MRC Clinical Trials Unit

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PROTOCOL DEVIATIONS

VERSION 2.0

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All appropriate approvals must have been completed prior to uploading to SOPbox. The effective date of this SOP is the day on which it was signed by the SOPbox Administrator and is available to use.

For the Revision History please see the Version History Summary in SOPbox.

PROTOCOL DEVIATIONS

TABLE OF CONTENTS

The following symbols may be used in this SOP:

Indicates a link to a related document

Indicates instructions to document trial-specific processes elsewhere

Throughout this document the MRC Clinical Trials Unit at UCL, will either be referred to as ‘MRC CTU at UCL’ or ‘the unit’. In instances where neither read well in the sentence, ‘the CTU’ may be used.

1 DEFINITIONS

A **Protocol Deviation** is defined as any change, divergence, or departure from study design or procedures as described in the approved study protocol[1]. i.e. any instance where an instruction in the protocol is not followed is a protocol deviation. **Important Protocol Deviations** are a subset of protocol deviations that may **significantly** impact the completeness, accuracy, and or reliability of the study data or that may **significantly** affect a subject's rights, safety, and/or well-being.

For example, **Important Protocol Deviations** may include enrolling participants in violation of key eligibility criteria designed to ensure participant safety and to define a specific participant population. Or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.

Critical and Major deviations would constitute **"Important Protocol Deviations".**

The following definitions should be used for studies run by the unit:

1. Critical protocol deviation
   Any change, divergence, or departure from study protocol **that significantly impacts** the integrity and or reliability of study results or significantly impacts subjects' rights, safety and or well-being.

   e.g. An example of a critical deviation could be recruitment of an ineligible patient who subsequently receives a drug that is not safe for them to be treated with, following which the patient experiences harm

2. Major protocol deviation
   Any change, divergence, or departure from study protocol **that potentially could significantly impact** the completeness, accuracy and or reliability of study data or the subjects' rights, safety and/or well being.

   e.g. A major deviation could be an ineligible patient recruited, but they are still safe to receive the drug and no harm came to that patient.

3. Minor protocol deviation
   A minor deviation is any change, divergence, or departure from study protocol that will not adversely affect subjects/data but should be dealt with appropriately.

   Note: A minor or major protocol deviation that is repeated multiple times by one study site (or across multiple sites) can be upgraded to a major or critical protocol deviation respectively upon discussion within the TMT. The TMT may consider consultation with the Trial Management Group (TMG) or the Research Governance Committee (RGC) where necessary.

It is acknowledged that the terms protocol violation and important protocol deviation are often used interchangeably to refer to a significant departure from protocol requirements. However the ICH E3 guideline, defines a **Protocol Violation** as any change, divergence or departure from study procedures, whether by a subject or an investigator, which resulted in a **subject's withdrawal from**

[1] ICH E3 - EMA Q&A Document Revised (rev1) July 2012

study participation[2]. Based on opinion outlined in ICH E3 Guideline, sponsors are encouraged to use only the term “protocol deviation” and avoid using “protocol violation”. It is, however, important for the Trial Management Team (TMT) to have a process in place to record whether any protocol deviation resulted in a subject’s withdrawal from study participation.

[2] Annex IVa, Subject Disposition of the ICH E3 guideline

2 PURPOSE

- The purpose of this standard operating procedure (SOP) is to provide definitions and grading for protocol deviations
- To define roles and responsibilities of the CTU study teams as well as study staff at participating sites
- To outline the procedures of identifying, reviewing, recording and reporting protocol deviations

This SOP does not cover specific procedures to be followed when a possible serious breach of GCP and/or approved protocol is identified. Please see below SOP for further information.

MRC CTU SOP 019 – Serious Breach, Research Fraud and Financial Irregularity

This SOP is also not intended to cover specific onward reporting requirements for studies with international sites (for example reporting to competent authorities or ethics committees, or other international bodies). Study teams that have international participating sites should develop study-specific working practices covering reporting requirements of each participating country. The processes for identifying, recording and reporting (internally to MRC CTU) should follow the principles of this SOP at international sites unless another process is stipulated by the study sponsor.

