

NEONATAL ADVERSE EVENTS GRADING

GRADING SCALE ADAPTED FROM DAIDS/NAESS

Purpose of this document: to standardize the classification and severity of adverse events in NeoSep1 clinical trial.

In general, and where appropriate, the parameters refer to the associated neonatal conditions e.g., “apnoea” is “neonatal apnoea”; “Respiratory Distress Syndrome” is “Neonatal Respiratory Distress Syndrome”, etc.

The requirement for an intervention does not mean that the intervention has to be available e.g. requiring urgent blood transfusion would be the need for an urgent blood transfusion whether the blood was available or not.

Parameter	Grade 0 Normal	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening	Grade 5
RESPIRATORY						
Apnoea	No apnoeas	Self-limiting apnoea	Apnoea responsive to stimulation AND/OR temporary FiO ₂ increase	Apnoea requiring sustained FiO ₂ increase AND/OR requiring non-invasive ventilation AND/OR other major care changes required	Apnoea with life-threatening respiratory and/or haemodynamic compromise AND/OR urgent care change required	Death
Bronchopulmonary Dysplasia	No evidence of BPD by definition	Supplemental oxygen at 28 days AND breathing room air at 36 weeks postmenstrual age (PMA) in infants born at <32 weeks' gestation OR by 56 days postnatal age (PNA) in infants born at >32 weeks gestation OR breathing room air at discharge	Supplemental oxygen at 28 days AND need for up to 30% oxygen at 36 weeks PMA in infants born at <32 weeks' gestation OR by 56 days PNA in infants born at >32 weeks gestation OR need for up to 30% oxygen at discharge	Supplemental oxygen at 28 days AND need for >30% oxygen OR positive pressure ventilation at 36 weeks PMA in infants born at <32 weeks' gestation OR by 56 days PNA in infants born at >32 weeks gestation OR need for >30% oxygen OR positive pressure at discharge	Supplemental oxygen at 28 days AND need for >30% oxygen AND positive pressure ventilation at 36 weeks PMA in infants born at <32 weeks' gestation OR by 56 days PNA in infants born at >32 weeks gestation OR need for >30% oxygen AND positive pressure at discharge	Death
For conversion of oxygen administered by different modalities to FiO ₂ : see for example http://nicutools.org/MediCalcs/ActualO2.php3						

Parameter	Grade 0 Normal	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening	Grade 5
Persistent Pulmonary Hypertension of the Newborn (PPHN)	No signs of PPHN	Evidence of PPHN with no clinical symptoms	Evidence of PPHN with moderate clinical symptoms AND/OR an oxygenation index <25 AND/OR minor care changes required	Evidence of PPHN with severe clinical symptoms AND/OR an oxygenation index ≥25 and <40 AND/OR major care changes required	Evidence of PPHN with life threatening respiratory and/or hemodynamic compromise AND/OR oxygenation index >40 AND/OR ECMO required	Death
Pneumothorax	No evidence of pneumothorax	Evidence of pneumothorax with no clinical signs AND no care change required	Evidence of pneumothorax with minor clinical signs AND/OR minor care changes required	Evidence of pneumothorax with significant clinical signs AND/OR major care change	Evidence of pneumothorax with life-threatening respiratory and/or haemodynamic compromise AND/OR urgent major care change required	Death
Pulmonary Haemorrhage	No evidence of pulmonary haemorrhage	Evidence of pulmonary haemorrhage with no care change required	Evidence of pulmonary haemorrhage without relevant increase in pCO ₂ or decrease in oxygenation AND/OR minor care changes required	Evidence of pulmonary haemorrhage with relevant increase in pCO ₂ or decrease in oxygenation AND/OR major care change required	Evidence of pulmonary haemorrhage with life-threatening respiratory and/or hemodynamic compromise	Death
Respiratory Distress Syndrome (RDS)/Insufficiency	No evidence of respiratory distress	Clinical evidence of mildly increased respiratory distress with no apparent change in baseline functioning AND no care change required	Clinical evidence of increased respiratory distress with minor care changes required	Clinical evidence of increased respiratory distress with relevant deterioration in gas exchange AND/OR major care changes required	Clinical evidence of increased respiratory distress with life-threatening respiratory and/or haemodynamic compromise AND/OR urgent care changes required	Death
CARDIOVASCULAR						
Coagulation disorder	No coagulation abnormality	Minor biochemical coagulation abnormalities without clinical signs AND no care change required	Biochemical or clinical coagulation abnormalities with clinical signs AND/OR increased monitoring required	Biochemical or clinical coagulation abnormalities AND intervention required	Biochemical or clinical coagulation abnormalities with life threatening consequences AND/OR urgent major care changes required	Death
Congenital Heart Disease	No congenital heart disease	Minor congenital heart disease AND no treatment required	Minor congenital heart disease AND future treatment may be required	Major congenital heart disease AND no immediate treatment required	Major congenital heart disease AND immediate treatment required	Death
Hypertension	No blood pressure (BP) performed	Self-limiting hypertension AND no care change required	Persistent hypertension AND no care change required	Persistent hypertension AND need for antihypertensive medication	Persistent hypertension with life-threatening consequences	Death

