SERIOUS BREACHES (HOSTED)

Research & Development

Standard Operating Procedure for Notification of Serious Breaches of GCP in HOSTED Clinical Trials at West Hertfordshire Hospitals NHS Trust

SOP Number : SOP-31-06	**Effective Date:** October 2021
Version Number: v06	**Review Date:** 2-3 years

1.0 BACKGROUND

This document sets out the procedures to be followed by all West Hertfordshire Hospitals Trust (WHHT) staff who are involved in Clinical Trials of Medicinal Products (CTIMPs) and non-CE marked Medical Devices.

It provides guidance on how serious breaches of Good Clinical Practice (GCP)/protocol must be identified and managed.

Deviations from clinical trial protocols and GCP occur commonly in clinical trials. The majority of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial. These cases should be documented e.g. in the case report form (CRF) for the trial or the Trial Master File (TMF), in order for appropriate Corrective And Preventative Actions (CAPA) to be taken. In addition, these deviations should be included and considered when the clinical study report is produced, as they may have an impact on the analysis of the data. However, not every deviation from the protocol needs to be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) as a serious breach. The reporting procedures for protocol violation/deviation are usually defined in the clinical trial protocol.

The judgement on whether a breach is likely to have a significant impact on the scientific value of the trial depends on a variety of factors including the design of the trial, the type and extent of the data affected by the breach, the overall contribution of the data to key analysis parameters, the impact of excluding the data from the analysis etc.

It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the trial. Anyone who is unsure whether a breach has occurred can contact the R&D Office to discuss the situation and clarify whether a breach is classed as serious (examples of possible serious breaches can be found in Appendix 2).

2.0 PURPOSE

- To outline procedures for identifying a potential serious breach of GCP or protocol violation.
- To describe the process for notification of serious breaches of GCP or the approved trial protocol.
- To ensure appropriate assessments are carried out by relevant parties and fully documented.
- To outline the role of the Research & Development Steering Group (RDSG) in assessing the reported serious breaches and the escalation process.

3.0 APPLICABLE TO

Any Trust employees involved with clinical research including, but not limited to, Unit Heads, Chief Investigators (CI), Principal Investigators (PI), Consultants, Co-Investigators, Clinical Trial Pharmacists, Research Managers, Statisticians, Research Nurses, Trial Coordinators, RDSG & Data Managers.

4.0 RESPONSIBILITIES

4.0.1 All researchers must ensure all possible serious breaches are reported to the PI immediately (within 24 hours) or as stated in the protocol.

