



Oak Hill Bio

Training Module:
International Neonatal Consortium's
Neonatal Adverse Event Severity Scale

INC 2020 training module adapted for use by Oak Hill Bio

Introduction

An **adverse event (AE)** is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE is a term that is a unique representation of a specific event used for **medical documentation and scientific analyses**.

Indicating the **severity** of an AE helps to understand the importance of an AE and facilitates comparison of AEs among trials and centers. It is commonly done in 5 grades: **mild, moderate, severe, life-threatening and death**.

INC NAESS provides **criteria for severity assessment** of AEs which have been defined by consensus.

However, AE severity is **not synonymous** with AE seriousness.

INC NAESS: Generic and specific severity criteria

Generic severity criteria have been developed as a framework for severity grading in every neonatal adverse event.

There are **disease specific severity criteria** provided for 35 common neonatal AEs in this first version of INC NAESS.

- ➡ If specific criteria are available: use the specific criteria for severity grading.
- ➡ If no specific criteria are available: apply the generic criteria for severity grading.

INC NAESS: Generic and specific severity criteria

AEs in INC neonatal AE severity scale	
Neurological	Respiratory
Neonatal Convulsion	Infantile Apnea
Neonatal Epileptic Seizure	Neonatal Respiratory Insufficiency
Neonatal Intraventricular Hemorrhage	Neonatal Respiratory Distress Syndrome
Retinopathy of Prematurity	Neonatal Pulmonary Hemorrhage
Hypoxic Ischemic Encephalopathy	Persistent Pulmonary Hypertension of the Newborn
Periventricular Leukomalacia	Neonatal Pneumothorax
Infant Irritability	Bronchopulmonary Dysplasia
Infant Sedation	Gastrointestinal
Cardiovascular	Necrotizing Enterocolitis
Neonatal Hypotension	Neonatal Diarrhea
Neonatal Hypertension	Infantile Vomiting
Neonatal Sinus Tachycardia	Feeding Intolerance
Neonatal Sinus Bradycardia	Neonatal Gastrointestinal Bleeding
Neonatal Tachyarrhythmia	Neonatal Spontaneous Intestinal Perforation
Neonatal Bradyarrhythmia	Neonatal Constipation
Neonatal Edema	General
Neonatal Coagulation Disorder	Neonatal Rash
Infectious	Neonatal Administration Site Complication
Neonatal Culture Positive Sepsis	Neonatal Fever
Neonatal Culture Negative Sepsis	

➡ If AE is any of these diagnoses: apply the respective specific criteria

Generic criteria

In INC NAESS, severity grading of neonatal adverse events is based on 3 main components:

- **Changes in age-appropriate behavior** (e.g. feeding behavior, crying, voluntary movements, perception of pain, social interactions, ...)
- **Changes in basal physiological processes** (e.g. oxygenation, ventilation, tissue perfusion, metabolic stability, organ functioning)
- **Changes in care or monitoring**
 - **Minor care changes**: e.g. brief, local, non-invasive or symptomatic treatments
 - **Major care changes**: e.g. surgery, addition of long-term treatment, upscaling care level

For all components, only AE-related **changes from baseline condition** are considered.

- e.g., Incapacity to feed orally or need for ventilatory support should not be considered in the severity assessment of a given AE if they were already present before the occurrence of the AE and if they are unaffected by the AE.

Generic criteria

The 3 main components are combined in the generic severity scale of INC NAESS:

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild	Moderate	Severe	Life threatening	Death
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no change in baseline age-appropriate behavior*; no change in baseline care or monitoring indicated***	Moderate; resulting in minor changes of baseline age-appropriate behavior*; requiring minor changes in baseline care or monitoring***	Severe; resulting in major changes of baseline age-appropriate behavior* or non-life threatening changes in basal physiological processes**; requiring major change in baseline care or monitoring***	Life-threatening; Resulting in life-threatening changes in basal physiological processes**; requiring urgent major change in baseline care***	Death related to AE
*Age-appropriate behavior refers to oral feeding behavior, voluntary movements and activity, crying pattern, social interactions and perception of pain. **Basal physiological processes refer to oxygenation, ventilation, tissue perfusion, metabolic stability and 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 If the different factors of this scale result in conflicting severity grades, the highest grade should be reported.				

