



## Standard Operating Procedure (SOP) 009

### Safety monitoring

#### Scope

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- To outline the procedure for safety monitoring in the PICnIC study, including the recording and reporting of adverse events (AEs).
- The procedures and processes laid out below are in accordance with Good Clinical Practice (GCP).
- This is for patients on the intervention arm (SDD administration) and will be collected from intervention commencement until PICU discharge.

#### Responsibilities

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- Responsibility for safety monitoring lies with the Principal Investigator (PI), however this can be delegated to another member of the site research staff if they have been authorised and it has been recorded in the study Delegation Log (Section 12: Site Staff Information, of the ISF).
- Patients should be monitored for AEs during Period Two until PICU discharge.

#### Definitions

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- **Adverse event**
  - Any untoward medical occurrence or effect in a patient participating in the study, which does not necessarily have a causal relationship with study treatment.
- **Serious adverse event**  
An AE that:
  - results in death
  - is life-threatening (the subject must have been at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
  - requires in-patient hospitalisation or prolongation of existing hospitalisation
  - results in persistent or significant disability/incapacity
  - is a congenital anomaly/birth defect
  - is otherwise considered medically significant by the PI

Important AEs that are not immediately life-threatening, do not result in death or hospitalisation but may jeopardise the subject or require intervention to prevent one or any of the other outcomes listed in the definition above should also be considered as serious.

- **Unexpected and Related serious adverse event**

- A suspected AE related (possibly, probably or definitely) to the treatment that is both unexpected (i.e. not consistent with the expected outcomes of the treatment being offered) and serious.

## Assessment

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### Severity

Assessment of severity will be graded based on the PI's (or other delegated investigators') clinical judgement using the following definitions:

- 0 **None**: indicates no event or complication
- 1 **Mild**: complication results in only temporary harm and does not require clinical treatment
- 2 **Moderate**: complication requires clinical treatment but does not result in significant prolongation of hospital stay. Does not usually result in permanent harm and where this does occur the harm does not cause functional limitation to the patient
- 3 **Severe**: complication requires clinical treatment and results in significant prolongation of hospital stay and/or permanent functional limitation
- 4 **Life threatening**: complication may lead to death
- 5 **Fatal**: indicates that the patient died as a direct result of the complication/AE

### Relatedness

The PI or other delegated investigator(s) should use clinical judgement to determine the relationship between the study treatment and the occurrence of each AE using the following definitions:

- **None**: there is no evidence of any relationship to the study treatment
- **Unlikely**: there is little evidence to suggest a relationship to the study treatment, and there is another reasonable explanation of the event
- **Possibly**: there is some evidence to suggest a relationship to the study treatment, although the influence of other factors may have contributed to the event
- **Probably**: there is probable evidence to suggest a relationship to the study treatment, and the influence of other factors is unlikely
- **Definitely**: there is clear evidence to suggest a relationship to the study treatment and other possible contributing factors can be ruled out

### Expectedness

Expected: the event is specified as an expected AE, as listed below

Unexpected: the event is not listed as an expected AE

## Adverse events in PICnIC

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### Expected Adverse Events

- AEs which might be expected in PICnIC are listed on the Safety Monitoring Case Report Form and below:
  - NG tube blockage
  - Choking on paste
  - Allergic reaction to SDD

NB: This list is not exhaustive.

AEs will be recorded during Period Two from enrolment until PICU discharge. All adverse events will be recorded in the medical notes of the patients.

For patients receiving SDD intervention, only AEs deemed possibly, probably or definitely related to the trial intervention should be reported to the ICNARC CTU, apart from NG tube blockages which should be reported even if not deemed related. Events should continue to be recorded for patients readmitted to PICU from another inpatient area who are receiving SDD until the end of their treatment period (30 days from being identified as eligible).

For patients on Usual care, only NG tube blockages should be reported under 'adverse events (specified)', relatedness should not be completed. NG tube blockages should continue to be recorded for any patients readmitted to PICU from another inpatient area, until 30 days from being identified as eligible.

