MANAGEMENT OF PROTOCOL AND GCP DEVIATIONS AND VIOLATIONS

DOCUMENT NO.:	**CR010 v7.0**
AUTHOR:	**Lorn Mackenzie**
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1 INTRODUCTION

1.1 The Academic & Clinical Central Office for Research & Development (ACCORD) is a joint office comprising clinical research management staff from NHS Lothian (NHSL) and the University of Edinburgh (UoE).

1.2 The Chief Investigator (CI)/Principal Investigator (PI) should not implement any deviation from, or changes to the protocol without prior review of an amendment, and documented approval/favourable opinion from the Sponsor/Research Ethics Committee (REC) and the Competent Authority and R&D (if applicable), except where necessary to eliminate an immediate hazard(s) to trial subjects.

1.3 A departure from the approved clinical trial protocol or from Good Clinical Practice (GCP) must be identified and recorded as a deviation or a violation (definitions and examples are provided in the Table below);

	Definition	Examples
Deviation	Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subjects rights, safety, or well-being, or study outcomes.	• Visit date outside the study visit window; • Missed or incomplete study procedure (e.g. lab test); • Missed or incomplete study evaluation (e.g. exam).
Violation	A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being	• Failure to obtain informed consent; • Enrolment of participants that do not meet the inclusion/exclusion criteria; • Undertaking a trial procedure not approved by REC, Licensing Authority or NHS R&D (unless for immediate safety reasons); • Failure to report adverse events, serious adverse events or SUSARs in accordance with requirements, such that trial participants, or the public, are put at significant risk or risk of harm; • Investigational Medicinal Product(s) dispensing, labelling or dosing error.

2 PURPOSE

2.1 To document the procedure of identifying, recording and reporting deviations and violations in studies sponsored by NHSL and/or UoE, and the management of these reports by ACCORD Quality Assurance (QA).

3 SCOPE

3.1 This procedure is relevant to researchers conducting studies sponsored by NHSL and/or UoE, and all members of ACCORD personnel who manage, coordinate or advise on clinical research sponsored or co-sponsored by NHSL and/or UoE.

3.2 Study specific requirements for reporting protocol deviations and violations will be detailed in the study protocol.

4 RESPONSIBILITIES

4.1 The PI, and clinical team on site, are responsible for identifying deviations or violations as they occur.

4.2 Responsibility for completing the violation forms and maintaining the deviation log may be delegated to suitably qualified named persons on the Study Delegation Log.

4.3 The PI is responsible for review of deviations and violations at their site.

4.4 The CI or designee (e.g. Trial Manager) is responsible for ensuring sites report deviations to the Sponsor in accordance with protocol requirements.

4.5 The QA Manager and/or QA Coordinator, are responsible for reviewing, logging and tracking reported deviations and violations in the ACCORD Quality Management System (QMS).

4.6 The QA Administrator and/or QA Coordinator are responsible for completing deviation reporting spot checks.

4.7 The QA Manager and/or QA Coordinator are responsible for seeking guidance from NHSL and UoE Sponsor representatives and the CI, where corrective and preventative actions required have the potential to impact the study.

4.8 The QA Manager and/or QA Coordinator are responsible for trending deviations and violations and reporting results to the Senior Clinical Trials Monitor and Heads of Research Governance (NHSL and UoE). They are also responsible for assessing violations to determine if they constitute a serious breach of the protocol or GCP.

4.9 The Senior Clinical Trials Monitor is responsible for reviewing deviation/violation trend reports, and for taking necessary action to address study specific trends and other significant findings, where applicable.

4.10 The Heads of Research Governance (NHSL and UoE) are responsible for reviewing deviation/violation trend reports, and for reviewing study specific deviations/violations where requested by the QA Manager/QA Coordinator.