3 RESPONSIBILITY AND ROLES

The following table lists the roles relevant to this SOP and a brief description of their responsibilities.

This SOP will be circulated for Read and Understand to all appropriate roles identified in the training matrix.

ROLE	RESPONSIBILITIES
Trial Management Team (TMT)	• Oversight of study sites to ensure identification of protocol deviations as well as recording/reporting requirements are fulfilled • Providing sites with training on protocol deviations • Liaising with study sites to ensure site-specific protocol deviation logs are sent through to the TMT for review on a regular basis • Grading protocol deviations reported to the TMT as well as logging them onto the Trial-specific protocol Protocol Deviation (PD) Log • Performing required onwards reporting of protocol deviations as necessary • Liaising with study sites to ensure that appropriate CAPAs are developed and implemented, as required • Escalating reports of protocol deviations to the RGC and TMG where necessary • Maintaining records of protocol deviations in the Trial Master File (TMF)
Trial Management Group (TMG)	• Review and input on protocol deviation grading or CAPAs as necessary

4 PROCEDURES

The Trial Management Team (TMT) should ensure appropriate and effective oversight systems are in place to monitor study activity and protocol compliance. Such systems can include central monitoring (including cleaning or statistical analysis of collected data) and on-site monitoring. These systems should be included in the study monitoring plan and be reviewed regularly. Protocol deviations may also be identified by clinical sites and reported to the TMT.

Study teams must develop study-specific working practices covering reporting requirements for protocol deviations, procedures for management of protocol deviations and mechanisms for clinical site identified protocol devitions to be reported to the TMT and subsequently the TMG. These working practices which should be in place prior to study start (as part of the monitoring plan).

Study teams may also want to produce a list of possible protocol deviations and associated grade to ease identification. Such a list should be reviewed and updated over time as the trial progresses and experience of the real life scenarios is gained.Studies with international sites should also consider and document any reporting requirements to relevant authorities on a country-level.

4.1 REPORTING AND RECORDING PROTOCOL DEVIATIONS

The monitoring plan should detail the process for ensuring any protocol deviations identified is added to a trial-specific protocol deviation log. This should also include (but not limited to) any protocol deviations identified as a part of any on-site monitoring, central monitoring, statistical analysis or via direct reports from sites.

The TMT is responsible for logging and regularly reviewing all protocol deviations reported on to a trial-specific protocol deviation log. Frequency of review should be defined in the monitoring plan.

MRC CTU TT 0473 – Template Trial-Specific Protocol Deviation Log

As part of the regular review of the trial-specific deviation log the delegated trial statistician should specifically review for protocol deviations which might impact on the data or analysis.

The TMT will assess and grade each deviation (or confirm grade provided by site team) according to the definitions outlined in **Section 1** and any listing developed under **Section 4**. The TMT should also consider and log whether a protocol deviation resulted in a subject's withdrawal from study participation.

Once a protocol deviation is graded by the TMT an appropriate action plan should be put in place. This should be in the form of a formal Corrective and Preventative Action Plan (CAPA) for Major and Critical protocol deviations or an action plan detailed in the trial-specific protocol deviation log for minor protocol deviations. Any actions highlighted should be follow-up regularly until resolution.

The protocol deviations should be a standing item on TMT and TMG agendas to ensure adequate follow-up of issues. For some trials it may be necessary to hold specific protocol deviation review meetings to ensure adequate time to cover all issues.

MRC CTU TT 0404 – Template Corrective and Preventative Action Plan

Documentation relating to protocol deviations and their CAPAs should be filed in the Trial Master File (and in the investigator site file held at site where applicable).

4.2 IDENTIFICATION OF PROTOCOL DEVIATIONS BY SITE

At study initiation, the TMT is responsible for providing training to the clinical sites on how to identify, grade, record and report potential protocol deviations. During site initiation, clinical sites should be provided with appropriate tools and templates for recording and reporting protocol deviations.

MRC CTU TT 0474 – Template Site-Specific Protocol Deviation Log

On identification of a protocol deviation at site, the site study team should grade and record the deviation onto the site-specific protocol deviations log. The investigator is ultimately responsible for reviewing and signing off the log.

For critical protocol deviations the TMT should be informed within 1 working day after the investigator becomes aware of the protocol deviation. For major deviations the TMT should be informed within 2 weeks after the investigator become aware. The site-specific protocol deviation log containing all site deviations should be requested from sites and reviewed by the TMT periodically as defined in study-specific monitoring plan (e.g. 6-monthly).

Where there is a discrepancy between the grading of the protocol deviation between site and TMT, the TMT is responsible for initiating further discussion with the site in order to come to a consensus. Ultimate responsibility for final grading of a protocol deviation lies with the Sponsor.

It is important that any site-related protocol deviations are communicated to the site study team if these are identified centrally by the TMT.

4.3 IDENTIFICATION OF PROTOCOL DEVIATIONS AT A MONITORING VISIT

During a monitoring visit a number of issues can be identified, many of which will be related to documention and process issues rather than compliance with the protocol. i.e. a monitoring finding is not necessarily a protocol deviation.

If a protocol deviation is identified at a monitoring visist, it should be discussed with the site and included in the monitoring report in accordance with the trial Monitoring Plan. In addition, the protocol deviation should be logged on the site-specific protocol deviation log and on the trial-specific protocol deviation log as described in **Section 4.1**.

4.4 IDENTIFICATION OF PROTOCOL DEVIATIONS FROM DATA REVIEW

Protocol deviations may be identified from review of the trial data either by the data management team on receipt of the data or by the statistical team in analyses and review of the data.

If a protocol deviation is identified in either of these ways, it should be checked to ensure that it is a true deviation rather than a data collection, entry or processing error in accordance with the trial Data Management Plan. Confirmed protocol deviations identified from data review should be logged

on the site-specific protocol deviation log and on the trial-specific protocol deviation log and classified and reported as described above.

4.5 NOTIFICATION OF PROTOCOL DEVIATION TO RGC AND TMG

Where a protocol deviation is considered critical by the TMT this should be reported to the RGC and TMG within 3 working days following TMT awareness.

MRC CTU TT 0427 – Notification Report for Research Governance Committee (RGC)

Reporting to the RGC and TMG should also be considered in the following circumstances:

- Where similar major protocol deviations have been reported or discovered across multiple sites in the study
- It may be possible that a large group of minor protocol deviations has been identified that might warrant upgrade to critical

RGC and TMG will advise on any further action to be taken as a result of the protocol deviation.

4.6 POTENTIAL SERIOUS BREACH

Where the TMT considers that a protocol deviation(s) could fulfil the criteria for a potential serious breach of GCP or the Protocol, the SOP on Serious Breach should be consulted and followed.

MRC CTU SOP 019 – Serious Breach, Research Fraud and Financial Irregularity

4.7 URGENT SAFETY MEASURES

Where the TMT feel that the protocol deviation may necessitate the implementation of an urgent safety measure, the SOP on Urgent Safety Measures should be consulted and followed.

MRC CTU SOP 062 – Urgent Safety Measures

4.8 TRIAL REPORTING

ICH E3[3] states that all important protocol deviations related to study inclusion or exclusion criteria, conduct of the study, patient management or patient assessment should be described in any clinical study report. The CONSORT Guidelines[4] should also be consulted to guide how protocol deviations should be reported in any study publications.

Please refer to the Pandemic Contigency Plan SOP for more information on reporting protocol deviations which arise as a result of a Pandemic.

MRC CTU SOP 097 – Pandemic Contingency Plan

[3] Annex IVa, Subject Disposition of the ICH E3 guideline

[4] Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine 2010, 8:18. (24 March 2010)

5 RELATED DOCUMENTS

For further information on this topic, see also:

MRC CTU SOP 019 – Serious Breach, Research Fraud and Financial Irregularity
MRC CTU SOP 062 – Urgent Safety Measures
MRC CTU SOP 013 – Statistical Principles
MRC CTU TT 0473 – Template Trial-Specific Protocol Deviation Log
MRC CTU TT 0474 – Template Site-Specific Protocol Deviation Log