### **Other Adverse Events**

Any AE not listed as 'expected' and therefore an unexpected reaction to the study medication should be listed on the Safety Monitoring CRF under 'other'. These events should only be reported for patients receiving SDD.

All patients in PICnIC are very ill, and due to the complexity of their existing medical conditions, are at increased risk of AEs. Many of these events may be expected as a result of either the patient's medical condition or additional treatment that is not part of the study treatment. The following events are exempt for reporting as AEs or SAEs, but should be recorded in the patients notes.

- Deterioration of condition or death that is not related to the trial intervention
- AEs of other drugs not specified in the protocol.

Pre-existing conditions do not qualify as AEs unless they worsen, however they should be documented in the patient's medical notes.

## **Recording and Reporting of Events (also see figure 1)**

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- All AEs should be recorded on the Safety Monitoring CRF, and if applicable, because the severity is classed as severe, life-threatening or fatal, on the Serious Adverse Event Reporting Form.
  - For AEs that might be expected, staff should indicate whether or not they occurred. If an event did not occur, '0' (None) should be entered in the severity box. If the event happened more than once, this can be recorded on Macro using the dropdown option. The Safety Monitoring CRF should be completed once and updated if further events occur. (Also see SOP 007\_Guidance for completion of Case Report Forms).
  - The date (dd/mm/yyyy) and time (24 hour clock) of the start of the event should be recorded.
  - If the AE (specified or other) is classified as severe, life threatening or fatal they must be reported on the Serious Adverse Event Reporting Form (from Section 8: Case Report Forms, of the ISF) and uploaded on to Macro within 24 hours of the study team becoming aware of the event. This should happen by:

- 1) Uploading a hard copy of the completed Serious Adverse Event Reporting Form page (which should have the minimum essential criteria listed below) on to Macro.
- 2) Directly inputting required data (which should have the minimum of the essential criteria listed below) on the Serious Adverse Event Reporting Form page on Macro.