Parameter	Grade 0 Normal	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening	Grade 5
Hypotension	No BP performed	Hypotension with no effect on perfusion AND no care change required	Persistent hypotension with no effect on perfusion AND/OR minor care changes required	Persistent hypotension affecting perfusion AND/OR major care changes required	Hypotension with life-threatening consequences AND/OR urgent care changes required	Death
Oedema	No oedema	Mild oedema AND no care change required	Moderate oedema AND/OR minor care changes required	Severe oedema AND/OR major care change required	Severe oedema with life threatening consequences AND/OR urgent major care changes required	Death
Patent Ductus Arteriosus (PDA)	No evidence of PDA	Diagnosis of PDA AND no care change required	PDA AND minor care changes required	Diagnosis of PDA AND major care changes required	Diagnosis of PDA AND surgical ligation required	Death
Tachycardia	No tachycardia	Self-limiting episodes of tachycardia AND asymptomatic AND no care change required	Persistent tachycardia AND minor care changes required	Persistent tachycardia resulting in non-life-threatening haemodynamic compromise AND/OR major care changes required	Persistent tachycardia resulting in life-threatening consequences AND/OR urgent major care changes required	Death
Bradycardia	No bradycardia	Self-limiting episodes of bradycardia AND no care change required	Persistent bradycardia AND minor care changes required	Persistent bradycardia resulting in non-life-threatening haemodynamic compromise AND/OR major care changes required	Persistent bradycardia resulting in life-threatening consequences AND/OR urgent major care changes required	Death
GASTROINTESTINAL						
Feeding Intolerance	No feeding intolerance	Mild feeding intolerance AND no apparent discomfort AND no care change required	Moderate feeding intolerance with apparent minor discomfort or alteration of drinking behaviour AND/OR minor care changes required	Severe feeding intolerance AND/OR major change in feeding support required	Severe feeding intolerance AND life-threatening consequences	Death
Necrotising Enterocolitis (NEC)	No gastrointestinal dysfunction	<i>See note†</i>	<i>See note†</i>	NEC confirmed AND major care change required	NEC with bowel perforation AND/OR life-threatening consequences AND/OR urgent major care change required	Death

†If NEC is not confirmed (Bell stages I): please record severity of individual symptoms (e.g. feeding intolerance)

