Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0

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DAIDS Regulatory Support Center (RSC) Safety Office

Site Specific Training Webinar
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DAIDS RSC Regulatory Support Center

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Objectives

At the end of this session, participants should be able to demonstrate an understanding of:

- The purpose of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE GT)
- How to use the DAIDS AE GT
- Changes in the new version of the DAIDS AE GT

Background

- **Adverse event (AE) data is collected during clinical trials sponsored by DAIDS support the safety and efficacy analysis of investigational products**
  - All AEs must be graded for severity
  - Incorrect and inconsistent grading can:
    - Lead to inaccurate data analyses and interpretation
    - Negatively impact the well-being of study participants and future patients using the product

Purpose

- **The DAIDS AE GT:**
  - Standardizes the evaluation of severity grading
  - Promotes consistency in AE term reporting
- **The DAIDS AE GT should be used for all DAIDS supported studies, unless otherwise stated in the study protocol**
- **Sites need to report the parameter as written if the clinical diagnosis is appropriate**

DAIDS AE Grading Table Version 1.0

Assessment of AEs

- **All AEs need to be assessed for:**
  - Seriousness
  - **Severity**
  - Relationship
  - Expectedness

Seriousness is NOT the same as Severity

Seriousness

- Based on outcome of the AE and is a factor in determining reportability (regulatory definition)
- Determined using the SAE criteria

Severity

- Based on the intensity of the AE and is not a factor in determining reportability (clinical description)
- Determined using the DAIDS AE grading table

DAIDS Grading Scale

- **Events are graded on a severity scale of 1-5:**
  - **1** – Mild
  - **2** – Moderate
  - **3** – Severe
  - **4** – Potentially Life-threatening
  - **5** – Death

Points to Consider

- **Determination of the AE term**
  - Select the term that best describes what the participant experienced
  - Use AE terms as written in the DAIDS AE GT v1.0, if applicable
    - FDA guidance: Investigators need to be consistent and use scientific terminology when reporting AEs
  - For DAERS reporting: Primary AE vs. Other Events
    - Other Events: Clinically significant events associated with the Primary AE that more fully describe the nature, severity, or complications of the Primary AE
    - Severity grade of the Other Events must be lower than or equal to the severity grade of the Primary AE

Points to Consider

- **Laboratory Values**
  - Asymptomatic abnormal laboratory findings without an accompanying AE do not qualify for expedited reporting, unless specified in the protocol
  - Any value between ULN and grade 1 or LLN and grade 1 should not be graded and reported as AE
  - If local normal values fall within GT laboratory ranges, severity grading is based on GT ranges, unless there is a protocol specific grading criterion for the laboratory value

Points to Consider

- Use age and sex values as applicable
- The parameters should be used for grading both adult and pediatric populations unless a distinction has been made
- Select the higher grade if the severity of an AE falls between two grades
- Unless noted, laboratory values are for term neonates; preterm neonates are assessed using local lab normal ranges

Points to Consider

- **All pregnancy outcome parameters should be reported using mother's participant ID (PID)**
  - If infant is not enrolled in the same study as mother, report any identified birth defects using mother's PID
  - If infant is enrolled in the same study as mother, report any identified birth defects using infant's PID
  - Refer to applicable network standards for reporting abnormal pregnancy outcomes on CRFs

Points to Consider

- Use the below table for estimating the severity grade of a clinical AE not specifically listed in the GT

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

Points to Consider

- **Addenda 1-3: Used in Microbicide studies as the primary grading tables, but may be used in other protocols as the main table or adjuncts to the main GT, if specified in the protocol**
  - Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies
  - Addendum 2 – Male Genital Grading Table for Use in Microbicide Studies
  - Addendum 3 – Rectal Grading Table for Use in Microbicide Studies

Case Study Discussions

Case Study 1: Narrative

- **26 May 2014: 36 year old HIV infected Black female subject enrolled at ~28 weeks gestation in mother-infant study; mother started on study agents ABC and XYZ**
- **11 Aug 2014: Mother delivered at 39 weeks gestation by cesarean section**
  - At birth, infant's Apgar scores were 6 at 5 minutes and 9 at 10 minutes, weight = 3.35 kg, length = 47.5 cm, HR = 140 bpm, RR = 62 bpm; PE = pale, flexed, not crying; infant started on oral zidovudine per local standard of care

