CLI 00125

ReCePI PROTOCOL, v8.0

A Randomized, Double-Blinded, Controlled, Parallel Group, Non-inferiority, Phase III Study to Evaluate the Efficacy and Safety of the INTERCEPT Blood System for Red Blood Cells in Patients undergoing Complex Cardiac Surgery Procedures (the ReCePI study)

April 6, 2023

NCT03459287

PROTOCOL

TITLE:	A Randomized, Double-Blinded, Controlled, Parallel Group, Non-inferiority, Phase III Study to Evaluate the Efficacy and Safety of the INTERCEPT Blood System for Red Blood Cells in Patients undergoing Complex Cardiac Surgery Procedures (the ReCePI study)
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SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company:
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Not applicable</td></tr>
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<tr><td>Title of Study:</td><td colspan="4">A Randomized, Double-Blinded, Controlled, Parallel Group, Non-inferiority, Phase III Study to Evaluate the Efficacy and Safety of the INTERCEPT Blood System for Red Blood Cells in Patients undergoing Complex Cardiac Surgery Procedures (the ReCePI study)</td></tr>
<tr><td colspan="5">Investigators / Study Sites/Blood Centers: 15-20 clinical sites and up to 4 blood centers</td></tr>
<tr><td colspan="5">Publication (reference): NA</td></tr>
<tr><td colspan="3">Studied period (years): To Be Determined (TBD)
Date of first enrollment: November 21, 2018
Date of last completed: TBD</td><td colspan="2">Phase of development: 3</td></tr>
<tr><td colspan="5">Objective:
The objective of this study is to evaluate the efficacy and safety of red blood cell (RBC) transfusion for support of acute anemia in cardiovascular surgery patients based on the clinical outcome of renal impairment following transfusion of RBCs treated with the INTERCEPT Blood System for Red Blood Cells compared to patients transfused with conventional RBCs.</td></tr>
<tr><td colspan="5">Methodology:
The study is a prospective, multicenter, randomized, double-blinded, active controlled, parallel-design, non-inferiority study.</td></tr>
<tr><td colspan="5">Primary Endpoints:
Primary
Efficacy:
The primary efficacy endpoint is the proportion of patients who have received at least one study transfusion with a diagnosis of renal impairment defined as:
• Any raised serum creatinine (sCr) level, occurring after transfusion of a study RBC, of ≥0.3 mg/dL (or 26.5 µmol/L) from the pre-surgery baseline within 48±4 hours of the end of surgery.
Safety:
The primary safety endpoints are:
• Proportion of patients with any treatment-emergent adverse events (TEAEs) possibly, probably or</td></tr>
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definitely related to study RBC transfusion through 28 days after the last study transfusion; and

- Proportion of patients with treatment-emergent antibodies with confirmed specificity to INTERCEPT RBCs by the end of study (i.e., 75±15 days after the last study transfusion).

Study Procedures:

Screening/Recruitment

In order to minimize the number of patients who enroll in the study but do not require RBC transfusion, only patients with a relatively high likelihood to receive a RBC transfusion as determined by the Investigator (e.g., patients receiving aspirin, clopidogrel (or analogs) and/or GPIIb/IIIa inhibitors), or patients with a TRUST Score of ≥3 will be eligible for enrollment. Patients ≥11 years of age undergoing complex cardiac surgery may be identified through pre-operative scheduling procedures in advance of their surgery.

Patients undergoing urgent or emergent cardiac surgery are eligible for the study, subject to institutional review board (IRB) approval of an appropriate informed consent process.

All potentially eligible patients will be approached for study consent/assent within 30 days prior to their surgical procedure. Subjects who consent/assent to the study will be assigned a subject ID number and undergo screening.

Screening will include documentation of the patient's pre-surgical exposure to radiographic contrast media and number of prior pregnancies (females). Screening data may be derived from the medical record when performed within 30 days prior to their surgical procedure. Eligibility status and other study data including all TRUST components will be entered into the clinical database via an electronic data capture (EDC) system using electronic case report forms (eCRFs). Patients who fail eligibility for any or multiple inclusion/exclusion criteria may be rescreened for eligibility closer to the time of surgery.

Randomization and Blinding

Eligible subjects will be randomized up to 7 days before or on the day of scheduled surgery (Day 0). An Interactive Web Response System (IWRS) will be used for electronic randomization of eligible patients. Randomization (in 1:1 ratio for Test:Control) stratified by site, pre-existing renal impairment (baseline sCr ≥1.2 mg/dL vs. < 1.2 mg/dL), and cardiac surgery group (more at risk for renal complications vs. less at risk) will be employed. Screened subjects who receive a red cell transfusion prior to randomization will no longer be considered for randomization, and their participation in the study will end. Patients may be rescreened for eligibility closer to the time of surgery.

Treatment

Once a subject is randomized, only study RBCs (Test or Control, per the subject's randomization) should be dispensed and transfused during the acute transfusion support period (Day 0 to Day 7 post surgery, hospital discharge, or death, whichever is first), as clinically indicated and determined by the treating physician.

In rare exceptions where study RBCs are unavailable or patient's need for RBC transfusions exceeds the quantity of study RBCs in inventory at the hospital blood bank (e.g., during a Massive Transfusion Protocol), a

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transfusion using non-study RBC (conventional) may be given to provide the patient with an appropriate and necessary treatment. In this case, a protocol deviation should be documented. If a study RBC transfusion is given after randomization before surgery commences, a protocol deviation should also be documented.