Parameter	Grade 0 Normal	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening	Grade 5
Spontaneous Intestinal Perforation	No evidence of intestinal perforation	-----	-----	Presence of spontaneous intestinal perforation AND non-urgent medical stabilisation and surgical intervention indicated	Presence of spontaneous intestinal perforation resulting in life-threatening consequences AND urgent intervention indicated	Death
Vomiting (infantile)	No increase in vomiting from baseline	Increase in vomiting over baseline AND self-limiting	Persistent increase in vomiting over baseline with no dehydration AND/OR minor changes in feeding support required	Persistent increase in vomiting over baseline with signs of dehydration AND/OR major changes in feeding support required	Persistent increase in vomiting with life-threatening consequences	Death
Neonatal Diarrhoea	No diarrhoea	Increase of 2 - 4 stools per day over baseline OR mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline OR moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline OR severe increase in ostomy output compared to baseline AND/OR signs of dehydration	Neonatal diarrhoea with life-threatening consequences	Death
Neonatal Gastrointestinal (GI) bleeding	No GI bleeding	Mild, self-limiting bleeding AND no care change required	Moderate bleeding AND/OR minor care change required AND/OR change in monitoring required	Severe bleeding AND/OR non-life-threatening haemodynamic consequences AND/OR major care change required	GI bleeding with life-threatening consequences AND/OR urgent major care change required	Death
HEPATOBILIARY						
Jaundice	No jaundice	Mild jaundice AND no treatment or care change required	Jaundice requiring minor care change AND/OR change in monitoring	Jaundice requiring major care change	New onset acute bilirubin encephalopathy	Death
CENTRAL NERVOUS SYSTEM						
Intraventricular Haemorrhage	No intraventricular haemorrhage noted or not assessed	Germinal matrix haemorrhage	Blood in ventricle AND no ventricular enlargement	Blood in ventricle AND ventricular enlargement	Parenchymal haemorrhage AND/OR ventricular drainage required	Death
Encephalopathy including Hypoxic Ischaemic Encephalopathy	No encephalopathy	-----	Mild, transient clinical signs (as per modified Sarnat) of encephalopathy AND increased observations required AND/OR	Moderate clinical signs of encephalopathy AND/OR meeting the criteria for therapeutic hypothermia	Severe clinical signs of encephalopathy with life threatening consequences	Death

Parameter	Grade 0 Normal	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening	Grade 5
			additional care required			
Neonatal Convulsion	No convulsions	Single, self-limited suspected seizure AND no treatment required	Suspected seizures controlled with 1 anti-seizure drug	Suspected seizures uncontrolled with 1 anti-seizure drug OR requiring 2 or more anti-seizure drugs	Suspected seizures with life threatening consequences AND/OR suspected status epilepticus [‡] despite multiple anti-seizure drugs	Death related to suspected seizures
[‡] >30 minutes duration of convulsions within a 60-minute period						
Periventricular leukomalacia (PVL)	No PVL OR not assessed	Transient periventricular echo densities persisting for > 7 days and resolving completely	Transient periventricular echo densities evolving into small localised frontoparietal cysts or persistent diffuse echodensities	Periventricular echodensities, evolving into extensive cystic periventricular lesions OR densities extending into the deep white matter	-----	-----
Infant Irritability	No irritability	Mild, self-limiting irritability not affecting feeding and sleeping	Moderate irritability AND minor changes in feeding and sleeping behaviour AND/OR minor additional care required	Severe irritability with major changes in feeding behaviour and/or requiring support other than oral feeding AND/OR requiring long term medical treatment	Life threatening irritability with loss of autonomic control of temperature or heart rate AND/OR urgent care changes required	-----
Retinopathy of Prematurity (ROP)	Normal vascularisation or not assessed	Incomplete vascularisation AND no care changes required	Pre-threshold ROP AND/OR more frequent ophthalmic monitoring than routine	Threshold ROP AND/OR major care changes required	Unilateral retinal detachment	Blindness (bilateral retinal detachment,
GENITOURINARY/RENAL						
Renal Dysfunction	Wet nappies/diapers documented	Evidence of mild renal dysfunction	Evidence of moderate renal dysfunction	Evidence of severe renal dysfunction	Evidence of life-threatening renal dysfunction	Death
INFECTIONS/INFESTATIONS						
Sepsis (Culture positive or Culture negative)	No signs or symptoms of sepsis	Evaluation for sepsis AND no anti-infectives started	Suspected sepsis with mild or ambiguous signs AND/OR anti-infectives initiated	Sepsis with severe signs AND/OR supportive care initiated or escalated AND/OR anti-infective treatment escalated AND no signs of septic shock and/or meningitis	Sepsis with life-threatening consequences AND urgent major care change required	Death

