# Safety and incident reporting

GUIDANCE SHEET 9

The safety reporting window for this trial will be from **randomisation up to 12 months after the end of pregnancy for the woman and infant(s)**.

**MAMA SAEs of special interest**

- Maternal death
- Stillbirth (fetal loss greater than or equal to 24 weeks' gestation)
- Neonatal death up to 28 days of life
- All infant in-patient (>24 hours) hospitalisations that occur after neonatal/postnatal discharge

**All SAEs of special interest must be reported on the SAE Reporting Form to the MAMA Coordinating Centre immediately and within 24 hours of the site becoming aware of the event.**

In this population we anticipate day-to-day fluctuations of pre-existing conditions, new conditions, and a small number of pregnancy losses. As a result, many adverse events are foreseeable due to the nature of the participant population and their routine care/treatment. Consequently, **only those adverse events or adverse reactions identified as serious (SAEs) and of special interest** will require expedited reporting for the trial.

## Definitions and acronyms

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| Adverse Event (AE) | Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| Adverse Reaction (AR) | An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.<br>The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.<br>All cases judged by either the reporting medically qualified professional or the Sponsor as having a |

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| | reasonable suspected causal relationship to the trial medication qualify as adverse reactions. |
| Serious Adverse Event (SAE) | A serious adverse event is any untoward medical occurrence that:<br>• Results in death<br>• Is life-threatening<br>NOTE: *The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*<br>• Requires inpatient hospitalisation or prolongation of existing hospitalisation<br>NOTE: *The term hospitalisation refers to any in-patient admission, regardless of length of stay, and does not need to be overnight. This includes precautionary measures for observation. It does not include hospital admission for elective procedures or for pre-existing conditions which have not worsened.*<br>• Results in persistent or significant disability/incapacity<br>• Consists of a congenital anomaly or birth defect<br>• Is another important medical events.<br>NOTE: *May be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.* |
| Serious Adverse Reaction (SAR) | An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: |



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| | • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product<br>• in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question. |

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

## What to report?

Although the following SAEs are known to occur in this population, they will be required to be reported immediately:

- Maternal death
- Stillbirth (fetal loss greater than or equal to 24 weeks' gestation)
- Neonatal death up to 28 days of life
- All infant in-patient (>24 hours) hospitalisations that occur after neonatal/postnatal discharge

## When to report?

All SAEs of special interest must be reported on the SAE Reporting Form to the MAMA Coordinating Centre immediately and within 24 hours of the site becoming aware of the event.

### Notification of SAEs via the MAMA App

Women will be able to notify the trial team of infant hospitalisations via the MAMA app. When a potential SAE is reported via the app or a CRF you will be sent an alert. This will also be sent to NPEU CTU.

On receiving an alert you will need to do the following:

- Investigate if admission fits the SAE of special interest criteria:
  - All infant in-patient (>24 hours) hospitalisations that occur after neonatal/postnatal discharge
- If the admission **does** fit these criteria: complete the SAE Reporting Form immediately

### Notification of SAEs from Status check

You will be prompted via an email alert to check existing medical sources (e.g. medical records, MBRRACE-UK Perinatal and Maternal Mortality Data, NHS Spine) at pre-specified intervals to check that the woman and her infant(s) are both alive.

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In the event of a death you will need to do the following:

- Confirm whether the event fits the SAE of special interest criteria::
  - Maternal death
  - Stillbirth (fetal loss greater than or equal to 24 weeks' gestation)
  - Neonatal death up to 28 days of life
- If the event **does** fit these criteria: complete the SAE Reporting Form immediately

**All SAEs of special interest must be reported on the SAE Reporting Form to the NPEU CTU trial team immediately and within 24 hours of the site becoming aware of the event.**

## How to report?

**Anyone can report an SAE. No personal identifiers should be included in the report.**

There are three ways of reporting the SAE:

1) Complete online: Complete the MAMA SAE Form online on OpenClinica
2) Complete paper form: Copies of the paper MAMA SAE Form can be found in the Site Document Box. Once complete, inform the MAMA study team by email and send using the NPEU Upload tool.
3) Report via phone: Call the MAMA study team using the details at the bottom of the guidance sheet during office hours in order to report the SAE verbally. Once you have made the team aware of the event, you must still complete a SAE form as detailed above.

**A copy of the SAE form along with any follow up information should be filed in the woman's medical notes and also in the electronic Investigator Site File (e-ISF).**

## Completing the SAE Form

There are completion instructions on the SAE Form. In MAMA both women and their infants can be affected by SAEs. In Section 3. Participant detail please enter the following:

**Study number**: Woman's study number (even if the SAE relates to the infant)
**Date of birth**: This may be for an infant, or the woman, depending on who is affected by the SAE
**Sex**: This may be for an infant, or the woman, depending on who is affected by the SAE

Where one infant of mutiples is affected please include which infant the SAE relates to in the SAE Narrative box e.g. TWIN 1 or TWIN 2… Do **not** include infant names.

The MAMA Coordinating Centre will call to confirm details if required.

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## Completing Causality Assessment

The relationship of each adverse event to the trial medication must be determined by a medically trained doctor according to the following definitions:

- Unrelated: Where an event is not considered to be related to the IMP
- Possibly: Although a relationship to the IMP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible
- Probably: The temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP
- Definitely: The known effects of the IMP, its therapeutic class or based on challenge testing suggest that the IMP is the most likely cause.

**All SAEs labelled possibly, probably, or definitely will be considered as related to the IMP.**

**Do not delay SAE reporting whilst awaiting a causality assessment.**

## Expectedness Assessment

**For SAEs that require reporting, expectedness will be determined by NPEU CTU.**

## Incident Reporting

A trial-related Incident or deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process) or from GCP or any applicable regulatory requirements. Document all incidents / deviations from protocol in electronic Incident Forms as soon as practically possible.

Once completed, these documents should be uploaded via the NPEU Upload Tool. Further instructions are on the Incident Forms themselves.

NPEU CTU staff will complete an assessment of the incident and, where applicable, complete the relevant corrective and preventative action plan. File final signed copies in the eISF.



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