

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

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**Corrected Version 2.1  
July 2017**

**Division of AIDS  
National Institute of Allergy and Infectious Diseases  
National Institutes of Health  
US Department of Health and Human Services**



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# Glossary and Acronyms

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase ( <i>serum glutamic pyruvic transaminase</i> )
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase ( <i>serum glutamic-oxaloacetic transaminase</i> )
AV	Atrioventricular
Basic Self-care Functions	<p><u>Adult</u> Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding.</p> <p><u>Young Children</u> Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.</p>
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio

# Glossary and Acronyms

Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	<p>Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example:</p> <p><u>Adults</u> Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby.</p> <p><u>Young Children</u> Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.</p>
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

# Introduction

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The Division of AIDS (DAIDS) oversees more than 300 clinical trials domestically and internationally, which evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

Over the years, DAIDS scientific knowledge and experience have expanded, necessitating revisions of the DAIDS grading table which serves as a guide for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in DAIDS-sponsored and -supported clinical trials. The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* updates and replaces version 2.1 (March 2017).

DAIDS is grateful to the DAIDS Grading Table Working Group, numerous government and non-government affiliated medical subject matter experts and reviewers who were instrumental in the revision of the DAIDS grading table.

# Instructions for Use

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## General Considerations

The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term “severe” is not the same as the term “serious” in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note: This grade is not specifically listed on each page of the grading table*).

Other points to consider include:

- Use age and sex values as applicable.
- Unless noted, laboratory values are for term neonates. Preterm neonates should be assessed using local laboratory normal ranges.
- Where applicable, Standard International (SI) units are included in italics.

## Selecting and Reporting a Primary AE Term

When selecting a primary AE term to report, sites should select the term that best describes what occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report “Acute Allergic Reaction” as the primary AE term.

Primary AE terms should be reported using the DAIDS Adverse Experience Reporting System (DAERS) only if they meet expedited reporting criteria. However, all primary AE terms should be reported using protocol-specific case report forms (CRFs). Because the reported information is stored in different databases (i.e., safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

# Instructions for Use

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When reporting using DAERS, other clinically significant events associated with a primary AE term that more fully describe the nature, severity, or complications of the primary AE term should be entered in the “Other Events” section. However, the severity grade for these events must be lower than or equal to the severity grade of the primary AE term. In the example above, dyspnea and angioedema of the face may be entered in the “Other Events” section, because they are more descriptive and provide additional information on the severity of the acute allergic reaction. However, their severity grades must be lower than or equal to the severity grade of the primary AE term of “Acute Allergic Reaction”.

Differences exist in the reporting and recording of information (e.g., signs and symptoms, clinically significant events) in DAERS and CRFs. Therefore, sites should refer to their protocols and CRF requirements for further instructions.

## **Grading Adult and Pediatric AEs**

When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If no distinction between adult and pediatric populations has been made, the listed parameter should be used for grading an AE in both populations.

## **Reporting Pregnancy Outcomes**

In the *Pregnancy, Puerperium, and Perinatal* section, all parameters are pregnancy outcomes and should be reported using the mother's participant ID. If an infant is not enrolled in the same study as the mother, any identified birth defects should be reported using the mother's participant ID. However, if an infant is enrolled in the same study as the mother or in another study, any identified birth defects should be reported using the infant's participant ID. Sites should refer to the applicable network standards for reporting abnormal pregnancy outcomes on the CRFs.

## **Determining Severity Grade for Parameters between Grades**

If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

## **Laboratory Values**

*General.* An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the clinical case report forms.

*Values below Grade 1.* Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

*Overlap of Local Laboratory Normal Values with Grading Table Ranges.* When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory

# Instructions for Use

value. For example, "Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory's normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant's magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

## Appendix Usage

Appendix A takes priority over the main grading table in all assessments of total bilirubin for term and preterm neonates.

## Using Addenda 1-3: Grading Tables Used in Microbicide Studies

In protocols involving topical application of products to the female and male genital tracts or rectum, strong consideration should be given to using Addenda 1-3 (see below) as the primary grading tables for these areas. Although these grading tables are used specifically in microbicide studies, they may be used in other protocols as adjuncts to the main grading table (i.e., the *Division of AIDS (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0*). It should be clearly stated in a protocol which addendum is being used as the primary grading table (and thus takes precedence over the main grading table) and which addendum is being used in a complementary fashion.

- Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies- <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>
- Addendum 2 – Male Genital Grading Table for Use in Microbicide Studies – <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>
- Addendum 3 – Rectal Grading Table for Use in Microbicide Studies – <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>

## Estimating Severity Grade for Parameters Not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event <b>NOT</b> identified elsewhere in the grading table	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

# Major Clinical Conditions

## Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Arrhythmia</b> (by ECG or physical examination) <i>Specify type, if applicable</i>	No symptoms <u>AND</u> No intervention indicated	No symptoms <u>AND</u> Non-urgent intervention indicated	Non-life-threatening symptoms <u>AND</u> Non-urgent intervention indicated	Life-threatening arrhythmia <u>OR</u> Urgent intervention indicated
<b>Blood Pressure Abnormalities<sup>1</sup></b> <b>Hypertension</b> (with the lowest reading taken after repeat testing during a visit) ≥ 18 years of age	140 to < 160 mmHg systolic <u>OR</u> 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic <u>OR</u> ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic <u>OR</u> ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) <u>OR</u> Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95 <sup>th</sup> to < 99 <sup>th</sup> percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99 <sup>th</sup> percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) <u>OR</u> Hospitalization indicated
<b>Hypotension</b>	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms <u>AND</u> IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
<b>Cardiac Ischemia or Infarction</b> <i>Report only one</i>	NA	NA	New symptoms with ischemia (stable angina) <u>OR</u> New testing consistent with ischemia	Unstable angina <u>OR</u> Acute myocardial infarction
<b>Heart Failure</b>	No symptoms <u>AND</u> Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) <u>OR</u> Intervention indicated (e.g., oxygen)	Life-threatening consequences <u>OR</u> Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

<sup>1</sup> Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

## Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Hemorrhage</b> (with significant acute blood loss)	NA	Symptoms <u>AND</u> No transfusion indicated	Symptoms <u>AND</u> Transfusion of $\leq 2$ units packed RBCs indicated	Life-threatening hypotension <u>OR</u> Transfusion of $> 2$ units packed RBCs (for children, packed RBCs $> 10$ cc/kg) indicated
<b>Prolonged PR Interval or AV Block</b> <i>Report only one</i> <i>&gt; 16 years of age</i>	PR interval 0.21 to $< 0.25$ seconds	PR interval $\geq 0.25$ seconds <u>OR</u> Type I 2 <sup>nd</sup> degree AV block	Type II 2 <sup>nd</sup> degree AV block <u>OR</u> Ventricular pause $\geq 3.0$ seconds	Complete AV block
<i><math>\leq 16</math> years of age</i>	1 <sup>st</sup> degree AV block (PR interval $>$ normal for age and rate)	Type I 2 <sup>nd</sup> degree AV block	Type II 2 <sup>nd</sup> degree AV block <u>OR</u> Ventricular pause $\geq 3.0$ seconds	Complete AV block
<b>Prolonged QTc Interval</b> <sup>2</sup>	0.45 to 0.47 seconds	$> 0.47$ to 0.50 seconds	$> 0.50$ seconds <u>OR</u> $\geq 0.06$ seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
<b>Thrombosis or Embolism</b> <i>Report only one</i>	NA	Symptoms <u>AND</u> No intervention indicated	Symptoms <u>AND</u> Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

<sup>2</sup> As per Bazett's formula.

# Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Alopecia</b> (scalp only)	Detectable by study participant, caregiver, or physician <u>AND</u> Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection <u>AND</u> Causing greater than minimal interference with usual social & functional activities	NA	NA
<b>Bruising</b>	Localized to one area	Localized to more than one area	Generalized	NA
<b>Cellulitis</b>	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
<b>Hyperpigmentation</b>	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
<b>Hypopigmentation</b>	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
<b>Petechiae</b>	Localized to one area	Localized to more than one area	Generalized	NA
<b>Pruritus<sup>3</sup></b> (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
<b>Rash</b> <i>Specify type, if applicable</i>	Localized rash	Diffuse rash <u>OR</u> Target lesions	Diffuse rash <u>AND</u> Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions <u>OR</u> Ulceration of mucous membrane involving two or more distinct mucosal sites <u>OR</u> Stevens-Johnson syndrome <u>OR</u> Toxic epidermal necrolysis

<sup>3</sup> For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

## Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Diabetes Mellitus</b>	Controlled without medication	Controlled with medication <u>OR</u> Modification of current medication regimen	Uncontrolled despite treatment modification <u>OR</u> Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
<b>Gynecomastia</b>	Detectable by study participant, caregiver, or physician <u>AND</u> Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection <u>AND</u> Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes <u>AND</u> Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
<b>Hyperthyroidism</b>	No symptoms <u>AND</u> Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities <u>OR</u> Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities <u>OR</u> Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
<b>Hypothyroidism</b>	No symptoms <u>AND</u> Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities <u>OR</u> Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities <u>OR</u> Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
<b>Lipoatrophy<sup>4</sup></b>	Detectable by study participant, caregiver, or physician <u>AND</u> Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection <u>AND</u> Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

<sup>4</sup> Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

## Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Lipohypertrophy<sup>5</sup></b>	Detectable by study participant, caregiver, or physician <u>AND</u> Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection <u>AND</u> Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

