Notification of Serious Breach

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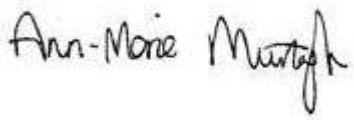
Signature and approval date	 02/01/2026

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1. BACKGROUND AND PURPOSE

This SOP describes the process for the identification, assessment, and follow up of Serious Breaches.

This SOP has been developed in accordance with:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended), Part 4:
  - Paragraph 29A. which states:
    - *(1) The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of—*
      - *(a) the conditions and principles of good clinical practice in connection with that trial; or*
      - *(b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25,*
    - *within 7 days of becoming aware of that breach.*
    - *(2) For the purposes of this regulation, a "serious breach" is a breach which is likely to effect to a significant degree—*
      - *(a) the safety or physical or mental integrity of the subjects of the trial; or*
      - *(b) the scientific value of the trial.*

- ICH GCP E6 (R3), Section II. PRINCIPLES OF ICH GCP:
  - Principle 6.3 which states:
    - *Strategies should be implemented to avoid, detect, address and prevent recurrence of serious noncompliance with GCP, the trial protocol and applicable regulatory requirements.*

Regulation 49 in the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) lists the regulations that if contravened, result in an offence. The contraventions are listed in Section 7 of this SOP: Offences (below). While Regulation 49 is concerned with criminal liability, these offences will be treated as Serious Breaches for the purposes of this SOP.

2. SCOPE

This SOP applies to all Clinical Trials sponsored by KHP.

3. PROCEDURE

3.1 Trial Location identifying a possible Serious Breach

Task	Responsibility	Activity

1	Principal Investigator or delegate	The PI or delegate must ensure that all possible deviations from Good Clinical Practice (GCP), the approved protocol, or applicable Regulations are promptly identified and accurately documented. Deviations must be recorded in the deviation log and appropriately referenced within the ISF and/or participant source records, as applicable.
2	Principal Investigator or delegate	The PI or delegate must review each possible deviation to determine whether it may constitute a possible Serious Breach, taking into account the nature, impact, and context of the deviation. In particular, the following must be considered: • Eligibility errors: All participants must meet the inclusion and exclusion criteria at the point of Clinical Trial entry. Any failure in eligibility assessment must be escalated as a possible Serious Breach. • Critical to quality factors: Deviations affecting factors that are fundamental to participant safety, the reliability and interpretability of Clinical Trial results, or decisions based on those results must be considered for escalation (in line with ICH GCP E6 (R3) principles). • Protocol waivers: Any intentional or prospective deviation from protocol requirements (i.e. protocol waivers) must be reported as a possible Serious Breach. • Cumulative impact: A Serious Breach may arise from the cumulative effect of multiple deviations over time or across Trial Locations, even where individual deviations would not independently meet the Serious Breach threshold.
3	Principal Investigator or delegate	Where a deviation is assessed as a possible Serious Breach, the PI or delegate must report it to the Non-Commercial Trials Manager (NCTM) as soon as possible, without waiting for confirmation or completion of corrective actions. The report should include, as a minimum: • PI name and Trial Location name • Clinical Trial title and identifiers (IRAS number, REC reference, protocol number/version where available) • Clear description of the deviation(s) and why it is considered a possible Serious Breach • Date(s) the issue occurred and was identified • Initial assessment of potential impact on participant safety and/or Clinical Trial integrity • Details of any immediate actions already taken or planned All correspondence and supporting documentation must be retained in the ISF.