Treatment assessments will be divided into an acute transfusion support period starting the day of surgery (Day 0 up to Day 7) during which study RBC (Test or Control) are administered, a post-surgical follow-up period of a minimum of 28 days after the last study transfusion to collect additional safety data, a clinical assessment at day 30 after surgery specifically for mortality and RRT status, and a visit at day 75 (±15) after the last study transfusion to assess mortality and RRT status, and collect samples for serological screening for antibodies specific to INTERCEPT RBCs.

In all patients, anesthesia and surgical procedures will be performed according to the local standards of care. Following the acute transfusion support period, subjects may receive conventional RBC components if additional transfusions are needed, as indicated by their treating physician.

Study Assessments: Monitoring and Follow-up

Baseline through Acute Transfusion Support Period (Pre-Op Day -1 up to Post-Op Day 7)

A screen for antibodies specific for INTERCEPT RBCs should be performed every time that a routine IAT is performed during the acute 7-day study transfusion period.

A blood sample for sCr will be taken at 48 ±4 hours after completion of surgery for both transfused and non-transfused subjects., A sCr will be determined on a daily basis during the acute transfusion support period up to 7 days post-surgery. Other parameters including additional sCr will be collected on eCRFs only when available in the medical record.

Randomized subjects who do not receive an RBC transfusion following randomization within the first 48 hours after surgery will be discontinued from the study and replaced.

Daily sCr assessments will be recorded up to and including 48 ±4 hours for transfused and non-transfused subjects. Other post baseline laboratory parameters and adverse events (AEs) will not be collected for non-transfused subjects. Vital status will be reported for randomized and non-transfused subjects at the time of discontinuation.

Hemodynamic and laboratory measures will be assessed pre-operatively (Day -1, Baseline) and daily as available in the medical record from post-operative Day 1 through Day 7, hospital discharge or death, whichever occurs first. If a subject is discharged prior to Day 7 but returns to the study site for a standard of care visit on Day 7, blood samples should be obtained on that day for a complete blood count and sCr determination.

Hemodynamic parameters that will be collected if available, include heart rate, blood pressure, mean arterial pressure, central venous pressure (CVP), and peripheral oxygen saturation via pulse oximetry probe.

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Laboratory parameters that will be captured on eCRFs include BUN, creatinine , AST, ALT, fibrinogen, bilirubin, troponin, hemoglobin, and platelet counts.

Transfusion reactions (TRs), adverse events (AEs) and serious adverse events (SAEs) will be assessed on a daily basis and documented in the eCRF from the start of surgery or the start of the first study transfusion (whichever is first) through post-operative Day 7 and as available through day 28 after the last study transfusion. Vital status will be reported for randomized and non-transfused subjects at the time of discontinuation.

NOTE: The following applies to randomized transfused subjects only.

Post-operative Day 8 (or Post-discharge, if earlier) through 28 Days After Last Study Transfusion. Subjects will be monitored for TRs, AEs and SAEs following the 7-day acute transfusion support period, through 28 days after the last study transfusion or death, whichever occurs first, according to the local standard of care. In an outpatient setting, weekly telephone surveillance calls to the subject will be performed in order to collect safety events until the next follow-up visit.

28 (±3) Days After Last Study Transfusion or Premature Discontinuation from study.

Subjects who have been discharged should be scheduled for the follow up visit 28 (±3) days after the last study transfusion to obtain additional safety information, including patient-reported AEs/ SAEs; laboratory results including sCr, DAT/ IAT; a sample for HLA antibodies and antibodies specific to INTERCEPT RBCs will be obtained. All randomized subjects who receive any study RBC transfusion must have their vital status documented at this visit, or earlier, if the subject dies prior to the visit. If a subject has been discharged, other safety information (e.g., AEs and SAEs) may be obtained through medical records, the subject's physician, or a telephone interview with either the subject or a family member.

30 Days After Surgery

All randomized subjects who receive a study RBC transfusion must have their vital status and need for RRT (defined as hemodialysis or peritoneal dialysis) documented at Day 30 after surgery. RRT that is provided prophylactically during surgery while patient is on a bypass machine (the pump), does not meet this endpoint. The vital status and RRT assessment on Day 30 can be performed either from the medical records, from a phone call to the subject or family, or during the visit 28±3 days after the last study transfusion (only if the last study transfusion was given at day 2 or later in the acute transfusion support period).

End of Study: 75 (±15 Days) After last Study Transfusion

75 (±15) days after the last study transfusion (End of Study), serum samples for antibodies specific for INTERCEPT RBCs will be obtained, either in hospital, at a clinic visitor or offsite. Mortality and the need for RRT will be assessed.

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Data and Safety Monitoring Board (DSMB)

The study will be monitored by an independent Data and Safety Monitoring Board (DSMB). The primary mission of the DSMB is to ensure patient safety and review protocol compliance for data collection. The DSMB will be assembled by the Sponsor and composed of transfusion medicine and other experts as per the DSMB charter. DSMB members will be independent of the Sponsor.

Interim Analysis and Early Stopping Rule

Aside from the blinded interim analysis for sample size re-estimation performed in October 2021, no other interim analysis is planned for this study to compare treatment differences with respect to efficacy or safety at any time prior to the completion of the study. Specific stopping rules, defined for safety considerations, are defined in Section 4.6 of the protocol.

Number of patients:

A total of at least 292 evaluable, randomized and transfused patients, 146 per arm, are planned to generate sufficient efficacy and safety data for the Test and Control components in patients undergoing cardiac surgery procedures.