<sup>5</sup> Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

## Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Anorexia</b>	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences <u>OR</u> Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
<b>Ascites</b>	No symptoms	Symptoms <u>AND</u> Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
<b>Bloating or Distension</b> <i>Report only one</i>	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	NA
<b>Cholecystitis</b>	NA	Symptoms <u>AND</u> Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
<b>Constipation</b>	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
<b>Diarrhea</b> <i>≥ 1 year of age</i>	Transient or intermittent episodes of unformed stools <u>OR</u> Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools <u>OR</u> Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period <u>OR</u> IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
<i>&lt; 1 year of age</i>	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools <u>OR</u> Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
<b>Dysphagia or Odynophagia</b> <i>Report only one and specify location</i>	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
<b>Gastrointestinal Bleeding</b>	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

## Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Mucositis or Stomatitis</b> <i>Report only one and specify location</i>	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations <u>OR</u> Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) <u>OR</u> Tissue necrosis <u>OR</u> Diffuse spontaneous mucosal bleeding
<b>Nausea</b>	Transient (< 24 hours) or intermittent <u>AND</u> No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours <u>OR</u> Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
<b>Pancreatitis</b>	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
<b>Perforation</b> (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
<b>Proctitis</b>	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities <u>OR</u> Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities <u>OR</u> Operative intervention indicated	Life-threatening consequences (e.g., perforation)
<b>Rectal Discharge</b>	Visible discharge	Discharge requiring the use of pads	NA	NA
<b>Vomiting</b>	Transient or intermittent <u>AND</u> No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension <u>OR</u> Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

# Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Arthralgia</b>	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
<b>Arthritis</b>	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
<b>Myalgia (generalized)</b>	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
<b>Osteonecrosis</b>	NA	No symptoms but with radiographic findings <u>AND</u> No operative intervention indicated	Bone pain with radiographic findings <u>OR</u> Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
<b>Osteopenia<sup>6</sup></b> <i>≥ 30 years of age</i>	BMD t-score -2.5 to -1	NA	NA	NA
<i>&lt; 30 years of age</i>	BMD z-score -2 to -1	NA	NA	NA
<b>Osteoporosis<sup>6</sup></b> <i>≥ 30 years of age</i>	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
<i>&lt; 30 years of age</i>	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

<sup>6</sup> BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

# Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Acute CNS Ischemia</b>	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
<b>Altered Mental Status</b> (for Dementia, see <i>Cognitive, Behavioral, or Attentional Disturbance</i> below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium <u>OR</u> Obtundation <u>OR</u> Coma
<b>Ataxia</b>	Symptoms causing no or minimal interference with usual social & functional activities <u>OR</u> No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
<b>Cognitive, Behavioral, or Attentional Disturbance</b> (includes dementia and attention deficit disorder) <i>Specify type, if applicable</i>	Disability causing no or minimal interference with usual social & functional activities <u>OR</u> Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities <u>OR</u> Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities <u>OR</u> Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions <u>OR</u> Institutionalization indicated
<b>Developmental Delay</b> <i>&lt; 18 years of age</i> <i>Specify type, if applicable</i>	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
<b>Headache</b>	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 <u>OR</u> Hospitalization indicated <u>OR</u> Headache with significant impairment of alertness or other neurologic function

# Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Neuromuscular Weakness</b> (includes myopathy and neuropathy) <i>Specify type, if applicable</i>	Minimal muscle weakness causing no or minimal interference with usual social & functional activities <u>OR</u> No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions <u>OR</u> Respiratory muscle weakness impairing ventilation
<b>Neurosensory Alteration</b> (includes paresthesia and painful neuropathy) <i>Specify type, if applicable</i>	Minimal paresthesia causing no or minimal interference with usual social & functional activities <u>OR</u> No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
<b>Seizures</b> <i>New Onset Seizure</i> $\geq 18$ years of age	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) <u>OR</u> Difficult to control (e.g., refractory epilepsy)
$< 18$ years of age <i>(includes new or pre-existing febrile seizures)</i>	Seizure lasting $< 5$ minutes with $< 24$ hours postictal state	Seizure lasting 5 to $< 20$ minutes with $< 24$ hours postictal state	Seizure lasting $\geq 20$ minutes <u>OR</u> $> 24$ hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) <u>OR</u> Difficult to control (e.g., refractory epilepsy)
<i>Pre-existing Seizure</i>	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) <u>OR</u> Difficult to control (e.g., refractory epilepsy)
<b>Syncope</b>	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness <u>AND</u> Hospitalization or intervention required	NA

## Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Stillbirth</b> (report using mother's participant ID) <i>Report only one</i>	NA	NA	Fetal death occurring at $\geq 20$ weeks gestation	NA
<b>Preterm Birth</b> (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
<b>Spontaneous Abortion or Miscarriage</b> <sup>7</sup> (report using mother's participant ID) <i>Report only one</i>	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

<sup>7</sup> Definition: A pregnancy loss occurring at < 20 weeks gestational age.

# Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Insomnia</b>	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
<b>Psychiatric Disorders</b> (includes anxiety, depression, mania, and psychosis) <i>Specify disorder</i>	Symptoms with intervention not indicated <u>OR</u> Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated <u>OR</u> Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated <u>OR</u> Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others <u>OR</u> Acute psychosis <u>OR</u> Behavior causing inability to perform basic self-care functions
<b>Suicidal Ideation or Attempt</b> <i>Report only one</i>	Preoccupied with thoughts of death <u>AND</u> No wish to kill oneself	Preoccupied with thoughts of death <u>AND</u> Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so <u>OR</u> Hospitalization indicated	Suicide attempted

# Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Acute Bronchospasm</b>	Forced expiratory volume in 1 second or peak flow reduced to $\geq 70$ to $< 80\%$ <u>OR</u> Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to $< 70\%$ <u>OR</u> Symptoms with intervention indicated <u>OR</u> Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to $< 50\%$ <u>OR</u> Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow $< 25\%$ <u>OR</u> Life-threatening respiratory or hemodynamic compromise <u>OR</u> Intubation
<b>Dyspnea or Respiratory Distress</b> <i>Report only one</i>	Dyspnea on exertion with no or minimal interference with usual social & functional activities <u>OR</u> Wheezing <u>OR</u> Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities <u>OR</u> Nasal flaring <u>OR</u> Intercostal retractions <u>OR</u> Pulse oximetry 90 to $< 95\%$	Dyspnea at rest causing inability to perform usual social & functional activities <u>OR</u> Pulse oximetry $< 90\%$	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

## Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Hearing Loss</b> ≥ 12 years of age	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) <u>OR</u> Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) <u>OR</u> Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
<b>Tinnitus</b>	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
<b>Uveitis</b>	No symptoms <u>AND</u> Detectable on examination	Anterior uveitis with symptoms <u>OR</u> Medical intervention indicated	Posterior or pan-uveitis <u>OR</u> Operative intervention indicated	Disabling visual loss in affected eye(s)
<b>Vertigo</b>	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
<b>Visual Changes</b> (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

# Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Acute Allergic Reaction</b>	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
<b>Chills</b>	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	NA
<b>Cytokine Release Syndrome<sup>8</sup></b>	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for $\leq 24$ hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
<b>Fatigue or Malaise</b> <i>Report only one</i>	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	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
<b>Fever</b> (non-axillary temperatures only)	38.0 to $< 38.6^{\circ}\text{C}$ or 100.4 to $< 101.5^{\circ}\text{F}$	$\geq 38.6^{\circ}\text{C}$ to $< 39.3^{\circ}\text{C}$ or $\geq 101.5$ to $< 102.7^{\circ}\text{F}$	$\geq 39.3$ to $< 40.0^{\circ}\text{C}$ or $\geq 102.7$ to $< 104.0^{\circ}\text{F}$	$\geq 40.0^{\circ}\text{C}$ or $\geq 104.0^{\circ}\text{F}$
<b>Pain<sup>9</sup></b> (not associated with study agent injections and not specified elsewhere) <i>Specify location</i>	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

<sup>8</sup> Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

<sup>9</sup> For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

## Systemic

<b>Serum Sickness<sup>10</sup></b>	Mild signs and symptoms	Moderate signs and symptoms <u>AND</u> Intervention indicated (e.g., antihistamines)	Severe signs and symptoms <u>AND</u> Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
<b>Underweight<sup>11</sup></b> <i>&gt; 5 to 19 years of age</i>	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
<i>2 to 5 years of age</i>	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
<i>&lt; 2 years of age</i>	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
<b>Unintentional Weight Loss</b> (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline <u>OR</u> Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

<sup>10</sup> Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

<sup>11</sup> WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs:  
[http://www.who.int/growthref/who2007\\_bmi\\_for\\_age/en/](http://www.who.int/growthref/who2007_bmi_for_age/en/) for participants > 5 to 19 years of age and  
[http://www.who.int/childgrowth/standards/chart\\_catalogue/en/](http://www.who.int/childgrowth/standards/chart_catalogue/en/) for those ≤ 5 years of age.

