STAMPEDE

Site Deviation Working Practices

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1. OVERVIEW

This document provides guidance and describes the procedures to be followed for parties involved in the identification, classification, reporting and resolution of deviations from the protocol of the STAMPEDE Trial.

The trial will be coordinated and/or managed by the Medical Research Council's Clinical Trials Unit at UCL (MRC CTU at UCL) referred to as MRC CTU in this document. The primary contacts at MRC CTU are listed below:

Main Contacts:
MRC Clinical Trials Unit at UCL
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REVISION HISTORY

Version	Version date	Amended by	Reason for amendment

2. RESPONSIBILITIES

2.1. Trial Site Staff

The tasks undertaken by each member of the site trial team are listed below:

2.1.1. Principal Investigator (PI)

- Has the ultimate responsibility for any protocol deviation (PD) occurring at site. Although a member of staff can be delegated to take on this task.
- Oversight of completion of PD reporting, recording, follow up, review and sign-off of the **Site Deviations and Concerns Log.**
- Ensuring PDs are processed in compliance with the trial's requirements and appropriate regulators.

2.1.2. Site Staff

- Identifying PDs.
- Classifying PDs according to the **Site Deviation Working Practise** provided by MRC CTU.
- Ensuring all identified PDs are added to the **Site Deviations and Concerns Log.**
- Ensuring the PI is aware of the PD.
- Reporting to MRC CTU within appropriate timelines.
- Completing, documenting and following up Action Items.
- Filing documentation including CAPAs, File notes and email correspondence of the PD in the ISF.

2.2. MRC CTU Trial Management Team (TMT)

The tasks undertaken by each member of the MRC CTU trial team are listed below:

2.2.1. Trial Managers (TM)

- To review any deviations raised by site members.
- To make sites aware of deviations identified centrally.
- To add any PDs to the **Central Deviations and Concerns Log** and ensure it's well maintained.
- Review Corrective and Preventative Action (CAPA) plans, file notes and action Items of PDs completed by sites.

3. DEFINITIONS

Key definitions regarding protocol deviations can be found within **Table 1.**

Table 1: Definitions

Terminology	Definition
Protocol Deviation	Any change, divergence, or departure from study design or procedures as described in the approved study protocol.
Critical 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.
Major Deviation[1]	Any change, divergence, or departure from study protocol that may significantly impact the completeness, accuracy and/or reliability of study data or the subjects' rights, safety and/or well-being.
Other Deviation[1]	Any deviation that is a change, divergence, or departure from study protocol that will not adversely affect subjects/data but should be dealt with appropriately.
Serious Breach	A breach of the protocol or of the conditions or principles of Good Clinical Practice in connection with that trial which is likely to affect to a significant degree (a) The safety or physical or mental integrity of the subjects of the trial; or (b) The scientific value of the trial.

[1] An "other" 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 and TMG.

4. Procedures

Whilst it is impossible to foresee the volume of protocol deviations, protocol non-compliance are likely to occur during the course of a trial. It is paramount that deviations are actively monitored throughout the lifespan of a trial and that accurate documentation is maintained to describe them.

4.1. Site Identified Protocol Deviations

All PDs discovered by the site research team will be internally circulated to appropriate site staff as soon as possible. The PD will be added to the **Site Deviations and Concerns Log.** The PD will also be forwarded to the STAMPEDE team at the CTU (mrcctu.stampede@ucl.ac.uk) to be assessed, a member of the STAMPEDE team will liaise with the site staff member if further information is required. The timeframe in which PDs need to be reported to the CTU by sites can be found in **Table 2**. A TM will acknowledge receipt of the deviation within 1 working day of receipt.

Table 2 Site Reporting Deviation Timeframe

Deviation Type	Action Required
Critical	Sites should document the deviation in an email, to the CTU, **within 1 working day** of the site becoming aware of the deviation. The **Site Deviations and Concerns Log** should also be submitted where possible but no later than a week from initially reporting the deviation.
Major	Sites should document the deviation in an email, to the CTU**, within 2 weeks** of the site becoming aware of the deviation. The **Site Deviations and Concerns Log** should also be submitted where possible but no later than a week from initially reporting the deviation.
Other	Should be reported on the **Site Deviations and Concerns Log** and sent to the CTU upon request.

