Research Governance
and Integrity Team

This is a controlled document.
The master document is posted on the RGIT website and any print-off of this document will be classed as uncontrolled.

Researchers and their teams may print off this document for training and reference purposes but are responsible for regularly checking the RGIT website for more recent versions.

Notification of Serious Breaches of GCP or the Trial Protocol

SOP Reference: RGIT_SOP_021	
Version Number: 10.0	
Effective Date: 27/04/2026	Review by: 31/12/2027
Author: Thomas Lewis, Ethics and Research Governance Coordinator	
Approved by: Amalia Ndoutoumou, Acting Head of Research Governance and Integrity	Date: Amalia Ndoutoumou Digitally signed by Amalia Ndoutoumou Date: 2026.04.27 19:11:17 +01'00'

Version	Date	Reason for Change
Version 1.0	31 May 2007	1st Edition
Version 2.0	15 Jul 2008	CRO name change
Version 3.0	08 Feb 2010	Formation of Joint Research Office
Version 4.0	14 Jul 2011	Annual Review
Version 5.0	03 Dec 2012	Annual Review
Version 6.0	18 Feb 2015	Scheduled Review
Version 7.0	25 Oct 2017	Scheduled Review
Version 8.0	19 Oct 2020	Scheduled Review Templates removed & administrative changes. JRCO name change to RGIT
Version 9.0	14 Mar 2024	Scheduled Review
Version 10.0	27/04/2026	Updates following legislative changes

TABLE OF CONTENTS

1. PURPOSE

This SOP describes the process for notification of serious breaches of GCP or the approved trial protocol. This SOP also outlines the processes taken at the RGIT to assess and report a serious breach of a clinical trial which is sponsored by Imperial College or Imperial College Healthcare Trust to the MHRA.

2. INTRODUCTION

As of the Medicines for Human Use (Clinical Trials) Regulations 2025, under regulation 29A of the Clinical Trials Regulations, the sponsor of a clinical trial shall notify the licensing authority, in writing, of any serious breach of:

(a) the conditions and principles of GCP in connection with that trial

(b) the protocol relating to that trial

A "serious breach" is considered to be any breach which is likely to effect to a significant degree either:

(a) the safety or physical or mental integrity of the subjects of the trial

(b) the scientific value of the trial.

These stipulations were incorporated into regulation to:

1. Enhance the safety of trial subjects/patients by seeking to ensure that the licensing authority is promptly informed of such serious breaches, in order to take appropriate action in response to the breach.

2. To take the information regarding serious breaches into account when assessing future applications for clinical trial authorisation, and applications for marketing authorisation, which include data from trials affected by serious breaches.

Under the new regulations, it is a requirement that serious breaches of GCP or the trial protocol are reported to the Medicines and Healthcare products Regulatory Agency (MHRA). It is the responsibility of the trial sponsor, or person legally authorised by the sponsor, to carry out the notification procedure **within 7 days** of becoming aware of the breach. This responsibility can be delegated by the sponsor.

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 and thus do not constitute as serious breaches. These cases should be documented as per RGIT_SOP_037_Management of protocol deviations, violations and urgent safety measures. 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.

The judgement on whether a breach is likely to have a significant impact on the scientific value of the trial or safety of the participants depends on a variety of factors (e.g. 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 RGIT Clinical Trial Manager and/or Research Governance Manager to discuss the situation and clarify whether a breach is classed as serious (examples of possible serious breaches can be found in Appendix 2).

3. PROCEDURE

The procedure for notification of serious breaches is outlined below:

1. Identified by study team who must notify the Sponsor of the potential serious breach.
2. Assessment of the potential serious breach (against the conditions of GCP or Protocol) by the Sponsor liaising with the study team (RGIT Staff to ensure all suspected/confirmed serious breaches are recorded on the RGIT Serious breach tracker located on the Q: Drive (Q:\fomcentre\cro\JRCO CTIMP Team\12. Serious Breach Tracker)).
3. Initial notification (initial report) to the MHRA within 7 days of initially becoming aware (should it meet the conditions of a serious breach).
4. Confirmation of receipt of initial notification to be received the GCP inspector who will review the initial notification.
5. Affirmation of the classification of the serious breach (i.e. is it actual a serious breach or not) by the GCP inspector and request for additional information (if applicable).
6. REC to be informed as soon as the MHRA inspector has confirmed the event is a serious breach.
7. Provision of additional information (FU report/s) to the MHRA inspector including the planned corrective and preventative actions (CAPAs).
8. Closure of this serious breach report by the MHRA inspector subject to the agreed CAPAs being implemented recorded by the Sponsor and study team.
9. Sponsor auditing of the CAPA implementation plan and its effectiveness.