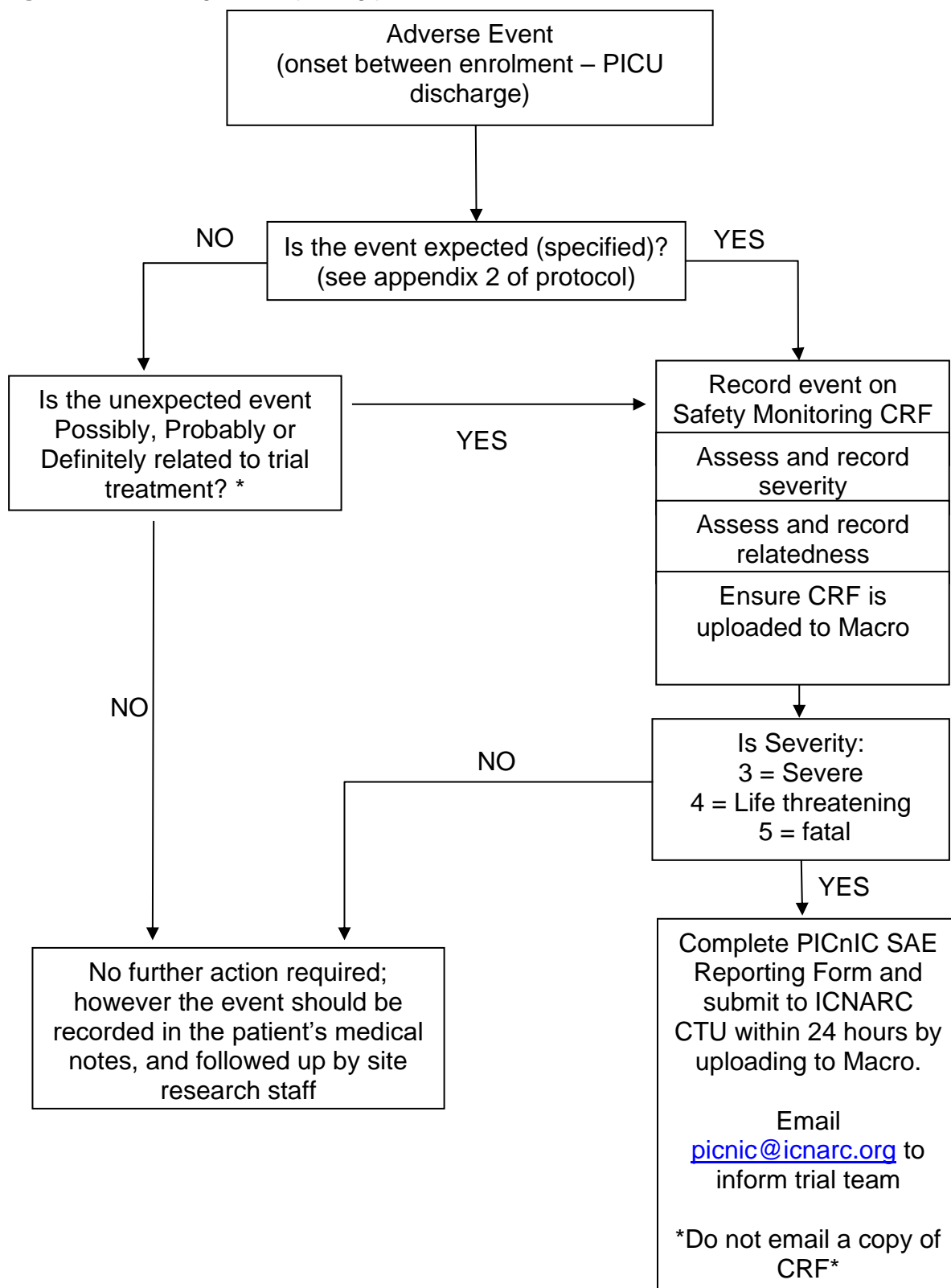
Please ensure any updates that follow are reflected on both the hard copy upload and direct data entry on the Serious Adverse Event Reporting Form page on Macro.

- Sites should also email [picnic@icnarc.org](mailto:picnic@icnarc.org) within 24 hours of becoming aware of the event to inform the PICnIC trial team that it has been uploaded for review. **Do not email a copy of the CRF.**
- Staff should not wait until all information about the event is available before sending the SAE notification. Information not available at the time of the initial report must be documented and submitted as it becomes available. However, essential criteria regarding date and time onset, event name, severity and relatedness of the event to the study treatment must be recorded in the first instance.
- On receipt of the SAE report on to Macro, a clinical member of the PICnIC Management Group (TMG) will evaluate the event for seriousness, relatedness and expectedness to determine whether or not the case qualifies for expedited reporting to the Research Ethics Committee (REC) (see below).
- The PI may be contacted to provide further details about the SAE.
- Following review by the ICNARC CTU, an SAE may be upgraded in terms of relatedness but cannot be downgraded.
- All SAEs must be followed-up until resolution. The site PI or other delegated investigator(s) must provide follow-up SAE report(s) if the SAE has not been resolved at the time of the initial report submission and ensure the report(s) are signed off.
- If the event is evaluated by either the CI or a clinical member of the PICnIC Trial Management Group (TMG) as an unexpected and related SAE, the ICNARC CTU will submit a report to the REC within 15 calendar days.

## Additional safety monitoring

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- The ICNARC CTU will also monitor data for documented AEs that are not considered to be related to the study treatment.
  - In the event that any study procedure does appear to be resulting in AEs, the TMG will be contacted for their opinion. If it is declared necessary to review the conduct of the study, the ICNARC CTU will inform the REC as appropriate.

**Figure 1.** Recording and Reporting process of Adverse Events



\*If there is any uncertainty about whether the AE is associated with trial treatment, then it should be reported. Unexpected events should only be recorded for patients receiving SDD treatment