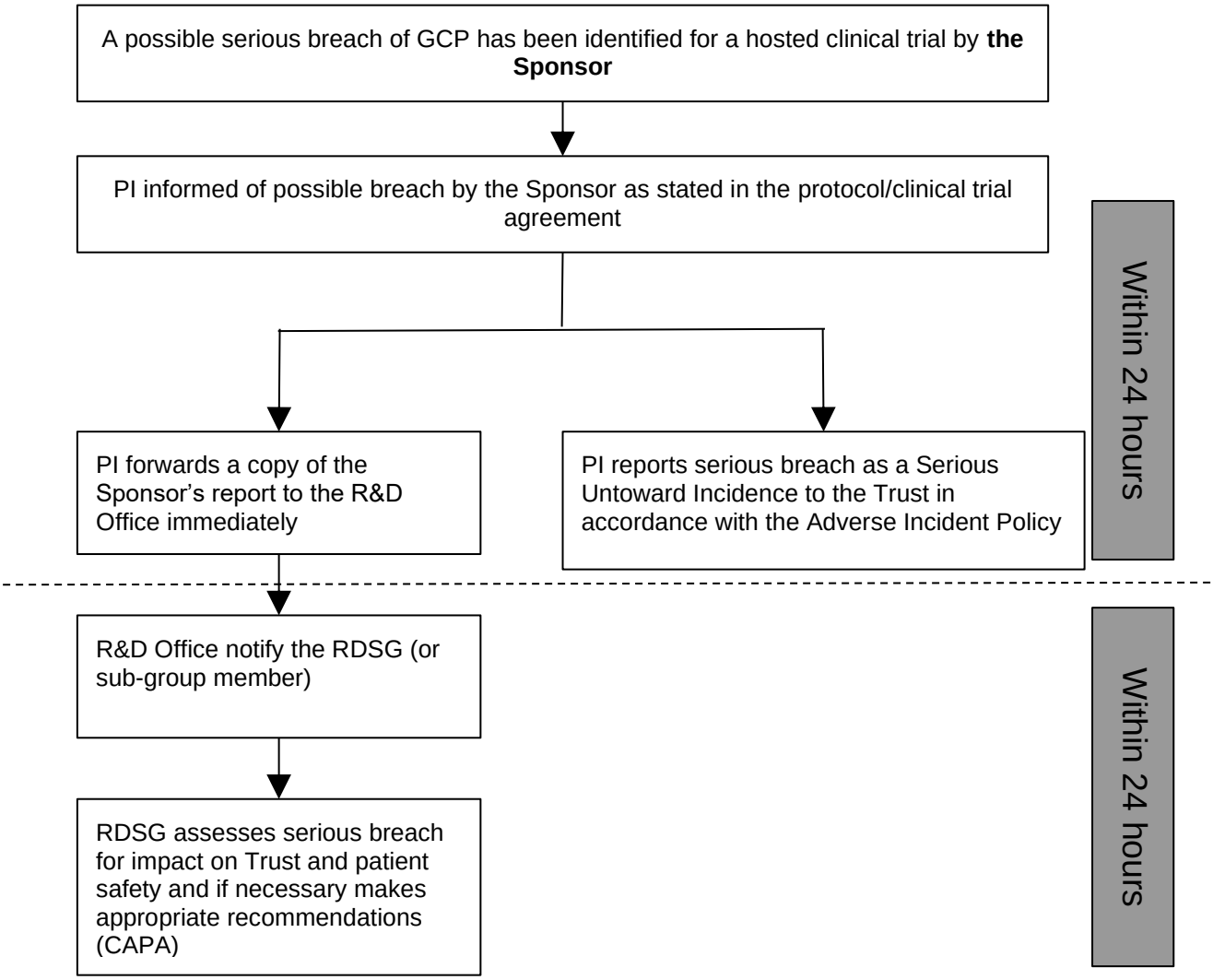
4.0.2 The PI or delegated individual (DI) of the study shall ensure that the Serious breach is reported to the CI, Sponsor and the R&D Office (within 24 hours).

4.0.3 For any possible serious breaches identified by the R&D Office, the RDSG shall ensure that they are assessed immediately and appropriate recommendations are made to the PI regarding further management of the breach and notification to patients.

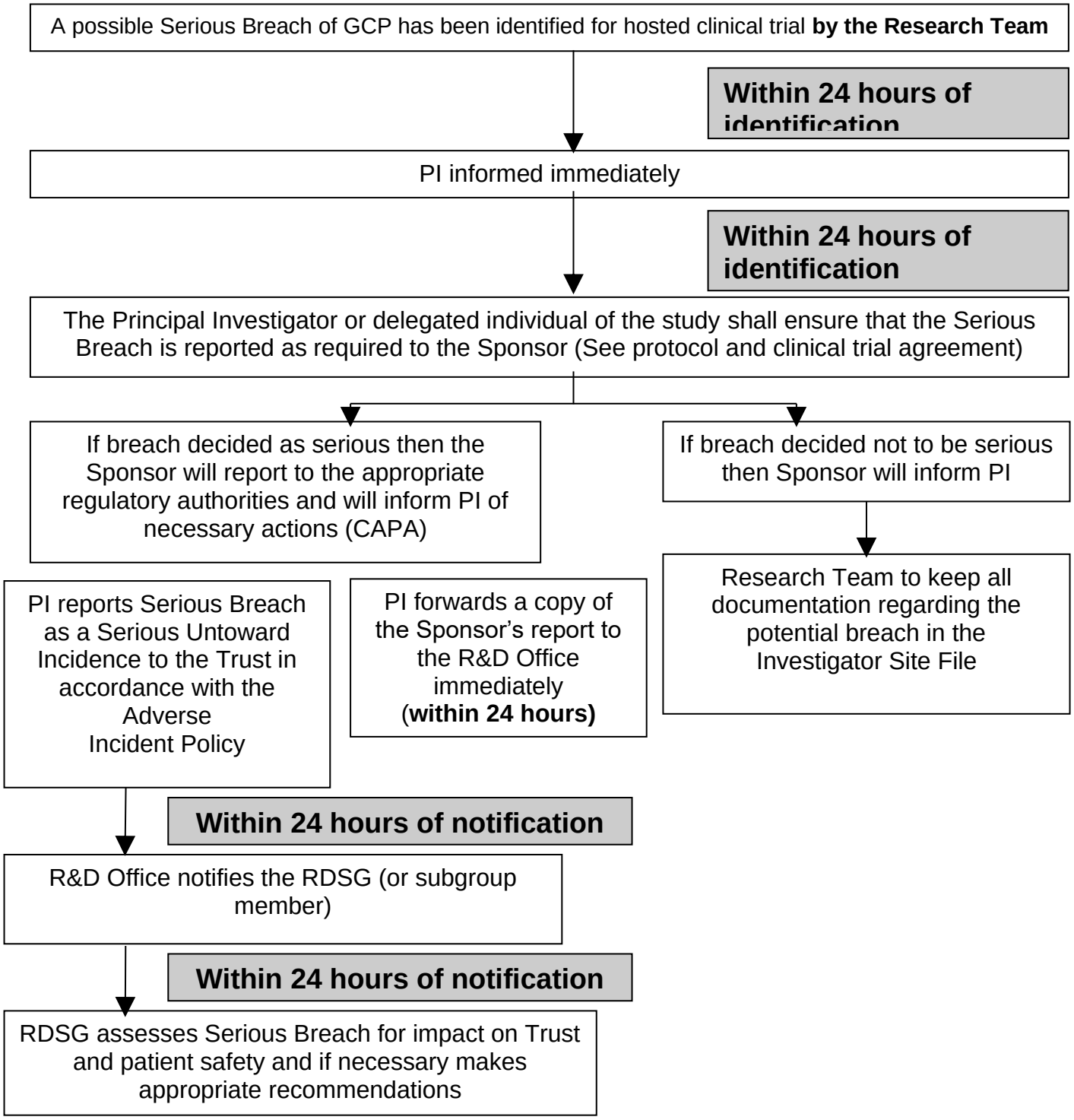
4.0.4 For any possible serious breaches reported to the R&D Office, the RDSG shall ensure that they are assessed for their impact on the Trust and patient safety and if required shall provide appropriate recommendations on behalf of the Trust.