For detailed information kindly read: The impact of SI 2006/1928 (*cited on 24Feb2026*).

3.1. Identifying and Notifying Sponsor of a Serious Breach

It is the responsibility of the Chief Investigator and Principal Investigator(s) to continually monitor the conduct of the clinical trial. This may be delegated to a suitably qualified or experienced member of the research team or sub-contracted to an appropriately qualified party. In addition, RGIT may audit the trial as part of their Quality Assurance procedures. Any breaches identified either through monitoring, audit or by other means must be reported to the RGIT Clinical Trial Manager (CTM) **within 24 hours of the breach being identified and confirmed.**

Initial reporting to the CTM should be carried out via telephone, email or in person and should inform of (but not limited to) the following information:

1. Name of Chief Investigator & Principal Investigator at the site where the breach occurred.
2. Full title of the clinical trial and Sponsor reference number (EDGE)
3. An explanation of how the breach was identified
4. Details of the breach
5. Details of any initial corrective actions
6. Assessment of the impact the breach will have on the trial participants and/or scientific integrity of the study.

If the initial notification is performed via telephone, the reporting applicant should follow up with written notification of the potential serious breach as soon as possible. The 7-day reporting period begins on day 0 (i.e. the day the sponsor is informed of the potential serious breach). The initial report should be made to the RGIT CTIMP generic mailbox (rgit.ctimp.team@imperial.ac.uk) copying in the RGIT Clinical Trials Manager (CTM).

If the incident relates to research misconduct and/or fraud, please refer to RGIT_SOP_36_Research Fraud and Misconduct.

3.2. Assessment of a Serious Breach

Upon receipt of an initial serious breach report, the RGIT CTM will discuss the issue with the Chief/Principal Investigator to identify which section of GCP, or the protocol has been breached and how the breach impacts participant safety and/or the scientific integrity of the trial.

The RGIT CTM, with the support of other members of the CTIMP team, will meet with the Chief/Principal Investigator and study team to discuss the breach and compile evidence to support notification to the MHRA. Any concerns should be escalated to the QA Manager and/or Head of Research Governance and Integrity.

The RGIT CTM will work with the Chief/Principal Investigator to identify the extent of the breach and to initiate any Urgent Safety Measures that may be required. For steps on urgent safety measures, please refer to RGIT_SOP_037_Management of protocol deviations, violations and urgent safety measures which can be found on the SOP, Associated Documents & Templates page (*cited on 24Feb2026*).

3.3. Initial Notification of Breach to MHRA

The RGIT CTM will collate all available information and complete the “Notification of Serious Breaches of GCP or the Trial Protocol” form. This form can be obtained from the Notification_of_Serious_Breach_Form_v7.docx (*cited on 24Feb2026*).

The form will be submitted via e-mail to the MHRA within the 7-day reporting period defined in regulation. The form will be sent to: GCP.SeriousBreaches@mhra.gov.uk

The CTM will be the contact person for all correspondence with the MHRA.

3.4. Provision of additional information to the MHRA

Once the initial notification has been submitted to the MHRA, the RGIT will review the serious breach in full to identify the extent of the breach. The RGIT CTM will forward all new information to the MHRA.

The Chief/Principal Investigator will compile a project report for submission to the MHRA. The project report will include (but is not limited to):

1. Full title of trial, ethics approval number, EudraCT number (as relevant), version number, date of commencement
2. Name of Chief Investigator
3. List of Sites
4. Number of subjects recruited

5. Brief description of the trial
6. Summary of the breach including rationale
7. Summary of actions taken
8. Assessment of impact of breach to subject/participant safety and/or scientific integrity of trial
9. Statement from Chief Investigator (if not the person completing the report)

The RGIT CTM will review the project report and submit to the MHRA. The MHRA may request additional information such as a copy of the protocol, ethics application, SOP's etc. The RGIT CTM will liaise with the study team to obtain additional documents and submit them to the MHRA.