3.2 CRA identifying a possible Serious Breach

Task	Responsibility	Activity
1	Clinical Research Associate	The Clinical Research Associate (CRA) must ensure that any possible deviations from GCP, the approved protocol, or applicable Regulations identified during monitoring activities are promptly recognised and appropriately documented. Deviations must be recorded in the deviation log and appropriately referenced within the TMF.
2	Clinical Research Associate	The CRA must consider each identified deviation to determine whether it may constitute a possible Serious Breach, taking into account the nature, impact, and context of the deviation. In particular, the CRA must consider: • Eligibility errors: Any failure to ensure that participants met the inclusion and exclusion criteria at the point of Clinical Trial entry must be escalated as a possible Serious Breach. • Critical to quality factors: Deviations affecting factors that are fundamental to participant safety, the reliability and interpretability of Clinical Trial results, or decisions based on those results, in line with ICH GCP E6 (R3) principles. • Protocol waivers: Any intentional or prospective deviation from protocol requirements identified during monitoring must be escalated as a possible Serious Breach. • Cumulative impact: A Serious Breach may arise from the cumulative effect of multiple deviations across time, participants, or Trial Locations, even where individual deviations would not independently meet the Serious Breach threshold. The CRA must not attempt to independently determine whether a deviation meets the regulatory definition of a Serious Breach, but must escalate any reasonable suspicion.
3	Clinical Research Associate	Where a deviation is assessed as a possible Serious Breach, the CRA must report it to the Non-Commercial Trials Manager (NCTM) as soon as possible, without waiting for Trial Location confirmation, completion of corrective actions, or resolution of the issue. The report should include, as a minimum:

		• CRA name • Clinical Trial title and identifiers (IRAS number, REC reference, protocol number/version where available) • Trial Location(s) affected • Clear description of the deviation(s) and why it is considered a possible Serious Breach • Date(s) the issue occurred and was identified • Initial assessment of potential impact on participant safety and/or Clinical Trial integrity • Details of any immediate actions already taken or recommended Record activities per SOP 3.0 Clinical Trial Monitoring.

3.3 KHP-CTO identifying a possible Serious Breach

Task	Responsibility	Activity
1	Non-Commercial Trials Manager	Upon receipt of a report of a possible Serious Breach, the NCTM must acknowledge receipt promptly and ensure the report is logged within the TMF. If the Chief Investigator is not already aware of the issue, the NCTM must inform the CI without delay. The Sponsor-level assessment of seriousness must commence immediately. The point at which the NCTM becomes aware of the possible breach must be recorded, as this triggers the 7-calendar-day statutory reporting timeline should the breach be confirmed as serious. The NCTM is responsible for coordinating the assessment on behalf of the Sponsor. The NCTM must ask the CRA and CI for any additional information required to support the assessment. All correspondence must be retained in the TMF.
2	Clinical Research Associate	The CRA is responsible for procuring the information requested by the NCTM, providing the information is primarily accessed by the CRA. All requests for information and responses must be documented and retained in the TMF.
3	Chief Investigator or delegate	The CI or delegate is responsible for procuring the information requested by the NCTM, providing the information is primarily accessed by:

		• The CI • The Sponsor Team • The Principal Investigators (PIs) • The Trial Locations. All requests for information and responses must be documented and retained in the TMF.
4	Principal Investigator or delegate	All requests for information and responses must be documented and retained in the ISF.
5	Non-Commercial Trials Manager	When the appropriate information has been collated, the NCTM should ask the CI to assess the impact of the breach on: • Participant safety or physical or mental integrity • Scientific validity or interpretability of Clinical Trial data All requests for information and responses must be documented and retained in the TMF.
6	Chief Investigator	When assessing the impact of the breach on the scientific validity or interpretability of Clinical Trial data, the CI must consider: • The Clinical Trial design • The nature, scope, and integrity of affected Clinical Trial data • The relevance of affected Clinical Trial data to primary and secondary endpoints • Whether the breach compromises the interpretability of Clinical Trial data The outcome of the CI's assessment must be documented in the TMF and provided to the NCTM.
7	Non-Commercial Trials Manager	The NCTM may seek advice from experts not involved in the Clinical Trial to support the assessment of the impact of the breach on: • Participant safety or physical or mental integrity • Scientific validity or interpretability of Clinical Trial data • Regulatory compliance Any advice sought and received must be documented and filed in the TMF.
8	Non-Commercial Trials Manager	The NCTM, on behalf of the Sponsor, and taking into account the CI's assessment and any advice from experts not involved in the Clinical Trial, must assess whether the breach meets the regulatory definition of a Serious Breach. Such assessment should consider: • Actual or likely impact on participant safety or physical or mental integrity