For the primary efficacy endpoint, the proportion of patients with a ΔsCr $\geq$0.3 mg/dL from pre-surgery baseline to within 48±4 hours after surgery, a non-inferiority test will be conducted to assess for treatment difference (Test – Control). By assuming an event rate of 30% in the Control group and no more than 50% increase from the Control rate as the non-inferiority margin, a sample size of 292 patients (146 per arm) will provide approximately 80% power to declare non-inferiority at the two-sided 0.05 alpha level, assuming the true treatment difference is zero.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Age $\geq$ 11 years of age
2. Weight $\geq$ 40 kg
3. Scheduled complex cardiac surgery or thoracic aorta surgery. The procedure may be performed either on or off cardiopulmonary bypass machine (CBP or "pump"). For the purposes of this protocol "Repeat procedure" means that the subject had a previous cardiac surgery. Procedures that qualify as complex cardiac surgery include but are not limited to, the following:
   - Single Vessel Coronary Artery Bypass Graft, first or repeat procedure
   - Multiple Coronary Artery Bypass Grafts, first or repeat procedure
   - Single Valve Repair or Replacement, first or repeat procedure
   - Multiple Valve Repair or Replacement, first or repeat procedure

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- Surgery involving both Coronary Artery Bypass Graft(s) and Valve Repair(s), first or repeat procedure
- One or more of the following procedures, with or without Coronary Bypass Graft(s):
  - left ventricular aneurysm repair
  - ventricular and/or atrial septal defect repairs
  - Batista procedure (surgical ventricular remodeling)
  - surgical ventricular restoration
  - congenital cardiac defect repair
  - aortic procedures
  - other cardiac surgery or thoracic aorta surgery types with a high probability of bleeding.

4. TRUST probability score (Alghamdi, Davis et al. 2006) ≥ 3, or currently on a regimen of aspirin (any dose), clopidogrel (or analogs) and/or GPIIb/IIIa inhibitors or at a high probability for need of a transfusion during or after surgery at the discretion of the Investigator
5. Female subjects of child-bearing potential must meet the 2 criteria below at screening:
   - Negative serum or urine pregnancy test
   - Use at least one method of birth control that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized partner
6. Signed and dated informed consent/assent form.

<u>Exclusion criteria:</u>

1. Confirmed positive baseline serum/plasma antibody specific to INTERCEPT RBCs (S-303 specific antibody) screening panel prior to randomization.
2. Pregnant or breast feeding
3. Refusal of blood products or other inability to comply with the protocol in the opinion of the Investigator or the treating physician
4. Treatment with any medication that is known to adversely affect RBC viability, such as, but not limited to dapsone, levodopa, methyldopa, nitrofurantoin, and its derivatives, phenazopyridine and quinidine.
5. Planned cardiac transplantation
6. Active autoimmune hemolytic anemia

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7. Left ventricular assist device (LVAD) or extracorporeal membrane oxygenation (ECMO) support pre-operatively or planned need post-operatively
8. Cardiogenic shock requiring pre-operative placement of an intra-aortic balloon pump (IABP) (NOTE: IABP done for unstable angina or prophylactically for low ejection fraction is not excluded).
9. Planned use of autologous or directed donations.
10. RBC transfusion during current hospitalization prior to enrollment and randomization (within 7 days).
11. Participation in an interventional clinical study concurrently or within the previous 28 days. This includes investigational blood products, pharmacologic agents, imaging materials (including dyes), surgical techniques, or devices. Observational studies of FDA cleared or approved products or nutrition, psychology, or socioeconomic issues are not grounds for exclusion.
12. Patients with a current diagnosis of either chronic kidney disease or acute kidney injury and with sCr ≥1.8 mg/dL at screening and patients requiring RRT. *(NOTE: If sCr at screening is <1.8 mg/dL, a patient with a diagnosis of chronic or acute kidney injury alone is not excluded).*
13. Patients with a current diagnosis of either chronic or acute hepatic insufficiency and with a total serum bilirubin ≥ 2.0 mg/dL (≥34.2 µmol/L). *(NOTE: If total serum bilirubin at screening is <2.0 mg/dL, a patient with a diagnosis of chronic or acute hepatic failure alone is not excluded).*
14. Pre-existing antibody(ies) to RBC antigens that may make the provision of compatible study RBC components difficult.
15. History of TRs requiring washed RBCs, volume reduced RBC, or RBCs with additive solution removed.
16. Patients with documented IgA deficiency or a history of severe allergic reactions to blood products.
17. Patients who require gamma-irradiated RBC blood components.
18. Positive DAT as defined below:

    A polyspecific DAT reaction strength > 2+, or

    A polyspecific DAT (any strength) in conjunction with pan-reactivity with a commercial IAT antibody screening panel that precludes the identification of underlying alloantibodies or indicates the presence of autoantibody.

Test product, dose and mode of administration:

The test device is the INTERCEPT Blood System for RBC. The INTERCEPT treatment process uses amustaline and glutathione together with a processing solution in a single-use disposable set and results in pathogen and leukocyte inactivated RBCs suspended in SAG-M additive solution (INTERCEPT RBCs). The INTERCEPT treatment will be performed on leukoreduced RBC components prepared from whole blood

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collections and suspended in AS-5 additive solution within 24 hours of collection. The test component is allogeneic INTERCEPT RBCs suspended in SAG-M and stored at 1°C to 6° for up to 35 days post-donation and administered intravenously. The treating physician will determine dose and schedule of RBC transfusions.

