APPENDIX 3: SAES EXEMPTED FROM EXPEDITED REPORTING

SERIOUS ADVERSE EVENTS (SAES) NOT REQUIRING EXPEDITED REPORTING WITHIN 24 HOURS OF THE INVESTIGATOR BECOMING AWARE OF THE EVENT

Adverse events are relatively common in the neonatal population due to immaturity and concomitant disease processes. Given that such events are frequent in this high-risk population but are unlikely to be considered related to the interventions under study, if an SAE meets the criteria below then it will be exempted from expedited reporting within 24 hours of occurrence of the event. Please see **Section 9.1** in the protocol for definitions of SAEs and SARs.

CRITERIA FOR EXEMPTION FROM EXPEDITED SAE REPORTING

Those events that:

EITHER

- **are listed in Appendix Table 2 below**

  AND
- **are not considered related** to any of the trial antibiotics (any of the antibiotics listed in protocol **Section 6**)

  AND
- **have a typical clinical course and are not more severe than would be expected** by the local clinician in this population

  AND
- **are not fatal**

OR

- **occur more than 2 days (≥48h) after stopping trial antibiotics** (any of the antibiotics listed in protocol **Section 6**)

  AND
- **are not considered related** to any of the trial antibiotics listed in protocol **Section 6**

  AND
- **are not fatal**

will be recorded and reported in the eDC within 7 days but are exempt from expedited reporting to the Sponsor and regulatory bodies within 24h of the investigator becoming aware of the event (see protocol **Section 9.3**). **Appendix 3 Appendix 3** Table 1 and **Appendix 3 Figure 1** outline the process for expedited reporting.

The events included in **Appendix 3**

Table 3 are adapted from the foreseeable SAEs as outlined in a previous UK neonatal randomised controlled trial (DOLFIN randomised controlled trial: Developmental Outcome of Long-term Feed Supplementation in Neonates) and are exempt from expedited reporting if the above criteria are also met. Any condition stated in the Reference Safety Information (RSI) for any of the interventions under study has been excluded from **Appendix 3**

Table 3. Any condition included in the RSI for one or more of the interventions under study **or** where an anticipated non-fatal SAE is of atypical severity within the clinical experience of the local investigator would require expedited reporting (**Appendix 3 Appendix 3** Table 1). All fatal and non-fatal serious adverse reactions (SARs), i.e. events deemed serious and related to a study intervention, **and** any fatal SAEs/SARs, require expedited reporting within 24 hours of becoming aware of the event. The Investigator **must report all deaths within 24 hours** of becoming aware of the event.

Appendix 3 Table 1: Expedited reporting criteria for SAEs/SARs

EVENT	ACTION
Fatal SAE/SAR	Requires expedited reporting
Non-fatal SAR	Requires expedited reporting
Non-fatal SAE (not SAR) not included in Appendix Table 3 below occurring on trial antibiotics or within 2 days (48h) of stopping trial antibiotics	Requires expedited reporting
Non-fatal SAE (not SAR) included in Appendix Table 3 below AN**D** atypical clinical course or severity	Requires expedited reporting
Non-fatal SAE (not SAR) not included in Appendix Table 3 below occurring 2 days (48h) or more after stopping trial antibiotics	Exempt from expedited reporting
Non-fatal SAE (not SAR) included in Appendix Table 3 below **AND** typical clinical course or severity	Exempt from expedited reporting