Case Study 1: Narrative

- **12 hours after birth: Infant developed tachypnea, RR = 62 bpm, Pulse Ox on room air = 70%**
- **Transferred to NICU, 100% oxyhood, Pulse Ox on room air = 80%, pH = 7.48, pCO2 = 27, pO2 = 251, HCO3 = 20**
  - PE: Systolic murmur heard along left sternal border
  - Echo: Moderate PDA, ASD, patent foramen ovale, mild TR, trivial MR
- **The subject was diagnosed with respiratory distress**

Case Study 1: Grading Table

- **What table section and parameter will be used?**
  - Reference the Respiratory section; *Dyspnea or respiratory distress, Pediatric ≤ 14 years* parameter

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pediatric ≤ 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

Case Study 1: Severity Grade

- **What is the severity grade?**
  - Grade would be assessed as severity grade 3 because subject had pulse oximetry of 70-80%

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pediatric ≤ 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

Case Study 2: Narrative

- **10 Jan 2014: 30 year old HIV-infected Black male subject enrolled and started on study agent XYZ**
- **12 May 2014: Subject was hit by a car while walking and sustained a leg fracture**
  - Admitted to the hospital with a diagnosis of left tibia and ankle fracture that requires surgical repair
  - Given pain medication and prepared for surgery
- **13 May 2014: Subject's fractures were repaired with plate insertions, given pain medication and antibiotics**
- **20 May 2014: Subject was ambulatory with walker, discharged with pain medication**

Case Study 2: Grading Table

- **What table section and parameter will be used?**
  - Reference the Estimating Severity Grade section

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

Case Study 2: Severity Grade

- **What is the severity grade?**
  - Grade would be assessed as severity grade 4 because of hospitalization for surgical repair to prevent persistent disability

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

Case Study 3: Narrative

- **15 June 2014: 40 year old HIV-infected White female subject enrolled and started on study agent XYZ**
  - No significant medical history, PE normal, routine blood draw
  - CBC showed ANC=559.70 cells/mm3, subject was called for a redraw
- **16 June 2014: Redraw ANC= 490.62 cells/mm^3, PE normal**
- **12 Sep 2014: ANC was 2402.10 cells/mm^3**

Case Study 3: Grading Table

- **What table section and parameter will be used?**
  - Reference the Laboratory-Hematology section; *Absolute neutrophil count (ANC), Adult and Pediatric > 7 days* parameter

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Adult and Pediatric > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*

Case Study 3: Severity Grade

- **What is the severity grade of the ANC on 15 June 2014?**
  - Grade would be assessed as severity grade 3 because 559.70/mm^3 falls between 500-749/mm^3

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Adult and Pediatric > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*

Case Study 3: Severity Grade

- **What is the severity grade of the ANC on 16 June 2014?**
  - Grade would be assessed as severity grade 4 because 490.62/mm^3 is less than 500/mm^3

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Adult and Pediatric > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*

DAIDS AE Grading Table Version 2.0

Why a new DAIDS AE GT version?

- **Since the publication of v1.0 (with clarification in 2009):**
  - DAIDS scientific knowledge and experience have expanded
  - Regulatory reporting regulations emphasize the use of MedDRA (Medical Dictionary for Regulatory Activities) to harmonize and standardize AE term reporting

New DAIDS AE GT Development

- **Work began in 2011 to revise the GT**
  - Collaborative effort included NIH, Subject Matter Experts (SMEs) from DAIDS and other NIH Institutes, DAIDS MOs, DAIDS SPT, DAIDS RSC Safety Office staff
  - Input on draft versions sought from NIH and external reviewers including DAIDS-affiliated Data Management Centers (DMCs), Operation Centers, and numerous government and non-government affiliated medical SMEs

What's new?

- **Added new medically important AE terms and removed terms that were no longer medically relevant or too general for the HIV-infected population**
- **Revised some grading descriptions to appropriately reflect current information:**
  - Certain hematology parameters
  - FDA guidance on the use of local laboratory reference values
  - Ethnic differences in parameter limits among certain healthy adolescent and adult populations

What's new?

- **Updated the following sections:**
  - Glossary and Acronyms
  - Instructions for Use
  - Appendix A
- **Created new medical condition parameters:**
  - Pregnancy, Puerperium, and Perinatal
- **Added a Table of Contents**

Where to Get Help

- **DAIDS RSC Safety Office:**
  - E-mail: DAIDSRSCSafetyOffice@tech-res.com
  - Telephone: +1-301-897-1709
    or 1-800-537-9979 (USA only)
  - FAX: +1-301-897-1710
    or 1-800-275-7619 (USA only)
  - Business Hours: Monday through Friday
    8 a.m. to 5 p.m. EST

- **DAIDS RSC Website:** http://rsc.tech-res.com/

Questions?