# STORC Clinical Management Study Specific Procedure Manual

**Abbreviations**

| | |
|---|---|
| AE | Adverse Event |
| AF | Amniotic Fluid |
| CRF | Case Report Form |
| CS | Cesarean section |
| DAIDS | Division of AIDS |
| | |
| EBL | Estimated Blood Loss |
| FDA | Food and Drug Administration |
| FGGT | Female Genital Toxicity Table |
| ICH-E6 | International Conference on Harmonization Consolidated Guidance for Good Clinical Practice |
| ICU | Intensive Care Unit |
| NICU | Neonatal Intensive Care Unit |
| PP | Postpartum |
| PSRT | Protocol Safety Review Team |
| SAE | Serious Adverse Event |
| SOF/VEL | sofosbuvir/velpatasvir (Epclusa®) |
| SSP | Study Specific Procedure |
| WNL | Within Normal Limits |

**Introduction**

This document provides information related to adverse event (AE) reporting and participant safety monitoring specific for the STORC study. Please also refer to the following resources relevant to AE assessment and reporting:

- Safety, Tolerability, and Outcomes of Velpatasvir/SofosbuviR in Treatment of Chronic Hepatitis C Virus during Pregnancy (STORC) study protocol, current version
- DAIDS Table for Grading Adult and Pediatric Adverse Events (DAIDS Tox Table), Version 2.1 dated July 2017, including:
    - Addendum 1: Female Genital Grading Table for Use in Microbicide Studies (FGGT), November 2007
- Epclusa® sofosbuvir/velpatasvir Package Insert, current version

## 1.1 Adverse Event (AE)

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) defines an AE as any untoward medical occurrence in a clinical research participant administered an investigational product that does not necessarily have a causal relationship with the investigational product. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

The ICH-E6 definition is applied to all maternal and infant participants, beginning at the time a maternal participant is enrolled through when the mother and the infant terminate from the study, respectively. Study staff must document all applicable AEs reported by or observed in study participants, regardless of severity and presumed relationship to study product.

AEs for the study will be entered into REDCap using the Adverse Event Instrument. All AEs must be reviewed by and relationship to investigational product determined by a site PI/designee. The site PI/designee must log into REDCap and personally sign and date each AE after determining relationship.

The REDCap AE Instrument will include the following details related to the AE:

- Date reported to site
- AE term/diagnosis (guidance is provided in this document to standardize AE terms among sites)
- Whether the AE is a maternal or infant AE
- Onset date

- Severity grade (tables are included in this document to standardize grading among sites)
- Relationship to study product (related or not related and alternate etiology as determined by a site PI/designee)
- Rationale for relatedness determination (documented by site PI/designee)
- Study product administration as related to the AE
- Outcome status
- Outcome date (or ongoing at time of final study visit)
- AE treatment
- Whether the AE is serious per ICH guidance (see definition below section 1.2)
- Whether the AE is a worsening of a baseline/pre-existing medical condition
- Additional comments/details related to the AE

### 1.1.1 Adverse Event Severity Grading

The term severity is used to describe the intensity of an AE. The severity of all AEs identified must be graded on a five-point scale:

Grade 1 = Mild
Grade 2 = Moderate
Grade 3 = Severe
Grade 4 = Potentially life-threatening
Grade 5 = Death

Severity is not the same as seriousness, which is based on the outcome or action associated with an event.

The severity of all AEs identified will be graded using the:
- Protocol-specific grading tables as outlined in this document
- *DAIDS Table for Grading Adult and Pediatric Adverse Events* (hereafter referred to as the Toxicity Table), Version 2.1 dated July 2017 or most current version, if updated
- *Female Genital Grading Table for Use in Microbicide Studies* (hereafter referred to as the FGGT), dated November 2007 or most current version, if updated

Importantly:
- AEs listed in both the FGGT and the Toxicity Table should be graded according to the FGGT.
- AEs not listed in the FGGT should be graded according to the Toxicity Table.
- AEs not listed in the FGGT or the Toxicity Table should be graded according to the "Estimating Severity Grade" row of the Toxicity Table listed below.

| **ESTIMATED SEVERITY GRADE** | | | | | |
|---|---|---|---|---|---|
| **PARAMETER** | **Grade 0 Normal** | **Grade 1 MILD** | **Grade 2 MODERATE** | **Grade 3 SEVERE** | **Grade 4 POTENTIALLY LIFE-THREATENING** |
| Clinical adverse event NOT identified elsewhere in the grading table | N/A | Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated | Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated | Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated | Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death |

Both the DAIDS Toxicity Table and FGGT can be accessed on the DAIDS RSC web site (http://rsc.tech-res.com/safetyandpharmacovigilance ).

### 1.1.2 Adverse Event Relationship to Study Product

One of two relationship categories must be assigned to each reportable AE:

**Related:** There is a reasonable possibility that the AE may be related to the study product.

**Not related:** There is not a reasonable possibility that the AE is related to the study product.

- The relationship must be determined and documented (signed/dated in REDCap) by a site physician investigator.
- For both 'related' and 'not related' assignments, a rationale (such as alternative etiology or explanation) is required to be provided within the Rationale for Relatedness Determination Section of each AE CRF. Recording "no other cause identified" is not adequate.
- Although an AE's relationship status defers to clinician discretion, some clinical explanation is helpful to present a more complete safety profile of the study product.
    - *For example: understanding* w*hat investigations were performed, knowing if the problem resolved spontaneously or only with cessation of study product use, and determining the onset date of the AE in relation to study product exposure.*
- Familiarity with previously identified adverse drug reactions (adverse events with a possibility of a causal relationship) may aid in determining relationship status. This information can be found in the current sofosbuvir/velpatasvir (Epclusa®) Package Insert.
- The relationship status of an AE may be changed if new information becomes available at a later date, after the AE is first reported. If the relationship status is changed at a later date, update the "Relationship to Study Product" item in the AE Instrument. Review the entire form for completeness. The physician investigator must review and re-sign/date the form and add additional rationale supporting the modified relationship in the Comments Rationale for Relatedness Determination Section.
    - *For example: a participant-reported "headache" is documented as an AE and deemed 'related' in the "Relationship to Study Product" item with the rationale that the headache presented after the participant started using Epclusa®. Days later, the participant was diagnosed with preeclampsia. At this point the site might conclude that the headache is now determined to be associated with preeclampsia. In this instance:*
        - *The "Relationship to Study Product" item of the AE Log entry should be updated from "related" to "not related".*
        - *Additional notes should be added the Comments* Rationale for Relatedness Determination *Section to clarify the rationale of changing the relationship by documenting preeclampsia as the causality.*
        - *The AE form should be re-signed and dated by the physician investigator making the update.*

### 1.1.3 Pre-existing conditions

For maternal participants, relevant medical conditions, problems, signs, symptoms, and findings identified *prior to enrollment* are documented within the REDCap Preexisting Conditions Mother Instrument (whether the conditions are ongoing at enrollment or not).

- If the pre-existing condition worsens (increases in severity or frequency per the Toxicity Table) after enrollment, the worsened condition is considered an AE.
- If a pre-existing condition resolves after enrollment, but then recurs at a later date, the recurrence is considered an AE.
- Medication allergies should be documented in the baseline medical history and listed on the Pre-existing conditions Instrument with the allergic reaction listed in the comments section and graded as "non-gradable".

Since infant participants are exposed to study drug in utero, all conditions identified at/following birth will be reported as AEs and not captured as 'pre-existing' conditions.

### 1.1.4 Adverse Events that are not reportable

Per protocol, the following AEs are not reportable:

- Uterine cramping that is judged by the clinician to be within the range normally anticipated post-delivery
- Perineal pain that is judged by the clinician to be within the range normally anticipated post-delivery
- Lower extremity edema that is judged by the clinician to be within the range normally anticipated during pregnancy
- Decreased fetal movement; however, AEs identified in the course of clinical evaluation of decreased fetal movement will be captured
- Large for Gestational Age (LGA) is not considered an AE; reassess at birth; AEs associated with macrosomia (e.g. shoulder dystocia, hypoglycemia) should be reported. Small for Gestational Age (SGA): see below for grading
- Findings on electronic fetal monitoring tracings
    - NOTE: AEs identified in the course of clinical evaluation of concerning electronic fetal monitoring will be captured
- Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths); however, untoward maternal conditions that either result in or result from fetal losses are reported as AEs
    - NOTE: All fetal losses will be reported by sites on the REDCap Pregnancy Outcome Instrument and will be considered during safety reviews conducted by PSRT
- Physiologic discharge associated with pregnancy
- Lochia judged to be within the range of normal experienced in the post-partum period
- Vaginal bleeding that is judged by the clinician to be within the range normally anticipated in the postpartum period
- Incisional pain or discomfort after cesarean delivery that is judged to be within the range normally anticipated after cesarean section
- Monitoring in the hospital for neonatal opioid withdrawal syndrome
- Perinatal HCV transmission
    - NOTE: Perinatal HCV transmission will be collected and reported as a secondary outcome

Note that any condition or issue above that is outside of the range normally anticipated during pregnancy is considered an AE.

### 1.1.5 Miscellaneous AE Guidance

Further clarifications, guidelines, and tips for grading the severity of AEs are as follows:

- If the severity of an AE falls into more than one grading category on the FGGT or the Toxicity Table, assign the higher of the two grades to the AE.
- If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, and the diagnosis is not specifically listed in the FGGT or Toxicity Table, assign the AE the highest severity grade among each of the associated signs and symptoms. Record the diagnosis as the AE term and record each associated sign and symptom in the AE CRF comments section.
- Seasonal allergies should be graded according to the “Estimating Severity Grade” row of the Toxicity Table (not the “acute systemic allergic reaction” row).
    - For example, seasonal allergies that require medication (e.g. allergy shots or over-the-counter allergy medication as needed), would be a Grade 2
- When grading adverse events per the “Estimating Severity Grade’ row (i.e. for AEs not listed specifically in the FGGT or Toxicity Table), ‘intervention’ should be defined as: “medical, surgical or other procedures for the treatment of an adverse event.” If a participant reports treatment, the AE is graded as at least a Grade 2. Importantly, clinicians should note that grading is dependent on participant-reported impact of symptoms on her life, and whether intervention (defined as above) is *indicated,* regardless of whether the treatment was actually provided or taken by the participant. It is at the discretion of clinician to determine whether intervention was indicated for the reported AE. In the event that an intervention was indicated but not taken, the treatment should be marked as “other” rather than ‘medications’ and additional details should be included in the line provided. The AE severity grade, per the Toxicity Table, would be assigned Grade 2.

- Adverse events may be identified by review of chart notes, laboratory results, and/or participant complaints. In some cases, a medical release may need to be signed to obtain records and additional details (e.g. if the AE was diagnosed/evaluated outside of the site's facility). Source documents pertinent to the AE should be maintained in the participant's research record. Attempts to obtain additional information from the participant or from outside facilities should be noted in the participant's record to clearly document efforts to get additional information.

### 1.2 Serious Adverse Events (SAEs)

ICH-E6 defines a serious adverse event (SAE) as an AE following any exposure to study product which:

- Results in death,
- Is life-threatening,
  ***NOTE:*** *The term "life threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. A Grade 4 severity grading on the DAIDS Grading Table does not necessarily mean that an event is life-threatening. When determining whether a Grade 4 event meets the ICH definition of "life threatening", consider the event in the context of any related symptoms the participant may have experienced.*
- Requires in-patient hospitalization or prolongs an existing hospitalization,
  *The following types of hospitalizations are not considered Adverse Events, serious or otherwise:*
  - *Any admission unrelated to an AE (e.g., for labor/delivery, including cesarean section)*
  - *Admission for diagnosis or therapy of a condition that existed before enrollment AND has not increased in severity per the DAIDS Grading Table since baseline*
  - *Admission of the neonate for observation for neonatal opioid withdrawal syndrome according to standard practice at the site hospital.*
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above.
- ICH guidance (E2A) also states that medical and scientific judgment should be exercised in deciding whether other adverse events not listed above should be considered serious.

SAEs are a subset of all reportable AEs. For each AE identified in STORC, an authorized study clinician must determine whether the AE meets the ICH definition of "serious". The RedCap AE Instrument includes a specific question to record this determination.

When assessing whether an AE meets the definition of serious, note that seriousness is not the same as severity, which is based on the intensity of the AE.

#### 1.2.1 Reporting SAEs

All adverse events will be reported to Gilead Sciences on a monthly basis by the Data Management Team. All SAEs that are considered unexpected and related to the study medication will be reported to the respective site Institutional Review Board/Research Ethics Board as applicable and per local reporting guidelines. The site PI/designee must notify the Protocol Chair and PSRT via email within 7 days of becoming aware of the SAE. Entry of an SAE form in the REDCap SAE form will automatically notify the STORC Data Management team and the Protocol Chair of the occurrence of an SAE. Additionally, the site PI/designee will also complete an FDA MedWatch Form if the event meets the reporting requirements (is serious, unexpected and related). The MedWatch form must be completed and sent to the Protocol Chair and (University of Pittsburgh) Regulatory Affairs Coordinator within 5 days of site awareness and as outlined in the REDCap instructions within the SAE Instrument. The Protocol Chair will be responsible for notifying Gilead Sciences within 15 days of becoming aware of an SAE. The University of Pittsburgh Regulatory Affairs Coordinator will report SAEs that require completion of MedWatch Forms to the FDA within 7 days of awareness/per reporting guidelines and will report other SAEs per FDA reporting guidelines or at the time of annual renewal through the local University of Pittsburgh's IND office.

### 1.3 Reporting Considerations for Pregnant Participants

AEs that are deemed related to the pregnancy, worsened by the pregnancy, or require changes in clinical management of the pregnancy should be reported, as clinically indicated. Use the appropriate pregnancy related terms or indicate the AE is during pregnancy by adding 'antepartum' or 'postpartum' when describing the AE diagnosis on the REDCap AE Instrument. Some events are inherently related to pregnancy (e.g., eclampsia); there is no need to add "antepartum" or "postpartum" to these AE descriptions.

Fetal losses (of any kind) are not reportable AEs. However, maternal complications or side effects associated with fetal loss that would otherwise be reported as an AE are considered AEs and should be reported.

- *For example: vaginal bleeding associated with miscarriage OR pelvic cramping associated with spontaneous abortion should be reported as AEs as further described below*

#### 1.3.1 Vaginal bleeding, Pelvic Pain, Contractions

Bleeding and pelvic pain or contractions are common complaints in pregnancy and may accompany a fetal loss. Depending on the circumstances, pain and bleeding experienced during pregnancy may be reported as AEs.

- In general, bleeding associated with delivery (intrapartum and/or postpartum) is not considered an AE, provided the bleeding does not exceed the expected amount (see Table 2, Grade 0 for bleeding amounts that are considered normal).
- Contractions at term are considered normal and should not be reported as an AE.
- Pain during pregnancy, with the exception of term contractions, should be captured as an AE.
- Bleeding prior to the onset of labor (and not associated with delivery) should also be captured as an AE.
- "Intrapartum hemorrhage" should be used to describe bleeding that occurs during labor, but not at delivery or after delivery. For example, a participant in labor with a placental abruption or a previa who presents with bleeding, should be considered to have an "intrapartum hemorrhage." Should it be difficult to ascertain whether the bleeding occurred "intrapartum" or "postpartum" from the record, but it is clear there was excessive bleeding at the time of delivery, record "postpartum hemorrhage."
- If a participant reports bleeding, not associated with delivery study staff should investigate the source of the bleeding (i.e. via review of medical records). If a pelvic exam finding such as a vaginal laceration, a cervical polyp, or hemorrhoids, is identified as the source of the bleeding, the finding should be recorded as the AE and an explanation provided in the comments section of the AE Instrument that the finding was associated with bleeding.

See Table 1 for additional guidance on reporting these AEs during pregnancy. Events classified as "NOT AE" in Table 1 are not recorded in the REDCap AE Instrument and should be documented as such in a chart note.

**Table 1: Adverse Event Reporting During Pregnancy by Gestational Age**

| **Parameter** | **Gestational Age** | | |
|---|---|---|---|
| | **0-20 weeks** | **20-37 weeks** | **Term ≥37 weeks** |
| Painful Cramping/Uterine Contractions *either associated with or not associated with pregnancy loss or delivery* | Record as "Pelvic Pain in Pregnancy" (grade per Pain row of FGGT) | Record as "Preterm Contractions" (grade per Preterm Contraction row of FGGT) | NOT an AE |
| Vaginal Bleeding *not associated with pregnancy loss or delivery* | Record as "Bleeding Prior to Onset of Labor" (grade per Bleeding during pregnancy, prior to the onset of labor in Table 2 below) | | |
| Vaginal Bleeding *associated with pregnancy loss or delivery* | Record as "Vaginal Bleeding Associated with Miscarriage" (grade per | NOT an AE unless: EBL is greater than WNL at any point in delivery. | NOT an AE unless: EBL is greater than WNL at any point in delivery. |

| | | | |
|---|---|---|---|
| | Bleeding during pregnancy, prior to the onset of labor in Table 2 below) | If EBL > WNL, record as "Intrapartum Hemorrhage" or "Post-Partum Hemorrhage" (grade per Intrapartum Hemorrhage or Post-Partum Hemorrhage in Table 2 below) | If EBL > WNL, record as "Post-Partum Hemorrhage" (grade per Post-Partum Hemorrhage in Table 2 below) |
| Fetal Loss | NOT an AE | NOT an AE | NOT an AE |

Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) are not considered AEs; however, untoward maternal conditions that either result in or result from fetal losses are reported as AEs

- NOTE: All fetal losses will be reported by sites on the REDCap Pregnancy Outcome Instrument and will be considered during safety reviews conducted by PSRT

## 1.4 Protocol Specific Grading Scales and Primary & Secondary Endpoint Definitions

### Protocol Specific Grading Scales

Protocol-specific grading scales will be used for the AEs outlined in Table 2 below to help ensure consistency of reporting and grading AEs between sites. All conditions that are Grade 1 or higher should be reported as AEs using the appropriate terms.

*For Example: If a participant has Preeclampsia with severe features, use the term of "Hypertensive disorders of pregnancy" as the AE term/description and grade as a Grade 3.*

### Primary & Secondary Endpoint Definitions

All AEs should be reported and graded in a timely fashion, with particular attention to the AEs listed as Protocol Endpoints. Use of the grading scales and guidance in this document will help to ensure consistency in reporting and grading among study sites.

Preterm delivery (spontaneous and iatrogenic) prior to 37 weeks' gestation is a Primary Endpoint for the STORC study.

- Preterm Delivery should be indicated on the REDCap Pregnancy Outcome Instrument.
- Preterm Delivery is not an AE; however, the reason for the Preterm Delivery should be reported as the event

  *For Example:*
  - *A Preterm Delivery that occurs after Spontaneous Preterm ROM: Spontaneous Preterm ROM is the AE term*
  - *A Preterm Delivery that occurs after spontaneous labor: Preterm Contractions is the AE term.*
  - *A Preterm Delivery that occurs as a result of Preeclampsia: Preeclampsia is the AE term*

A Secondary Objective of the STORC study is to evaluate maternal and neonatal safety of HCV treatment. Secondary Endpoints related to Maternal and Neonatal/Infant Safety are defined in the protocol. Table 2 below provides guidance to standardize reporting and grading of these AEs across the sites. These (Secondary Endpoints) conditions should also be noted as a complications of pregnancy on the REDCap Pregnancy Outcome Instrument.

If the verbatim term for the protocol-outlined Secondary Endpoint is not documented in the medical record, but a condition is presumed based on chart review by an experienced site clinician, the verbatim term should still be reported on the REDCap Pregnancy Outcome Instrument.

Secondary Endpoint measures also include Severe Maternal Morbidity as defined by the CDC and found utilizing the following link:
https://www.cdc.gov/reproductivehealth/maternalinfanthealth/smm/severe-morbidity-ICD.htm

## Table 2: Protocol Specific Grading Tables

| PARAMETER | Grade 0 Normal | Grade 1 MILD | Grade 2 MODERATE | Grade 3 SEVERE | Grade 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|---|
| Bleeding during pregnancy, prior to the onset of labor | N/A | Spotting or bleeding less than menses | Bleeding like menses* or heavier, no intervention indicated<br>**note: "menses like" refers to several days of moderate bleeding* | Profuse bleeding with dizziness or orthostatic hypotension, transfusion | Potentially life-threatening profuse bleeding and/or shock |
| Hypertensive disorders of pregnancy | N/A | Gestational hypertension | Preeclampsia without severe features | Preeclampsia with severe features | Eclampsia;<br>HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) syndrome, eclampsia, or life-threatening sequelae of preeclampsia (e.g., pulmonary edema, stroke, etc) |
| Gestational diabetes | N/A | Diet-controlled, no or minimal interference with usual social and functional activities | Medication prescribed | Evidence of adverse effects on pregnancy secondary to diabetes | N/A |
| Chorioamnionitis | N/A | Fever of 38°C – 38.4°C<br>(or 100.4°F-100.9°F) with more than one of the following:<br>FHR > 160 BPM, maternal HR > 120, uterine tenderness between contractions, purulent AF, or preterm labor | Grade 1 plus fever of 38.5°C -40°C<br>(or 101°F-104°F) | Grade 2 plus fetal distress or fever > 40°C<br>(or 104°F) | Grade 3 plus fetal demise or maternal symptoms of shock |
| Puerperal sepsis and endometritis | N/A | Low grade fever and uterine tenderness, resolved with oral antibiotics | Moderate symptoms, treated by ≤ 3 days of parenteral antibiotics | Severe symptoms treated with > 3 days of IV antibiotics or addition of heparin | Severe infection or infection for which operative intervention is indicated |
| Preterm rupture of membranes (PROM) | N/A | N/A | Preterm rupture with hospitalization but not resulting in delivery at less than 37 weeks' gestation | Delivery at 33-36 weeks' gestation or 1501-2500 grams birth weight | Delivery < 33 weeks' gestation or ≤ 1500 grams birth weight |
| Postpartum hemorrhage | Estimated blood loss (EBL) < 500 mL for vaginal delivery or < 1000 mL after CS or reported as normal | EBL 500-1000 mL for vaginal delivery or 1000-1500 mL for CS or<br>reported as slightly increased | EBL > 1000 mL or vaginal delivery or > 1500 mL for CS, with or without mild dizziness, no transfusion required | Hemorrhage at a level for which transfusion of 1-2 units of packed cells,<br>but no other blood products indicated | Hemorrhage with shock or coagulopathy, for which transfusion of > 2 units of packed cells or any amount of other blood components is indicated |
| Intrapartum hemorrhage | Within the anticipated amount | N/A | Above the anticipated amount but not requiring transfusion | Hemorrhage at a level for which transfusion of 1-2 units of packed cells,<br>but no other blood products indicated | Hemorrhage with shock or coagulopathy, for which transfusion of > 2 units of packed cells or any amount of other blood components is indicated |
| Cholestasis of Pregnancy | | Serum bile acids <100umol/L, delivery at 37 or greater weeks' gestation | Serum bile acids >100umol/L, delivery 37 or greater weeks' gestation | Requiring delivery at <37 weeks' gestation | N/A |

### 1.4.1 Hypertensive Disorders of Pregnancy

The following definitions should be followed when reporting hypertensive disorders of pregnancy[1]:

**Gestational hypertension** (i.e. pregnancy-induced hypertension, grade 1): Pregnancy >20 weeks and NEW diagnosis of hypertension (≥140 mmHg systolic and/or ≥ 90mmHg) WITHOUT severe features of pre-eclampsia or proteinuria

**Pre-eclampsia WITHOUT severe features** (i.e. mild pre-eclampsia, grade 2): Pregnancy >20 weeks and NEW diagnosis of hypertension (≥140 mmHg systolic and/or ≥ 90mmHg) AND proteinuria BUT **NO** severe features which include:

- Severely elevated blood pressures, with systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg, which is confirmed after only minutes (to facilitate timely antihypertensive treatment)
- Development of a severe headache (which can be diffuse, frontal, temporal or occipital) that generally does not improve with over the counter pain medications (such as acetaminophen)
- Development of visual changes (including photopsia, scotomata, cortical blindness)
- Eclampsia, or new-onset grand mal seizures in a patient with preeclampsia, without other provoking factors (such as preexisting seizure disorder). Seizures are often preceded by headaches, visual changes or altered mental status
- New onset thrombocytopenia, with platelet count <100,000/μL
- New onset of nausea, vomiting, epigastric pain
- Transaminitis (AST and ALT elevated to twice the upper limit of normal)
- Liver capsular hemorrhage or liver rupture
- Worsening renal function, as evidenced by serum creatinine level greater than 1.1 mg/dL or a doubling of the serum creatinine (absent other renal disease)
- Oliguria (urine output <500 mL/24 h)
- Pulmonary edema (confirmed on clinical exam or imaging)

**Pre-eclampsia WITH severe features** (i.e. severe pre-eclampsia, grade 3**)**: Pregnancy >20 weeks and NEW diagnosis of hypertension (≥140 mmHg systolic and/or ≥ 90mmHg) AND severe features as listed above.

For participants with chronic hypertension with superimposed pre-eclampsia (SIPE), then chronic hypertension should be noted as a pre-existing condition and then the severity of pre-eclampsia should be graded as previously noted.

### 1.4.2 Perineal trauma

First and second-degree lacerations are normal occurrences after a vaginal delivery. Unless these tears are associated with excessive pain and/or infection, they should not be reported as adverse events. Third- and fourth-degree lacerations are unusual occurrences after a vaginal delivery and should be captured as an AE. The event should be graded by the "Estimating Severity Grade" row of the toxicity table.

### 1.4.3 Abdominal Pain

For pregnant participants, the terms and guidance as outlined in table 2 above should be used to report pelvic pain. General guidance is provided below.

- After delivery, uterine cramping, perineal pain, and bleeding that is judged by the clinician to be within the range normally anticipated in the postpartum period (approximately 6 weeks following delivery) are not reportable as an AE.

[1] Rouse CE, et al. Hypertensive disorders of pregnancy: Case definitions & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016 Dec 1;34(49):6069-6076. doi: 10.1016/j.vaccine.2016.03.038. Epub 2016 Jul 15

- For participants who are no longer pregnant, when reporting abdominal pain as an AE, pain that is gastrointestinal in nature must be differentiated from pain that is genitourinary or reproductive in nature.
- If abdominal pain is assessed as gastrointestinal in nature and no other overarching or unifying diagnosis is available, the term “abdominal pain” should be used to describe the AE on the AE Instrument. Do not report “upper abdominal pain” or “lower abdominal pain”. The term “abdominal pain” is sufficient.
- If the pain is assessed as genitourinary and a specific anatomic location is known, the term reported within the AE Instrument should be described as such (i.e., “bladder pain”).
- If the pain is assessed as reproductive in nature and a specific anatomic location is known, the term reported within the AE Instrument should be described as such (e.g., “adnexal pain”, “uterine pain”). Pain associated with menstruation is reproductive in nature and the term reported within the AE Instrument should be described using the term “dysmenorrhea”.
- If the pain cannot be localized to a specific organ, it should be described within the AE Instrument using terms that identify a reproductive or genitourinary anatomical location (e.g., “pelvic pain”, “urinary tract pain”).

### 1.4.4 Weight Loss

Unintentional weight loss prior to the pregnancy outcome should be graded and reported per the Toxicity Table.

The Toxicity Table parameter for unintentional weight loss excludes postpartum weight loss. Therefore, maternal weight loss will not be graded after pregnancy outcome in this study.

### 1.4.5 Additional Adverse Events

When the below AEs are identified, please use the following guidance on the reporting terminology:

Respiratory Tract Infection:
- Use the terms “upper respiratory tract infection” or “lower respiratory tract infection” only.
- Do *not* use “upper respiratory-bacterial” or “upper respiratory-viral”.
- Note: If a participant is suspected or confirmed to have COVID-19, “COVID-19” should be reported as the AE term.
- If deemed not to be related to COVID-19, this should be indicated in the comments along with the rationale (for example, the participant has a negative COVID-19 test result).

Viral Illness:
- Use the terms “viral illness” rather than “flu-like illness” to refer to a generalized illness presumed to be due to a virus.
- This does not apply to acute seroconversion illness in the setting of acute HIV infection, which should be reported as “seroconversion illness.”
- Note: If a participant is suspected or confirmed to have COVID-19, “COVID-19” should be reported as the AE term.
- If deemed not to be related to COVID-19, this should be indicated in the comments along with the rationale (for example, the participant has a negative COVID-19 test result).

COVID-19:
- If a participant is suspected or confirmed to have COVID-19, “COVID-19” should be reported as the AE term. It is not necessary to include details on whether suspected or confirmed in the comments.
- Grade based on the “estimating severity grade” row of the toxicity table.

Anemia:
- If treatment, including diet recommendations, are offered, use the term “anemia”.
- If no instruction is provided to the participant, report “decreased hemoglobin”.

- It is anticipated that most participants will be informed of low hemoglobin and encouraged to increase iron-rich foods. Therefore, “anemia” will be more commonly reported.
- Anemia and decreased hemoglobin should be graded based on the hemoglobin result on the DAIDS tox table.

Diarrhea:
- Use the terms “diarrhea” rather than “diarrhea infectious etiology,” “infectious diarrhea” or “diarrhea related to bacterial infection.”
- It is not necessary to specify the cause of the diarrhea in the AE term.

Gastroenteritis:
- Use the term “gastroenteritis” for clinical conditions of nausea and diarrhea.
- No need to specify “viral” or “bacterial” gastroenteritis.

Intrauterine growth restriction (IUGR)
- Refer to the FGGT for grading in the “poor fetal growth” row

### 1.4.6 Hospitalizations, ICU/NICU Admissions, Surgical Procedures

Hospitalization or admission to the ICU/NICU should not be captured as an AE/SAE; rather the underlying condition which lead to the admission should be considered an AE /SAE as applicable.
- Hospitalization for delivery is not an AE; a normal delivery is not an AE
- If a condition is considered immediately life-threatening or the condition and its resultant surgery result in a prolonged hospitalization, it will be considered a SAE.
- Prolongation of a hospitalization, including for a delivery, is deemed a SAE with the reason for the prolonged stay being the event description
- Admission to the ICU/NICU is deemed a SAE with the reason for the admission being the event description (note: admission of the infant for routine observation for neonatal opioid withdrawal is not considered an AE).

Likewise, procedures should not be captured as AEs; rather the underlying condition which lead to the procedure may be considered an AE.

*For example:*
- *An infant is hospitalized to undergo a lumbar procedure for presumed sepsis—sepsis would be considered an AE, not the lumbar puncture.*
- *A mother that undergoes a cesarean hysterectomy for post-partum hemorrhage— post-partum hemorrhage would be considered an AE, not the hysterectomy.*

### 1.4.7 Cesarean Sections

A “cesarean section” would not be considered an AE; however, the indication for the cesarean section may be reportable as either a maternal or fetal AE.

*For example:*
- *Maternal conditions (i.e., hemorrhage, preeclampsia, etc.) or fetal conditions (i.e. fetal distress, or meconium aspiration syndrome) which result in a cesarean section should be captured as AEs.*
- *If the cesarean was performed for failure to progress in labor (including conditions such as cervical dystocia, contracted maternal pelvis, large fetus, poor contraction pattern) the event should be captured as an AE but the preferred term should be ”arrest of dilation” or “arrest of descent,” as appropriate. AEs reported for cephalo-pelvic disproportion should be reported as Grade 2.*
- *A scheduled repeat cesarean section or primary cesarean section for malpresentation would not be expected to have an AE associated; however most intrapartum cesarean sections would.*

Maternal complications following cesarean section (hemorrhage, infection, scar disruption, post procedural pain, etc.) will be considered AEs regardless of the indication for the surgery. If the complication results in re-hospitalization or a prolonged hospital stay, it will be considered a SAE.

### 1.4.8 Postpartum Events

The postpartum period (approximately 6-12 weeks following delivery) is a period of physiologic transition where some adverse events are considered normal and not reportable as AEs.

- **Uterine Cramping/Perineal Pain:** After delivery, uterine cramping and perineal pain that is judged by the clinician to be within the range normally anticipated in the postpartum period are not reportable as an AE.
- **Vaginal bleeding/Discharge:** Vaginal bleeding and discharge associated with pregnancy/postpartum period (lochia) within the range of normal for the postpartum period are also considered expected and not reported as AEs.
- **Weight Loss:** The Toxicity Table excludes weight loss during the postpartum period as a reportable condition.
- **Lower extremity edema** that is judged by the clinician to be within the range normally anticipated during pregnancy is not considered to be an AE.
- **Other PP Conditions:** Outside of the conditions specified in the protocol as "not reportable" during the postpartum period, other new or worsening postpartum conditions (or, conditions listed above but judged to be outside of the range of what the investigator would consider "normal") identified during follow-up should be reported as adverse events.
- **Breast-feeding Issues/Disorders of Lactation:** Breastfeeding-related AEs (e.g. mastitis) may be observed in the postpartum period and should be reported and graded using the "Estimating Severity Grade" row of the Toxicity Table.
- **Fatigue:** Fatigue due to sleep disturbances, while expected, is also considered an AE and should be reported.
- **Post-partum mood disorders**: Mood disorder AEs (e.g. anxiety, depression, psychosis) may be observed in the postpartum period (new events or worsening of pre-existing disorders) and should be reported.

## 1.5 Infant/Fetal AE Reporting

Infant/fetal AEs are defined as outlined above (untoward medical occurrence that does not necessarily have a causal relationship with the investigational product), with the exception that infants/fetuses are not administered study product. Rather, fetal drug exposure will be considered to start in utero at the time of maternal participant enrollment.

Reporting conventions for diagnosed conditions related to the fetus will depend on whether the AE is or is not considered a congenital anomaly.

### 1.5.1 Fetal Adverse Events That Are Not Congenital Anomalies

- Report on the maternal AE Instrument at the time of diagnosis.
- Isolated findings such as abnormal fetal heart rate should <u>not</u> be reported as an AE, only the outcome if relevant—for example, fetal distress.
- Poor fetal growth (as defined in the FGGT) or any other fetal abnormalities diagnosed by ultrasound (e.g. echogenic intracardiac focus) doppler, or other means that are not considered congenital anomalies should also be reported as AEs within the maternal section of REDCap.
- Some fetal AEs may resolve prior to pregnancy outcome, but if not resolved while the participant is still pregnant, AEs related to the fetus should be resolved at the time of delivery. Any infant-associated conditions that are present after birth should be opened as new AEs in the infant section of RedCap using the Infant AE Instrument.

  *For example:*
  - *Intrauterine growth restriction (IUGR) is diagnosed on ultrasound. This should be reported in real time on the maternal AE Instrument. At delivery, the AE should be marked "resolved." If, after delivery, the infant is found to be low birth weight and/or small for gestational age, a new AE should be reported using the infant AE Instrument.*

### 1.5.2 Fetal Adverse Events That Are Congenital Anomalies

- Congenital anomaly AEs (i.e. congenital, familial, and genetic disorders) identified while the fetus is in utero (e.g. on ultrasound) should be source documented in chart notes, but only reported as an AE after the infant is born and a full evaluation can be conducted. In most cases, reporting of congenital anomalies will be done using the Infant AE Instrument**.**
  *For example:*
  - *A fetus is diagnosed with an atrial septal defect on ultrasound. The site team should source document this in the maternal study file at the time the defect is identified, but no AE reporting is required at this time. Upon delivery, a full evaluation of the infant should be conducted and, if the atrial septal defect (or another cardiac defect) is confirmed, a new AE should be reported using the infant AE Instrument (enrolled infants).*

Infant AEs should be graded using the DAIDS Toxicity Table, version 2.1, dated July 2017.

In addition, the following protocol-specific grading tables should be used:

| PARAMETER | Grade 0 Normal | Grade 1 MILD | Grade 2 MODERATE | Grade 3 SEVERE | Grade 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|---|
| Creatinine (neonates 0-28 days old) | N/A | 1.1 mg/dL to <1.6 mg/dL | 1.6 mg/dL to <2.1 mg/dL | 2.1 mg/dL to 3.0 mg/dL | >3.0 mg/dL |
| Creatinine (infants >28 days old) | N/A | 0.5 mg/dL to <0.7 mg/dL | 0.7 mg/dL to <0.9 mg/dL | 0.9 mg/dL to 1.2 mg/dL | >1.2 mg/dL |

As noted above and the STORC protocol, fetal losses (Stillbirth, Preterm Birth, and Spontaneous Abortions/Miscarriages) will not be reported as AEs however they are captured as a primary outcome on the pregnancy outcome CRF. Maternal conditions that either result in or result from fetal losses are reported as AEs.

### 1.5.3 Common Infant Conditions AE Reporting Guidance

There are conditions that are common within the first year of an infant's life, some of which are summarized in this section with guidance for preferred AE reporting term and grading. Appropriate referrals should be made, as applicable, whenever infant AEs are identified.

**Concomitant medications:**
Medication use should be documented in the Infant Concomitant Medication Instrument.

- Include medications given at birth, including erythromycin ophthalmic ointment and vitamin K
- Infant vaccines should be recorded
- Topical steroid and antifungals (drops, shampoo, creams) should also be recorded
- Over the counter diaper creams like Desitin or A+D are not necessary to record, however prescriptions like Pittsburgh paste should be included
- Vitamin D use as a supplement is not necessary to record
- Other medications used for a medical event or adverse event should be recorded

**Rashes:**
The following are rashes common in the newborn and are not considered adverse events. Rather they should be documented in the research record note as variants of normal.

- Acne neonatorum
- Irritant/contact dermatitis from saliva (around mouth and chin)
- Miliaria rubra (heat rash)
- Milaria
- Erythema toxicum neonatorum

- Transient neonatal pustular melanosis
- Milia
- Seborrheic dermatitis (cradle cap) not requiring prescription shampoo
- Irritant diaper rash (candida diaper rash should be reported)
- Congenital dermamelanosis/dermal melanosis/mongolian spots
- Nevus simplex/Stork bites (pink flat birthmarks on back of neck, forehead, eyelids, nose)
- Strawberry hemangioma, unless location requires an intervention
- Isolated café-au-lait spots

The following rashes/skin issues would be adverse events:

- Infectious rashes (viral, fungal, bacterial) should be documented as AEs. If treatment is required, grade as grade 2.
- Atopic dermatitis (eczema)
- Skin injury from birthing process (forceps, scalp electrode or birth canal)

| PARAMETER | Grade 0 Normal | Grade 1 MILD | Grade 2 MODERATE | Grade 3 SEVERE | Grade 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|---|
| Atopic dermatitis/eczema | N/A | Mild transient rash requiring topical steroid treatment | Moderate rash requiring systemic treatment (such as, antimicrobials for superimposed infection) | Severe rash requiring hospital admission | N/A |
| Candida infections including thrush and candida diaper dermatitis | N/A | Mild infection resolved with topical treatment (for diaper), Oral nystatin for thrush | Moderate infection requiring a repeat course of treatment | Severe infection requiring hospital admission | N/A |

All other rashes should be graded according to the "Estimating Severity Grade" row of the Toxicity Table

**Thrush (candida infection):**

- Thrush should be reported as candida infection. If the infant is a newborn (< 28 days), report as neonatal candida infection.
- Report associated maternal AEs as appropriate (i.e. Nipple Thrush).

**GENERAL INFANT FINDINGS**

The following infant events are common issues in newborns/infants are not considered adverse events:

- Isolated feeding issues without gradable weight loss
  - For feeding issues that result in a gradable weight loss, see next section
- Teething
- Ankyloglossia
- Ligamentous Hip clicks

- Plagiocephaly
- Torticollis
- Soft 1-2/6 murmurs.
- Constipation
- Sacral dimple (not requiring follow up MRI; initial US is OK)

**INFANT WEIGHT LOSS/POOR WEIGHT GAIN**

Note: use appropriate WHO growth curves for infants that are born at term or Fenton Preterm Growth Chart if infant born at <37 weeks to determine percentiles

AAP has replaced the term FTT with the new "Growth Faltering or Weight Faltering". See the following link:

Failure to Thrive or Growth Faltering: Medical, Developmental/Behavioral, Nutritional, and Social Dimensions | Pediatrics In Review | American Academy of Pediatrics (aap.org)

Zero – one month of age:

- Birth weights should be graded per the table below with the AE term "small for gestational age".
- AEs reported for small for gestational age should remain as ongoing until either weight-for-age measurements resolve to non-gradable OR until 28 days old.
- Average expected weight gain:
  - Weight loss is accepted until 14 days of life, after that weight should be greater than birth weight
  - 0 – 4 months of life: typically expect 20 - 30g/day weight gain
- Newborns (defined as infants < one month of age) should be assessed for poor weight gain, if <15 grams/day of weight gain then the correct AE term should be "growth faltering"
- Also NBs with weight < 3rd percentile or down-crossing 2 major percentile lines should be labeled as "growth faltering".
- If grading criteria are met for 'growth faltering' in infants older than one month of age(see next bullet below), a new AE for 'growth faltering' should be reported and followed to resolution or stabilization.

| PARAMETER | Grade 0 Normal | Grade 1 MILD | Grade 2 MODERATE | Grade 3 SEVERE | Grade 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|---|
| Small for Gestational Age* | At or above 10th percentile | <10th percentile but ≥ 3rd percentile | N/A | < 3rd percentile | N/A |
| Growth faltering (only for first month) | weight loss <10% of birth weight in the first 10 days; and/or gaining 15-20 gr per day | 10-12% weight loss in the first week; gaining 10-15 gr/day | 12-14% weight loss in the first week; gaining 5-9 gr/day | 15-19% weight loss in the first week active weight loss (< 5gr/day or no gain) | 20% or greater weight loss in the first week; active weight loss (no gain) |

*Small for gestational age should be determined by fetal growth ultrasound or by birthweight percentile for gestational age at newborn exam.

Greater than one month of age:

Average expected weight gain:

- At about 4 months of life expect approximately 15-20g/day weight gain
- At around 6 months of life expect closer to 10-15g/day weight gain

**Undernutrition, stunting, and wasting (growth faltering):**

- Growth faltering is typically diagnosed when height, weight or weight for length measurements are < 3rd percentile OR the height or weight crosses two major growth percentiles on the growth curve.

| PARAMETER | Grade 0 Normal | Grade 1 MILD | Grade 2 MODERATE | Grade 3 SEVERE | Grade 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|---|
| Growth Faltering (>28 days) | N/A | 3rd-10th%ile on appropriate growth curves (weight, length or weight for length) | 0.1-3rd %ile on appropriate growth curve (weight, length or weight for length) OR crossing two growth percentiles | <0.1%ile on appropriate growth curve (weight, length or weight for length) | < 0.1% ile on appropriate growth curve, with life threatening consequences |

**Infant diarrhea:**

- Grade using the Diarrhea < 1 year of age row of the Toxicity Table below.
- Report as "diarrhea" or "infectious diarrhea".
- If the infant is a newborn (< 28 days), report "neonatal diarrhea" or "neonatal infectious diarrhea".

| PARAMETER | Grade 0 Normal | Grade 1 MILD | Grade 2 MODERATE | Grade 3 SEVERE | Grade 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|---|
| Diarrhea <1 year of age | N/A | Liquid stools (more unformed than usual) but usual number of stools | Liquid stools with increased number of stools OR mild dehydration | Liquid stools with moderate dehydration | Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock) |

**Infant vomiting:**

- Report if determined to be vomiting based on clinical judgement (i.e. not spit up).
- Grade using the vomiting row of the Toxicity Table below.

| PARAMETER | Grade 0 Normal | Grade 1 MILD | Grade 2 MODERATE | Grade 3 SEVERE | Grade 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|---|
| Vomiting | N/A | Transient or intermittent AND no or minimal interference with oral intake | Frequent episodes with no or mild dehydration | Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated (e.g. IV fluids) | Life-threatening consequences (e.g., hypotensive shock) |

**Lower respiratory tract infection (bacterial or viral infection):**

- Report as "lower respiratory tract infection".
- Characterized in infants by poor feeding, irritability and lethargy, grunting/cyanosis, fever, cough/wheeze, chest drawing in.

- Grade using the Dyspnea or Respiratory Distress row of the Toxicity Table below.

| PARAMETER | Grade 0 Normal | Grade 1 MILD | Grade 2 MODERATE | Grade 3 SEVERE | Grade 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|---|
| Dyspnea or Respiratory Distress | N/A | Dyspnea on exertion with no or minimal interference with usual social & | Dyspnea on exertion causing greater than minimal interference with usual social & | Dyspnea at rest causing inability to perform usual social & functional | Respiratory failure with ventilator support indicated (e.g., |

| | | | | | |
|---|---|---|---|---|---|
| | | functional activities OR wheezing OR minimal increase in respiratory rate for age | functional activities OR nasal flaring OR intercostal retractions OR pulse oximetry 90 to < 95% | activities OR pulse oximetry < 90% | CPAP, BPAP, intubation) |

**Neonatal Opioid Withdrawal Syndrome**:

- Some maternal study participants will have opioid use disorder (OUD) and may be prescribed either methadone or buprenorphine as treatment.
- Infants who are exposed to these medications often experience neonatal opioid withdrawal syndrome (NOWS). Given that this is an expected outcome for this treatment, NOWS will not be reported as an AE. Many hospitals caring for opioid exposed infants require a standard period of observation in the hospital and those who require pharmacologic treatment for NOWS can remain in the hospital for up to a month. Stays beyond the expected observation for issues/concerns or are treated for NOWS would be captured as an AE/SAE.
- The site pediatric co-investigators will review all infant delivery records to ensure that there are no hospital events that are outside the scope of standard NOWS findings
    - For example: pneumonia, sepsis, and hypoglycemia. Since these events are outside of the standard NOWS findings, they would be captured as AEs.

### 1.5.4 Severe Neonatal Morbidity Admission to Neonatal Intensive Care Unit (NICU)

The following events are Neonatal Safety protocol defined Secondary Endpoints.

- Severe neonatal morbidity admission to neonatal intensive care unit
    - Perinatal *preterm* (<37 weeks) composite defined as:
        - fetal or neonatal death,
        - severe bronchopulmonary dysplasia (grade 3),
        - intraventricular hemorrhage grades III-IV,
        - necrotizing enterocolitis (proven – Bell Stage 2A or greater),
        - periventricular leukomalacia,
        - retinopathy of prematurity stage III-V, or
        - proven sepsis (early or late)
    - Perinatal *term* (>= 37 weeks) composite defined as:
        - fetal or neonatal death,
        - respiratory support (defined as any mechanical ventilation, any high flow nasal cannula or continuous positive airway pressure for >4 hours),
        - Apgar score ≤ 3 at 5 minutes,
        - hypoxic ischemic encephalopathy,
        - seizure,
        - infection (sepsis or pneumonia),
        - birth trauma,
        - meconium aspiration syndrome,
        - intracranial or subgaleal hemorrhage, or
        - hypotension requiring vasopressor support

The event(s) that lead to a NICU admission should be listed as the SAE term(s). As a reminder, use a diagnosis if available rather than individual symptoms/signs/laboratory findings related to the diagnosis. The details including individual symptoms/signs/laboratory findings related to the diagnosis should be included in the Comments Section of the SAE.

## 1.6 Reporting Congenital Anomalies

Congenital Anomalies may be considered SAEs. Note that all congenital anomalies (major/minor) should be reported on the REDCap Pregnancy Outcome Instrument and on an Infant AE Instrument, regardless of whether they are reported as a SAE.

The European Surveillance of Congenital Anomalies (EUROCAT) Guide 1.4: Instruction for the registration of congenital anomalies (EUROCAT Central Registry, University of Ulster) should be used as the reference which defines minor and major anomalies for STORC. https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/JRC-EUROCAT-Full-Guide-1-4-version-01-Dec-2020.pdf

- Chapters 3.2 (Minor Anomalies for Exclusion) defines minor anomalies
- Chapter 3.3 (EUROCAT Subgroups of Congenital Anomalies) defines major anomalies

Clinically insignificant physical findings at birth, including those regarded as normal variants, do not meet reporting criteria as an SAE. Examples of conditions considered to be minor anomalies are summarized in EUROCAT guidelines Chapters 3.2 (Minor Anomalies for Exclusion). However, if a clinically significant anomaly is reported, all other findings (including those of no individual significance) should be included in the same SAE report.

*For example:*

- *An isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant with no other findings would not be reported as a SAE, but polydactyly or Mongolian spot occurring with a major cardiac defect would be reported and included in the SAE report.*

Sites should always overreport versus not report and potentially miss an important primary outcome.

Conditions outlined in the EUROCAT guidelines Chapter 3.3 (EUROCAT Subgroups of Congenital Anomalies) are reportable to FDA as SAEs through a MedWatch Form if thought to be related to the study medication. Although organized slightly differently, the major anomalies listed in EUROCAT cover those listed in the Guidelines for Conducting Birth Defects Surveillance, National Birth Defects Prevention Network (NBDPN). An event that is not included in the list, but is deemed important by the site investigator, should also be reported to FDA utilizing a MedWatch Form. MedWatch Forms must be emailed to the Protocol Chair and University of Pittsburgh Regulatory Coordinator within 5 days as detailed in REDCap.

### 1.7 Reporting Maternal or Infant Deaths

- All deaths related to an AE are to be classified as grade 5 and reported as an SAE.
- In the event of a maternal or infant death, sites should capture as much information as possible related to the circumstances of the death.
- An autopsy report should be pursued, if possible. SAE and AEs should be updated as appropriate if new information becomes available as a result of the autopsy.

### 1.8 Adverse Event Outcomes and Follow-Up Information: During the Study

All AEs identified must be followed clinically until they resolve (return to baseline) or stabilize (persist at a certain severity grade above baseline for one month).

- At each follow-up visit, an authorized study clinician should review all previously identified ongoing AEs and evaluate/document their current status.
- For all AEs, outcomes must be reported within the AE Instrument and chart notes, as applicable
- In many cases, the final outcome of a reportable AE may not be available when the AE Instrument is first completed. In such cases, the AE Instrument should be updated when the final outcome becomes available.
- Resolution dates for AEs of any AE requiring treatment should be based on the date when all associated symptoms resolve or when treatment is completed (whichever occurs later).
- For asymptomatic STIs, the resolution date is the date the participant completes treatment.

Clinical management and follow-up of AEs detailed in the protocol should take precedence. If an AE is not addressed in the protocol, follow-up evaluations should be performed at an appropriate schedule as determined by the clinician until resolution or stabilization (the same grade for 30 days) has been documented. In general, evaluations of an AE may be performed at any time if required to properly monitor and/or manage participant safety, at the discretion of the site PI or designee. It is acceptable for AE follow-up/evaluation to be conducted over the phone or by review of the medical record, as clinically appropriate.

### 1.9 Adverse Event Outcomes and Follow-Up Information: After the participant's final study visit or after completion of the entire study

A subset of AEs must be followed after a participant's final visit.

- SAEs that are ongoing at the participant's final visit:
- AEs that are found to have increased in severity at the participant's final visit
- Any new grade 3 AE uncovered at the participant's final visit

For any AE that fall into one of the categories above, the site PI/designee must establish a clinically appropriate follow-up plan.

- At a minimum, the AE must be re-assessed by study staff 30 days after the participant's study exit visit; additional evaluations also may take place at the discretion of the site PI/designee.
- If the AE is not resolved or stabilized at the time of re-assessment, additional assessments should occur at the following frequency:
    - If the study is ongoing, continue to reassess at least once per month while the study is ongoing until resolution/stabilization.
    - If the AE has not resolved by study end (i.e., once all participants have completed the study), these AEs should be re-assessed at least once within 30-60 days after the study end date. The site is to send a summary regarding the case to the PSRT at the time of reassessment. The PSRT may request additional follow-up.

For AEs that are continuing at the participant's final visit but do not meet the criteria above, the site PI/designee may determine whether the AE needs to continue to be followed.

*For example:*

- *A maternal participant has depression noted at her 6-week follow-up visit and was referred for further evaluation. The site PI/designee may determine that follow-up is warranted. In this case, the plan and frequency for clinical management will be determined by the site PI/designee. The PSRT may be consulted as needed.*

Importantly, site will adhere to the following documentation guidelines for AEs that are re-assessed after a participant's termination visit:

- Information on the status of the AE at the time of re-assessment will be recorded in REDCap, and may be communicated to the PSRT, if applicable
- All AEs that are ongoing at the time of final clinic visit should have a status/outcome marked as "continuing at the end of study participation."
- Regardless of whether a participant has an ongoing AE requiring reassessment per protocol or clinical discretion, or if lab results from samples drawn during her final visit are still pending, the termination date should be documented as the date of her final visit.

### 1.10 Reporting Recurrent Adverse Events

If an AE previously reported within an AE Instrument resolves and then recurs at a later date, the second occurrence may be reported as a new AE on a separate AE Instrument, or the previous occurrence of this same AE may be reopened and documented as ongoing, depending on participant well-being and site preference.

Regular occurrences of the same adverse event that are expected in follow-up are not typically considered separate adverse events.

*For example:*

- *A participant reports a single episode of Grade 1 acid reflux that the site PI determines not related to study product. Acid reflux is captured as an AE with an onset and outcome date. At the next visit, the participant notes that Grade 1 acid reflux is now a recurring 1-2 times a week. Rather than open a separate AE for each occurrence of acid reflux, the site can update the first AE for acid reflux and note in the comments section that this is a recurring event. The status should be changed to ongoing.*

Some participants may have chronic, episodic, pre-existing conditions. In these situations, if the participant experiences an episode of the condition during follow-up that has not increased in severity or frequency from the baseline condition, it would not be considered an AE.

*For example:*

- *If a participant reports that she has ear pain about three times a month before the study, and this continues at the same frequency and severity during the study, ear pain should not be reported as an AE.*

### 1.11 STORC Safety Monitoring, Review, and Oversight

Participant safety is of paramount importance. Primary safety monitoring and safeguarding of individual study participants is the responsibility of local study staff, under the direction of the site-PI. Any study staff member who is regularly involved in the source documentation of safety data for this trial (including documentation of participant symptoms, physical or obstetric exam findings, pelvic exam findings etc.) should be licensed/trained and listed as a sub-investigator on the FDA Form 1572. Decisions regarding relationship to study product and study product management must be done by a study physician listed on the FDA Form 1572 and should be completed directly in RedCap.

The site PI/designated study staff are responsible for completing Instruments within RedCap according to the STORC Study Data Management Plan, in order for the safety data to be available in a timely manner for study-specific safety monitoring procedures.

The STORC PSRT will be charged with reviewing participant safety data as no DSMB is planned for this study. The PSRT will routinely review safety data reports prepared by the STORC Data Management Team. The PSRT will meet remotely on a regular basis to discuss study safety data and any potential safety concerns, as outlined in the protocol. PSRT meetings will have an open session in which all team members will be present and able to participate. Following the open session, the external safety physicians will have a closed session to determine if the study should proceed as designed, proceed with design modifications, or be discontinued. Ad hoc meetings will also be conducted in a similar fashion.

The STORC Study Management Team will meet separately to review STORC study progress, including rates of participant accrual, retention, completion of primary and secondary endpoint assessments, and any study related issues as outlined in the STORC Study Management Plan and Risk Mitigation Plan.

The STORC Clinical Management SSP, Version 2.0, has been reviewed and approved by the Protocol Chair, Dr. Catherine Chappell, MD, MSc.

DocuSigned by:
Catherine Chappell
Catherine Chappell, MD, MSc
Signer Name: Catherine Chappell
Signing Reason: I approve this document
Signing Time: 12/14/2022 | 6:37:00 AM CST
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12/14/2022
Date