## Urinary

<b>PARAMETER</b>	<b>GRADE 1 MILD</b>	<b>GRADE 2 MODERATE</b>	<b>GRADE 3 SEVERE</b>	<b>GRADE 4 POTENTIALLY LIFE- THREATENING</b>
<b>Urinary Tract Obstruction</b>	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

## Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Injection Site Pain or Tenderness</b> <i>Report only one</i>	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function <u>OR</u> Hospitalization indicated
<b>Injection Site Erythema or Redness<sup>12</sup></b> <i>Report only one</i> <i>&gt; 15 years of age</i>	2.5 to < 5 cm in diameter <u>OR</u> 6.25 to < 25 cm <sup>2</sup> surface area <u>AND</u> Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter <u>OR</u> ≥ 25 to < 100 cm <sup>2</sup> surface area <u>OR</u> Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter <u>OR</u> ≥ 100 cm <sup>2</sup> surface area <u>OR</u> Ulceration <u>OR</u> Secondary infection <u>OR</u> Phlebitis <u>OR</u> Sterile abscess <u>OR</u> Drainage <u>OR</u> Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
<i>≤ 15 years of age</i>	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) <u>OR</u> Ulceration <u>OR</u> Secondary infection <u>OR</u> Phlebitis <u>OR</u> Sterile abscess <u>OR</u> Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
<b>Injection Site Induration or Swelling</b> <i>Report only one</i> <i>&gt; 15 years of age</i>	Same as for <b>Injection Site Erythema or Redness, &gt; 15 years of age</b>	Same as for <b>Injection Site Erythema or Redness, &gt; 15 years of age</b>	Same as for <b>Injection Site Erythema or Redness, &gt; 15 years of age</b>	Same as for <b>Injection Site Erythema or Redness, &gt; 15 years of age</b>
<i>≤ 15 years of age</i>	Same as for <b>Injection Site Erythema or Redness, ≤ 15 years of age</b>	Same as for <b>Injection Site Erythema or Redness, ≤ 15 years of age</b>	Same as for <b>Injection Site Erythema or Redness, ≤ 15 years of age</b>	Same as for <b>Injection Site Erythema or Redness, ≤ 15 years of age</b>
<b>Injection Site Pruritus</b>	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized <u>OR</u> Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

<sup>12</sup> Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

# Laboratory Values\*

## Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Acidosis</b>	NA	pH $\geq$ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
<b>Albumin, Low</b> (g/dL; g/L)	3.0 to < LLN 30 to < LLN	$\geq$ 2.0 to < 3.0 $\geq$ 20 to < 30	< 2.0 < 20	NA
<b>Alkaline Phosphatase, High</b>	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	$\geq$ 10.0 x ULN
<b>Alkalosis</b>	NA	pH > ULN to $\leq$ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
<b>ALT or SGPT, High</b> <i>Report only one</i>	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	$\geq$ 10.0 x ULN
<b>Amylase (Pancreatic) or Amylase (Total), High</b> <i>Report only one</i>	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	$\geq$ 5.0 x ULN
<b>AST or SGOT, High</b> <i>Report only one</i>	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	$\geq$ 10.0 x ULN
<b>Bicarbonate, Low</b> (mEq/L; mmol/L)	16.0 to < LLN 16.0 to < LLN	11.0 to < 16.0 11.0 to < 16.0	8.0 to < 11.0 8.0 to < 11.0	< 8.0 < 8.0
<b>Bilirubin</b> <i>Direct Bilirubin</i> <sup>13</sup> , <b>High</b> > 28 days of age	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
$\leq$ 28 days of age	ULN to $\leq$ 1 mg/dL	> 1 to $\leq$ 1.5 mg/dL	> 1.5 to $\leq$ 2 mg/dL	> 2 mg/dL
<b>Total Bilirubin, High</b> > 28 days of age	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	$\geq$ 5.0 x ULN
$\leq$ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

\*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

<sup>13</sup> Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

## Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Calcium, High</b> (mg/dL; mmol/L) ≥ 7 days of age	10.6 to < 11.5 2.65 to < 2.88	11.5 to < 12.5 2.88 to < 3.13	12.5 to < 13.5 3.13 to < 3.38	≥ 13.5 ≥ 3.38
< 7 days of age	11.5 to < 12.4 2.88 to < 3.10	12.4 to < 12.9 3.10 to < 3.23	12.9 to < 13.5 3.23 to < 3.38	≥ 13.5 ≥ 3.38
<b>Calcium (Ionized), High</b> (mg/dL; mmol/L)	> ULN to < 6.0 > ULN to < 1.5	6.0 to < 6.4 1.5 to < 1.6	6.4 to < 7.2 1.6 to < 1.8	≥ 7.2 ≥ 1.8
<b>Calcium, Low</b> (mg/dL; mmol/L) ≥ 7 days of age	7.8 to < 8.4 1.95 to < 2.10	7.0 to < 7.8 1.75 to < 1.95	6.1 to < 7.0 1.53 to < 1.75	< 6.1 < 1.53
< 7 days of age	6.5 to < 7.5 1.63 to < 1.88	6.0 to < 6.5 1.50 to < 1.63	5.50 to < 6.0 1.38 to < 1.50	< 5.50 < 1.38
<b>Calcium (Ionized), Low</b> (mg/dL; mmol/L)	< LLN to 4.0 < LLN to 1.0	3.6 to < 4.0 0.9 to < 1.0	3.2 to < 3.6 0.8 to < 0.9	< 3.2 < 0.8
<b>Cardiac Troponin I, High</b>	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
<b>Creatine Kinase, High</b>	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
<b>Creatinine, High</b> *Report only one	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
<b>Creatinine Clearance<sup>14</sup> or eGFR, Low</b> *Report only one	NA	< 90 to 60 ml/min or ml/min/1.73 m <sup>2</sup> OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m <sup>2</sup> OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m <sup>2</sup> OR ≥ 50% decrease from participant's baseline or dialysis needed
<b>Glucose</b> (mg/dL; mmol/L) <b>Fasting, High</b>	110 to 125 6.11 to < 6.95	> 125 to 250 6.95 to < 13.89	> 250 to 500 13.89 to < 27.75	≥ 500 ≥ 27.75
<b>Nonfasting, High</b>	116 to 160 6.44 to < 8.89	> 160 to 250 8.89 to < 13.89	> 250 to 500 13.89 to < 27.75	≥ 500 ≥ 27.75