3.5. Planning and Implementing the CAPA

The RGIT will work with the study team to devise a formal CAPA to address the breach. The CAPA will be submitted to the MHRA on their request. In the event where the MHRA has confirmed the reported breach is not classified as a serious breach, a CAPA plan should remain.

Depending on the initial assessment of seriousness and impact, the RGIT may carry out a full audit of the trial and general trial management systems and procedures.

The RGIT will publish general information on the breach, in an anonymised form to educate and inform researchers about errors that can occur in the trial process and to facilitate an open environment for reporting such occurrences.

3.6. Serious breach reporting for non-CTIMPs studies

When notified of a potential serious breach, the event should be reviewed in a timely manner by the Research Governance Manager (RGM). The RGM should request further information in order to assess the severity of the breach and whether it meets the serious breach definition.

If the breach is considered a serious breach, the RGM/CI should report to the research ethics committee (REC) **within 7 days of becoming aware of the breach**. The CI/RGM should provide details to REC of when the breach occurred, the location, who was involved, the outcome and any information given to participants. An explanation should be given, and the REC informed what further actions will be taken to correct the issue.

In the event consideration by the REC is no longer appropriate, for example where the study has closed, any reports provided may be referred to the Health Research Authority at breaches.nres@nhs.net for consideration.

If the breach is not considered a serious breach, the CI should create a CAPA plan (with the support of the RGM if required) and ensure this is implemented.

4. REFERENCES

Medicines: clinical trials hub - GOV.UK (*cited 24 Feb 2026*)

Statutory instrument 2004/1031: The Medicines for Human Use (Clinical Trials) Regulations 2004 (*cited 24 Feb 2026*)

The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 (*cited 24 Feb 2026*)

Statutory Instrument 2006/1928: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (*cited 24 Feb 2026*)

ICH_E6(R3)_Step4_FinalGuideline_2025_0106.pdf (*cited 24 Feb 2026*)

Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol, MHRA. Version 6 dated 08/07/2020 (*cited 24 Feb 2026*)

SOPs and Associated Documents-Templates | Research | Imperial College London (*cited 24 Feb 2026*)

Standard Operating Procedure for Research Ethics Committee v7.6 (*cited 20 Mar 2023*)

5. APPENDICES

Appendix 1 – MHRA expectations for Specific Serious Breach Topics

Should proof of fraud relating to clinical trial records or data be reported as a serious breach?
If the fraud is likely to have a significant impact on the integrity of trial subjects or the scientific value of the data, this will be a serious breach. Although not a legal requirement under Regulation 29A, the MHRA GCP Inspectorate encourages the reporting of all confirmed instances of clinical trial fraud occurring at sites in the UK, which the Sponsor becomes aware of. The reason for this is that, although fraud at one particular trial location may not have a significant impact on scientific value or subject integrity for that particular trial, the MHRA would wish to assess the impact on other trials or subjects/patients at that site. If clinical trial fraud is identified at a non-UK trial location, for a trial that is also being conducted in the UK, a serious breach notification should be submitted to MHRA if the fraud is likely to have a significant impact on the integrity of trial subjects in the UK or on the overall scientific value of the trial. A site refers to any site involved in the trial, for example, a CRO or other contracted organisation and not solely to investigator sites (such as laboratories analysing samples from UK patients/subjects).

Should a breach of GCP or the protocol leading to the death, hospitalisation or permanent disability of a trial subject in the UK be reported as a serious breach?
Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) resulting from a breach of the conditions and principles of GCP or a breach of the protocol, will constitute a serious breach. However, it should be noted that not every SAE or SUSAR would routinely be classified as a serious breach.
Also, submission of a serious breach notification to the MHRA Inspectorate *does not obviate the requirement for a SUSAR report* (where applicable) to be submitted to the concerned competent authorities, for example, via the EudraVigilance database. If the breach also resulted in a *temporary /permanent halt* to the trial, a *substantial amendment* would need to be submitted to the MHRA CTU and a further amendment approved to re-start the trial.