Control product, dose and mode of administration:

The control transfusion component is a conventional leukoreduced RBC component in an FDA approved additive solution (AS-1, AS-3 or AS-5) stored at 1°C to 6°C for up to 35 days post-donation and administered intravenously. The Control RBC components will be handled and labeled in a manner to maintain blinding. The treating physician will determine dose and schedule of RBC transfusions.

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint is the proportion of patients, who have received at least one study transfusion with a diagnosis of renal impairment defined as:

- Any raised sCr level, occurring after transfusion of a study RBC, of ≥0.3 mg/dL (or 26.5 µmol/L) from the pre-surgery baseline within 48±4 hours of the end of surgery.

If any subject meets this criterion before receiving a study transfusion, that particular event will not be included in this analysis.

Secondary efficacy outcome measures include:

- The proportion of patients with a diagnosis of stage I, II or III Acute Kidney Injury (KDIGO 2012) based on changes in sCr levels from pre-surgery baseline and the need for renal replacement therapy (RRT) post-surgery.
- Mortality or the need for RRT by 30 days post-surgery.

Safety:

The primary safety outcome measures are the:

- Proportion of patients with any treatment-emergent adverse events (TEAEs) possibly, probably or definitely related to study RBC transfusion through 28 days after the last study transfusion; and
- Proportion of patients with treatment emergent antibodies with confirmed specificity to INTERCEPT RBCs by end of study (i.e., 75±15 days after the last study transfusion).

Additional safety assessments will include:

- Treatment-emergent AEs through 28 days after the last study transfusion.
- Treatment-emergent SAEs through 28 days after the last study transfusion.

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- Transfusion reactions (as defined by the CDC National Healthcare Safety Network [NHSN] Hemovigilance Module protocol) through 28 days after last study transfusion.
- Treatment-emergent immunization to RBC allo-antigens through 28±3 days after the last study transfusion.
- Treatment-emergent immunization to HLA allo-antigens through 28±3 days after the last study transfusion.

Statistical methods:

For the primary efficacy endpoint, the treatment difference (Test – Control) and its two-sided 95% confidence interval (CI) will be estimated from Cochran-Mantel-Haenszel (CMH) test stratified by baseline sCr (sCr ≥1.2 mg/dL vs. < 1.2 mg/dL) and cardiac surgery group (more at risk for renal complications vs. less at risk) performed. The upper bound of the two-sided 95% CI will be compared with the 50% of the observed Control rate. Non-inferiority will be achieved if the upper bound is less than the 50% of the observed Control rate. For the non-inferiority test, the null and alternative hypotheses (H0 and H1, respectively) will be formulated as follows:H_0: $P_{Test} - P_{Control} \geq 50\% \times \hat{P}_{Control}$ $vs.$ H_1: $P_{Test} - P_{Control} < 50\% \times \hat{P}_{Control}$,

where P_{Test} and $P_{Control}$ are the event rates for Test (INTERCEPT) and Control groups, respectively, and $\hat{P}_{Control}$is the observed Control rate.

Same CMH test will be used for assessment of treatment differences for the secondary efficacy endpoints. As a sensitivity analysis, logistic regression will be utilized to estimate the treatment differences after controlling for baseline sCr, cardiac surgery group performed and other covariates to be detailed in the statistical analysis plan (SAP). Treatment-emergent AEs (defined as AEs with an onset date/time that is on or after the start date/time of the first study transfusion) will be summarized by treatment group, system organ class (SOC), and preferred term.

Subgroup analysis by the randomization stratification variables (clinical site, pre-surgery renal impairment, and cardiac surgery group) and by demographic variables such as age group (≤18, 19 to 65, and >65 years old), sex, and race will be presented for primary and secondary efficacy endpoints. Additional subgroup analysis may also be presented as suggested by the data.

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AABB	American Association of Blood Banks
ADL	Activities of Daily Living
AE	Adverse Event
AHG	Anti-human Globulin
AHTR	Acute Hemolytic Transfusion Reaction
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
AS	Additive Solution
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
ATR	Acute Transfusion Reaction
BP	Blood Pressure
bpm	Beats per minute
BUN	Blood Urea Nitrogen
BVDV	Bovine Viral Diarrhea Virus
C	Celsius
CABG	Coronary Artery Bypass Graft
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CFU	Colony Forming Units
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus
CPB	Cardiopulmonary Bypass
CP2D	Citrate Phosphate Double Dextrose
CPD	Citrate Phosphate Dextrose
CRF	Case Report Form
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
CVP	Central Venous Pressure
DAT	Direct Antiglobulin Test. Also referred to as the direct Coombs test.

Device Malfunction	The failure of a medical device to function according to its requirements.
DHBV	Duck Hepatitis B Virus
DHTR	Delayed Hemolytic Transfusion Reaction
dL	Deciliter
DNA	Deoxyribonucleic Acid
ds DNA	Double stranded DNA
2,3-DPG	2,3-Diphosphoglycerate
DSMB	Data and Safety Monitoring Board
DSTR	Delayed Serological Transfusion Reaction
EC	Ethics Committee
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EIA	Emerging Infectious Agents
EKG	Electrocardiogram
EOS	End of Study
F	Fahrenheit
FDA	Food and Drug Administration
FNHTR	Febrile Non-Hemolytic Transfusion Reaction
g	Gram
GCP	Good Clinical Practice
GSH	Glutathione
HA	Hemolytic anemia
Hb	Hemoglobin
HBV	Hepatitis B Virus
Hct	Hematocrit
HCV	Hepatitis C Virus
HELLP	A syndrome occurring in pregnancy. A combination of the breakdown of red blood cells (hemolysis: the H in the acronym, elevated liver enzymes (EL), and low platelet count (LP).
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HR	Heart rate
HSV	Herpes Simplex Virus
HTR	Hemolytic Transfusion Reaction
IABP	Intra-aortic Balloon Pump
IAT	Indirect Antiglobulin Test. Also referred to as the Indirect Coombs Test.
IBS	INTERCEPT Blood System (abbreviation used in preceding protocol versions)
ICF	Informed Consent Form