<sup>14</sup> Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m<sup>2</sup>). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

\*Reminder: Choose the method that selects for the higher grade.

## Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Glucose, Low</b> (mg/dL; mmol/L) ≥ 1 month of age	55 to 64 3.05 to <3.55	40 to < 55 2.22 to < 3.05	30 to < 40 1.67 to < 2.22	< 30 < 1.67
< 1 month of age	50 to 54 2.78 to < 3.00	40 to < 50 2.22 to < 2.78	30 to < 40 1.67 to < 2.22	< 30 < 1.67
<b>Lactate, High</b>	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life- threatening consequences	Increased lactate with pH < 7.3 with life- threatening consequences
<b>Lipase, High</b>	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
<b>Lipid Disorders</b> (mg/dL; mmol/L) <b>Cholesterol, Fasting, High</b> ≥ 18 years of age	200 to < 240 5.18 to < 6.19	240 to < 300 6.19 to < 7.77	≥ 300 ≥ 7.77	NA
< 18 years of age	170 to < 200 4.40 to < 5.15	200 to < 300 5.15 to < 7.77	≥ 300 ≥ 7.77	NA
<b>LDL, Fasting, High</b> ≥ 18 years of age	130 to < 160 3.37 to < 4.12	160 to < 190 4.12 to < 4.90	≥ 190 ≥ 4.90	NA
> 2 to < 18 years of age	110 to < 130 2.85 to < 3.34	130 to < 190 3.34 to < 4.90	≥ 190 ≥ 4.90	NA
<b>Triglycerides, Fasting, High</b>	150 to 300 1.71 to 3.42	>300 to 500 >3.42 to 5.7	>500 to < 1,000 >5.7 to 11.4	> 1,000 > 11.4
<b>Magnesium<sup>15</sup>, Low</b> (mEq/L; mmol/L)	1.2 to < 1.4 0.60 to < 0.70	0.9 to < 1.2 0.45 to < 0.60	0.6 to < 0.9 0.30 to < 0.45	< 0.6 < 0.30
<b>Phosphate, Low</b> (mg/dL; mmol/L) > 14 years of age	2.0 to < LLN 0.65 to < LLN	1.4 to < 2.0 0.45 to < 0.65	1.0 to < 1.4 0.32 to < 0.45	< 1.0 < 0.32
1 to 14 years of age	3.0 to < 3.5 0.97 to < 1.13	2.5 to < 3.0 0.81 to < 0.97	1.5 to < 2.5 0.48 to < 0.81	< 1.5 < 0.48
< 1 year of age	3.5 to < 4.5 1.13 to < 1.45	2.5 to < 3.5 0.81 to < 1.13	1.5 to < 2.5 0.48 to < 0.81	< 1.5 < 0.48
<b>Potassium, High</b> (mEq/L; mmol/L)	5.6 to < 6.0 5.6 to < 6.0	6.0 to < 6.5 6.0 to < 6.5	6.5 to < 7.0 6.5 to < 7.0	≥ 7.0 ≥ 7.0
<b>Potassium, Low</b> (mEq/L; mmol/L)	3.0 to < 3.4 3.0 to < 3.4	2.5 to < 3.0 2.5 to < 3.0	2.0 to < 2.5 2.0 to < 2.5	< 2.0 < 2.0

<sup>15</sup> To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

## Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Sodium, High</b> (mEq/L; mmol/L)	146 to < 150 <i>146 to &lt; 150</i>	150 to < 154 <i>150 to &lt; 154</i>	154 to < 160 <i>154 to &lt; 160</i>	≥ 160 ≥ 160
<b>Sodium, Low</b> (mEq/L; mmol/L)	130 to < 135 <i>130 to &lt; 135</i>	125 to < 130 <i>125 to &lt; 130</i>	121 to < 125 <i>121 to &lt; 125</i>	≤ 120 ≤ 120
<b>Uric Acid, High</b> (mg/dL; mmol/L)	7.5 to < 10.0 <i>0.45 to &lt; 0.59</i>	10.0 to < 12.0 <i>0.59 to &lt; 0.71</i>	12.0 to < 15.0 <i>0.71 to &lt; 0.89</i>	≥ 15.0 ≥ 0.89

# Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Absolute CD4+ Count, Low</b> (cell/mm <sup>3</sup> ; cells/L) <i>&gt; 5 years of age</i> (not HIV infected)	300 to < 400 300 to < 400	200 to < 300 200 to < 300	100 to < 200 100 to < 200	< 100 < 100
<b>Absolute Lymphocyte Count, Low</b> (cell/mm <sup>3</sup> ; cells/L) <i>&gt; 5 years of age</i> (not HIV infected)	600 to < 650 0.600 x 10 <sup>9</sup> to < 0.650 x 10 <sup>9</sup>	500 to < 600 0.500 x 10 <sup>9</sup> to < 0.600 x 10 <sup>9</sup>	350 to < 500 0.350 x 10 <sup>9</sup> to < 0.500 x 10 <sup>9</sup>	< 350 < 0.350 x 10 <sup>9</sup>
<b>Absolute Neutrophil Count (ANC), Low</b> (cells/mm <sup>3</sup> ; cells/L) <i>&gt; 7 days of age</i>	800 to 1,000 0.800 x 10 <sup>9</sup> to 1.000 x 10 <sup>9</sup>	600 to 799 0.600 x 10 <sup>9</sup> to 0.799 x 10 <sup>9</sup>	400 to 599 0.400 x 10 <sup>9</sup> to 0.599 x 10 <sup>9</sup>	< 400 < 0.400 x 10 <sup>9</sup>
<i>2 to 7 days of age</i>	1,250 to 1,500 1.250 x 10 <sup>9</sup> to 1.500 x 10 <sup>9</sup>	1,000 to 1,249 1.000 x 10 <sup>9</sup> to 1.249 x 10 <sup>9</sup>	750 to 999 0.750 x 10 <sup>9</sup> to 0.999 x 10 <sup>9</sup>	< 750 < 0.750 x 10 <sup>9</sup>
<i>≤ 1 day of age</i>	4,000 to 5,000 4.000 x 10 <sup>9</sup> to 5.000 x 10 <sup>9</sup>	3,000 to 3,999 3.000 x 10 <sup>9</sup> to 3.999 x 10 <sup>9</sup>	1,500 to 2,999 1.500 x 10 <sup>9</sup> to 2.999 x 10 <sup>9</sup>	< 1,500 < 1.500 x 10 <sup>9</sup>
<b>Fibrinogen, Decreased</b> (mg/dL; g/L)	100 to < 200 1.00 to < 2.00 OR 0.75 to < 1.00 x LLN	75 to < 100 0.75 to < 1.00 OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 0.50 to < 0.75 OR 0.25 to < 0.50 x LLN	< 50 < 0.50 OR < 0.25 x LLN OR Associated with gross bleeding
<b>Hemoglobin<sup>16</sup>, Low</b> (g/dL; mmol/L) <sup>17</sup> <i>≥ 13 years of age</i> (male only)	10.0 to 10.9 6.19 to 6.76	9.0 to < 10.0 5.57 to < 6.19	7.0 to < 9.0 4.34 to < 5.57	< 7.0 < 4.34
<i>≥ 13 years of age</i> (female only)	9.5 to 10.4 5.88 to 6.48	8.5 to < 9.5 5.25 to < 5.88	6.5 to < 8.5 4.03 to < 5.25	< 6.5 < 4.03

<sup>16</sup> For participants ≥ 13 years of age, hemoglobin is graded based on the predominant sex hormone present in the body, whether endogenous or exogenous, for at least 6 consecutive months.

