 to be 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, probably or definitely related,* the event is an adverse reaction

EXPECTEDNESS

Adverse reactions must be considered as unexpected if they add significant information on the specificity or severity of an expected adverse reaction. The expectedness of an adverse reaction shall be determined according to the reference documents as defined in the study protocol (e.g. Investigator Brochure or marketing information).

EXPECTED	Reaction previously identified and described in protocol and/or reference documents (e.g. Investigator's Brochure, summary of product characteristics (SMPC)
UNEXPECTED	Reaction not previously described in the protocol of reference documents

INTENSITY

The assessment of intensity will be based on the Investigator's 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