ICH	International Council on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INTERCEPT Blood System for RBCs	Name of the current Cerus' Investigational device
INTERCEPT RBC(s)	Red blood cell component (s) that have been processed/treated with the INTERCEPT Blood System for Red Blood Cells (also known as INTERCEPT RBCs or S-303 (treated) RBCs)
IP	Investigational product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
KDIGO	Kidney Disease Improving Global Outcomes
kg	Kilogram
LDH	Lactate Dehydrogenase
L	Liter
LVAD	Left Ventricular Assist Device
mg	milligram
mITT	Modified Intent-to-Treat
mL	Milliliter
mM	Millimole
µM	Micromole
MI	Myocardial Infarction
mm^3	Cubic millimeter
mm Hg	Millimeter of mercury
N	Number
NBG	Normalized Background
NCI	National Cancer Institute
$PaCO_2$	Partial pressure of carbon dioxide
PFU	Plaque Forming Unit
PP	Per Protocol
RBC	Red Blood Cell
ReCePI	Red Cell Pathogen Inactivation (acronym)
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease classification
RNA	Ribonucleic Acid
ROS	Reactive oxygen species
RR	Respiratory rate

RRT	Renal Replacement Therapy
ssRNA	Single Stranded Ribonucleic Acid
S-300	(N-(9-Acridinyl)-ß-alanine). The primary decomposition product of S-303.
S-303	Amustaline. [N,N-bis (2-chloroethyl)]-2-aminoethyl 3-[(acridin-9-yl) amino] propionate free base. May also refer to S-303 in solution (dissolved S-303 2HCl).
S-303•2HCl	S-303 in the salt form used for treating RBC components.
SAG- M	SAG-Mannitol: an RBC additive solution
SAE	Serious Adverse Event
SD	Standard deviation
SCD	Sickle Cell Disease
sCr	Serum creatinine
SIRS	Systemic Inflammatory Response Syndrome
SOC	System Organ Class (MedDRA)
SOP	Standard Operating Procedure
TACO	Transfusion Associated Circulatory Overload
TA-GVHD	Transfusion Associated Graft versus Host Disease
TEAE	Treatment Emergent Adverse Event
TR	Transfusion Reaction
TRALI	Transfusion Related Acute Lung Injury
TRS	Transfusion Related Sepsis
TRUST	Transfusion Risk Understanding Screening Tool
TTI	Transfusion-Transmitted Infection
UADE	Unanticipated Adverse Device Effect
ULN	Upper Limit of Normal
UO	Urinary output
U.S.	United States
USP	US Pharmacopeia
VSV	Vesicular Stomatitis Virus
WBC	White Blood Cells
WNV	West Nile Virus

2 BACKGROUND INFORMATION

2.1 GENERAL

Red blood cell (RBC) transfusion is a critical supportive therapy for healthcare. Patients and physicians assume, when required, blood transfusion will be available and safe. However, serious transfusion-transmitted infections (TTI) caused by viruses, bacteria and protozoa (Stramer 2009, MacLennan 2006); and fatal transfusion complications such as transfusion-associated graft-versus-host disease (TA-GVHD) still pose a threat to transfusion recipients (Kopolovic 2015). Currently, prevention of TTI includes pre-donation evaluation and selection of low-risk donors, followed by serologic and/or nucleic acid testing for selected known infectious pathogens.

The advent of testing has greatly reduced TTI from blood products, particularly viral disease, and sepsis associated with the transfusion of bacterially contaminated red cell blood components is generally regarded as a very rare event. However, from 1976 through September 1998, 26 fatalities thought to be secondary to contaminated whole blood or red cells were reported to the U.S. FDA (Lee 1999). The majority of deaths reported to the FDA involved *Yersinia enterocolitica*. The highest reported incidence of *Y. enterocolitica* contamination was reported in New Zealand, with an incidence rate of 1 in 65,000 and a fatality rate of 1 in 104,000 red cell units transfused (Theakston et al. 1997). Unrecognized cases, underreporting, and regional variation may account for observed differences in this incidence. Interestingly, passive reporting studies of bacterially contaminated red cells from the United States, France, and the United Kingdom that caused symptoms of infection show a relative paucity of *Y. enterocolitica* cases (Perez et al. 2001, Kuehnert et al. 2001, Serious Hazards of Transfusion report for 2000-2001). Of the reported deaths, one was due to a coagulase-negative Staphylococcus strain and seven were due to a variety of gram-negative organisms (including *Serratia liquefaciens* in three cases). These organisms are all capable of growth at refrigerated temperatures (1° to 6°C). Sepsis associated with the transfusion of red cells contaminated with gram-negative bacteria is typically severe and rapid in onset (Brecher and Hay 2005). Patients frequently develop high fever (temperatures as high as 109°F have been observed) and chills during or immediately following transfusion. From 1987 to February 1996, 20 recipients of *Y. enterocolitica* red cells were reported to the Centers for Disease Control (Cookson et al, 1996). Twelve of the 20 recipients died, and the median time to death was only 25 hours. Of the seven who developed disseminated intravascular coagulopathy, six died.