Age-appropriate behavior

Basal physiological processes

Care and monitoring

Generic criteria



IMPORTANT: the different components are combined by an “OR” relationship.

If the different components are conflicting, **the highest grade** should be reported.

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild	Moderate	Severe	Life threatening	Death
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no change in baseline age-appropriate behavior*; no change in baseline care or monitoring indicated ***	Moderate; resulting in minor changes of baseline age-appropriate behavior*; requiring minor changes in baseline care or monitoring ***	Severe; resulting in major changes of baseline age-appropriate behavior* or non-life threatening changes in basal physiological processes**; requiring major change in baseline care or monitoring ***	Life-threatening; Resulting in life-threatening changes in basal physiological processes**; requiring urgent major change in baseline care ***	Death related to AE
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e.g.

A given AE requires surgery (a **major care change** from baseline), however does not affect age-appropriate behaviour or basal physiological processes



grade as SEVERE

Specific criteria

For all 35 listed AEs disease specific criteria have been defined. These are listed in INC NAESS v1.0.

e.g.

EVS and MedDRA terms linked to AE

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild	Moderate	Severe	Life threatening	Death
Neonatal Convulsion Definition C154952 10028932 : Sudden, involuntary, rapid, rhythmic or stereotyped skeletal muscular contractions in a newborn.				
Single, self-limited suspected seizure, no treatment	Suspected seizures controlled with 1 anti-seizure drug (no recurrence within 3 days after treatment)	Suspected seizures uncontrolled with 1 anti-seizure drug (recurrence within 3 days after treatment or requiring 2 or more anti-seizure drugs)	Suspected seizures with life-threatening consequences (e.g. need for ventilation); suspected status epilepticus* despite multiple anti-seizure drugs	Death related to suspected seizures
* >30min duration of convulsions within any 60-minute period				

- ➡ If different components indicate conflicting severity, the **highest grade** should be reported.
- ➡ A single dash (-) indicates a severity grade is not available. **Not all grades are appropriate for all AEs.**



Examples

Example 1

Several hours after vaccination, a monitored preterm baby experienced a clinically significant apnea. The baby's oxygen saturation dropped (SpO_2 56%) and baby became moderately bradycardic (85 beats/min).

Tactile stimulation and repositioning did not result in improvement. After about 2 minutes without effective breathing mask ventilation was initiated. After a few positive pressure ventilations, the baby regained a normal breathing pattern.

A single loading dose of caffeine was administered to prevent reoccurrences.

- ➡ What is the adverse event (AE) term?
- ➡ Which severity criteria would you apply to the reported AE?
- ➡ What is the AE severity?

Example 1

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild	Moderate	Severe	Life threatening	Death
Infantile Apnea Definition C154938 10077322: <i>Cessation of air flow.</i>				
Self-limiting apnea	Apnea responsive to stimulation or intermittent FiO ₂ -increase.	Apnea requiring stimulation and sustained FiO ₂ increase; requiring non-invasive ventilation; *** reoccurrences requiring start of or relevant increase in dose of respiratory stimulants or other major care changes ***	Life-threatening respiratory and/or hemodynamic compromise; (semi-)urgent intubation required	Death

Care and monitoring

- ➡ Apnea
- ➡ **Specific** criteria are available for **Infantile Apnea** (incl. Apnea of Prematurity)
- ➡ This would be considered as a **SEVERE** AE

Example 2

An extremely preterm conventionally ventilated baby in a neuroprotection trial develops a pulmonary hemorrhage. A large quantity of clear red secretions is aspirated from the tube.

Heart rate increases, but respiratory condition remains stable (PCO_2 and PO_2 do not change significantly). Blood pressure drops and capillary refill time is lengthened to 5 seconds. Hemoglobin decreases until 6.5 g/dL.

PEEP is increased to 6.5 cm H_2O and the baby is urgently transfused.

- ➡ What is the AE term?
- ➡ Which severity criteria would you apply to the reported AE?
- ➡ What is the AE severity?