5.0 PROCEDURE

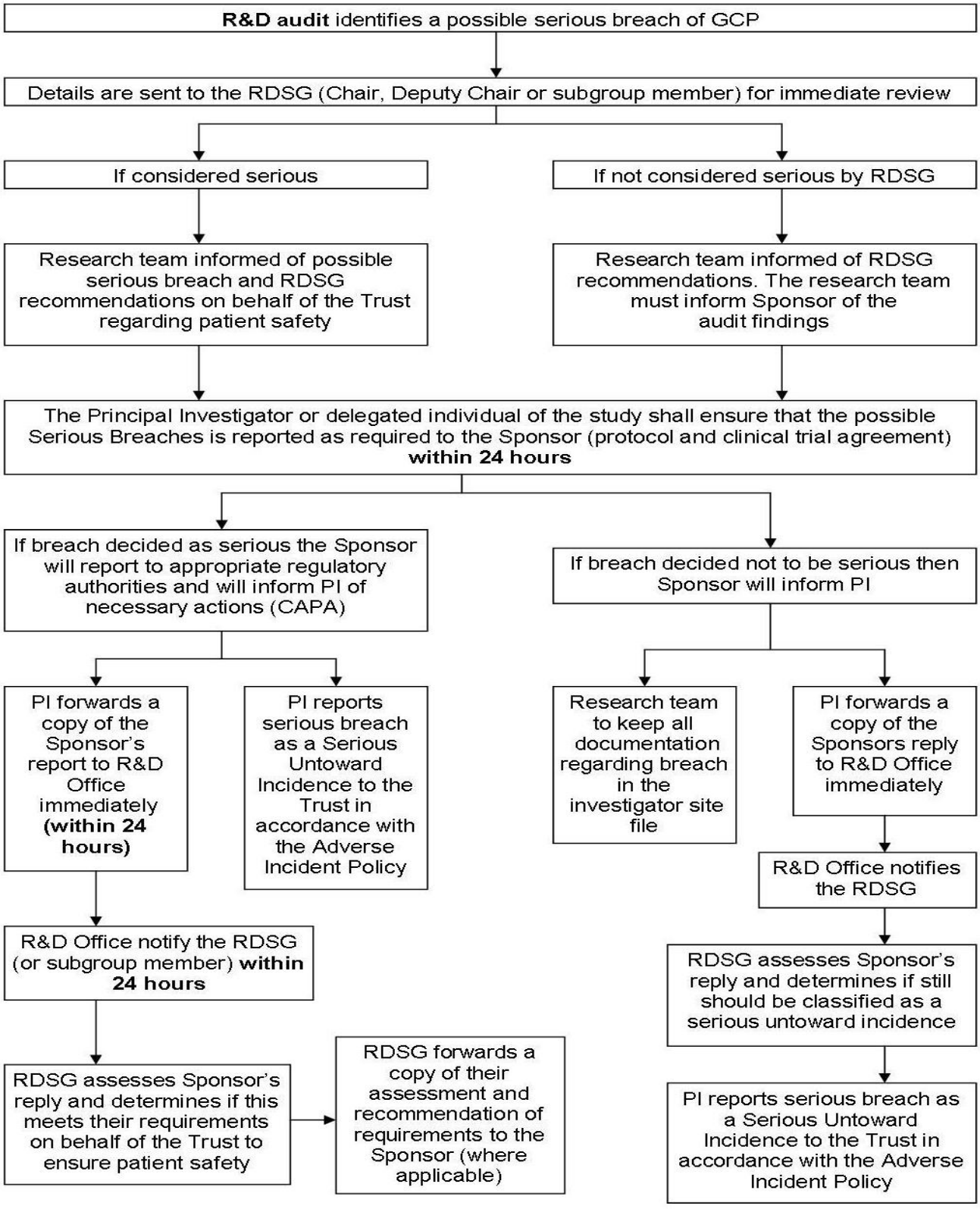
5.1 Procedure for possible Serious Breaches of GCP identified by Sponsor



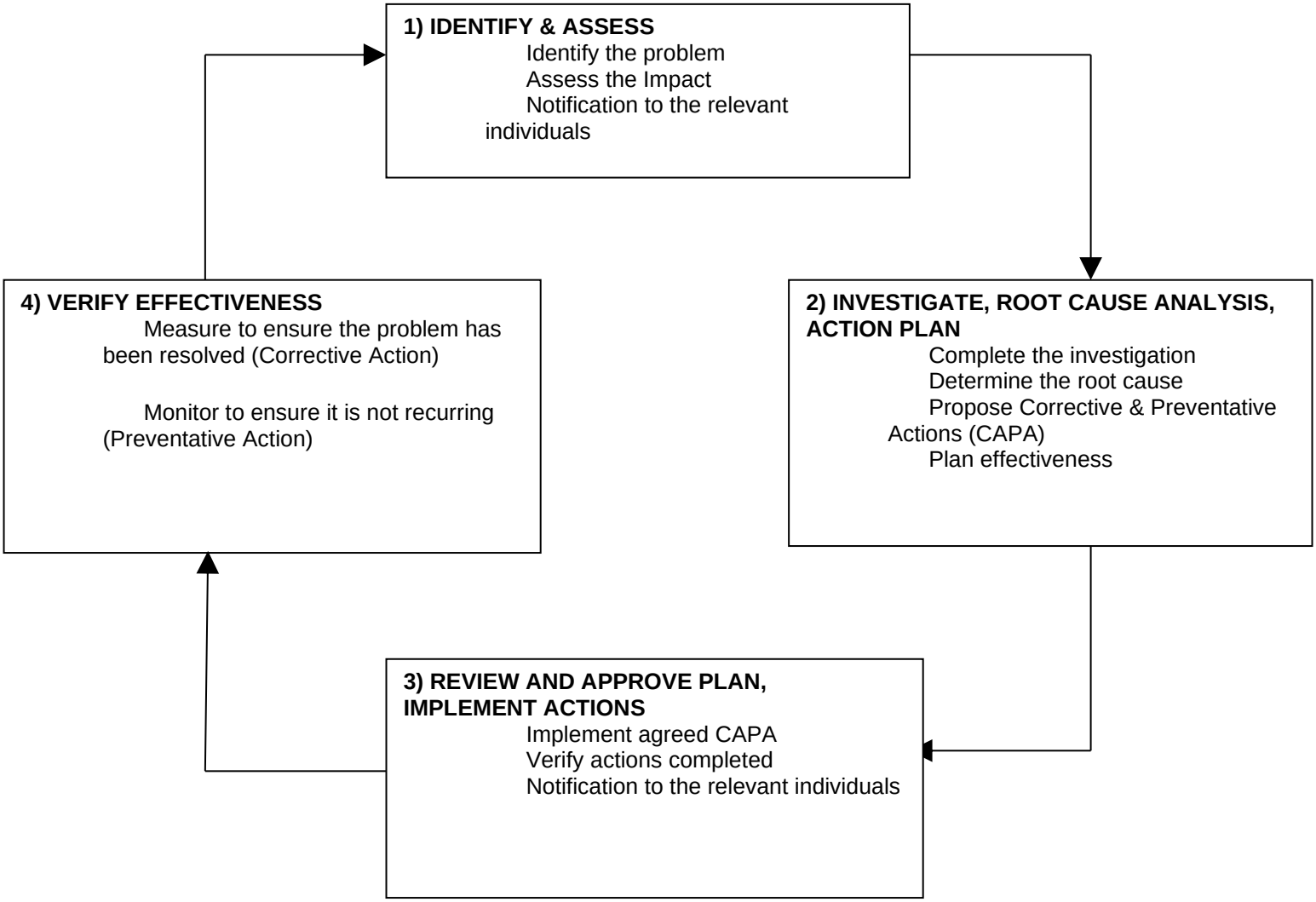
5.2 Procedure for possible Serious Breaches of GCP identified by Research Team



5.3 Procedure for possible Serious breaches of GCP identified by R&D audit



5.4 Corrective and Preventative Action (CAPA Cycle)



5.5 Provision of additional information to the Sponsor

5.5.1 Once the initial notification has been submitted to the Sponsor, the PI and R&D Office will review the breach in full to identify the extent of the breach and continue to update the Sponsor with new information.

5.5.2 The PI and R&D Office will also facilitate any related Sponsor audits and MHRA inspections related to the breach.

5.6 Other Reporting Requirements and Implementing CAPA

5.6.1 Any possible serious breach that occurs may also require reporting to the Trust's risk management team in accordance with the Trust policy. The R&D Office shall make recommendations to the PI/study team about where further reporting requirements apply.

5.6.2 The breach may also require reporting to the ethics committee if it is in breach of the ethical conditions of study approval.

5.6.3 Following the initial assessment of seriousness and impact of the GCP breach, the R&D Office may carry out a full audit of the trial and general trial management systems and procedures. The R&D Office will implement any relevant systems or operational changes as required.

6.0 RELATED DOCUMENTS

- Standard Operating Procedures Working Group Terms of Reference
- Membership of Standard Operating Procedures Working Group
- SOP-02- SAEs (Sponsored)
- SOP-04- Informed Consent
- SOP-05- SAEs (Hosted)
- SOP-06- Trial Master File
- SOP-07- Research Staff Training
- SOP-08 - Role of CI, pharmacy, nuclear medicine and R&D
- SOP-09- Amendments
- SOP-11- Sponsor oversight
- Statutory Instrument 2004/1031: The Medicines for Human Use (Clinical Trials) Regulations 2004
- Statutory Instrument 2006/1928: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006
- Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol, MHRA

7.0 APPENDICES

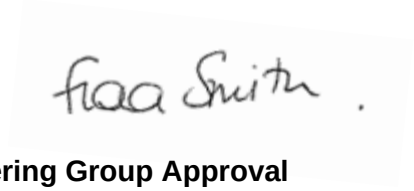
Appendix 1 - Definitions
Appendix 2 - Examples of Serious Breaches

8.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**
SOP-31-06	**October 2021**	1. Change from general Standard Operating Procedures (gSOP) to SOP 2. Removal of the '10.0 Agreement' from the template - all agreement signatures will be collated on a new 'SOP Signature Sheet Document' 3. Minor changes and clarifications of terms following review
gSOP-31-05	**October 2017**	Minor amendments following review
gSOP-31-04	**01/10/2015**	Minor amendments following review
gSOP-31-03	**22/05/2014**	Minor amendments following review
gSOP-31-02		SOP modified for implementation at ENHT/WHHT
gSOP-31-01 (MVCC)		SOP modified for implementation at MVCC

9.0 AUTHORSHIP & APPROVAL

Author

Signature  **Date** 28/10/2021

R & D Steering Group Approval

Signature  **Date** 28/10/2021

Appendix 1: Definitions

Adverse Event (AE)
An unfavourable outcome that occurs during or after the use of a drug or other intervention, but is not necessarily caused by it.

Case Record Form (CRF)
A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Chief Investigator (CI)
The investigator with overall responsibility for the research. In a multi-site study, the CI has co-ordinating responsibility for research at all sites. All applications for ethical review should be submitted by the CI.

Clinical Trial
A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions. A Study Type.

Delegated Individual (DI)
An individual delegated by a person of responsibility to carry out their task(s).

Good Clinical Practice (GCP)
Good Clinical Practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.

International Conference on Harmonisation (ICH)
International Conference for Harmonisation, a collaboration between regulators and the pharmaceutical industry in Europe, the United States and Japan to establish common standards for clinical trials. ICH GCP is a widely recognised standard for Good Clinical Practice in clinical trials.

Investigational Medicinal Products (IMP)
A pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a Clinical Trial, and includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial - a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation, b) used for an indication not included in the summary of product characteristics under the authorisation for that product, or c) used to gain further information about the form of that product as authorised under the authorisation.

MHRA Clinical Trial Authorisation (CTA)
This is the authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) to conduct a Clinical trial of an investigational medicinal product (CTIMP). No CTIMP 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.

Principal Investigator (PI)
The investigator responsible for the research site. There should be one PI for each research site. In the case of a single-site study, the chief investigator and the PI will normally be the same person.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
Any adverse event or adverse reaction that results in:

- death
- is life-threatening*
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- or is a congenital anomaly or birth defect

Comment: Medical judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important adverse events/reactions 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 of the other outcomes listed in the definition above, should also be considered serious.

* Life-threatening in the definition of a serious adverse event or serious adverse reaction 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 which hypothetically might have caused death if it were more severe.

Statutory Instrument (SI)
Legal means of implementation of EU Clinical Trials Directive into UK law. SI 1031 (2004), subsequently amended by SI 1928 (2006), SI 2984 (2006), SI 941 (2008) and SI 1184 (2009).

The Medicines & Healthcare products Regulatory Agency (MHRA)
The MHRA is the competent authority for the UK in relation to the Directive 2001/20/EC and the Clinical Trials Regulations, and for Medical Devices, the competent authority in relation to the Medical Devices Regulations 2002.

The Regulations
Medicines for Human Use (Clinical Trial) Regulations 2004 transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 no 1031. This became effective on the 1st May 2004. An amendment to implement Directive 2005/28/EC was made to the Regulations as Statutory Instrument 2006 no 1928.

Trial Master File
The Trial Master File contains all essential documents held by the sponsor/Chief Investigator which individually and collectively permits the evaluation of the conduct of a trial and the quality of the data produced.

Appendix 2: Examples of Serious Breaches

Category	Notifier	Details of Breach Reported	Is this a Serious Breach?
IMP	Sponsor	Dosing errors reported: 1) A subject was dosed with the incorrect IMP, which was administered via the incorrect route (the IMP used was from a completely different clinical trial to the one the subject was recruited to).	**Yes,** there was significant potential to impact the safety or physical or mental integrity of trial subjects.
		2) A subject was dosed with IMP from the incorrect treatment arm. In addition, some months later, the subjects in an entire cohort were incorrectly dosed with IMP three times daily when they should have been dosed once daily.	**Yes,** ● there was impact on the safety or physical or mental integrity of trial subjects or on the scientific value of the trial. ● this issue was systematic and persistent leading to a constant breach of the conditions and principles of GCP in connection with that trial or the trial protocol. ● this issue persisted despite the implementation of a corrective and preventative action plan.
		3) One subject was administered 6 additional doses of IMP. The subject was to receive IMP on day 1 and 8 but instead received IMP on days 1 to 8. The subject experienced a severe adverse event as a result.	**Yes,** there was impact on the safety or physical or mental integrity of trial subjects and on the scientific value of the trial.
		4) A subject took IMP that had expired two days ago. The subject did not experience any adverse events and this issue was not likely to affect the data credibility of the trial.	**No,** there was no impact on the safety or physical or mental integrity of the trial subject or on the scientific value of the trial. In addition, the assessment of the breach identified this as a single episode and a detailed corrective and preventative action plan was implemented.

Temperature monitoring		IMP temperature excursions reported	**Yes**, if the situation was not managed and subjects were dosed Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol Version 6, 08 Jul 2020 10(12) with IMP assessed as unstable, which resulted in harm/potential to harm subjects. **No,** if the excursions had been managed appropriately (e.g. IMP was moved to alternative location/quarantined as necessary and an assessment (by qualified personnel) illustrated that there was no impact on subject safety and data integrity.
IRT issues	Sponsor	Multiple issues with the Interactive Response Technology (IRT) system across several clinical trials leading to the dispensing of expired IMP and a shortage of IMP at investigator sites in time of subject visits.	**Yes,** there was impact on the safety or physical or mental integrity of trial subjects and this issue persisted leading to a constant breach of the conditions and principles of GCP in connection with that trial or the trial protocol, despite the implementation of a corrective and preventative action plan.
Potential Fraud	Sponsor Identified during inspection	On two separate occasions the sponsor identified issues with the same organisation. First with consenting and then with potential irregularities in recruitment and consenting. However, there was not unequivocal evidence of fraud at the time of reporting. One of the studies involved paediatric subjects. A potential serious breach was identified, but not reported (documentation in the Sponsor's TMF identified that there may have been fraud at an investigator site, re-use of previous time point data in later time points). The Sponsor had investigated and the issue was subsequently found to be a genuine error and not fraud.	**Yes,** this subsequently led to enforcement action against the organisation in question. **No**, on this occasion. *However, had this been identified as fraud impacting on the integrity of the data, then this serious breach would not have been notified within the regulatory timeframe (i.e. 7 day window).*
Source Data	Sponsor	Concerns were raised during monitoring visits about changes to source data for a number of subjects	**Yes** *Note: not all information was provided in the original notification, the sponsor*

		in a trial, which subsequently made subjects eligible with no explanation. An audit was carried out by the Sponsor and other changes to source data were noted without explanation, potentially impacting on data integrity. Follow-up reports sent to MHRA confirmed the Sponsor concerns over consenting and data changes made to source without an adequate written explanation.	*provided follow up updates*
Emergency unblinding	Sponsor	A clinical trial subject attended A&E who attempted to contact the pharmacy department (using the phone number listed on the emergency card issued to the subject) in order to break the unblinding code. Pharmacy were unable to code break in a timely manner, as a result, the subject withdrew from the clinical trial feeling unhappy that the pharmacy was not available in an emergency situation.	**Yes,** as this had significant potential to harm the subject if unblinding would have affected the course of the treatment.
Sample processing	CRO	A cohort had invalid blood samples as they were processed incorrectly. As a result one of the secondary endpoints could not be met. Therefore, a substantial amendment was required to recruit more subjects to meet the endpoint. Subjects were dosed unnecessarily as a result of this error.	**Yes**
Protocol compliance	CRO Identified during inspection	Subject safety was compromised because repeat electrocardiograms (ECGs) were not performed, as required by the protocol. The ECGs were required as part of the safety monitoring due to the pharmacology of the IMP. Also, there was inadequate quality control (QC) of the interim safety reports used for dose escalation which has potential for stopping criteria to be missed if adverse events (AEs) were not transcribed from the source to the safety report. Investigator site failed to reduce or stop trial medication, in response to certain laboratory parameters, as required by the protocol. This	**Yes** **Yes**

	Sponsor	occurred with several subjects over a one year period, despite identification by the monitor of the first two occasions. Subjects were exposed to an increased risk of thrombosis. Minor visit date deviation. *A common deviation in clinical trials.*	**No**, a minor protocol deviation, which does not meet the criteria for notification
SAE reporting	Contractor	The investigator failed to report a single serious adverse event (SAE) as defined in the protocol (re-training provided).	**No,** if this did not result in other trial subjects being put at risk, and if it was not a systematic or persistent problem. In some circumstances, failure to report a SUSAR could have significant impact on trial subjects. Sufficient information and context should be provided for the impact to be assessed adequately.
Consent	Sponsor	Patient information leaflet and informed consent updated, but at one trial site this was not relayed to the patients until approximately 2-3 months after approval. More information on the potential consequences of the delay should have been provided.	**No**, if this was not a systematic or persistent problem and if no harm to trial subjects resulted from the delay. **Yes**, if there was a significant impact on the integrity of trial subjects (e.g. there was key safety information not relayed to subjects in a timely manner.
Reporting	MHRA (CTU)	The GCP Inspectorate was notified that a substantial amendment had been submitted regarding changes to dosing on a first in human study, as a result of an SAE after dosing the initial subject. The sponsor had temporarily halted the trial and only after further investigation had assigned the SAE as unrelated. The sponsor had not notified the CTU of the "urgent safety measure" implemented or reported the SAE as a potential SUSAR.	**Yes**
Site Files	NRES	The early destruction of investigator site files (i.e. one study had only been completed a year earlier and one study was still ongoing).	**Yes**

Invitation of patients	Member of public	A member of public received a named invite to be a volunteer in a clinical trial (no specific trial mentioned). However, this person was not on the organisation's volunteer database and had not participated previously in a study. On further investigation by MHRA, it was revealed that the organisation had contracted the use of a mail shot organisation to send a generic mail shot to a list of people in a specific location, over a certain age. This had been approved by the REC.	**No**