Prospective bacterial cultures of whole blood or red cells, however, have shown a much higher incidence of bacterial contamination (Damgaard et al 2015). The organisms commonly cultured are Staphylococcus sp. or Propionibacterium sp.; those strains that have been reported to be isolated in association with adverse events linked to the transfusion of contaminated red cell concentrates include Pseudomonas sp., S. marcescens, Enterobacter sp., Klebsiella sp., S. epidermidis and B. cereus (Siblini et al 2004).

Newly-emerging infectious agents also remain important risks to blood safety. Estimates of per-unit and per-patient aggregate infectious risks for conventional RBCs, including known and potential emerging infectious agents (EIA, modeled based on chikungunya and dengue viruses) were calculated by Kleinman and Stassinopoulos (2015). Minimum and maximum per-unit risks were calculated as 0.0003% (1/323,000) and 0.12% (1/831), respectively. The minimum estimate is for known lower-risk pathogens while the maximal estimate also includes an EIA and endemic area Babesia sp. risk. For patients with hemoglobinopathies who receive repeated RBC transfusions such as sickle cell disease (SCD), at the minimum risk level it is estimated that approximately 1/450 (0.22%) of patients will acquire an infection during their entire course of transfusion therapy (approximately 30-50 years); at the maximum risk levels, infections risk increases to 43-45% for patients with hemoglobinopathies, or almost 1 in every 2 patients (Kleinman and Stassinopoulos 2015).

Leukoreduced RBC concentrates contain $<5 \times 10^6$ white blood cells (WBC) that may induce TA-GVHD and/or alloimmunization to human leukocyte antigen (HLA) antigens. Gamma irradiation can effectively prevent TA-GVHD in transfusion recipients. However, almost half the cases of TA-GVHD occur in patients in which their treating physicians failed to identify risk using current guidelines for blood irradiation, leading to substantial morbidity and mortality (Kopolovic 2015). Moreover, irradiation adversely affects post-transfusion RBC recovery (Dumont 2008) and is associated with raised extracellular potassium levels in the transfused concentrates.

To proactively address the risk of TTIs and TA-GVHD, Cerus has developed pathogen and leukocyte inactivation technology systems (INTERCEPT Blood System™) for platelet and plasma components and is currently developing a system for RBC concentrates. These systems use nucleic acid-targeted compounds that intercalate into, and upon activation, covalently bind to nucleic acids of viruses, bacteria, parasites and leukocytes that may contaminate blood components, and form irreversible adducts and crosslinks thus preventing replication and TTI. This

process does not depend on or generate reactive oxygen species (ROS) which can damage cells and proteins. RBCs do not require nucleic acid for therapeutic function and thus retain therapeutic efficacy after pathogen inactivation treatment. INTERCEPT treated RBC (INTERCEPT RBCs) components should not require gamma irradiation because the treatment process inactivates donor white blood cells with a high safety margin (Castro et al. 2016). It is also possible that INTERCEPT treatment may interfere with antigen presentation by donor leukocytes, thereby reducing the incidence of HLA alloimmunization.

Conventional leukoreduced RBC concentrates include approximately 20-40 mL of residual plasma that contains serum proteins and immunoglobulins; these are implicated in allergic TRs and Transfusion Related Acute Lung Injury (TRALI). The INTERCEPT RBC process includes a terminal washing step that reduces the concentration of plasma proteins and may reduce the incidence of these reactions.

The INTERCEPT Blood System for RBCs inactivates a variety of bacteria, viruses and protozoa. The organisms evaluated to date include examples representing a range of different characteristics, such as enveloped (HIV and DHBV) and non-enveloped (Bluetongue virus), RNA genome (HIV and BVDV) and DNA genome (DHBV), and single stranded (HIV) and double stranded (DHBV) genomes. The bacteria evaluated represent Gram negative bacilli (Yersinia sp., Serratia sp., *E. coli*, Salmonella sp. and Pseudomonas sp.) and Gram positive cocci (*S. epidermidis* and *S. aureus*) that are significant especially for RBC transfusion. The protozoan parasites evaluated to date are *Plasmodium falciparum* and *Babesia microti*. INTERCEPT RBCs have demonstrated adequate viability in terms of in vivo recovery and lifespan for transfusion (Cancelas 2015), and a recently completed Phase 3 clinical study (CLI 00076) in cardiovascular surgery patients conducted in Europe has demonstrated that INTERCEPT RBCs possess in vitro characteristics comparable to untreated RBCs with a comparable safety profile (Brixner 2015, Rico 2015).

The proposed phase 3 study in patients undergoing complex cardiac surgery is intended to demonstrate that INTERCEPT RBCs are non-inferior to conventional RBCs with regard to clinical safety and clinical efficacy for transfusion support of acute anemia during surgery with potential hemodynamic instability. The study is designed to support the licensure of the INTERCEPT Blood System for Red Blood Cells.

2.2 NAME AND DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

The INTERCEPT Blood System for RBCs is an investigational medical device used to prepare pathogen and leukocyte inactivated RBC components for transfusion.

