

### Procedures for Reporting Serious Adverse Events (SAEs)

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 **DOLFIN Study Protocol**.

The safety reporting window for this trial will be from the time the participant **starts supplementation up to two weeks after supplementation ends (at 12 months post Estimated Date of Delivery (EDD))**.

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

#### Definitions

**Adverse Event (AE):** Any untoward medical occurrence in a participant to whom a trial supplement has been administered, including occurrences which are not necessarily caused by or related to that product.

**Adverse Reaction (AR):** Any untoward and unintended response in a participant which is related to the trial supplement.

**Serious Adverse Event (SAE):** A serious adverse event is any untoward medical occurrence that:

1. results in death
2. is life-threatening
3. requires inpatient hospitalisation or prolongation of existing hospitalisation
4. results in persistent or significant disability/incapacity
5. consists of a congenital anomaly or birth defect

Other 'important medical events' may also be considered a serious adverse event 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.

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.

**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 the trial supplement, based on the information provided

**Unexpected Serious Adverse Reaction:** An SAE that, in the opinion of the CI (or safety delegate), is a result of the trial supplement and is not listed as an expected occurrence in the protocol.

## Reporting Serious Adverse Events (SAEs)

Due to the nature of the participant population and their routine care/ treatment, many adverse events are foreseeable and have been listed as non-reportable in the DOLFIN study protocol, even if they otherwise meet the definition of 'serious' as outlined above. During Neonatal Unit (NNU) admission, all unforeseeable SAEs, and foreseeable SAEs deemed causally related to the trial supplement must be reported to the DOLFIN study team. Approved Continuing Care Sites (CCSs) are asked to report any SAEs to the DOLFIN study team, who will notify the recruiting site.

### Events exempt from immediate reporting

The following foreseeable SAEs are pre-defined trial outcomes or events that could be reasonably expected to occur in this population. They do not require reporting as SAEs unless considered that they may be causally related to the study intervention (supplement), in which case they should be reported as detailed in the section reporting SAEs:

#### Foreseeable SAEs

1. Abnormalities of tone, posture and/or movement
2. Accidental injury
3. Acute cardio-respiratory event or failure
4. Anaemia
5. Clinically significant intracranial abnormality on cranial ultrasound scan – intracranial haemorrhage or white matter injury
6. Chronic lung disease / Broncho pulmonary dysplasia
7. Coagulopathy requiring treatment
8. Congenital anomalies
9. Constipation
10. Death (unless unforeseen in this population)
11. Difficulty establishing enteral feeding
12. Dysphagia/neurological feeding and drinking difficulties
13. Epilepsy
14. Food intolerances leading to exclusion diet (cow's milk, lactose, eggs, fish)
15. Fluid retention
16. Fine motor impairment
17. Gastrointestinal bleeding
18. Gastro-oesophageal reflux disease
19. Gastrostomy insertion
20. Global developmental impairment
21. Gross motor impairment
22. Haematuria
23. Haemothorax

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24. Hearing impairment
25. High blood creatinine level (defined as  $>100 \mu\text{mol/L}$ )
26. Hyperbilirubinemia (jaundice)
27. Hyperglycaemia
28. Hypoglycaemia
29. Hypotension
30. Hypoxic ischaemic encephalopathy
31. Hydrocephalus
32. Impaired renal function (urine output  $<0.5 \text{ ml/kg/hour}$ , and or serum creatinine  $> 100 \mu\text{mol/L}$ )
33. Incarcerated hernia
34. Jejunostomy or gastrojejunostomy extension tube insertion
35. Low sodium level/hyponatremia
36. Liver dysfunction
37. Non-iatrogenic meningitis
38. Necrotising enterocolitis
39. Neutropenia (defined as  $<1.0 \text{ mmol/L}$ )
40. Metabolic bone disease
41. Metabolic disturbance of electrolytes or minerals
42. Patent ductus arteriosus
43. Pneumothorax or air leaks
44. Pneumonia (including aspiration pneumonia)
45. Pulmonary haemorrhage
46. Pulmonary hypertension requiring treatment
47. Respiratory failure
48. Retinopathy of prematurity
49. Seizures
50. Sepsis / infection (except when associated with culture/growth of an unusual organism)
51. Sleep disordered breathing
52. Spontaneous intestinal perforation
53. Speech and language impairment
54. Thrombocytopenia
55. Tracheostomy placement
56. Upper airway obstruction
57. Ventriculo-peritoneal shunt insertion or replacement
58. Visual impairment