<sup>17</sup> The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

# Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<i>57 days of age to &lt; 13 years of age (male and female)</i>	9.5 to 10.4 5.88 to 6.48	8.5 to < 9.5 5.25 to < 5.88	6.5 to < 8.5 4.03 to < 5.25	< 6.5 < 4.03
<i>36 to 56 days of age (male and female)</i>	8.5 to 9.6 5.26 to 5.99	7.0 to < 8.5 4.32 to < 5.26	6.0 to < 7.0 3.72 to < 4.32	< 6.0 < 3.72
<i>22 to 35 days of age (male and female)</i>	9.5 to 11.0 5.88 to 6.86	8.0 to < 9.5 4.94 to < 5.88	6.7 to < 8.0 4.15 to < 4.94	< 6.7 < 4.15
<i>8 to ≤ 21 days of age (male and female)</i>	11.0 to 13.0 6.81 to 8.10	9.0 to < 11.0 5.57 to < 6.81	8.0 to < 9.0 4.96 to < 5.57	< 8.0 < 4.96
<i>≤ 7 days of age (male and female)</i>	13.0 to 14.0 8.05 to 8.72	10.0 to < 13.0 6.19 to < 8.05	9.0 to < 10.0 5.59 to < 6.19	< 9.0 < 5.59
<b>INR, High</b> (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
<b>Methemoglobin</b> (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
<b>PTT, High</b> (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
<b>Platelets, Decreased</b> (cells/mm <sup>3</sup> ; cells/L)	100,000 to < 125,000 <i>100.000 x 10<sup>9</sup> to &lt; 125.000 x 10<sup>9</sup></i>	50,000 to < 100,000 <i>50.000 x 10<sup>9</sup> to &lt; 100.000 x 10<sup>9</sup></i>	25,000 to < 50,000 <i>25.000 x 10<sup>9</sup> to &lt; 50.000 x 10<sup>9</sup></i>	< 25,000 < 25.000 x 10 <sup>9</sup>
<b>PT, High</b> (not on anticoagulation therapy)	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
<b>WBC, Decreased</b> (cells/mm <sup>3</sup> ; cells/L)				
<i>&gt; 7 days of age</i>	2,000 to 2,499 <i>2.000 x 10<sup>9</sup> to 2.499 x 10<sup>9</sup></i>	1,500 to 1,999 <i>1.500 x 10<sup>9</sup> to 1.999 x 10<sup>9</sup></i>	1,000 to 1,499 <i>1.000 x 10<sup>9</sup> to 1.499 x 10<sup>9</sup></i>	< 1,000 < 1.000 x 10 <sup>9</sup>
<i>≤ 7 days of age</i>	5,500 to 6,999 <i>5.500 x 10<sup>9</sup> to 6.999 x 10<sup>9</sup></i>	4,000 to 5,499 <i>4.000 x 10<sup>9</sup> to 5.499 x 10<sup>9</sup></i>	2,500 to 3,999 <i>2.500 x 10<sup>9</sup> to 3.999 x 10<sup>9</sup></i>	< 2,500 < 2.500 x 10 <sup>9</sup>

# Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Glycosuria</b> (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
<b>Hematuria</b> (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots <u>OR</u> With RBC casts <u>OR</u> Intervention indicated	Life-threatening consequences
<b>Proteinuria</b> (random collection tested by dipstick)	1+	2+	3+ or higher	NA

## Appendix A.

### Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<b>Total Bilirubin<sup>18</sup>, High</b> (mg/dL; $\mu\text{mol/L}$ ) <sup>19</sup>				
<b>Term Neonate<sup>20</sup></b> < 24 hours of age	4 to < 7 68.4 to < 119.7	7 to < 10 119.7 to < 171	10 to < 17 171 to < 290.7	$\geq 17$ $\geq 290.7$
24 to < 48 hours of age	5 to < 8 85.5 to < 136.8	8 to < 12 136.8 to < 205.2	12 to < 19 205.2 to < 324.9	$\geq 19$ $\geq 324.9$
48 to < 72 hours of age	8.5 to < 13 145.35 to < 222.3	13 to < 15 222.3 to < 256.5	15 to < 22 256.5 to < 376.2	$\geq 22$ $\geq 376.2$
72 hours to < 7 days of age	11 to < 16 188.1 to < 273.6	16 to < 18 273.6 to < 307.8	18 to < 24 307.8 to < 410.4	$\geq 24$ $\geq 410.4$
7 to 28 days of age (breast feeding)	5 to < 10 85.5 to < 171	10 to < 20 171 to < 342	20 to < 25 342 to < 427.5	$\geq 25$ $\geq 427.5$
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	$\geq 5.0$ x ULN
<b>Preterm Neonate<sup>20</sup></b> 35 to < 37 weeks gestational age	Same as for <b>Total Bilirubin, High, Term Neonate</b> (based on days of age).	Same as for <b>Total Bilirubin, High, Term Neonate</b> (based on days of age).	Same as for <b>Total Bilirubin, High, Term Neonate</b> (based on days of age).	Same as for <b>Total Bilirubin, High, Term Neonate</b> (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 171 to < 239.4	$\geq 14$ $\geq 239.4$
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 102.6 to < 171	$\geq 10$ $\geq 171$
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 85.5 to < 136.8	$\geq 8$ $\geq 136.8$
7 to 28 days of age (breast feeding)	5 to < 10 85.5 to < 171	10 to < 20 171 to < 342	20 to < 25 342 to < 427.5	$\geq 25$ $\geq 427.5$
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	$\geq 5.0$ x ULN

<sup>18</sup> Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

<sup>19</sup> A laboratory value of 1 mg/dL is equivalent to 17.1  $\mu\text{mol/L}$ .

<sup>20</sup> Definitions: Term is defined as  $\geq 37$  weeks gestational age; near-term, as  $\geq 35$  weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.