Example 2

Neonatal Pulmonary Hemorrhage				
Definition C154936	10082199 (v22.0): <i>Bleeding in the respiratory tract of a neonate.</i>			
Limited hemorrhagic secretion in ET tube	Hemorrhagic secretion in ET tube; without relevant increase in PCO ₂ or decrease in oxygenation ^{**} requiring minor changes in care ^{***} (e.g. increase PEEP)	Hemorrhagic secretion in ET tube; with relevant increase in PCO ₂ or decrease in oxygenation; requiring major change in ventilatory support or transfusion ^{***}	Life-threatening respiratory and/or hemodynamic compromise ^{**}	Death

Basal physiological processes

Care and monitoring

Several criteria result in conflicting severity assessment: the **highest** possible grade should be reported.

- ➡ Pulmonary Hemorrhage
- ➡ **Specific** criteria for **Neonatal Pulmonary Hemorrhage**
- ➡ This would be considered as a **LIFE THREATENING** AE

Example 3

A ventilated newborn with a congenital cardiopathy in a surgical trial, develops respiratory insufficiency 1 day after surgery: PO_2 decreases and PCO_2 increases, requiring a steadily increase of the ventilator pressures, rate and FiO_2 . An X-ray of the chest reveals a pleural effusion.

As the effusion increases over the following days, a pleural drainage is placed. Analysis of the pleural fluid suggests a chylous origin.

Respiratory condition stabilizes after drainage, however chest drain remains necessary for 2 weeks. During these 2 weeks there is continuous flow of chylous fluid, requiring suppletion with albumin. When enteral feedings are initiated, baby is started on a MCT formula.

- ➡ What is the AE term?
- ➡ Which severity criteria would you apply to the reported AE?
- ➡ What is the AE severity?

Example 3

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild	Moderate	Severe	Life threatening	Death
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no change in baseline age-appropriate behavior*; no change in baseline care or monitoring indicated	Moderate; resulting in minor changes of baseline age-appropriate behavior*; requiring minor changes in baseline care or monitoring***	Severe; resulting in major changes of baseline age-appropriate behavior* or non-life threatening changes in basal physiological processes**; requiring major change in baseline care or monitoring***	Life-threatening; Resulting in life-threatening changes in basal physiological processes**; requiring urgent major change in baseline care	Death related to AE
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steady increase of PCO₂
and decrease of PO₂

need for pleural drainage,
long term MCT diet

- ➡ Chylothorax
- ➡ No specific criteria available: **Generic** criteria should be used.
- ➡ This would be considered as a **SEVERE** AE

Example 4

An extremely preterm baby on full parenteral feeds develops hyponatremia (peak 151 mEq/L). The baby is asymptomatic. The humidity in the incubator is increased to 60% and an additional 10mL/kg/d of glucose 5% is added to the intravenous fluid.

- ➡ What is the AE term?
- ➡ Which severity criteria would you apply to the reported AE?
- ➡ What is the AE severity?

Example 4

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild	Moderate	Severe	Life threatening	Death
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only;* no change in baseline age-appropriate behavior*; no change in baseline care or monitoring indicated	Moderate; resulting in minor changes of baseline age-appropriate behavior*; requiring minor changes in baseline care or monitoring***	Severe; resulting in major changes of baseline age-appropriate behavior* or non-life threatening changes in basal physiological processes**; requiring major change in baseline care or monitoring****	Life-threatening; Resulting in life-threatening changes in basal physiological processes**; requiring urgent major change in baseline care	Death related to AE
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Asymptomatic, biochemical AE

Alteration of humidity in incubator and adjustment of fluid administration

Several criteria result in conflicting severity assessment: the **highest possible grade** should be reported.

Example 4

- ➡ Hybernatriemia
- ➡ No specific criteria available: **Generic** criteria should be used.
- ➡ This would be considered as a **MODERATE** AE
- ➡ Some people might argue that this is not an AE at all, as hypernatremia is a common finding in extremely preterm neonates which probably does not relate to any drug or treatment.



It is important to remember:

Severity assessment is unaffected by whether a plausible clausal relationship exists between the drug and the AE.

Event severity can be assessed irrespective of causality.



Thank you for going through this training module.

OHB has incorporated INC NAESS into the  naetohb.com online app.
Please submit questions or comments on the online app through the [Contact Us](#) page.