**All SAEs deemed causally related to the trial supplement must also be reported irrespective of whether they feature in the list of foreseeable adverse events.**

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## Reportable Serious Adverse Events

All SAEs other than those listed as foreseeable, and not deemed causally related, will be reported. In particular, the following events will need to be reported:

- Serious prolonged gastrointestinal disturbance (except from necrotising enterocolitis)
- Serious prolonged gastrointestinal disturbance associated with culture/growth of an unusual organism
- Sepsis associated with culture/growth of an unusual organism

**All SAEs deemed causally related to the trial supplement must also be reported irrespective of whether they feature in the list of foreseeable adverse events.**

## Reporting Serious Adverse Events

During Neonatal Unit (NNU) admission, all unforeseeable SAEs, and foreseeable SAEs deemed causally related to the trial supplement must be reported on the **DOLFIN Serious Adverse Event Report Form** to the DOLFIN study team at the NPEU Clinical Trials Unit (CTU) as soon as the **site becomes aware of the event**.

Following discharge from the NNU, parents will be asked to report SAEs to their local research nurse or local NHS clinical team using the contact details provided in **the DOLFIN Discharge Pack**. Parents will be reminded via the study app or an agreed alternative (text message/email) to report unplanned hospital admissions. When a report is received the site will be asked to assess whether the hospital admission requires reporting as an SAE. Parents will also be asked about the occurrence of unplanned hospital admissions at the time of parent reported outcome measure completion at 3, 6, and 12 months post EDD.

SAEs reported to the site (which meet the reporting criteria listed above), must be reported to the DOLFIN study team at the NPEU CTU via the **DOLFIN Serious Adverse Event Report Form**.

**Please make an initial report as soon as possible even if you do not have all the information.**

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

Follow up SAE information should be reported as necessary by the site staff and sent to the DOLIN study team, NPEU CTU.

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Recruiting sites may use one of the following SAE reporting methods:

1. Paper or electronic forms (found in the eISF and/or Document Box, or for CCS in the Transfer Pack). Staff without access to OpenClinica can fill out a copy on this and send to the **DOLFIN study team at NPEU CTU** via email or for recruiting sites via the **DOLFIN secure file transfer system**.
  - Completed editable PDFs can be printed and signed, or they can be signed using a secure electronic signature e.g. via AdobeSign (a signature cannot be typed as text or added as an image to the PDF).
  - Completed paper forms must be signed and an electronic copy emailed to the DOLFIN study team at NPEU CTU.
2. Staff at recruiting sites with access to Openclinica can complete an SAE form directly onto the system. An automatic email notification to the NPEU CTU staff will be triggered for SAEs reported electronically. Forms can also be signed directly on OpenClinica. For PI or safety delegate signatures, forms must be signed off using the account of the person signing the form, or the form can be printed and wet-signed.
3. Where the above routes are not possible, then the SAE may be reported to NPEU CTU by telephone and a completed SAE form provided as soon as practically possible.
4. Contact the team on 01865 617919 / 01865 617924 during office hours between 9:00 to 17:00 Monday to Friday. In the case of out-of-hours reporting, please phone 0800 1385 451. (See **Guidance Sheet 10 – Emergency Queries**).

Sites should retain a copy of any completed SAE forms as a hardcopy in the site folder and/or an electronic copy in the eISF (depending on how the form was completed and signed).

**Please do not include any personal identifiable information on SAE forms**

### Assessing causality of SAEs

The causal relationship of each adverse event to the study intervention (supplement) must be determined by a medically qualified individual delegated to assess SAE causality (safety delegate) as documented on the **DOLFIN Site Delegation Log**. For this reason, we recommend that **more than one person is delegated to complete causality assessment to cover any absences**. Continuing Care Sites (CCS) do not hold delegation logs and so causality can be completed by any medically qualified individual.