5 PROCEDURE

5.1 Recording and Reporting: Deviations (CTIMPs & Non-CTIMPs)

5.1.1 For Clinical Trials of Investigational Medicinal Products (CTIMPs) and non-CTIMPs, the PI will adhere to the deviation definition (section 1.3) and once identified, record the deviation in the Protocol / GCP Deviation Log (CR010-T01). Any divergence from an ACCORD / study specific standard operating procedure (SOP) in relation to a study will also be recorded using CR010-T01.

5.1.2 Corrective action is the immediate action taken when a deviation is discovered. The PI, or designee, will detail in the deviation log how the deviation was corrected (if applicable) at the time of discovery, and how this will be documented in the Investigator Site File (ISF).

5.1.3 Preventative action includes investigation into the root cause of the deviation, assessing possible impact and risk, and whether the event is part of a systemic issue. Actions taken to ensure the deviation is not repeated will also be detailed. The PI, or designee, will detail in the deviation log how recurrence of this deviation will be prevented and how this will be documented in the ISF.

5.1.4 Corrective and preventative action closure (i.e. when actions are complete) will be documented in the deviation log by the PI, or designee.

5.1.5 The PI, or designee (e.g. Trial Manager, Research Nurse), will send the deviation log to the Sponsor **quarterly,** unless a specific timeframe is detailed in the protocol. If no deviations are reported during the quarter, the PI or designee will inform the ACCORD office via email (QA@accord.scot). The QA Coordinator, or designee, will send quarterly email reminders to Trial Managers for studies subject to Combined Risk Assessment (SOP GS002).

5.1.6 A new deviation log will be started at the beginning of each reporting period, continuing the event number sequence from the previous deviation log.

5.1.7 Deviation logs can be sent to the ACCORD office by e-mail (QA@accord.scot). Alternative arrangements for sending deviation logs should be agreed with the QA team.

5.1.8 The QA Manager, or QA Coordinator, will acknowledge receipt by email to the individual who submitted the deviation log, copying the Trial Manager (where there is Trial Management support).

5.1.9 The QA Manager, or QA Coordinator, will assess the events in the log to ensure each event has been correctly classified as a deviation, and will review corrective and preventive actions to ensure they are adequate to remedy the event and prevent recurrence, where possible.

5.1.10 If the deviation has been incorrectly classified, the QA Coordinator, or designee, will advise accordingly and request the PI or designee annotate the entry on the deviation log e.g. score through N/A.

5.1.11 Any further issues or inconsistencies identified will be communicated to the individual who submitted the deviation log, the Trial Manager, and/or the PI.

5.1.12 If resolution cannot be achieved, the matter will be referred to the Heads of Research Governance (NHSL and UoE).

5.1.13 The QA Manager or QA Coordinator will log and track received deviation logs in the QA Deviations & Violations folder in the ACCORD QMS on SharePoint.

5.1.14 The QA Manager or QA Coordinator will review deviations for trends within each study and global trends, and report these to the Heads of Research Governance (NHSL and UoE) and the Senior Clinical Trials Monitor as a minimum quarterly.

5.1.15 The Senior Clinical Trials Monitor, QA Manager, or designee, will take actions to address study specific trends and other significant findings where applicable.

5.2 Recording and Reporting: Deviations (CIMD)

5.2.1 For Clinical Investigations of a Medical Device (CIMD), the PI or designee, will record the deviation using the following MHRA Deviation Log template (unless otherwise agreed with the Sponsor).

5.2.2 Details about the nature of the deviation, when it occurred, where it occurred, and any proposed corrective and preventative actions should be provided.

5.2.3 The PI, or designee (e.g. Trial Manager, Research Nurse), will send the deviation log to the Sponsor (QA@accord.scot) and MHRA (info@mhra.gov.uk) as soon as they have been made aware. New deviations

will be added to the deviation log as they occur. Specific details regarding the management of deviation reporting will be outlined in the study protocol and risk assessment (SOP GS002).

