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Management of Protocol Deviations, violations 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 and 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

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1. PURPOSE

This Standard Operating Procedure (SOP) describes the process for identifying and managing protocol deviations, violations 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 and related amendments, 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 protocol to protect the safety of a research participant, 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 the section three of this SOP.

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

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 defined visit schedule, or a variation in the management of a participant due to minor safety or logistical concerns. Deviations are occurrences which can be classed as minor and not affect participant safety or the integrity of the research.

2.2 A protocol violation 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). A violation 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 a violation if it occurs on multiple occasions and/or affects multiple participants.

Non-compliance with the inclusion and exclusion criteria is always classed as a significant protocol violation 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.

3. PROCEDURE

3.1. Identification of a Protocol Deviation or Violation

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.

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 a protocol violation and take appropriate measures to address the occurrence which may include audit or monitoring of the research project and 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 on safety or research integrity, this should be documented in a protocol deviation form, protocol deviation log, CRF and source documents explaining the action taken and its justification. For CTIMPs, RGIT or CTU should review the deviation log and upload to Documas. 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 deviation or violation they should seek advice from the sponsor to ensure appropriate action is taken.

3.2. Reporting a Protocol Violation

When a protocol violation 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 violation 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 violation and its relation to any other protocol compliance issues.

3.2.2 If the sponsor identifies a protocol violation during routine audit the process described in RGIT SOP 018 – RGIT Audit will be followed. For CTIMP trials requiring MHRA approval, should the violation 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.

3.2.3 Once a violation 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
- Time line for corrective action and amendment approval (if applicable)

3.2.4 If the protocol violation 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 subject from immediate harm.

3.3.1 Any urgent safety measure relating to a CTIMP trial must be notified to the sponsor, ethics committee and MHRA within three days of the action being taken. The notification should describe the event, the measures taken and justification for the measures taken. The MHRA can be contacted via email at clinicaltrialshelpline@mhra.gsi.gov.uk by titling the email 'Urgent Safety Measures'. The ethics committee will need to be informed in writing with a copy to the sponsor and the R&D department. For studies that have used the Combined Ways or Working (CWOW) IRAS system, USMs can be notified to the MHRA via IRAS rather than submitting via email. The outcome of the USM will be issued by the MHRA via email and the outcome will also be available to view in IRAS. For USMs that are accepted, applicants will then be able to submit a substantial amendment, identifying that the amendment is linked to an agreed USM.

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

RGIT_SOP_006– Amendments to Healthcare Research

RGIT_SOP_018– Research Governance and Integrity Team Audit

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.

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