The **DOLFIN Serious Adverse Event Report Form** can be sent to the DOLFIN study team initially without the causality assessment, with the causality assessment completed as soon as possible.

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The definitions for assessing causality are:

**Unrelated** – where an event is not considered to be related to the trial supplement.

**Possibly** – although a relationship to the trial supplement 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 trial supplement.

**Definitely** – the trial supplement is the most likely cause

If there is uncertainty regarding whether an event is related to the supplement or requires reporting, please discuss with the infant’s consultant, local Principal Investigator (PI) or local research nurse. If uncertainty remains, please report the event and contact the DOLFIN study team to discuss.

## Review of SAEs

The NPEU CTU will forward a copy of the SAE form to the CI / safety delegate as soon as possible on receipt. The CI /safety delegate (as well as the site PI) will also assess whether the SAE was related to the trial supplement (i.e. is it an SAE or a SAR). If assessed to be related, the CI / safety delegate will proceed to assess expectedness. In the event of the assessment of the causality differing, the assessors may discuss to see if agreement can be reached, but no coercion may take place. If agreement cannot be reached, the event must be treated as related for reporting requirements.

## Procedure for Recording and Reporting Incidents

### Incident Reporting

Any deviations from the DOLFIN Study Protocol, study-specific procedures, Good Clinical Practice (GCP) or regulatory requirements must be reported as incidents to the DOLFIN study team, using the **DOLFIN Incident and Deviation Reporting Form**.

Examples of incidents in this context might be a study activity performed by an individual not listed on the delegation log or who is listed on the delegation log but not delegated for that specific activity; forms not amended in accordance with GCP; consent forms not signed and dated correctly; and use of a superseded form.

Any staff member may report incidents. Approved Continuing Care Site (CCSs) are asked to report any incidents to the DOLFIN study team. The DOLFIN study team will notify recruiting sites of any incidents relevant to infants recruited at their site which are reported by CCS. The DOLFIN study team may, in some circumstances, complete a form on behalf of the site. In this case the form will be sent to the site for review and for filing locally.

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Incidents should be reported as soon as is practical. Sites can complete the form as an editable electronic PDF form (provided as part of the DOLFIN electronic Investigator Site File (e-ISF), or a paper form (provided in the DOLFIN Document Box or can be printed from eISF) can be completed and scanned copies sent to NPEU CTU via email [dolphin@npeu.ox.ac.uk](mailto:dolphin@npeu.ox.ac.uk) or the **DOLFIN secure file transfer system**. Incident forms **cannot** be completed on OpenClinica. Please complete any paper documentation clearly and legibly in black ink. If an error is made whilst completing the form, cross through the error with a single line with the initials of the person completing the form and date next to it.

**Please DO NOT send patient identifiable information to [dolphin@npeu.ox.ac.uk](mailto:dolphin@npeu.ox.ac.uk) instead please upload identifying information ONLY to the DOLFIN secure file transfer system.**

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 completed **DOLFIN Incident & Deviation Reporting Forms** relevant to the site should be filed in the e-ISF and/or hardcopies filed in the site folder.

## Serious Breaches

Incidents and protocol deviations will be defined as a serious breach if there is a breach of GCP or study 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 DOLFIN study team will assess all reported incidents to determine if they should be classified as a serious breach.

## Emergency Queries Contact Details

### During Office Hours

Any queries whether urgent or not should be directed to the DOLFIN study team during office hours (i.e. between 09:00- 17:00, Monday to Friday) on 01865 617919

**\*\*Important\*\*** Please DO NOT send patient identifiable information to [dolphin@npeu.ox.ac.uk](mailto:dolphin@npeu.ox.ac.uk) instead please upload identifying information ONLY to the DOLFIN secure file transfer system

### Out-of-Hours

In the case of urgent out-of-hours queries, please phone 0800 1385 451.  
Please see **Guidance Sheet 10: Emergency Queries** for further information

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