		• Actual or likely impact on the scientific value of the Clinical Trial • Whether the breach constitutes an offence under Regulation 49 The NCTM's assessment and rationale must be fully documented in the TMF.
9	Non-Commercial Trials Manager	Where the breach is assessed as serious, the NCTM must ensure that the breach is reported as soon as possible, and no later than 7 calendar days from the date the NCTM became aware of it. All individuals involved in the assessment (excluding experts not involved in the Clinical Trial) should be notified of the outcome. The Serious Breach must be reported to the MHRA (See Section 3.4 below for how to report). The Serious Breach should be reported to the REC if it 1) has ethical implications, or 2) affects participant safety, rights, dignity, or welfare (See Section 3.4 below for how to report). Note: If the Serious Breach will result in a Modification that'll be reviewed by the REC, the REC does not need to be given advanced noticed of the Serious Breach as the Modification will be the mechanism by which the REC is informed.
10	Chief Investigator or delegate	Where the breach is assessed as serious, the CI should share the outcome with individuals that were not involved in the assessment, if appropriate. For example: • The Trial Steering Committee • The Funder • The Data Monitoring Committee if applicable • The IMP manufacturer if applicable • The NIMP manufacturer if applicable Correspondence should be recorded in the TMF
11	Non-Commercial Trials Manager	Where the breach is assessed as non-serious, the NCTM must ensure that: • The rationale for the decision is clearly documented • The CI identifies appropriate corrective and preventive actions, records them using the CAPA template, and implements them using the CAPA template • All individuals involved in the assessment (excluding experts not involved in the Clinical Trial) are notified of the outcome The NCTM's assessment and rationale must be fully documented in the TMF.

3.4 KHP-CTO reporting a Serious Breach to the MHRA and REC

Task	Responsibility	Activity
1	Non-Commercial Trials Manager	The NCTM may, where appropriate, make initial contact with the MHRA by telephone to inform them of the confirmed Serious Breach. This contact is supplementary to, and does not replace, formal written notification. A written record of the call, including the date, MHRA contact, and issues discussed, must be prepared and retained in the TMF.
2	Non-Commercial Trials Manager	The NCTM must ensure that the MHRA Serious Breach Notification Form (see Section 5 below) is completed and submitted as soon as possible and no later than 7 calendar days from the date the NCTM became aware of the breach. The form must be submitted in accordance with the instructions provided on the MHRA Serious Breach Notification Form. The NCTM must be listed as the Sponsor contact for ongoing correspondence unless otherwise agreed. A copy of the completed form and the covering email must be retained in the TMF.
3	Non-Commercial Trials Manager	The NCTM must determine whether the Serious Breach requires notification to the REC. Notification to the REC is required where the breach: • Has ethical implications • Affects participant safety, rights, dignity, or welfare Where REC notification is required, the MHRA Serious Breach Notification Form (the same form that was sent to the MHRA) must be submitted to the REC, using IRAS, in a timely manner, and a copy of the submission and covering correspondence must be retained in the TMF. Note: If the Serious Breach will result in a Modification that'll be reviewed by the REC, the REC does not need to be given advanced noticed of the Serious Breach as the Modification will be the mechanism by which the REC is informed.
4	Non-Commercial Trials Manager	The NCTM must inform the Sponsor representative(s) of the confirmed Serious Breach in a timely manner, including as applicable: • The KCL Vice Principal (Health Schools) (for Clinical Trials co-sponsored by KCL) • The Director of RMID (for Clinical Trials co-sponsored by KCL)

