Maternal and Fetal Adverse Event Terminology (MFAET) v1.1, 2022

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Guidance on the use of the MFAET severity grading criteria[1]

Adverse Events

An adverse event (AE) is "any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment"[2]. Each AE is reviewed to determine (1) whether it meets the definition of 'serious'[2]:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or results in prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event or reaction

(2) whether it is possibly, probably or definitely related to the intervention (i.e. is a reaction). The event is then classified as:

	Serious	Reaction
Adverse event (AE)	x	x
Adverse reaction (AR)	x	✓
Serious adverse event (SAE)	✓	x
Serious adverse reaction (SAR)	✓	✓

Grading the severity of AEs provides additional safety information. It does not replace the regulatory requirements for AE assessment described above.

Adverse Event Terms

The terms used in these criteria reference the corresponding Lowest Level Terms (LLTs) from the Medical Dictionary for Regulatory Activities (MedDRA)[3].

Definitions

A brief definition is provided to clarify the meaning of each AE term. These definitions are not designed to be used for clinical diagnosis.

Adverse Event Grades

Grade refers to the severity of the AE. The grading of defined maternal AEs is based on the generic criteria from the NCI Common Terminology Criteria for Adverse Events (CTCAE), adapted for pregnancy. The grading of defined fetal AEs is based on the 'generic grading criteria for fetal adverse events' (page 9).

AEs are graded from 1 to 5:

Grade 1: mild

Grade 2: moderate

Grade 3: severe or medically significant

Grade 4: life-threatening

Grade 5: death

If an AE fulfils the criteria for more than one grade of severity, the highest applicable grade should be used.

Not all grades are appropriate for all AEs. A single dash (-) indicates that grade is not defined for a given AE.

Several fetal AEs only include definitions for grades 2 (moderate) and 4 (life-threatening). This is because current methods of investigating the fetus and predicting short- and long-term prognosis are often not sufficient to differentiate between mild and moderate events and between severe and life-threatening events.

Death resulting from any AE is graded as 5.

A semicolon indicates 'or' within the description of a grade.

Maternal and Fetal Adverse Events

Some AEs have the potential to differentially affect the pregnant woman and the fetus (haemorrhage in pregnancy, preterm premature rupture of membranes, chorioamnionitis and anaemia of pregnancy). It is not possible to have separate AE terms for the mother and the fetus within the structure of MedDRA, so these events should be reported using a single MedDRA term, with maternal and fetal severity gradings recorded within the trial records.

Maternal AEs not included in these criteria

Maternal procedural complications, such as pain and infection, should be identified by the appropriate MedDRA Lowest Level Term and graded according to CTCAE criteria.

Maternal thromboembolic events during pregnancy and the puerperium should be identified by the appropriate MedDRA Lowest Level Term (LLT *Venous thrombosis in pregnancy,* LLT *Postpartum venous thrombosis,* or LLT *Obstetrical pulmonary embolism*) and graded according to the CTCAE criteria for 'Thromboembolic event'.

Neonatal Adverse Events

Neonatal AEs should be graded using the International Neonatal Consortium (INC) Neonatal AE Severity Scale (NAESS).[4]

[1]Adapted from the introductory section to the CTCAE v5.0. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, 2017.

[2]International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use. ICH Harmonised Tripartite Guideline. Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting E2D. 2003.

[3]https://www.meddra.org/

[4]https://ncit.nci.nih.gov/ncitbrowser/ajax?action=create_src_vs_tree&vsd_uri=http://evs.nci.nih.gov/valueset/INC/C154914

MATERNAL ADVERSE EVENTS

Maternal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Haemorrhage in pregnancy: maternal MedDRA LLT: *Haemorrhage in pregnancy*	Staining, streaking of blood spotting noted on underwear or sanitary protection; blood loss < 50ml that has settled	Blood loss of 50 to <250ml with no signs of clinical shock	Blood loss of 250-1000ml with no signs of clinical shock	Blood loss >1000ml; signs of clinical shock
Definition: Bleeding from or in the genital tract during pregnancy, prior to the birth of the baby				
Postpartum haemorrhage MedDRA LLT: *Postpartum haemorrhage*	Estimated blood loss 501-1000ml without haemodynamic instability	Estimated blood loss 1001-2000ml; estimated blood loss 501-1000ml with haemodynamic instability	Estimated blood loss >2000ml; transfusion <5 units packed red cells; balloon tamponade; surgical intervention (excluding hypogastric or uterine artery ligation or hysterectomy); interventional radiology	Hysterectomy; hypogastric or uterine artery ligation; shock; transfusion of 5 units or more of packed red cells; coagulopathy
Definition: The loss of 500ml or more of blood from the genital tract within 24 hours of the birth of a baby				
Anaemia of pregnancy: maternal MedDRA LLT: *Anaemia of pregnancy*	Haemoglobin 7.0-10.5 g/dl; 4.4-6.5 mol/l; 70-105 g/l and no intervention indicated	Haemoglobin 7.0-10.5 g/dl; 4.4-6.5 mol/l; 70-105 g/l and haemodynamically stable but oral iron indicated	Haemoglobin <7.0 g/dl; <4.4 mmol/l; <70 g/l; transfusion indicated	Urgent intervention indicated; imminent cardiac compromise
Definition: Disorder characterised by a reduction in the amount of haemoglobin in the blood occurring during pregnancy or the puerperium, in the absence of haemoglobinopathies				