4.2. Grading And Management Of Site Identified Protocol Deviations

Any PDs identified by site teams will be reviewed by a TM to confirm the sites assigned severity of the PD and the required actions, review **Table 1** to aid in assigning a severity.

4.3. PI Review

The PI has ultimate responsibility for all deviations from the protocol as stated in **Section 2.1.1** and should be informed if any deviations have occurred. The PI will be responsible for the final review and sign off of any CAPAs also. To show evidence that the PI has reviewed all deviations, the **Site Deviation Log** contains the "PI sign off" tab. The STAMPEDE team will periodically request this to be signed. When requested, the tab should be printed, signed by the PI, submitted to the STAMPEDE team and stored within **ISF Section 16.**

4.4. Site Protocol Deviation Log Guidance

When using the log, first ensure the tab "**Deviations**" is selected at the bottom of the spreadsheet, and ensure your site name and site number is entered into the appropriate cells. Fill in a row for each single deviation, such as missed safety bloods, a missed blood pressure measurement or if the follow up has been missed entirely. The log should be updated when new deviations are discovered or when a current deviation has an update in their status, for example the STAMPEDE team has requested actions to be completed or the issue has been resolved. Guidance on each item included in the site-specific log can be found in **Table 3.**

Table 3 Site Deviation Log Column Guidance

Column	Details
Site Deviation No.	Running reference number for all deviations.
Staff Member Responsible	Free text box to state which Site member is responsible for the reporting of this deviation.
Deviation Summary	Free text box to state a brief summery about the deviation.
Date Site Became Aware	Enter the date your site became aware of the deviation, if reported to site by the sponsor enter that date instead.
Deviation Category?	Cell is validated with a drop down list for deviation categories, select the most appropriate category, for guidance about which category is most appropriate see **APPENDIX 1 – Deviation Examples.**
Description If Other	Free text box to state how the deviation falls into the "other category".
Patient(s) Affected ID	Free text box to state participant ID
Deviation Details	Free text box to state details about the deviation, possible timeline of events, general comments and the actions to be taken following the deviation.
Date STAMPEDE Team Informed	Enter the date your site informed the sponsor of the deviation, if reported to site by the sponsor add that date instead.
Severity	Cell is validated with a drop down list for deviation grades. Critical, Major, Other. For definitions see **Section 3**.
Actions Required (CAPA, File Note Etc.)	Free text to state the actions to be taken following the deviation, CAPA, File Note Etc.
Current Status? (Open or Closed)	Cell is validated with a drop down list, open or closed.

APPENDIX 1 – Deviation Examples

Deviation Category	Example
Eligibility: disease category incorrect	Not eligible T2 tumour
	Staging incorrect (met to non-met)
	Incorrect disease category
	GS incorrect – using tertiary score
Eligibility: inclusion/exclusion criteria	Patient not meeting inclusion/exclusion criteria
	Incorrect blood tests performed
	Incorrect start date for ADT
	Randomised despite ineligible co-morbidity
	Participant taking contra-indicated medication
Screening	Trial mandated screening (bloods/imaging) not completed
	ECG completed after randomisation
	Incorrect Radio therapy intentions given
Follow-up	Safety blood checks not completed
	Incorrect follow-up schedule
	Stopped follow-up early – not per protocol
Patient treatment	Medical event – didn't receive IMP
	Continued IMP post progression (ZA)
	Did not receive planned radiotherapy
	Continued AA
	Missed 2 months of hormone treatment
	Wrong dose of IMP given
	Given wrong IMP
	Patient not taking IMP
	Incorrect dose escalation
	Incorrect treatment change response to toxicity
	Started second line treatment without disease progression due to inadequate response to first line treatment
Trial documentation	Data overdue
	Re-consent not completed
	Study specific procedures prior to consent.
	No delegation log in pharmacy
	Staff members not on delegation log
	Patient consented on wrong version of consent
Imp issue – not directly treatment related	Not given trial stock but hospital stock
	Temperature excursion
	Out of date IMP
	Incorrect IMP labelling
	Destroyed trial stock without permission
Other	Findings with no clear category