GUIDANCE SHEET 6:
Safety & Incident Reporting

Procedures for Recording Adverse Events and Reporting Serious Adverse Events

This guidance sheet outlines the different types of events that need reporting; in what timeframe these must be reported; and how to report them. For more information on safety and incident reporting, please refer to the SurfON Protocol.

The safety reporting window for this trial for each participant will be from **randomisation to discharge home**.

- Any staff can report a safety event or incident
- Events can be defined as:
  - Adverse Events or Reactions (AE/AR)
  - Serious Adverse Events or Reactions (SAE/SAR)
  - Suspected Unexpected Serious Adverse Reactions (SUSAR)

Definitions

ADVERSE EVENT (AE) is any untoward medical occurrence in a participant, which does not necessarily have a causal relationship with the trial intervention.

ADVERSE REACTION (AR) is an untoward and unintended response in a participant to an investigational medicinal product that is related to any dose administered to that participant

SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Consists of a congenital anomaly or birth defect
- Other important medical events

Other 'important medical events' may also be considered as a SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

The term 'life-threatening' 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.

SERIOUS ADVERSE REACTION (SAR) is 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.

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SUSPECTED UNEXPECTED SERIOUS ADVERSE EVENT (SUSAR) is a serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out:

- In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product
- In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

For SurfON, the assessor must refer to the latest approved **SmPC as per SurfON Protocol** in order to assess expectedness. If the SAE is related to the IMP and the event is unexpected (i.e. is not consistent with SmPC) then this is a SUSAR.

Reporting of Adverse Events

In this trial population we anticipate day-to-day fluctuations of pre-existing conditions. As a result, many AEs are foreseeable due to the nature of the participant population and their routine care/ treatment. Consequently, **only those AEs identified as serious will be reported for the trial**.

Events exempt from immediate reporting as SAEs

The following SAEs are pre-defined trial outcomes and as such will only be recorded on the case report forms but not expeditiously reported:

- Pulmonary air leaks (pneumothoraces or pneumomediastinum)
- Late onset sepsis
- Need for mechanical ventilation via an ETT
- ECMO
- iNO

The following serious adverse events are a foreseeable occurrence in this population of infants and as such do not require reporting as SAEs:

- Common minor deviations from normal haematological values, including anaemia and thrombocytopenia
- Common minor deviations from normal biochemical values including hyponatraemia, hyperbilirubinaemia, and hypoglycaemia
- Patent ductus arteriosus

Reportable Serious Adverse Events

All SAEs, other than those listed above, will be reported. In particular, the following events will need to be reported:

- Death
- Transfer to another hospital related to early respiratory management
  - for escalation of care
  - for neonatal intensive care because of lack of intensive care cot capacity in the NICU or LNU of birth

  (Please note that transfers for a lower level of care (SCU) or for reasons unrelated to respiratory management do not need to be reported as an SAE.)
- Serious complication of ETT intubation such as hypoxia resulting in encephalopathy
- Severe pulmonary haemorrhage
- Severe intracranial haemorrhage

Reporting Serious Adverse Events and Reactions

SAEs must be reported **as soon as possible and within 24-hours of the site becoming aware of the event**. Anyone can report an SAE. There are three ways of reporting the SAE form:

1. Complete online:

Complete the SurfON SAE Form (CTIMP) online on OpenClinica and inform the SurfON study team by:

- Emailing to surfon@npeu.ox.ac.uk. Use the study number to notify the SurfON study team that the SAE form has been completed online. Do not send any personal identifiable information in this email (**OR**)
- Calling the team on 01865 289 437/ 738 during office hours between 9:00 to 17:00 Monday to Friday (**OR**)

2. Complete paper form:

Copies of the paper SurfON SAE Form (CTIMP) can be found in the Site Document Box. Once complete, inform the SurfON study team by:

- Emailing a scanned copy of the form from your nhs.net or trust account to ouh-tr.surfon@nhs.net so end-to-end encryption applies. Please check the email addresses thoroughly before sending (**OR**)

3. Complete via phone:

Call the SurfON study team using the above details during office hours in order to report the SAE verbally

In the case of out-of-hours reporting, please phone **0800 1385 451**.

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

Completing causality assessment

Do not delay SAE reporting whilst awaiting a causality assessment.