Parameter	Grade 0 Normal	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening	Grade 5
BLOOD/ELECTROLYTE/METABOLIC DISORDERS/LABORATORY ABNORMALITIES						
Only to be reported if deemed clinically significant						
Anaemia	No anaemia	Anaemia AND according to clinical judgment no additional monitoring required	Anaemia with more frequent monitoring required	Anaemia with no clinical signs AND requires blood transfusion	Anaemia with clinical signs of shock AND requires blood transfusion	Death
Electrolyte/Metabolic Disorders	No electrolyte/metabolic disorder	Electrolyte/metabolic disorder AND according to clinical judgment no treatment or additional monitoring required	Electrolyte/metabolic disorder with no systemic signs AND more frequent monitoring required AND/OR minor care changes required	Electrolyte/metabolic disorder requiring intravenous correction	Electrolyte/metabolic disorder with systemic signs AND/OR urgent invasive treatment required	Death
Leukopaenia	No leukopaenia	Leukopaenia AND according to clinical judgment no additional monitoring required	Leukopaenia with more frequent monitoring required	Clinically relevant leukopaenia requiring treatment AND/OR major care changes required	Life threatening leukopaenia AND/OR urgent major care change required	Death
Neutropaenia	No neutropaenia	Neutropaenia AND according to clinical judgment no additional monitoring required	Neutropaenia with more frequent monitoring required	Clinically relevant neutropaenia AND/OR GCSF treatment required AND/OR major care changes required	Life-threatening neutropaenia AND/OR white cell transfusion required AND/OR urgent major care changes required	Death
Thrombocytopenia	No thrombocytopenia	Thrombocytopenia AND according to clinical judgment no additional monitoring required	Thrombocytopenia with more frequent monitoring required	Thrombocytopenia with non-life-threatening bleeding	Life-threatening thrombocytopenia with associated life-threatening bleeding AND/OR platelet transfusion required AND/OR urgent major care changes required	Death
OTHER						
Administration site complication	No administration site complication	Painless oedema	Erythema with associated symptoms	Ulceration AND/OR necrosis AND/OR severe tissue damage AND/OR operative intervention indicated	Life-threatening consequences AND/OR urgent intervention required	Death

Parameter	Grade 0 Normal	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening	Grade 5
Neonatal rash	No rash	Localised rash	Diffuse rash AND/OR target lesions	Diffuse rash or vesicles AND/OR limited number of bullae AND/OR superficial ulcerations of mucous membrane limited to one site	Extensive or generalised bullous lesions AND/OR ulceration of mucous membranes involving ≥2 distinct mucosal sites AND/OR Stevens Johnson syndrome AND/OR toxic epidermal necrosis	Death
Congenital Anomalies	No congenital abnormalities	Minor congenital abnormality with no impairment of function	Minor congenital abnormality with no impairment of function AND future treatment may be needed	Major congenital abnormality with impairment of function AND no immediate treatment needed but future treatment may be needed	Major congenital abnormality with impairment of function AND urgent treatment needed	Death
Neonatal Abstinence Syndrome (NAS)	No history of NAS	NAS with signs AND no medical treatment required	NAS controlled with a single drug	NAS controlled with two drugs	NAS with seizures	Death
Any other AE	-----	Mild presentation AND asymptomatic or mild symptoms AND clinical or diagnostic observations only AND no change in baseline age-appropriate behaviour* AND no change in baseline care or monitoring indicated	Moderate presentation resulting in minor changes of baseline age-appropriate behaviour* AND/OR minor changes in baseline care or monitoring required***	Severe presentation resulting in major changes of baseline age-appropriate behaviour* or non-life-threatening changes in basal physiological processes** AND/OR major change in baseline care or monitoring required****	Life-threatening presentation resulting in life threatening changes in basal physiological processes** AND/OR urgent major change in baseline care required	Death

*Age-appropriate behaviour refers to oral feeding behaviour, voluntary movements and activity, crying pattern, social interactions and perception of pain. **Basal physiological processes refer to oxygenation, ventilation, tissue perfusion, metabolic stability organ functioning. ***Minor care changes constitute: brief, local, non-invasive or symptomatic treatments. ****Major care changes constitute: surgery, addition of long-term treatment, upscaling care level

BP = blood pressure; GI = gastrointestinal; Hb = haemoglobin; NEC = necrotising enterocolitis; PDA = patent ductus arteriosus; PMA = postmenstrual age; PNA = postnatal age
PPHN = persistent pulmonary hypertension of the newborn; PVL = periventricular leukomalacia; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity