



# Development of standard definitions and grading for Maternal and Fetal Adverse Event Terminology

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**Abstract**

**Objective:** Adverse event (AE) monitoring is central to assessing therapeutic safety. The lack of a comprehensive framework to define and grade maternal and fetal AEs in pregnancy trials severely limits understanding risks in pregnant women. We created AE terminology to improve safety monitoring for developing pregnancy drugs, devices and interventions.

**Method:** Existing severity grading for pregnant AEs and definitions/indicators of 'severe' and 'life-threatening' conditions relevant to maternal and fetal clinical trials were identified through a literature search. An international multidisciplinary group identified and filled gaps in definitions and severity grading using Medical Dictionary for Regulatory Activities (MedDRA) terms and severity grading criteria based on Common Terminology Criteria for Adverse Event (CTCAE) generic structure. The draft criteria underwent two rounds of a modified Delphi process with international fetal therapy, obstetric, neonatal, industry experts, patients and patient representatives.

**Results:** Fetal AEs were defined as being diagnosable in utero with potential to harm the fetus, and were integrated into MedDRA. AE severity was graded independently for the pregnant woman and her fetus. Maternal ( $n = 12$ ) and fetal ( $n = 19$ ) AE definitions and severity grading criteria were developed and ratified by consensus.

**Conclusions:** This Maternal and Fetal AE Terminology version 1.0 allows systematic consistent AE assessment in pregnancy trials to improve safety.

**Key points****What's already known about this topic?**

- Adverse event (AE) monitoring is central to assessing therapeutic safety. The lack of a comprehensive AE framework in pregnancy trials severely limits understanding risks in pregnant women

**What does this study add?**

- Through international consensus we systematically developed definitions and severity grading for maternal and foetal AEs: Maternal and Fetal AE Terminology Version 1.0. New fetal AE definitions were adopted by the Medical Dictionary for Regulatory Activities. This terminology should be used to monitor safety in pregnancy trials

**1 | INTRODUCTION**

Conducting clinical trials in pregnancy raises many challenges, primarily due to safety concerns for mother and fetus, and particularly when testing novel maternal and fetal therapies. The legacy of thalidomide and diethylstilbestrol, combined with more recent regulatory categorisation of pregnant women as vulnerable, has largely excluded this population, even limiting the inclusion of females of reproductive potential from clinical trials of novel therapies.<sup>1-5</sup> This contributes to underinvestment and inequality in women's health and the health of their unborn children.<sup>6</sup> The paucity of clinical trials in pregnancy has led to absent standard frameworks such as standardised severity grading for maternal and fetal adverse events (AEs), which renders clinical trials in pregnancy more difficult. All this compromises the health of pregnant participants in clinical trials.

An 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 product'.<sup>7,8</sup> AEs are important signals in clinical trials, facilitating swift and responsible communication of safety data between study investigators, sponsors and regulators. Regulatory guidelines require that AEs are recorded in medical records, reported to the sponsor and competent authority, and determination made as to whether they (a) meet European Medicines Agency (EMA)/ Food and Drug Administration (FDA)/ Medicines and Healthcare products Regulatory Agency (MHRA) definition of 'serious' and (b) are related to the administration of the Investigational Medical Product (IMP). This determines classification as a serious adverse reaction (SAR) (Figure S1).

Severity of AEs should be recorded using standard grading criteria. An example of why standardization is so critical is when

decisions around dose-escalation and the Maximum Tolerated Dose (MTD) are based on observation of Adverse Reactions (ARs) of given severity. The most widely used system, the Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0) comprises 837 potential AE, of which only 4 relate to ‘pregnancy, the puerperium and perinatal conditions’.<sup>9</sup> Some condition-specific severity grading for pregnancy-specific events have been developed (e.g., in HIV-AIDS and surgery).<sup>10–12</sup> However, there remain no standard general severity grading criteria. This contrasts with recent Delphi consensus work to integrate neonatal terminology and definitions into wider dictionaries.<sup>13,14</sup> We convened an international multidisciplinary group to develop standard definitions and severity grading criteria to enable objective reporting of AEs in all clinical trials involving pregnant women.

## 2 | METHODS

We undertook a stepwise consensus process through a Delphi approach, between January 2015 and December 2019 (Figure 1).<sup>15</sup> Following a comprehensive review of existing terminology, consensus statements and guidelines, draft maternal and fetal AE definitions and severity grading criteria were agreed by the Steering Group. New fetal AE terms were integrated with MedDRA (Medical Dictionary for Regulatory Activities) requirements and added to MedDRA terms list. The draft fetal and maternal AE definitions and severity criteria were reviewed by a Patient Public Advisory Group (PPAG) before undergoing a two-stage international modified Delphi consensus

process. A final set of maternal and fetal AE definitions and severity criteria were agreed.

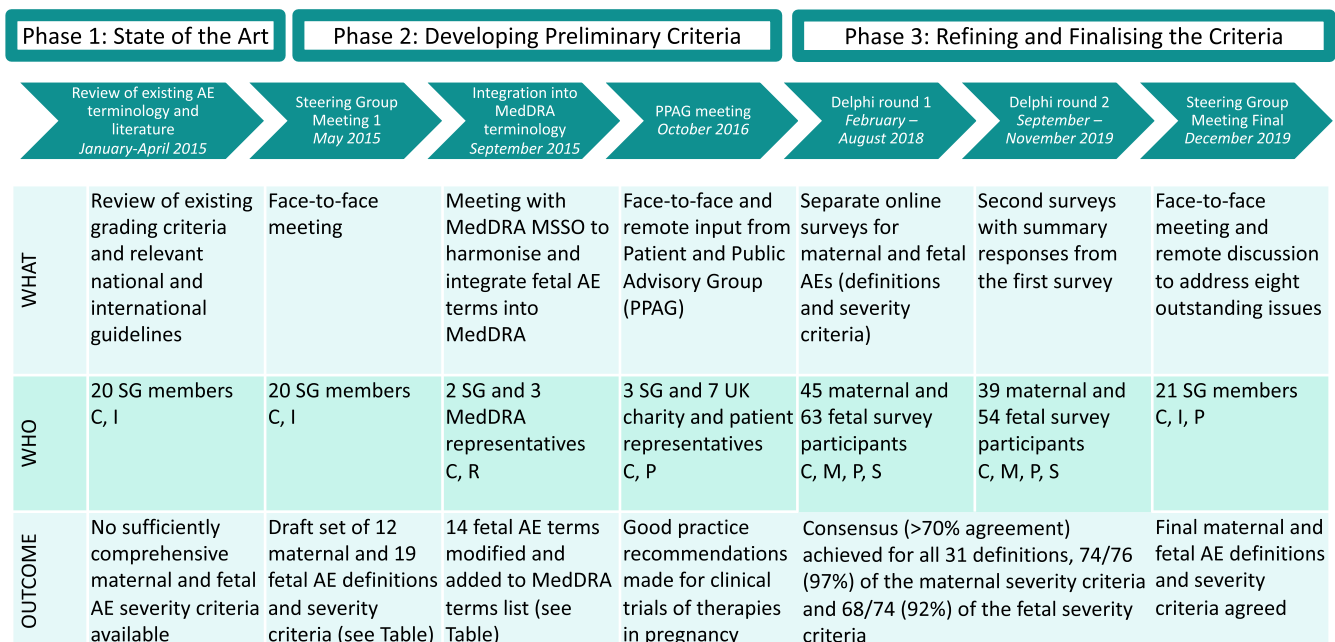
### 2.1 | Phase 1: state of the art

#### 2.1.1 | Review of existing AE terminology

In January 2015, we consulted internationally with academic and industry pregnancy and fetal therapy clinical trialists to identify existing maternal and fetal AE definitions and severity grading criteria for clinical trials in pregnancy (Table S1).<sup>10,11,16</sup> Existing definitions and severity grading criteria were reviewed with MedDRA preferred terms for AEs.

#### 2.1.2 | Review of consensus statements and guidelines literature

In March 2015, we performed a literature review to identify existing definitions and severity descriptors for maternal and fetal AEs in consensus development conferences, statements and practice guidelines (Figure S2). Between March and April 2015, the National Guideline Clearing House, International Guideline Library and Scottish Intercollegiate Guidelines Network were searched for pregnancy or neonatal care guidelines. Full guideline lists from National Colleges and Professional Societies were hand-searched (Table S2); key references were retrieved (March–April 2015)



**FIGURE 1** An overview of the three-stage development process of the standard maternal and fetal AE severity grading criteria. Stakeholder involvement is indicated by C (clinicians), S (scientists), I (industry), M (midwifery representatives), P (patient and/or charity representatives) and R (regulatory authority employees). MedDRA, Medical Dictionary for Regulatory Activities; MSSO, Maintenance and Support Services Organisation; PPAG, Patient Public Advisory Group; SG, EVERREST AE Consensus Steering Group [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

and reviewed for definitions and severity indicators (Table S3).<sup>10,11,17-62</sup>

## 2.2 | Phase 2: developing preliminary criteria

### 2.2.1 | Development of the preliminary AE definitions and severity grading criteria

The EVERREST AE Consensus Steering Group met in May 2015. Maternal AE definitions and severity grading criteria were developed based on relevant sections of the reviewed AE terminology and literature, starting with CTCAE generic grading criteria (Table 1). For fetal AEs a generic severity grading system was developed. Fetal AEs were identified by considering the potential impacts of maternal or fetal therapies on fetal organ systems. The effects of maternal AEs on the fetus were also considered. AE definitions were adapted from existing clinical definitions in the literature.

### 2.2.2 | Integration into MedDRA terminology

In September 2015, the Steering Group met with the Chief Medical Officer for the MedDRA Maintenance and Support Services Organisation (MSSO) to amend and integrate fetal AE terms with existing MedDRA terms, hierarchy, structure and functioning (<https://www.meddra.org/>).

### 2.2.3 | Review by Patient Public Advisory Group

In October 2016, the Steering Group presented preliminary AE definitions and severity grading criteria to the Guided Instrumentation for Fetal Therapy and Surgery (GIFT-Surg) project PPAG ([www.GIFT-Surg.ac.uk](http://www.GIFT-Surg.ac.uk)) with representatives from UK charities supporting patients with fetal abnormalities and pregnancy complications, together with neonatology, obstetric, fetal medicine and fetal surgery clinicians (Figure S3). The PPAG considered the definitions and criteria, proposing recommendations for good practice in clinical trials during pregnancy.

## 2.3 | Phase 3: refining and finalising the criteria

### 2.3.1 | Modified Delphi consensus process

The preliminary maternal and fetal AE definitions and severity grading criteria underwent a modified Delphi consensus process. Two rounds of online surveys were followed by Steering Group resolution of outstanding issues. Participants with expertise relevant to maternal and/or fetal AEs were identified by the Steering Group, including maternal and fetal medicine specialists, obstetricians, paediatric and fetal surgeons, neonatologists, clinical trialists, research midwives, fetal physiologists and pregnancy charity representatives. We ensured broad global coverage inviting participants from Europe, United States and Canada, South America, Middle East, Asia, Australasia and Africa. For each component of

TABLE 1 Agreed generic criteria for grading the severity of fetal AEs (top table)

Agreed generic grading of foetal AEs				
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
CTCAE generic severity grading for comparison <sup>9</sup>				
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated	Death related to AE

Note: The Common Terminology Criteria for Adverse Events (CTCAE) generic severity grading criteria are listed in the bottom table and will apply to maternal AEs.<sup>9</sup> A semicolon indicates 'or' within the description of the grade.

Abbreviation: AE, adverse event.

each severity grading criterion, participants had the option to: keep the criterion at the proposed level of severity; downgrade or upgrade it to a different severity (if applicable); remove it from the criteria.

Delphi participation was tracked through individual login details. In February 2018, we launched the first round for both maternal and fetal AE surveys which closed in August 2018 following three reminders. The second round launched in September 2019, closing in November 2019 after two reminders. Agreement of  $\geq 70\%$  participants was taken as consensus. Systematically missing responses where participants stopped part-way through the survey were excluded from analysis; non-systematically missing responses were included as non-agreement.

### 2.3.2 | Steering Group consensus meeting

The Steering Group finally convened to review Delphi consensus results (December 2019) and to resolve outstanding questions before agreeing a final set of maternal and fetal AE definitions and severity criteria.

## 3 | RESULTS

### 3.1 | Phase 1: state of the art

#### 3.1.1 | Review of existing AE terminology

Four sets of national or international AE severity grading criteria and a fifth set of industry criteria were reviewed by the Steering Group; the first four were not specifically pregnancy related AE systems. Two included no pregnancy-specific AEs<sup>63,64</sup> and the other three were considered insufficient to meet the needs of trials of maternal and fetal therapies, particularly as few fetal AEs were included.<sup>10,11,65</sup> MedDRA AE terms for 'f(o)etal complications' were limited and related generally to teratogenic effects, or fetal malposition and malpresentation in labour.

#### 3.1.2 | Review of consensus statements and guidelines literature

Handsearching full lists of guidelines from National Colleges and Professional Societies (Table S2) and the literature search of consensus statements and guidelines (March–April 2015) identified maternal AEs that were grouped into 10 categories. Identified documents were examined for definitions of AE terms and criteria used to indicate their severity. A summary was prepared for the Steering Group before the first meeting (Table S3).

### 3.2 | Phase 2: developing preliminary criteria

#### 3.2.1 | Development of preliminary AE definitions and severity grading criteria

The Steering Group considered general principles of assessing AE severity in pregnancy and the ways that this might differ from assessment in a non-pregnant population. Firstly, fetal AEs must be diagnosable in utero, with the potential, at their most severe, to cause a detrimental effect in utero. Current methods of investigating the fetus (imaging and fetal heart rate monitoring) and predicting short- and long-term prognosis can be challenging, potentially make it impossible to differentiate between mild and moderate events and between severe and life-threatening events. Therefore, the Steering Group decided that some AEs may only have severity criteria defined for grade 2 (moderate) and grade 4 (life-threatening), with grade 3 remaining undefined. AEs that only manifest after birth were considered to be neonatal AEs, even if they had originated in utero. For fetal AEs 'hospitalisation or prolongation of hospitalisation', which forms part of the CTCAE general criteria, was considered a poor indicator of severity. Maternity units often have a low threshold for admitting pregnant women to observe fetal well-being. In contrast, a well pregnant woman with a severely compromised fetus may be managed as an outpatient, in cases where fetal intervention is not deemed appropriate. A more useful indicator of fetal severity was considered to be a requirement for a change in pregnancy management, including additional fetal intervention, for example, blood transfusion, or delivery including termination of pregnancy. Generic criteria to assess fetal AE severity were developed (Table 1) based on the CTCAE generic criteria; the CTCAE generic criteria were assumed to apply to maternal AE severity.

Next the Steering Group decided that, in order to fully characterise the impact of any investigational intervention, AEs with potential to differentially affect the pregnant woman and her fetus should have separate maternal and fetal grading criteria. Four such AEs were proposed: Haemorrhage in pregnancy, Preterm premature rupture of membranes, Chorioamnionitis and Anaemia of pregnancy (Table 2). For example, preterm premature rupture of membranes (PPROM) at 20 weeks of gestation in the absence of chorioamnionitis would likely have significant impact on the fetus causing life-threatening pulmonary hypoplasia, but less impact on the pregnant woman's health.

The Steering Group agreed fetal AE definitions related to specific organs and systems (Table 2), namely abnormalities in the fetus detectable by imaging in the gastrointestinal, renal, brain or musculoskeletal systems, including fetal movement disorders and fetal fluid collection. Fetal AEs related to fetal heart rate abnormalities (bradycardia or tachyarrhythmia) and cardiac function abnormalities were defined. More non-specific AEs defined abnormal fetal growth, fetal neoplasm and a 'catch-all' term for fetal structural abnormalities: not otherwise classified. Fetal AE definitions were developed

TABLE 2 The maternal and fetal AE terms for which definitions and severity grading criteria were developed

Maternal AEs	Fetal AEs
Haemorrhage in pregnancy	Haemorrhage in pregnancy
Preterm premature rupture of membranes	Preterm premature rupture of membranes
Chorioamnionitis	Chorioamnionitis
Anaemia of pregnancy	Anaemia of pregnancy
Gestational hypertension	Fetal fluid collection <sup>a</sup>
Pre-eclampsia	Fetal bradycardia: non-labour <sup>a</sup>
Eclampsia	Fetal tachyarrhythmia <sup>a</sup>
Premature labour	Cardiac function abnormalities <sup>a</sup>
Puerperal infection	Fetal brain scan abnormal <sup>a</sup>
Postpartum haemorrhage (primary)	Fetal gastrointestinal tract imaging abnormal <sup>a</sup>
Retained placenta or membranes	Fetal musculoskeletal imaging abnormal <sup>a</sup>
Amniotic fluid embolism	Fetal renal imaging abnormal <sup>a</sup>
	Fetal movement disorders <sup>a</sup>
	Fetal neoplasm <sup>a</sup>
	Fetal structural abnormalities: not otherwise classified <sup>a</sup>
	Abnormal fetal growth <sup>a</sup>
	Fetal intraoperative injury <sup>a</sup>
	Procedural haemorrhage <sup>a</sup>
	Post-procedural haemorrhage <sup>a</sup>

Abbreviation: AE, adverse event.

<sup>a</sup>Added to the Medical Dictionary for Regulatory Activities terms list.

specifically for AEs related to fetal interventions (Table 2). Fetal intraoperative injury was defined as unintended damage to the fetus occurring as a result of a fetal interventional procedure, but excluding the effects of fetal haemorrhage. Separately two fetal AEs related to local or remote haemorrhage during (fetal procedural haemorrhage) or occurring after a fetal procedure (fetal post-procedural haemorrhage) were proposed; both AE definitions also included fetomaternal haemorrhage.

Finally the Steering Group agreed on a draft set of AE severity criteria which were then subjected to the two stage Delphi consensus (data not shown).

### 3.2.2 | Integration into MedDRA terminology

The Steering Group met the Chief Medical Officer for the MedDRA MSSO to integrate the new terminology into MedDRA (September 2015). The proposal for AEs differentially affecting the mother and the fetus to be recorded as separate AEs, for example, 'fetal chorioamnionitis' and 'maternal chorioamnionitis', could not be accommodated within the structure of MedDRA. Instead, it was agreed that one AE would be recorded ('chorioamnionitis') but that the maternal and fetal severity would be recorded separately.

The fetal AE terms were adapted to integrate with existing MedDRA High Level and Lowest Level Terms (Table S4). For example, the originally proposed AE 'fetal renal abnormalities' was changed to 'fetal renal imaging abnormal' to fit an existing higher level MedDRA term 'fetal and neonatal imaging procedures'. The modified AE terms were approved by the Steering Group and added to the MedDRA terms list v19.0 (Table 2).

### 3.2.3 | Review by Patient Public Advisory Group

The PPAG review supported the general principles of assessing AE severity in pregnancy proposed by the Steering Group and the preliminary generic and specific AE severity grading criteria. The group also identified broader considerations on the AE assessment in pregnancy (Table 3). Among these were the potential psychological effect of fetal AEs on the pregnant woman, the wider psychological impact of participating in clinical trials during pregnancy and considering the effect of AEs on future fertility and pregnancies. The PPAG indicated the importance of carefully documenting patient choices such as termination of pregnancy or palliative care after birth for those fetuses with life-threatening abnormalities.



**TABLE 3** Patient and Public Advisory Group recommendations for best practice in clinical trials of maternal and fetal therapies

- Define the timing of AE assessment in the clinical trial protocol. Depending on the intervention short-term, medium-term, and/or long-term AEs may be appropriate and the severity grading may change across these timepoints. Ideally report as much as possible, potentially as supplementary online information.
- Record information on antenatal decisions to terminate the pregnancy or to have only palliative neonatal care after birth. State in the clinical trial protocol how these outcomes will be analysed and consider them part of the same group when analysing data and measuring mortality.
- Mode of labour onset and mode of delivery are outcomes that should be reported, including whether the mode of delivery is likely to impact on decisions regarding delivery in future pregnancies (i.e., women undergoing classical Caesarean section or open fetal surgery are advised to delay another pregnancy for a year and to avoid labour).
- Assess the psychological impact of the intervention on the pregnant woman and her partner including the psychological impact of any fetal AEs. Evaluate using validated measures in comparison with an 'untreated' group with the same condition.
- Where possible include costs in clinical trial funding applications for psychological support for pregnant women and their partners and, especially in phase I trials, consider qualitative assessment of the women's experience.
- Include in the clinical trial protocol assessment methods to capture data about the fetal response to an intervention, including indications of fetal pain or stress. Appropriate measures are likely to vary depending on whether the intervention involves the fetus directly (fetal surgery) or indirectly (maternal medication).
- Capture data on subsequent fertility and pregnancies over a time period proportionate and relevant to the intervention under investigation. This should include whether women were trying to conceive, and their pregnancy outcomes and complications if they were successful.

### 3.3 | Phase 3: refining and finalising the criteria

#### 3.3.1 | Modified Delphi consensus process

The first round had 45 participants from 33 countries in the maternal AE survey and 63 participants from 34 countries in the fetal AE survey. For the second round, 39 participants (87%) completed the maternal AE survey, and 54 participants (86%) completed the fetal AE survey (Table S5). Table S6 lists the levels of agreement in each round; final definitions and criteria are in Table S7.

#### 3.3.2 | Maternal adverse events

Of the 12 proposed maternal AEs, 11 definitions reached consensus in the first survey; the final definition reached consensus in the second survey. Sixty-three of the 74 criteria (85%) reached consensus in the first survey; a further 9 reached consensus in the second survey (total 96%). One criterion, 'haemorrhage in pregnancy: maternal' was broken down further in the second survey, with two of three components reaching consensus. The two outstanding issues resolved by consensus within the final Steering Group Meeting were (1) classifying 'haemorrhage in pregnancy' with blood loss of 250–1000 ml and no signs of clinical shock as a grade 3 (severe) maternal AE, and (2) classifying 'retained placenta or membranes' requiring minimal, local or non-invasive intervention to deliver the placenta following vaginal birth as a grade 2 (moderate) maternal AE. This achieved consistency with the CTCAE generic guidelines whereby a grade 3 (severe) AE is medically significant and/or requires hospitalisation, whereas a grade 2 (moderate) AE requires minimal, local or non-invasive intervention.

#### 3.3.3 | Fetal adverse events

Of the 19 proposed fetal AEs, 18 definitions reached consensus in the first survey; the final definition and three modified definitions

reached consensus in the second survey. Fifty-nine of the 73 criteria (80%) reached consensus in the first survey; a further eight reached consensus in the second survey (total 92%). An additional criterion for 'preterm premature rupture of membranes: fetal' was added to the second survey and reached consensus.

Three outstanding issues were resolved by consensus within the final Steering Group Meeting. Firstly, for both the generic grading criteria and for 'fetal tachyarrhythmia' the proposed grade 2 (moderate) criterion 'resolves spontaneously with low risk of long-term consequences' did not reach consensus, with most participants in the second round (54% and 59%, respectively) considering that it should be downgraded to grade 1 (mild). The Steering Group agreed to this downgrading. Secondly, three of the proposed grade 3 (severe) criteria for 'fetal brain imaging abnormal' failed to reach consensus (cystic changes, abnormal cortical development and hydrocephalus). These were removed as specific criteria and would need to be graded according to the generic criteria if they occurred. Finally, the criterion 'imaging appearance highly suggestive of bowel necrosis or perforation', proposed as a grade 3 (severe) AE for 'fetal gastrointestinal tract imaging abnormal', achieved only 65% agreement in the first but 69% in the second round; the Steering Group agreed to retain this as a grade 3 (severe) AE.

## 4 | DISCUSSION

### 4.1 | Main findings

We describe the development of the most comprehensive set of maternal and fetal AE definitions and severity grading criteria available, which can guide investigators and clinicians in assessing the severity of AEs so as to increase the quality of safety information. By reviewing international guidelines and consensus statements, building on the existing CTCAE framework, liaising with MedDRA and seeking consensus from international experts through a modified Delphi consensus process we have made this terminology as robust as possible.

For clinical trials, recording and reporting AEs using standardised severity grading terminology allows comparison of safety data between clinical trials. For first-in-human or early-phase trials in particular, AE grading is vital to facilitate dose escalation by allowing the categorisation of Dose Limiting Toxicity (DLT) events in the mother and fetus, so as to derive the target toxicity level and then to define the Maximum Tolerated Dose (MTD). Without suitable AE grading and criteria for the mother and the fetus, it is not possible to define these trial endpoints, rendering early phase trial safety assessment impossible. The deficiency of appropriate regulatory language available to describe safety assessment until now may have contributed to the lack of investment in novel therapeutics for pregnancy diseases. A recent example of this phenomenon is the SarsCoV2 pandemic, a current and urgent situation in which the exclusion of pregnant women and those breastfeeding from many clinical trials of treatment or vaccination for COVID-19 has left a vacuum of information. This means that women and their healthcare providers have had to make treatment decisions without the appropriate safety information.<sup>66</sup> We hope that this terminology will now be adopted by triallists, industry and regulatory authorities to address this deficit in treatments for pregnant women and their fetuses.

## 4.2 | Interpretation

The MFAET version 1.0 system can also be used to standardise recording and severity grading of AEs in untreated populations, to provide comparison and valuable reproducible contextual 'control' data with which to interpret safety and AEs in interventional trials. The EVERREST prospective study, for example, is defining characteristics of pregnancies affected by severe early onset fetal growth restriction, generating control data for a future first-in-human intervention trial of maternal gene therapy.<sup>67</sup> The terminology is being used to derive the dose escalation plan of the Phase I clinical trial protocol. In addition, this terminology can be used simply to study safety in cohort studies of maternal and/or fetal intervention. A recent example used fetal AE MedDRA terms to define maternal and fetal complications after fetal surgery for myelomeningocele.<sup>68</sup>

The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) report to the US Secretary, Health and Human Services Congress, September 2018, identified the difficulties with developing safe and effective therapies for pregnant and lactating women, due to gaps in knowledge and research from limited existing scientific literature.<sup>69</sup> These new AE definitions and grading in MFAET version 1.0 will provide the nomenclature to fulfil their objectives which include prioritising data collection on therapeutic products.

Our approach of grading the severity of AEs separately for the pregnant woman and the fetus allows for greater detail and nuance in AE reporting. Many severe or life-threatening fetal AEs have little physical impact on the mother and may have been difficult to capture in the past given the previously limited fetal AE terms and severity

grading criteria. However, assessing fetal AEs raises specific challenges; current methods of investigating the fetus through imaging and fetal heart rate monitoring, and predicting short- and long-term prognosis are rarely sufficient to differentiate between mild and moderate events and between severe and life-threatening events. This is why many of the fetal AEs only have severity criteria defined for grade 2 (moderate) and grade 4 (life-threatening), with grade 3 remaining undefined. A recent study published in 2019 developed a more limited set of AEs in relation to thoraco-amniotic shunting. The authors adopted a similar generic grading system for fetal AEs, and again acknowledged the potential for maternal AEs such as haemorrhage to independently act as a fetal AE.<sup>70</sup>

## 4.3 | Strengths and limitations

The strength of our process is that we carefully examined existing terminology and literature to identify gaps in AE assessment for the mother and the fetus. Our Steering Group and Delphi consensus members included multiple key stakeholders involved in developing maternal and fetal drugs, devices and surgical interventions. We ensured international participation in the process with academic and non-academic clinicians and researchers, industry representatives, scientists, midwifery and parent representatives.

This terminology should however not be considered final or exhaustive. Future refinement and expansion, such as that undertaken by other AE severity grading systems, will continue to improve these criteria with revised versions to be released in the future. More criteria are likely to be added as the process matures, fetal anaemia being one such criterion that has not yet been included. Until the next version is available, triallists can apply the generic criteria to estimate the severity for AEs that may not be currently included in MFAET version 1.0. We did not specifically develop an AE definition for analysis of Cardiotocography (CTG, non-stress test 'NST') as this will be accommodated in the fetal heart rate AEs (Fetal Bradycardia and Fetal Tachyarrhythmia). Future versions may need to accommodate new methods of fetal assessment including objective fetal movement monitoring, computerised CTG analysis of short-term variability (STV) and machine learning algorithms.

Laboratory-based AEs for the pregnant woman such as abnormal liver or thyroid function are not included in any existing grading criteria such as CTCAE, DAIDS, etc., and will require future development. Deriving laboratory-based AEs for the fetus depends on data from invasive sampling of amniotic fluid, placental villi, fetal blood or urine which carries a risk of miscarriage or preterm labour. Historical data is available and has been used to develop non-invasive ultrasound Doppler methods to diagnose fetal anaemia.<sup>71</sup> As analysis of fetal circulating DNA, RNA and proteins in the maternal blood advances, it is possible that fetal laboratory-based AEs will be developed to further assess fetal well-being.<sup>72,73</sup>

The goal of a standardised AE severity scale is to reduce subjectivity in severity assessments and thus reduce interobserver



variability. We are currently planning prospective validation studies of agreement among observers in different countries for the generic and specific severity criteria for maternal and fetal AEs.

## 5 | CONCLUSION

This novel set of 12 maternal and 19 fetal AE definitions and severity grading criteria (MFAET version 1.0) has been developed through an international modified Delphi consensus process. This terminology fills a vital gap in maternal and fetal translational medicine research, supporting the development of therapies for pregnant women, a neglected patient group. We recommend their use to achieve systematic and consistent AE grading and reporting within and between clinical trials in pregnancy. Only by doing this will clinical trials provide a meaningful understanding of safety and the risk/benefit for mothers and their fetuses, lifting the mystique and reducing reluctance to undertake studies in pregnancy.

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## DATA AVAILABILITY STATEMENT

All data generated by this study are presented in the manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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