Maternal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Gestational hypertension MedDRA LLT: *Gestational hypertension*	Systolic BP 140-149 mmHg; diastolic BP 90-99 mmHg	Systolic BP 150-150 mmHg; diastolic BP 100-109 mmHg	-	-
Definition: New onset hypertension (diastolic BP 90 mmHg or more, systolic BP 140 mmHg or more) presenting after 20 weeks' gestation in the absence of indicators of pre-eclampsia				
Pre-eclampsia MedDRA LLT: *Pre-eclampsia*	Systolic BP 140-149 mmHg with significant proteinuria and without severe signs; diastolic BP 90-99 mmHg with significant proteinuria and without severe signs	Systolic BP 150-159 mmHg with significant proteinuria and without severe signs; diastolic BP 100-109 mmHg with significant proteinuria and without severe signs	Systolic BP >160 mmHg; diastolic BP >110 mmHg; platelets <100,000; severe persistent right upper quadrant or epigastric pain unresponsive to medication with no other cause; AST or ALT 2x upper limit of normal for pregnancy or more; serum creatinine >1.1 mg/dl; new-onset cerebral or visual disturbance	Pulmonary oedema; stroke; positive inotrope support; myocardial ischaemia or infarction; platelets <50,000; HELLP syndrome (haemolysis, elevated liver enzymes, low platelets)
Definition: New onset hypertension (diastolic 90 mmHg or more, systolic BP 140 mmHg or more) presenting after 20 weeks' gestation with one or more indicator of pre-eclampsia				
Eclampsia MedDRA LLT: *Eclampsia*	-	-	-	Eclampsia
Definition: Generalised maternal seizures between 20 weeks' gestation and up to 28 days after delivery, not attributable to any other condition				

Maternal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Preterm premature rupture of membranes: maternal MedDRA LLT: *Preterm premature rupture of membranes*	-	Preterm premature rupture of membranes	-	-
Definition: The rupture of membranes before labour and before 37 weeks of gestation				
Premature labour MedDRA LLT: *Premature labour*	-	Symptoms of premature labour	-	-
Definition: Symptoms of labour before 37 weeks of gestation, with or without preterm delivery				
Chorioamnionitis: maternal MedDRA LLT: *Chorioamnionitis*	Histological, biochemical or microbiological evidence of chorioamnionitis from placental or amniotic fluid examination in the absence of clinical signs in the fetus or mother	Maternal fever of 38-40 °C (100.4-104.0 °F) and: maternal leukocytosis (>15,000 cells/mm^3); fetal tachycardia (>160bpm); maternal tachycardia (>100bpm); foul odour of amniotic fluid; uterine tenderness between contractions	Clinically or pathologically diagnosed chorioamnionitis and fever >40 °C (104.0 °F) for <24 hours	Clinically or pathologically diagnosed chorioamnionitis and: fever >40 °C (104.0 °F) for >24 hours; septic shock; coagulopathy; adult respiratory distress syndrome;
Definition: Inflammation of the chorion, amnion, and/or placenta				

Maternal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Puerperal infection MedDRA LLT: *Puerperal infection*	-	Genital tract infection in the absence of severe or life-threatening symptoms, oral antibiotics indicated	Genital tract infection with severe symptoms requiring intravenous antibiotics	Genital tract infection and: septic shock; organ failure; requirement for admission to intensive care
Definition: Infection of the genital tract occurring from the time of giving birth to 6 weeks postnatally, excluding vaginal yeast infection				
Amniotic fluid embolism MedDRA LLT: *Amniotic fluid embolism*	-	-	Clinical diagnosis of amniotic fluid embolism in the absence of life-threatening features	Clinical diagnosis of amniotic fluid embolism with cardiac arrest; coma; seizures; disseminated intravascular coagulation; requirement for admission to intensive care unit
Definition: Embolisation of amniotic fluid into the maternal circulation				
Retained placenta or membranes MedDRA LLT: *Retained placenta or membranes*	Passage of placental tissue or membranes >24 hours after delivery, intervention not indicated	Minimal, local, or non-invasive intervention required to deliver the placenta following vaginal birth (not including routine active management); manual removal of placenta	Surgical evacuation of the uterus	-
Definition: Delayed delivery of the placenta and/or membranes according to local criteria				

