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Management of Protocol Deviations, Important Protocol Deviations and Urgent Safety Measures

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Version	Date	Reason for Change
Version 1.0	02 Feb 2012	New Procedure
Version 2.0	30 Nov 2012	Annual Review
Version 3.0	18 Feb 2015	Scheduled Review
Version 4.0	25 Oct 2017	Scheduled Review
Version 5.0	19 Oct 2020	Scheduled Review Templates removed & administrative changes to SOP. JRCO name change to RGIT.
Version 6.0	02 Nov 2021	Inclusion of submission via CWOW IRAS
Version 7.0	06 Feb 2024	3yr SOP review
Version 8.0	27 Apr 2026	Changes of terminology from “Violations” to “Important protocol deviations” as per updated ICH_GCP Guidance. Updated as per new legislation.

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1. PURPOSE

This Standard Operating Procedure (SOP) describes the process for identifying and managing protocol deviations, Important protocol deviations and urgent safety measures.

2. INTRODUCTION

A protocol that has received ethics approval (and regulatory approval as applicable) is a formal document defining what can and cannot be done as part of a research project and must be adhered to so that participant safety and research integrity can be maintained. This is of particular importance where a trial is being conducted under the Medicines for Human Use (Clinical Trials) Regulations 2004 ("the Clinical Trials Regulations"), as amended by the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, as there are strict legal requirements that must be upheld to ensure the legitimacy of research activity.

In some circumstances, it may be necessary to deviate from the protocol to protect the safety of research participants, which is classed as an urgent safety measure. For trials under the Clinical Trials Regulations, there are defined reporting requirements that will be explained in section three of this SOP.

Deviations from the protocol can occur for a number of reasons and, depending on the occurrence, can be classed as protocol deviation or an Important protocol deviation.

2.1 A protocol deviation occurs when a process or criteria has not been actioned in line with the approved protocol. For example, a study visit outside the defined visit schedule, or a variation in the management of a participant due to minor safety or logistical concern. Deviations are occurrences which can be classed as minor and do not affect participant safety or the integrity of the research.

2.2 An Important protocol deviation occurs when there is a consistent variation in practice from the defined protocol. For example, changes to the protocol that have not been approved by an ethics committee or regulator that are classed as substantial amendments (see RGIT_SOP_006). An Important protocol deviation is a significant occurrence or event which may affect participant safety or the integrity of the research.

2.3 An urgent safety measure occurs when a research participant has been identified as being at risk of harm in relation to their involvement in a research project and an urgent action, which deviates from the protocol, is required to manage the event and protect the participant.

A protocol deviation may become an Important protocol deviation if it occurs on multiple occasions and/or affects multiple participants.

Non-compliance with the inclusion and exclusion criteria is always classed as an Important protocol deviation regardless of how minor the deviation appears to be, as these criteria define the participant group in relation to the scientific requirements of the protocol.

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3. PROCEDURE

3.1. Identification of a Protocol Deviation or Important Protocol Deviation

The Chief Investigator (CI) of a research project is responsible for ensuring there are appropriate oversight systems in place to monitor research activity and identify any deviations from the study protocol. This responsibility may be shared with other members of the research team (e.g. a Trial Steering Committee).

3.1.1 All deviations identified must be reviewed by the CI to assess whether participant safety or study integrity has been affected by the deviation and to what extent the deviation has affected the project. Study Teams should periodically review all Protocol Deviations to ensure any which are being repeated are investigated and clarified whether collectively, the deviation being reported now constitutes an important Protocol Deviation (see reporting procedure below).

3.1.2 The CI will notify the sponsor if a deviation has an impact on safety or research integrity. The sponsor will advise whether the event is an Important protocol deviation and take appropriate measures to address the occurrence which may include audit or monitoring of the research project alongside defining a corrective action and preventative action (CAPA) plan to be implemented by the CI.

3.1.3 Where a protocol deviation is not judged to impact safety or research integrity, this should be documented in a protocol deviation form, protocol deviation log, CRF and source documents respectively explaining the action taken and its justification. All protocol deviations should be sent to the Trial Statistician prior to final analysis of the study and in the clinical study report.

3.1.4 If the CI is unsure whether an occurrence is a protocol deviation or an Important protocol deviation, they should seek advice from the sponsor to ensure appropriate action is taken as soon as possible.

3.2. Reporting an Important Protocol Deviation

When an Important protocol deviation is identified, it is essential to inform the appropriate parties of the occurrence and any corrective actions that have been implemented.

3.2.1 The CI must notify the sponsor of the Important protocol deviation immediately upon identifying the issue. The sponsor will advise on what action is required and may initiate a triggered audit or monitoring of research activity to assess the extent of the Important protocol deviation and its relation to any other protocol compliance issues.