Should a failure to report adverse events, serious adverse events or SUSARs in accordance with the legislation be reported as a serious breach?
If this failure results in trial subjects, or the public, in the UK being put at significant risk, then this will constitute a serious breach, for example, inadequate safety reporting in dose escalation studies may impact on the decision to escalate to the next dose level.

Should persistent or systematic non-compliance with GCP or the protocol be reported as a serious breach?

If this non-compliance has a significant impact on the integrity of trial subjects in the UK or on the scientific value of the trial, this will constitute a serious breach. For example, widespread and uncontrolled use of protocol waivers affecting eligibility criteria, which leads to harm to trial subjects in the UK or which has a significant impact on the scientific value of the trial. Another example would be an investigator repeatedly failing to reduce or stop the dose of an IMP in response to a trigger defined in the protocol (for example, abnormal laboratory results).

Should a failure to control investigational medicinal product(s) be reported as a serious breach?

This will constitute a serious breach if the failure results in trial subjects or the public, in the UK being put at significant risk or the scientific value of the trial being compromised. If a serious breach occurs due to an IMP defect, *a drug defect report may need to be submitted to the MHRA Defective Medicines Reporting Centre (DMRC)*, in addition to the serious breach notification.

For trials that are on-going in the UK, should serious breaches that occur at *non-UK sites* be reported?

If a serious breach is identified at an investigator site outside the UK that has a significant impact on the integrity of trial subjects at that non-UK site and is likely to have a significant impact on the integrity of trial subjects in the UK, then this will require notification to the MHRA. For example:

• The cause of the breach may be such that the breach may occur at other trial sites, e.g. death of a subject due to incorrect administration of IMP resulting from erroneous reconstitution instructions in the protocol. It should be noted that as well as having to notify the MHRA of the serious breach, other concerned competent authorities may also need to be informed.
• In relation to the example above, an urgent safety measure (USM) may need to be implemented to address the cause of the breach. If, in order to address the cause of a serious breach, an USM is implemented at UK sites, to amend the conduct of the trial or suspend the trial, the USM notification should be sent by the Sponsor to the MHRA Clinical Trials Unit within 3 days of identifying the measures to be taken (in accordance with Regulation 30), in addition to the serious breach notification to the MHRA Inspectorate.
• If a serious breach is identified at an investigator site outside the UK, which is likely to affect to a significant degree the overall scientific value of the trial and the result will impact on UK patients or the UK public (for example, data will be used in a marketing authorisation application that affects the UK), then this breach should be notified to the MHRA (other concerned competent authorities may also need to be informed).

Appendix 2 – MHRA Notification Examples

Notified by:	Issue:	Would MHRA have expected this case to be notified?
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	1) Yes, there was significant potential to impact the safety or physical or mental integrity of trial subjects. 2) Yes, • there was impact on the safety or physical or mental integrity of

	completely different clinical trial to the one the subject was recruited (to). 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. 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. 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.	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) Yes, there was impact on the safety or physical or mental integrity of trial subjects and on the scientific value of the trial 4) 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.
Sponsor	IMP temperature excursions reported.	Yes, if the situation was not managed and subjects were dosed 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.
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.
Sponsor	On two separate occasions the Sponsors identified issues with the same organisation. First with consenting and then with potential fraud in recruitment and consenting. However, there was not unequivocal evidence of fraud at the time of reporting. One of the	Yes, this subsequently led to enforcement action against the organisation in question.

	studies involved paediatric subjects.	
Sponsor	Concerns were raised during monitoring visits about changes to source data for a number of subjects 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.	Yes Note: not all of the information was provided in the original notification, the Sponsor provided follow-up updates.
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 treatment.
Researcher	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
Researcher	Subject safety was compromised because repeat ECGs were not performed, as required by the protocol. Also, there was inadequate QC of the interim safety reports used for dose escalation which has potential for stopping criteria to be missed.	Yes
Identified during inspection	Investigator site failed to reduce or stop trial medication, in response to certain laboratory parameters, as required by the protocol. This 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.	Yes

Researcher	Early destruction of investigator site files	Yes
Researcher	Patient Information Leaflet and Informed Consent updated, but at one trial location 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)
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