FETAL ADVERSE EVENTS

Generic grading criteria for fetal adverse events				
Grade 1 (mild)	**Grade 2 (moderate)**	**Grade 3 (severe)**	**Grade 4 (life-threatening)**	**Grade 5 (death)**
Clinical observation of uncertain significance; resolves spontaneously with low risk of long-term consequences	Likely to resolve spontaneously with low risk of long-term consequences; requires increased frequency of monitoring, but less than once a week; requires additional tests	Requires increased frequency of monitoring, once a week or more; likely to lead to significant neonatal morbidity	Likely to lead to fetal injury or permanent disability; likely to lead to neonatal death; requiring a substantive change in management including changing the course of an interventional procedure or necessitating delivery	Fetal death

Fetal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Fetal fluid collection MedDRA LLT: *Fetal compartment fluid collection*	-	New onset isolated pericardial, pleural, or peritoneal fluid collection or skin oedema, which is not life-threatening	New onset accumulation of fluid in at least two fetal compartments (hydrops) which resolves spontaneously	New onset accumulation of fluid in at least two fetal compartments (hydrops) which is sustained; life-threatening isolated pericardial, pleural, or peritoneal fluid collection
Definition: The collection of non-haemorrhagic fluid in one or more fetal compartment (pericardial space, pleural space, peritoneal cavity, and/or skin oedema)				
Fetal bradycardia MedDRA LLT: *Fetal bradycardia*	-	A decrease in the fetal heart rate of more than 30 beats per minute to a level below the lower limit of normal for gestation according to local criteria, lasting for less than 3 minutes	-	A decrease in the fetal heart rate of more than 30 beats per minute to a level below the lower limit of normal for gestation, according to local criteria, lasting for more than 3 minutes; a decrease in the fetal heart rate of more than 30 beats per minute requiring a change in the course of an interventional procedure or necessitating delivery
Definition: A decrease in the fetal heart rate of more than 30 beats per minute to a level below the lower limit of normal for gestation according to local criteria, lasting for more than 1 minute				

Fetal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Fetal tachyarrhythmia MedDRA LLT: *Fetal tachyarrhythmia*	Resolves spontaneously with a low risk of long-term consequences	-	-	Likely to lead to fetal injury or permanent disability; requiring a substantive change in management including changing the course of an interventional procedure or necessitating delivery
Definition: A sustained abnormal fetal heart rhythm with a fetal heart rate above the upper limit of normal for gestation according to local criteria				
Fetal cardiac function abnormalities MedDRA LLT: *Cardiac function test abnormal*	-	-	Non-life-threatening signs of cardiac failure, including cardiomegaly and valve regurgitation	Likely to lead to fetal injury or permanent disability; requiring a substantive change in management including changing the course of an interventional procedure or necessitating delivery
Definition: An abnormality in fetal cardiac function				
Fetal musculoskeletal imaging abnormal MedDRA LLT: *Fetal musculoskeletal imaging abnormal*	-	Limb or digit deformity not expected to cause long-term disability	Limb or digit loss; limb or digit deformity expected to cause long-term disability	-
Definition: New loss or deformity of a fetal limb or digit				

Fetal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Fetal brain scan abnormal MedDRA LLT: *Brain scan abnormal*	-	An abnormality of uncertain neurological significance which does not fulfil the criteria for Level 4 (life-threatening)	-	Haemorrhage; ischaemia; an abnormality likely to lead to permanent disability; an abnormality requiring a substantive change in management including changing the course of an interventional procedure or necessitating delivery
Definition: A newly identified change on fetal brain imaging, outside the scope of normal brain development				
Fetal movement disorders MedDRA LLT: *Fetal movement disorder*	-	-	-	A complete and sustained loss of fetal movement including breathing, swallowing, and limb movements; sustained fetal hypertonia or abnormal fetal posture suggestive of neurological damage
Definition: A new abnormality of fetal movement, observed on ultrasound scan				

Fetal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Fetal gastrointestinal tract imaging abnormal MedDRA LLT: *Fetal gastrointestinal tract imaging abnormal*	-	Hyperechogenic dilated bowel	Imaging appearance highly suggestive of bowel necrosis or perforation	-
Definition: New abnormality in the appearance of the fetal gastrointestinal tract on imaging				
Fetal renal imaging abnormal MedDRA LLT: *Fetal renal imaging abnormal*	Renal pelvis antero-posterior diameter 4 to <7mm in the second trimester; renal pelvis antero-posterior diameter 7 to <9mm in the third trimester	Reduced diuresis, as indicated by reduced bladder filling and/or oligohydramnios not attributable to another cause; hyperechogenic kidney(s); abnormal kidney size; renal pelvis antero-posterior diameter 7 to 10mm in the second trimester; renal pelvis antero-posterior diameter 9 to 15mm in the third trimester	Renal pelvis antero-posterior diameter >15mm in the third trimester	Sustained anuria, as evidenced by severe oligohydramnios or anhydramnios, which is likely to result from renal failure and which is either life-threatening or expected to have long-term consequences
Definition: New abnormality in the structure or function of the fetal kidney(s) on imaging				
Fetal neoplasm MedDRA LLT: *Neoplasm*	-	-	Newly diagnosed fetal neoplasm which is not life-threatening	Newly diagnosed life-threatening fetal neoplasm
Definition: A benign or malignant abnormal fetal mass (excluding any collection of blood or fluid, or haematoma)				