		• The sole Sponsor/NHS Co-Sponsor R&D Dept. All correspondence must be retained in the TMF.
5	Non-Commercial Trials Manager	All individuals involved in the assessment of the breach (excluding external experts not involved in the Clinical Trial) must be informed of the outcome of the seriousness assessment and the fact that regulatory notification has occurred.
6	Non-Commercial Trials Manager or delegate	The NCTM or delegate must ensure that any correspondence or requests received from the MHRA and/or REC are: • Reviewed promptly • Discussed with the Chief Investigator, as appropriate • Addressed within required timelines All correspondence and records of actions taken must be retained in the TMF

3.5 Producing the Project Report (including CAPA) after a Serious Breach is reported to the MHRA

Task	Responsibility	Activity

1	Chief Investigator	For all Serious Breaches reported to the MHRA, the Chief Investigator (CI) is responsible for ensuring the prompt preparation of a Project Report. The report may be drafted by a delegate; however, the CI retains overall responsibility for its accuracy and completeness.
		
		The Project Report must include, as a minimum:
		• Full Clinical Trial title
		• Clinical Trial identifiers, including IRAS number and applicable trial registration numbers (e.g. ISRCTN, ClinicalTrials.gov, EudraCT, CTIS)
		• Current protocol version and date
		• Date of first participant first visit
		• Name of the Chief Investigator
		• List of participating Trial Locations
		• Number of participants recruited at the time of the breach
		• Brief description of the Clinical Trial
		• Clear and factual summary of the Serious Breach, including how and when it was identified
		• Summary of immediate and interim actions already taken, including rationale where relevant
		• Assessment of the impact of the breach on:
		  ○ Participant safety and physical or mental integrity
		  ○ The scientific value, reliability, and interpretability of the Clinical Trial

		• Root Cause Analysis, identifying underlying and contributory causes • The appropriate corrective and preventive actions, recorded using the CAPA template • A signed statement from the CI confirming oversight and endorsement of the report (mandatory where the report is drafted by a delegate) The completed draft Project Report must be submitted to the NCTM for review and approval. The covering email and version-controlled document must be retained in the TMF.
2	Non-Commercial Trials Manager	The NCTM must review the draft Project Report and any associated CAPA to ensure they are complete, proportionate, and aligned with regulatory expectations. Approval must be formally documented, either through: • NCTM signature on the final document(s), or • Written confirmation from the NCTM by email. Records of approval must be retained in the TMF.
3	Non-Commercial Trials Manager or delegate	The NCTM or delegated representative must submit the approved Project Report and CAPA to the MHRA. Submission may occur: • As part of the initial Serious Breach notification, where the Project Report is available within the 7-calendar-day reporting period; or • As a follow-up submission, where further investigation and CAPA development were required. A copy of the final approved Project Report, CAPA, and covering correspondence to the MHRA must be retained in the TMF.
4	Non-Commercial Trials Manager or delegate	Following submission to the MHRA, the NCTM or delegate must ensure that: • Any MHRA feedback or requests for further information are addressed promptly • Approved CAPA actions are implemented within agreed timelines • Completion and effectiveness of CAPA actions are documented Evidence of implementation and effectiveness review must be retained in the TMF.

3.6 Other actions that may be required after a Serious Breach is reported

These actions may be required after a Serious Breach is reported:

- Urgent Safety Measures (USMs)
  - See SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation
- Modifications
  - SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation
- Temporary Halt of a Clinical Trial which may result in the permanent halt of a Clinical Trial aka End of Trial (EoT)
  - SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation

4. RELATED TEMPLATES

- SOP 3.0 Clinical Trial Monitoring
- SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation

5. RELATED DOCUMENTS

MHRA Serious Breach Notification Form
https://assets.publishing.service.gov.uk/media/5f22f5a6d3bf7f1b13f64f88/Notification_of_Serious_Breach_Form_v7.docx