2.2.1 Description of Investigational Product

The investigational device is the INTERCEPT Blood System for Red Blood Cells. The pathogen reduction process begins with a unit of RBCs derived from whole blood that is separated according to local regulations and standard operating procedures at the Blood Centers. RBCs are suspended in additive solution-5 (AS-5). Leukocyte-reduction of whole blood or RBCs will be performed per manufacturer's instructions. The INTERCEPT Blood System process is performed on a single unit of leukoreduced RBC in AS-5.

For a detailed description of the investigational product, please refer to the Investigator's Brochure.

2.3 SUMMARY OF NONCLINICAL AND CLINICAL STUDIES

The INTERCEPT treatment process uses amustaline and glutathione together with a processing solution in a single-use disposable set to produce pathogen inactivated RBCs in SAG-M additive solution. Cerus' pre-clinical and clinical development program has evaluated the efficacy of amustaline for pathogen inactivation and safety profiles of treated RBCs and breakdown products with regard to systemic toxicity, genotoxicity and carcinogenicity in accordance with International Council on Harmonization (ICH) standards for RBCs development of pharmaceuticals. These data are presented in detail in the Investigator's Brochure.

2.3.1 Safety

No physiologically relevant toxicity using INTERCEPT RBCs at doses higher than planned for this trial was observed in pre-clinical studies. Additional information about the toxicological evaluations of the treatment system is provided in detail in the Investigator's Brochure.

2.3.2 Immunogenicity

The mechanism of action of S-303 can also lead to reactions with macromolecules other than nucleic acids in the blood components, such as constituents of the red cell membrane. In early studies of the pathogen inactivation process for RBCs (referred to as "Original process") there was evidence of antibody formation directed against INTERCEPT RBCs (also referred to as S-303-specific RBC antibodies) in two patients participating in a chronic RBC transfusion study. In order to minimize these non-specific and unwanted reactions with RBC surface molecules, an increased level of the quencher, glutathione (GSH), has been included in the current, pathogen inactivation process (referred to as "Current process").

Additional information regarding the potential for immunogenicity, and the studies that have been conducted is provided in the Investigator's Brochure.

2.3.3 Clinical Studies

Four clinical studies have been completed with the current process of the INTERCEPT Blood System for RBCs. The studies are summarized in **Table 2.1** below and additional detail is provided in the Investigator's Brochure.

Table 2.1 Summary of Clinical Studies with INTERCEPT Blood System for RBCs Current Process

Study ID	Number of Study Centers	Design	Study & Ctrl Drugs (Dose, route & regimen)	Study Objective	# subjects (entered, completed)	Diagnosis	Primary Endpoint(s)	Main Findings
CLI00062 (RBC08001)	2	Randomized, single blinded, controlled, 2 period, cross-over	Single transfusion of 5-15 mL of ^{51}Cr-labeled Test (S-303) or Control RBCs (35 day storage), intravenous	Recovery of IBS treated autologous RBCs; safety and tolerability	26/26	Healthy adult subjects	24 hour recovery and life span of 35 day old autologous RBCs	IBS-treated RBCs met FDA recommended criteria for 24 hour recovery with no significant difference between IBS-treated and control RBC Survival was significantly different between Test (32.8 days) and Control (39.5 days) but T50 of Test was within published reference range (28-35 days) No physiologically meaningful differences at end of storage between Test and Control RBC
CLI00073		Single-blinded, randomized crossover	Single transfusion µ10-30 mL of 51Cr-labeled Test (S-303) or Control RBCs (35 day storage), intravenous	Compare survival and recovery of autologous S 303 RBCs to conventional RBCs	42 enrolled/ 26 completed	Healthy subjects	24 hour post-infusion dual label recovery of autologous RBCs stored for 35 days	The 24-hour post-transfusion recovery (both dual- and single-label) of autologous IBS RBCs following infusion after 35-days of storage met all the FDA criteria for the evaluation of RBC products. No immunologic reactivity developed to Test RBC.
CLI00070	3	Randomized, controlled, double blinded, parallel	IBS treated or untreated RBC transfusions for up to 7 days starting on day of surgery; dose and frequency per treating physician	In vitro characterization of IBS RBCs relative to EU criteria for RBC for transfusion Obtain clinical data to support design of add'l studies	87 randomized; 51 treated (25Test, 26Control)	Patients undergoing complex cardiac surgery with high likelihood of requiring RBC transfusion	Primary in vitro endpoint Hb content/unit Primary clinical endpoint = safety Exploratory endpoints indicative of tissue oxygenation include renal or	IBS RBC demonstrated equivalence to untreated RBC regarding hemoglobin content; the proportion of IBS RBCs satisfying the EDQM guidelines was higher than for conventional RBCs. The incidence of renal insufficiency was 15.7% (Test 5, Control 3, p=0.41). The incidence of hepatic insufficiency was 2% (Test 1, Control 0, p=0.37). There was no statistical difference between Test and Control groups for the