5.2.4 The QA Manager, or QA Coordinator will review the deviation log following sections 5.1.8 – 5.1.14.

5.3 Deviation Spot Checks.

5.3.1 The QA Administrator, in consultation with the QA Manager and/or QA Coordinator and the Senior Clinical Trials Monitor(s), will conduct regular deviation log spot checks following ACCORD Work Instruction CR010-WI01.

5.3.2 The spot checks will reconcile the data captured in the QA protocol deviation assessment tracker with the deviation logs (CR010-T01) retained in the Trial Master File (TMF)/Sponsor File. These spot checks will include confirming that trial sites have submitted protocol/GCP deviation logs following section 5.1 of this procedure.

5.4 Recording and Reporting: Violations

5.4.1 If a deviation is assessed as a violation, a Protocol / GCP Violation Reporting Form (CR010-F01) must be completed by the site PI. It is not necessary to complete a corresponding entry in the deviation log (CR010-T01).

5.4.2 Corrective action is the immediate action taken when a violation is discovered. The PI, or designee, will detail in the violation report form how the violation was corrected (if applicable) at the time of discovery, and how this will be documented in the ISF.

5.4.3 Preventative action includes investigation into the root cause of the violation, assessing possible impact and risk, and whether the event is part of a systemic issue. Actions taken to ensure the violation is not repeated will also be detailed. The PI, or designee, will detail in the violation report form how recurrence of this violation will be prevented and how this will be documented in the ISF.

5.4.4 Corrective and preventative action closure (i.e. when actions are complete) will be documented in the violation report form by the PI, or designee.

5.4.5 The PI, or designee, will document their investigation conclusion in the violation report form i.e. has the violation had an actual impact on the participants safety, rights or wellbeing and/or the study outcomes and how this is known.

5.4.6 Violation forms must be submitted to the ACCORD office **within 3 days** of becoming aware of the violation.

5.4.7 Forms can be submitted by e-mail (QA@accord.scot). Alternative arrangements for sending violation logs should be agreed with the QA team.

5.4.8 The QA Manager, or QA Coordinator, will acknowledge receipt by email to the individual who submitted the violation form, copying the Trial Manager (where there is Trial Management support).

5.4.9 The QA Manager or QA Coordinator will log received violation reports in the QA Deviations & Violations folder in the ACCORD QMS on SharePoint.

5.4.10 The QA Manager, QA Coordinator, or designee, will assess the event to ensure it has been correctly classified as a violation, and will review corrective and preventive actions to ensure they are adequate to remedy the event and prevent recurrence, where applicable.

5.4.11 If the violation has been incorrectly classified, the QA Coordinator, or designee, will request the PI or designee to annotate the violation form e.g. score through N/A (i.e. to confirm downgrade to deviation). The QA Coordinator, or designee, will request the non-compliance be recorded on CR010-T01 and reported at the end of the current reporting quarter following section 5.1.

5.4.12 On review of section 4 of the Protocol / GCP Violation Reporting Form (CR010-F01), where actions required have the potential to impact the study, the QA Manager, QA Coordinator, or designee may seek guidance from NHSL and UoE sponsor representatives as well as the CI.

5.4.13 Any further issues or inconsistencies identified will be communicated to the individual who submitted the report, the Trial Manager and/or the PI/CI.

5.4.14 If resolution cannot be achieved, the matter will be referred to the Heads of Research Governance (NHSL and UoE).

5.4.15 The QA Manager, QA Coordinator, or designee, will assess if the violation could meet the criteria for a serious breach of the study protocol/GCP in accordance with SOP CR003 (Suspected Serious Breaches). This assessment will be documented in the QA Deviations & Violations tracker in the ACCORD QMS on SharePoint.

5.4.16 If the violation constitutes an Urgent Safety Measure (USM), as described in SOP CR005 (Identifying, Recording and Reporting AEs and USMs for CTIMPs), this should be indicated on the violation form.

5.4.17 The QA Manager or QA Coordinator will review violations for trends within each study and global trends and report these to the Heads of Research Governance (NHSL and UoE) and the Senior Clinical Trials Monitor as a minimum quarterly.

5.4.18 The Senior Clinical Trials Monitor, or designee, will take actions to address study specific trends and other significant findings where applicable.

5.5 Filing Deviation Logs and Violation Reports

5.5.1 Original deviation logs and violation forms are essential documents and will be retained in the Investigator Site File (ISF) by the PI, or designee.

5.5.2 Copies of these documents will be retained in the Trial Master File (TMF) and/or Sponsor File, together with any communication, including ACCORD email receipt, resolution of corrective/preventative actions or the change of status of a non-compliance.

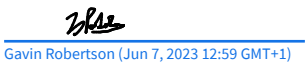
6 REFERENCES AND RELATED DOCUMENTS

- CR010-F01 Protocol / GCP Violation Reporting Form
- CR010-T01 Protocol / GCP Deviation Log
- CR005 Identifying, Recording and Reporting AEs and USMs for CTIMPs
- CR003 Suspected Serious Breaches
- GS002 Combined Risk Assessment
- CR010-WI01 Deviation Log Spot Checks
- The Medicines for Human Use (Clinical Trials) Act (SI 1031), as amended
- The Medical Devices Regulation 2002 (SI 618)
- ICH-GCP E6(R2) Guidelines

7 DOCUMENT HISTORY

Version Number	Effective Date	Reason for Change
1.0	22 MAR 2011	New Procedure.
2.0	07 MAY 2013	Change to deviation log timelines and reviewer. Minor adjustment to violation definition.
3.0	30 MAY 2016	New SOP template and SOP title. Changes in responsibilities for review, logging, trending and reporting deviations/violations, including confirmation of receipt by signing log/form. Additional information added to 5.1.11/5.2.12 regarding resolution of issues. Formatting and wording changed throughout document including changes to Sponsor website and e-mail address. Additional information added to sections 5.1-5.3 regarding retention of documents electronically on the ACCORD QMS and in TMFs/ISFs/Sponsor Files.
4.0	15 SEPT 2016	Additional information added to section 5.2.11 regarding input sponsor representatives and the CI. Section 5.2.12 updated to include the CI.
5.0	01 OCT 2018	Requirement to inform ACCORD when no deviations are reported added to 5.1.5. Update to CAPA requirements 5.1.2, 5.1.3, 5.2.2 and 5.2.3. Change of author and minor clarifications and administrative updates throughout.
6.0	11 JUN 2021	Responsibility added for the CI or designee (e.g. Trial Manager) to ensure trial sites are reporting deviations to the Sponsor in accordance with protocol requirements. Associated forms updated (CR010-F01 & CR010-T01), including the removal of the requirement for ACCORD QA signature and visual changes. CR010-F02 (Fax Cover Sheet) has been discontinued. ACCORD QA will send quarterly email reminders for studies subject to Combined Risk Assessment (SOP GS002). Minor administrative changes throughout.
7.0	23 JUN 2023	Clarification added to section 5.1.1 that form CR010-T01 may be used to record SOP deviations related to the study. Section 5.2 added outlining details of deviation reporting for device trials. Section 5.1.10 and 5.4.11 added to detail change of non-compliance status. Addition of CR010-W01 at section 5.3.

8 APPROVALS

Sign	Date
 AUTHOR: Lorn Mackenzie, QA Manager, NHS Lothian, ACCORD	Jun 8, 2023
 Heather Charles (Jun 7, 2023 13:04 GMT+1) APPROVED: Heather Charles, Head of Research Governance, NHS Lothian, ACCORD	Jun 7, 2023
 Gavin Robertson (Jun 7, 2023 12:59 GMT+1) AUTHORISED: Gavin Robertson, QA Coordinator, NHSL, ACCORD	Jun 7, 2023

CR010 Management of Protocol and GCP Deviations and Violations v7.0

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