CAPA template

6. CHANGE HISTORY

CHANGE HISTORY			
Date	Version Number	Change details	Approved by
12 Feb 2010	2.0	Change to King's Health Partners Livery and amend MHRA notification contact details.	Jackie Powell
24 Jan 2012	2.0	Reviewed and no change required.	Jackie Powell
11 Feb 2013	3.0	Change to reflect rebranding of JCTO and to reflect new guidance issued by MHRA.	Jackie Powell
24 Feb 2016	4.0	Scheduled review including consistency check of Glossary terms.	Jackie Pullen
01 Oct 2018	4.1	Minor amendment to include trials managed by KHP-CTO and amend Jackie Pullen's title to Director KHP-CTO.	Jackie Pullen

12 Mar 2019	5.0	Scheduled review, inclusion of requirement to notify Research Ethics Committee of serious breach at same time as MHRA.	Jackie Pullen
08 Mar 2023	6.0	Scheduled review, minor revisions.	Jackie Pullen
31 Aug 2025	7.0	Scheduled review, minor revisions.	Ann-Marie Murtagh
01 Jan 2026	8.0	• SOP template updated • Addition of regulation contraventions • Required actions following assessment of reported Serious Breach listed in more detail	Ann-Marie Murtagh

7. OFFENCES

Regulation 49 in the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) lists the regulations that if contravened, result in an offence. This is the list of contraventions:

- Investigator brochure not amended or validated annually
- Clinical Trial starts before required approvals are granted
- IMP given to those who are not participants
- Modifications made to the Clinical Trial before required approvals are granted
- Breach of transparency requirements
- Clinical Trial starts after approvals have lapsed
- Failure to submit the EoT notification where such failure is likely to significantly affect participant safety, regulatory oversight, or the scientific value of the Clinical Trial
- Failure to adhere to the principles of GCP
- Failure to adhere to protocol
- Failure to report Serious Breach
- Failure to submit notification of USM
- Failure to create and maintain an adequate TMF
- Failure to create and maintain adequate records of SAEs, or failure to use those records to minimise and prevent risk by taking appropriate measures
- Failure to report SAEs to the Sponsor as required by the protocol, or failure by the Sponsor to keep adequate records of reports
- Failure to report SUSARs
- Failure to submit DSURs
- IMP (or IMP modules if there's modular manufacture of the IMP) not manufactured per the Human Medicines Regulations 2012
- IMP manufacturer fails to follow GMP
- IMP manufacturer fails to have a Qualified Person
- NIMP not manufactured per the Human Medicines Regulations 2012

- NIMP manufacturer fails to follow GMP
- NIMP not listed in the investigational medicinal product dossier
- IMP labelling does not meet regulatory requirements

8. GLOSSARY

Adverse Event (AE) - Any untoward medical occurrence in a participant who has been administered an IMP, which does not necessarily have a causal relationship with that IMP.

Corrective and Preventive Action (CAPA) - A structured quality management process used to identify, investigate, and address the root causes of actual or potential non-compliance, deviations, or quality issues, with the aim of preventing recurrence and improving systems and processes.

Chief Investigator (CI) – The overall lead researcher for a Clinical Trial (Outside the UK the term 'Coordinating Investigator', 'Principal Investigator' or 'Investigator' may be used for the overall lead researcher for a Clinical Trial). Chief Investigators are responsible for the overall conduct of a Clinical Trial.

Clinical Research Associate (CRA) – A staff member employed by the KHP-CTO who conducts monitoring activities for a Clinical Trial, including but not limited to the initiation phase, routine phase, and close down phase.

Clinical Trial aka Clinical Trial of an Investigational Medicinal Product (CTIMP) - Any investigation in human participants (other than a non-interventional trial) intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products and/or to identify any adverse reactions to one or more such products and to study absorption, distribution, metabolism and excretion of one or more such products with the object of ascertaining the safety and/or efficacy of those products. Includes clinical trials of ATMPs.