SAE = serious adverse event; SAR = serious adverse reaction

Appendix Figure 2: Expedited reporting flow diagram for SAEs/SARs

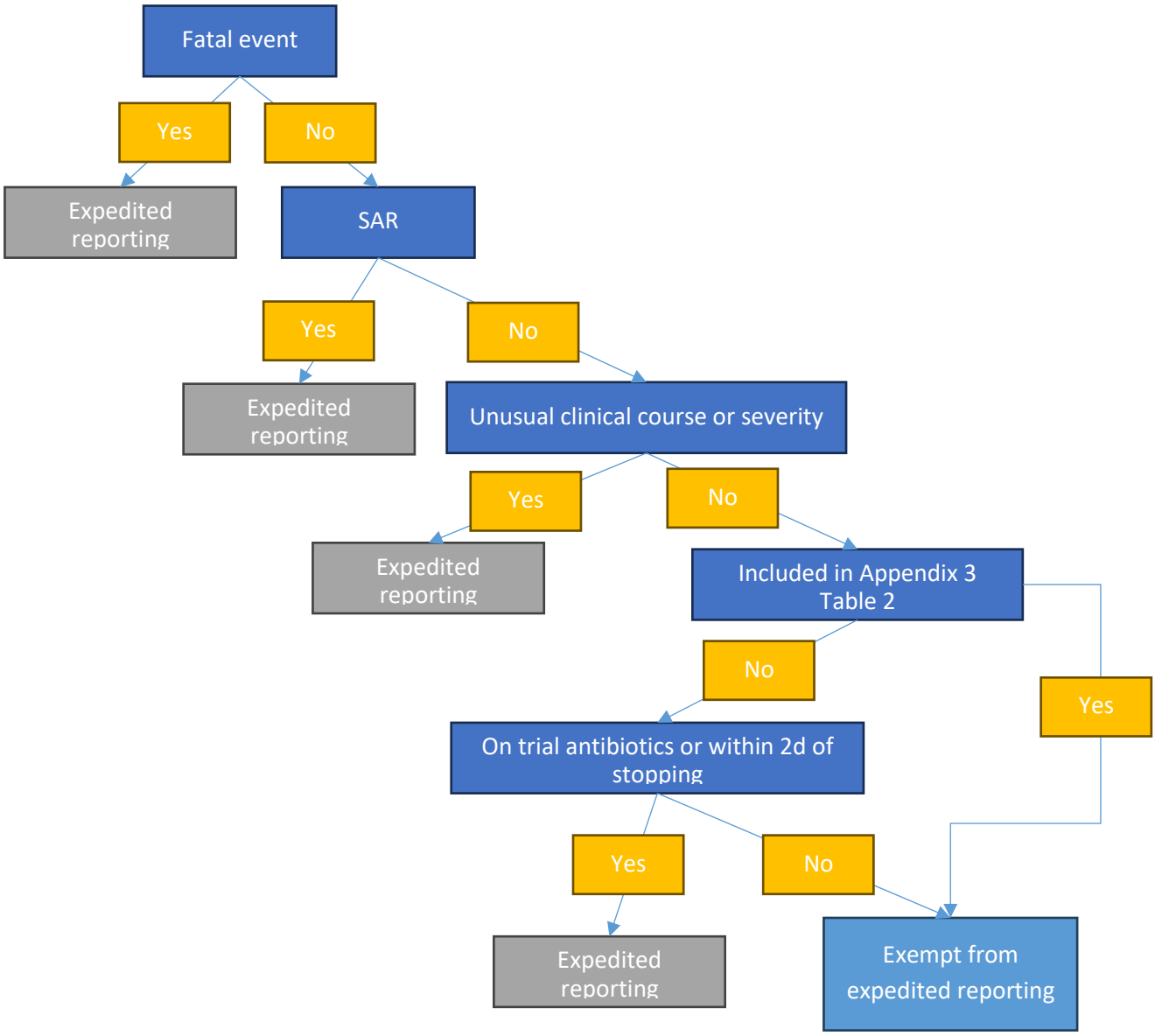

Table 3: Anticipated serious adverse events

SERIOUS ADVERSE EVENT
Abnormalities of tone, posture and/or movement
Administration site complication/Extravasation injury (serious, permanent scarring and/or/joint deformity)
Chronic lung disease/Bronchopulmonary dysplasia
Congenital anomalies
Difficulty establishing enteral feeding
Dysphagia/neurological feeding and drinking difficulties
Food intolerances leading to exclusion diet (cow's milk, lactose)
Fine motor impairment
Gastrointestinal bleeding
Global developmental impairment
Gross motor impairment
Haemothorax
Hyperglycaemia
Hypoglycaemia
Hypotension
Hypoxic ischaemic encephalopathy/Other Encephalopathies
Hydrocephalus
Intracranial abnormality on cranial ultrasound scan – clinically significant intracranial haemorrhage or white matter injury
Non-iatrogenic meningitis
Necrotising enterocolitis
Metabolic bone disease
Neonatal abstinence syndrome
Patent ductus arteriosus
Pneumothorax or air leaks
Pulmonary haemorrhage
Persistent pulmonary hypertension of the newborn requiring treatment
Respiratory failure
Retinopathy of prematurity
Sleep disordered breathing
Spontaneous intestinal perforation
Tracheostomy placement
Upper airway obstruction