Fetal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Fetal structural abnormalities: not otherwise classified MedDRA LLT: *Fetal malformation*	-	-	Newly diagnosed fetal structural abnormality which is not life-threatening	Newly diagnosed life-threatening fetal structural abnormality
Definition: A new abnormality in the structural development of the fetus, not classified elsewhere				
Haemorrhage in pregnancy: fetal MedDRA LLT: *Haemorrhage in pregnancy*	-	-	-	Evidence of fetal compromise including pathological cardiotocograph, signs of fetal anaemia or need for delivery
Definition: Bleeding from or in the maternal genital tract during pregnancy, prior to the birth of the baby				
Anaemia of pregnancy: fetal MedDRA LLT: *Anaemia of pregnancy*	-	-	-	Pathological cardiotocograph; fetal indication for delivery
Definition: A disorder characterised by a reduction in the amount of haemoglobin in the maternal blood occurring during pregnancy, in the absence of haemoglobinopathies				

Fetal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Preterm premature rupture of membranes: fetal MedDRA LLT: *Preterm premature rupture of membranes*	Membrane separation without confirmed rupture of membranes; inter-twin membrane disruption not leading to amniotic fluid leakage	Confirmed rupture of membranes between 32+0 and 33+6 weeks of gestation	Confirmed rupture of membranes with persistently reduced amniotic fluid, as identified by a deepest vertical pool of less than 2 cm on ultrasound scan, between 22 and 32 weeks of gestation	Confirmed rupture of membranes with persistently reduced amniotic fluid, as identified by a deepest vertical pool of less than 2 cm on ultrasound scan, < 22 weeks of gestation
Definition: The rupture of membranes before labour and before 37 weeks of gestation				
Chorioamnionitis: fetal MedDRA LLT: *Chorioamnionitis*	-	Clinically or pathologically diagnosed chorioamnionitis with fetal tachycardia >160 beats/min but without a pathological cardiotocograph	-	Clinically or pathologically diagnosed chorioamnionitis with pathological cardiotocograph; Clinically or pathologically diagnosed chorioamnionitis with fetal indication for substantive change in management, including need for delivery
Definition: Inflammation of the chorion, amnion, and placenta				

Fetal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Abnormal fetal growth MedDRA LLT: *Fetal growth abnormality*	-	New onset increase in fetal growth velocity from that which would be expected, which is likely to have adverse consequences or results in a substantive change in management, including necessitating delivery	-	New onset decrease in fetal growth velocity from that which would be expected, which is likely to have adverse consequences or results in a substantive change in management, including necessitating delivery
Definition: A change in fetal growth velocity from that which would be expected				
Fetal procedural haemorrhage MedDRA LLT: *Procedural haemorrhage*	-	Haemorrhage which does not have life-threatening physiological consequences for the fetus and which does not require intervention	-	Haemorrhage which results in life-threatening consequences for the fetus; Haemorrhage requiring a substantive change in management including necessitating delivery
Definition: A local or remote haemorrhage occurring after, and as a result of, a fetal interventional procedure, including haemorrhage in the fetus, feto-maternal haemorrhage and maternal haemorrhage				

Fetal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Fetal post-procedural haemorrhage MedDRA LLT: *Post procedural haemorrhage*	-	Haemorrhage which does not have life-threatening physiological consequences for the fetus and which does not require intervention	-	Haemorrhage which results in life-threatening consequences for the fetus; Haemorrhage requiring a substantive change in management including necessitating delivery
Definition: A local or remote haemorrhage occurring after, and as a result of, a fetal interventional procedure, including haemorrhage in the fetus, feto-maternal haemorrhage and maternal haemorrhage				
Fetal intra-operative injury MedDRA LLT: *Intraoperative injury*	-	Unintended damage to a fetal organ, not requiring treatment	Unintended damage to a fetal organ which requires future intervention but is not life-threatening and is not expected to result in long-term disability	Unintended damage to a fetal organ which is life-threatening or is expected to result in long-term disability
Definition: Unintended damage to the fetus occurring as a result of fetal interventional procedure (excluding the effects of haemorrhage)				