Clinical Trial Authorisation (CTA) – Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) to conduct a Clinical Trial. No Clinical Trial can commence in the UK without both a CTA and a favourable ethical opinion. Applications to the MHRA and the Research Ethics Committee (REC) may be made in parallel.

Co-Sponsors – Two organisations that take responsibility for the initiation, management and financing (or arranging of the financing) in relation to a Clinical Trial. The Co-Sponsors agree how the Sponsor functions for the Clinical Trial are divided between themselves and document this accordingly.

Development Safety Update Report (DSUR) - A common standard for periodic reporting on drugs under development (including marketed drugs that are under further study).

End of Trial (EoT) – The end of the trial as defined in the protocol. The end of the trial is typically expressed as a condition-based event, not a predetermined date.

Good Clinical Practice (GCP) - An international ethical and scientific quality standard for designing, conducting, recording, and reporting Clinical Trials that involve human participants. It ensures the safety, well-being, and rights of participants are protected while

maintaining the credibility and accuracy of trial data. GCP is crucial for safeguarding participants and ensuring Clinical Trials produce reliable, scientifically valid results.

Good Manufacturing Practice (GMP) - A system of quality standards that ensures medicinal products are consistently produced and controlled in accordance with their intended use and the requirements of their Marketing Authorisation or CTA. The GMP that applies in the UK is a version of the EU GMP, historically known as EudraLex Volume 4, and this version is maintained and published by the MHRA.

Health Research Authority (HRA) – The national body in England responsible for protecting and promoting the interests of patients and the public in health and social care research.

ICH GCP E6 (R3) – The International Council for Harmonisation – Good Clinical Practice, Guideline E6 (Revision 3). This is an internationally recognised ethical and scientific quality standard for the design, conduct, oversight, recording, and reporting of Clinical Trials.

Integrated Research Application System (IRAS) - The online application system used to apply for most permissions and approvals for research in health and social care in the UK.

Investigational Medicinal Product (IMP) – A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a Clinical Trial. This includes products with marketing authorisation when used in a way different from the approved form, for an unapproved indication, or to gain further information about an approved use.

Investigator Site File (ISF) – The Trial Location-specific set of essential documents held at the Trial Location by the Principal Investigator, demonstrating how the trial was conducted at that particular location and that the investigator complied with the protocol, Sponsor instructions, and GCP.

KHP-CTO Non-Commercial Team - Comprises the Non-Commercial Trials Manager, CRA(s), Clinical Trial Administrator(s), and Training Executive(s).

King's Health Partners (KHP) - King's College London, Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, and South London and Maudsley NHS Foundation Trust.

K**ing's Health Partners Clinical Trials Office (KHP-CTO)** – The department established by KHP to 1) undertake the governance, contracting and financial management for commercial research hosted by KHP, and 2) undertake the monitoring and regulatory oversight for non-commercial research sponsored by KHP.

Marketing Authorisation – A regulatory approval granted by the competent authority that permits a medicinal product to be placed on the market, confirming that its quality, safety, and efficacy have been adequately demonstrated.

Medicines & Healthcare products Regulatory Agency (MHRA) – The UK government agency responsible for regulating medicines, medical devices, and Clinical Trials. In the context of Clinical Trials, the MHRA i) acts as the licensing authority for Clinical Trials, ii) reviews the scientific, quality, and safety aspects of a Clinical Trial application, iii) issues CTAs, iv) oversees GCP and GMP inspections, v) monitors pharmacovigilance and safety reporting, and vi) enforces compliance with UK medicines legislation.

Modification - Any change to a Clinical Trial after initial approval that affects the information or conditions on which the Clinical Trial was authorised. Includes minor modifications, Modifications of an Important Detail (MOIDs), Route A and Route B substantial modifications.

Monitoring Plan - A Sponsor-approved document that sets out how Clinical Trial monitoring will be conducted, managed, and documented, using a risk-based approach to ensure participant safety, data integrity, and compliance with the approved protocol and applicable regulations.

Non-Commercial Trials Manager (NCTM) – The most senior member of the KHP-CTO Non-Commercial Team.