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The causal relationship of each adverse event to the IMP must be determined. This must be completed by a **delegated clinician** listed on the **SurfON Delegation Log**. For this reason, we recommend that **more than one person is delegated to complete causality assessment to cover any absences**.

If the initial SAE form was completed online, print the form in order to get the causality assessment completed. Do this by accessing the SAE form relating to the study ID in OpenClinica using 'review only' mode (or the magnifying glass icon). Then use the print icon to print the form.

The SAE form may be sent to the SurfON study team initially without the causality assessment. If the delegated clinician completing causality assessment completes a paper form, the updated form must be sent to the SurfON study team once complete. If they complete the causality assessment online, this will trigger an automated email to the SurfON study team so there is no need to send a separate email or copy of the form.

Causality cannot be downgraded by others. The definitions for assessing causality are:

- **Not related** – 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

If the event is considered to be a SAR, it is assessed for expectedness against the known adverse reaction profile of the IMP. If there is uncertainty regarding whether an event is related to the intervention/or requires reporting, please discuss with the infant's consultant, local Principal Investigator or Research Nurse. If uncertainty remains, please report the event.

Follow up Information

Sites can provide follow-up information to the SurfON Study Team using paper or online on Openclinica. This can be completed by adding information to the original SAE paper form, e.g. causality assessment, in a Good Clinical Practice (GCP) compliant way i.e. initialled and dated.

Alternatively, this can be completed online by starting a new SAE report form and ticking the 'follow-up information' box. You will notice that Openclinica will automatically mark this as form 2. Multiple follow-up forms may be used for an SAE.

It is to be noted that any unchanged information in the 'initial SAE report form' need not be re-reported in the follow up form). Only 'new or missing information' will need to be reported in the follow up form.

Follow up information should continue to be provided until the SAE is:

- Resolved (the subject's health has returned to their baseline status or all variables have returned to normal)
  OR
- Resolved with sequelae (the Investigator does not expect any further improvement or worsening of the event).

Outcome of SAE

The outcome of events "Resolving" or "Not Resolved" must be followed up until the status of the SAE changes.

Procedures for Recording and Reporting Incidents

Incident Reporting

Any deviations from the protocol, trial procedures, Good Clinical Practice or regulatory requirements must be reported as incidents to the SurfON study team, using the **SurfON Incident and Deviation Reporting Form**. Any member of the team can report incidents.

Examples of incidents in this context might be a trial activity performed by a practitioner not listed on the delegation log; forms not amended in accordance with GCP; and not emailing consent forms securely to ouh-tr.surfon@nhs.net.

Incidents should be reported as soon as practical and can be reported by either:

1. Completing the Incident & Deviation Reporting Form (kept in the SurfON Documents Box). Please fill in all documentation clearly and legibly in black ink. If you make a mistake, please cross through this with a single line and put your initials and date next to it. Written forms should be emailed to surfon@npeu.ox.ac.uk.

   For the purpose of anonymity, all paperwork should have the Study number only and no further identifiable information. If the form does need to contain personal identifiable information, please always ensure end-to-end encryption is applicable by using nhs.net or trust id when emailing the form to ouh-tr.surfon@nhs.net.

   OR

2. Verbally via phone. However, this must be followed up in writing.

If you are unable to complete the 'resolution' section of the form in the first instance, send the partially completed form and re-send the form with 'resolutions' at a later date.

Copies of all incident reports relevant to the site should be kept in the ISF.

Serious Breaches

Incidents and protocol deviations will be defined as a serious breach if there is a breach of GCP or trial protocol which is likely to affect to a significant degree either:

- The safety, physical or mental integrity of the subjects of the trial
- The scientific value of the trial

The SurfON study team will conduct an assessment of all reported incidents to determine if they will be classified as a serious breach.

Emergency Queries Contact Details

During Office Hours

Any queries whether urgent or not should be directed to the SurfON study team during office hours (i.e. between 09:00- 17:00, Monday to Friday) on 01865 289 437 / 738. **Important** Please DO NOT send patient identifiable information to surfon@npeu.ox.ac.uk instead please send identifying information ONLY to ouh-tr.surfon@nhs.net from your **nhs.net or trust** email id, so it remains end-to-end encrypted.

Out-of-Hours

In the case of urgent out-of-hours queries, please phone 0800 1385 451.
Please see **Guidance Sheet 9: Emergency Queries** for further information.

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