3.2.2 If the sponsor identifies an Important protocol deviation during routine audit the process described in RGIT_SOP_018 – RGIT Audit will be followed. For CTIMP trials requiring MHRA approval, should the Important protocol deviation be identified as a serious breach of good clinical practice or the trial protocol, the sponsor will follow RGIT_SOP_021 – Notification of Serious Breaches of GCP or the Trial Protocol, and inform the MHRA of the incident within seven days of being notified of the event.

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3.2.3 Once an Important protocol deviation has been identified, it may be necessary to inform the ethics committee and/or regulator of the incident and any corrective actions. The sponsor will inform the CI of reporting requirements and direct them to submit a report explaining the event. Key areas to include in a report are:

- An overview of the incident and its cause
- Description of CAPA
- An assessment of likelihood of reoccurrence
- Outline of any changes to the protocol that may be required
- Timeline for corrective action and amendment approval (if applicable)

3.2.4 If the Important protocol deviation is deemed to be of a serious nature, the sponsor will suspend the research project until all necessary corrective actions have been taken.

3.3. Management of Urgent Safety Measures (Clinical Trials)

Under the Medicine for Human Use (Clinical Trials) Regulations the sponsor, Chief Investigator or Principal Investigator may carry out urgent safety measures (USM) to protect trial subjects from immediate harm.

3.3.1 If the USM is implemented, then no later than 3 days after the measures are taken (but ideally within 24 hours), the sponsor should contact the licensing authority through the Clinical Trial Helpline (020 3080 6456) to discuss the USM. The REC should also be notified of the USM via a phone call. If the sponsor is unable to report the USM by telephone, they should email clintrialhelpline@mhra.gov.uk with contact details, the trial's IRAS ID, a description of the USM, and an explanation as to why it was not reported via phone. The licensing authority will then contact the sponsor with further actions. Failure to notify the licensing authority of the implementation of an USM for safety reasons may be considered a serious breach.

Following the initial telephone conversation with the licensing authority, regardless of whether the measures discussed are informally agreed to be a USM, the sponsor must provide written notification to the licensing authority, describing the events requiring action to be taken, and the measures taken in response to those events, including any additional actions requested by the licensing authority. The REC should also be provided written notice via email.

Per regulation 30 of the Clinical Trials Regulations, this must be done within 7 calendar days from the date the measures are taken or as soon as possible during any period where a disease is pandemic and is a serious or potentially serious risk to human health.

mailto:clinicaltrialshelpline@mhra.gov.ukTo submit a written notification:

- If any of the clinical trials affected were approved through the combined review process, submit through IRAS rather than via email as per the paragraph above. Guidance on submitting an urgent safety measure notification through IRAS can be found in the Step-by-step guide to using IRAS for combined review (Step by step guide to using IRAS for combined review - Health Research Authority)

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- If all of the clinical trials affected were approved through separate applications to the licensing authority and the ethics committee, email the notification to the licensing authority (clintrialhelpline@mhra.gov.uk).

The licensing authority will review the written notification and may request additional information by email (and through IRAS, if this route of submission was used). Once the licensing authority has sufficient information, it will decide whether the measure taken is a USM and communicate the outcome to the sponsor by email (and through IRAS, if this route of submission was used).

If the licensing authority agrees that the measure is a USM, the sponsor should submit a substantial modification that covers the USM (with no additional changes) using the same process as other applications for a substantial modification (although in this case the modifications will have already been implemented) within 2 weeks of the date on which the licensing authority was first informed (via telephone) of the USM. The sponsor should agree any potential delays with the licensing authority during the initial or a follow-up telephone call.

If the licensing authority does not agree that the measure is a USM, it will confirm with the sponsor whether any further actions are needed.

A temporary halt can also be part of an urgent safety measure (USM). In this case, the notification of the temporary halt of a trial should be done via the usual process and following the usual timelines for reporting USMs. Failure to notify the licensing authority of the implementation of a temporary halt for safety reasons may be considered a serious breach.

The process is summarised in Figure 4: Flowchart summarising the process of notifying the licensing authority about a potential urgent safety measure (Fig4. USMs.pdf).

3.3.2 The sponsor must be notified of the USM before submitting to the MHRA and ethics to advise on content and process, and to ensure the sponsor is aware of the event should the ethics committee or regulator contact for further information.

4. REFERENCES

Statutory instrument 2004/1031: The Medicines for Human Use (Clinical Trials) Regulations 2004. *(cited 24 Feb 2026)*
Statutory Instrument 2006/1928: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006. *(cited 24 Feb 2026)*
The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 *(cited 24 Feb 2026)*

ICH GCP E6 (R3) *(cited 24 Feb 2026)*

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