Non-Investigational Medicinal Product (NIMP) - Any medicinal product (licensed or unlicensed) used in a Clinical Trial for reasons other than testing its safety or efficacy.

Partner Trusts – Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, and South London and Maudsley NHS Foundation Trust.

Principal Investigator (PI) – The individual at a Trial Location who has primary responsibility for the conduct of the Clinical Trial at that Trial Location.

Project Report - A formal, Sponsor-controlled document produced following the identification and reporting of a Serious Breach to the MHRA, which provides a comprehensive account of the breach, its causes, impacts, and the actions taken or proposed in response.

Qualified Person (QP) - An individual who is legally designated and appropriately qualified to ensure that each batch of a medicinal product, including an IMP, has been manufactured, tested, and released in compliance with applicable legislation, GMP, the terms of the CTA, and the terms of the Manufacturing Authorisation if applicable.

Regulations – The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended).

Research & Development Department (R&D Dept.) – The NHS department at a Trial Location that's responsible for research and development at that Trial Location.

Research Ethics Committee (REC) – A national independent body consisting of healthcare professionals and non-medical members, whose responsibility is to protect the rights, safety and well-being of human subjects involved in a Clinical Trial, and to provide public assurance of that protection by, among other things, expressing an opinion on the Clinical Trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform Clinical Trial participants and obtain their informed consent.

Serious Adverse Event (SAE) - An Adverse Event that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect.

Serious Adverse Reaction (SAR) - An Adverse Event that is both serious and suspected to be causally related to an IMP. In other words, it is an untoward and unintended response to

the IMP that results in death, is life-threatening, requires or prolongs hospitalisation, results in persistent or significant disability or incapacity, involves a congenital anomaly or birth defect, or is otherwise judged to be a medically important event.

Serious Breach - Under Part 4, paragraph 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended), a serious breach is defined as a breach of the conditions and principles of good clinical practice, or of the approved clinical trial protocol (as amended in accordance with regulations 22 to 25), which is likely to affect to a significant degree either the safety or the physical or mental integrity of trial participants, or the scientific value of the clinical trial. Where such a breach occurs, the sponsor is required to notify the licensing authority in writing within seven days of becoming aware of the breach.

Source Documents - The original documents, data, and records in which information about a participant is first recorded.

Sponsor - The person or body who takes on ultimate responsibility for the initiation, management and financing (or arranging of the financing) of a Clinical Trial. The Regulations allow for two or more persons or bodies to take on responsibility for Sponsor functions.

Sponsor Team – The team selected by the CI to undertake the sponsorship functions of the Clinical Trial.

Standard Operating Procedures (SOPs) - Detailed, written instructions to achieve uniformity of the performance of a specific function. SOPs are the basis upon which Quality Systems and Processes are conducted and monitored against.

Suspected Unexpected Serious Adverse Reaction (SUSAR) - A Serious Adverse Reaction to an IMP that is suspected to be causally related to that IMP and is unexpected, meaning that the nature or severity of the reaction is not consistent with the applicable product information (such as the Investigator's Brochure or Summary of Product Characteristics).

Trial Location - Means a hospital, health centre, surgery or other establishment, or facility or premises at or from which a Clinical Trial, or any part of such a Clinical Trial, is conducted.

Trial Location Team - The team selected by the PI to undertake the Trial Location functions of the Clinical Trial.

Trial Master File (TMF) - A standard filing system which contains all essential documents which individually and collectively permits the evaluation of the conduct of a Clinical Trial and the quality of the data produced. The filing system can be in the form of a single project file or a number of files/filing cabinets, depending on what is deemed most appropriate for a particular Clinical Trial given its size and complexity. The regulatory documents and approvals within the TMF will be maintained alongside Case Report Forms and source documentation.

Urgent Safety Measure (USM) - An urgent safety measure that must be taken to protect Clinical Trial participants against an immediate hazard to their health or safety.