Study ID	Number of Study Centers	Design	Study & Ctrl Drugs (Dose, route & regimen)	Study Objective	# subjects (entered, completed)	Diagnosis	Primary Endpoint(s)	Main Findings
				to support registration of IBS for RBC			hepatic insufficiency and 6MWT	assessments of the 6MWT at the time of first ambulation post-surgery and at day 13 or discharge. No statistical differences in the overall incidence of AE rates, or in possibly related AEs between Test and Control, with similar distribution of SAEs between groups. The events observed were those expected in this population.
CLI 00076	3	Randomized, controlled, double blinded, two-period, crossover, non-inferiority	Six transfusion episodes of Test (INTERCEPT) or Control RBC; each treatment period to include 2 wash-in episodes and 4 study transfusion episodes; subjects will be transfused to maintain the same target hemoglobin level specified by treating physician in each study period	Evaluate the efficacy and safety of INTERCEPT RBCs in subjects who require chronic transfusion support due to thalassemia major	86 randomized, 81 treated	Subjects with thalassemia major who require chronic transfusion of RBC components	Hgb consumption during each efficacy evaluation period (episodes 4 to 6) measured as the Hgb mass transfused per subject adjusted for episode-specific body weight and duration (Hgb g/kg body weight/day). Incidence of a treatment-emergent antibody with confirmed specificity to INTERCEPT treated RBCs associated with clinically significant hemolysis	The non-inferiority of INTERCEPT RBC components for the primary efficacy endpoint was robustly achieved consistently for both the ITT and PP analysis groups. No treatment emergent antibodies to INTERCEPT RBC were detected. Adverse events were equally distributed between Test and Control periods.

2.4 SUMMARY OF POTENTIAL RISKS

The potential risks of this study include those adverse reactions that are recognized to occur following any transfusion of RBC components and could be anticipated to occur with either control or INTERCEPT-treated components including, but not limited to, delayed serologic transfusion reactions (DSTRs), acute hemolytic transfusion reactions (AHTRs), delayed hemolytic transfusion reactions (DHTRs), febrile non-hemolytic transfusion reactions (FNHTRs), allergic (urticarial) reactions, anaphylaxis, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion-related sepsis (TRS), or transfer of an infectious agent via transfusion/transfusion transmitted infection (TTI), respectively, transfusion- associated graft-vs-host disease (TA-GVHD), and allo-immunization to RBC and HLA antigens.

The development of antibodies to INTERCEPT RBCs, or to neoantigens formed as a result of acridine binding to red cells, could occur as a result of transfusion with INTERCEPT RBCs. Acridine-specific antibodies were observed in an early and current ongoing blinded studies (as described in the Investigator's Brochure) and many could be neutralized with acridine in solution, thereby defining specificity for this moiety. The occurrence of these antibodies was not associated with any clinical events or observations. The Current process has been optimized to decrease the likelihood of this event.

A screening study was performed to evaluate the prevalence of natural antibodies with specificity for INTERCEPT RBCs (SUD 00742). Five plasma samples from 998 subjects requiring chronic transfusion support for anemia and 12 plasma samples from 10,721 hospital subjects demonstrated low titer cross-reactions with INTERCEPT RBCs. The cumulative prevalence of cross-reactive antibodies to INTERCEPT RBCs was 0.15%. Each of the antibodies identified was characterized and none were found to be IgG_1 or IgG_3 subclass, the antibody subclasses most associated with physiologic hemolytic activity. The majority demonstrated specificity for acridine.

Several instances of treatment emergent antibodies with specificity for INTERCEPT RBCs were reported during the ongoing Phase III clinical investigations. In each event, the antibodies were shown to be non-clinically significant without evidence of patient harm. These studies remain blinded and it is not known whether the patients received Test of Control RBCs.

Natural antibodies to INTERCEPT RBCs are expected to occur in ongoing clinical trials. Risk mitigation is in place to protect patients and further evaluate clinical significance. All study subjects are screened before enrollment for INTERCEPT RBC-specific antibodies and subjects with natural cross-reactive antibodies are excluded. Subjects are regularly screened during the study including at approximately 75 days after the last study RBC transfusion in all ongoing clinical trials. Subjects with treatment emergent antibodies are withdrawn from receiving study RBC and are fully evaluated for evidence of hemolysis. Stopping rules are in place related to the occurrence of delayed serological and hemolytic TRs associated with treatment emergent antibodies to INTERCEPT RBCs.

Additional risks associated with Control components, that INTERCEPT treatment is designed to reduce, include risk of infectious contamination by viral or protozoan agents, such as HIV, HCV, HBV, malaria, and emerging viruses such as Zika, Dengue and Chikungunya.

The risk of bacterial contamination is considered to be negligible with INTERCEPT RBC components and, although it has not been measured directly, is expected to be less than the risk of bacterial contamination with conventional RBC components, thus providing a potential benefit of receiving INTERCEPT-treated components.

Finally, human error, clerical error and transfusion of RBC to the wrong patient remain risks of red cell transfusion.

2.5 DESCRIPTION OF AND RATIONALE FOR TREATMENT

Patients undergoing cardiac surgery are an appropriate study population because (i) these patients commonly require multiple RBC transfusions for support of acute anemia and might be expected to manifest complications ascribed to exposure to allogeneic blood, (ii) cardiac surgery patients comprise a large group of recipients with acute anemia requiring RBC transfusion and on a national basis account for a significant proportion of blood component utilization, and (iii) following cardiopulmonary bypass surgery, patients are in a pro-inflammatory state which might make them particularly vulnerable to adverse consequences of RBC transfusion, especially decreased tissue and organ oxygenation. While other types of surgical patients receive blood for acute anemia, they are either difficult to study in a clinical trial setting (e.g., trauma patients) or they may have high rates of autologous blood transfusion use (e.g., orthopedic patients). Cardiac surgery is also one setting where a liberal RBC transfusion policy has been documented to increase overall survival, suggesting an important role in ensuring tissue oxygenation (Murphy 2015).

The acute nature of the transfusion support in the setting of surgical blood loss with many confounding variables unrelated to the properties of RBC components limits the utility of measuring post-transfusion hemoglobin increments, and other direct measures of therapeutic benefit (Weiskopf 1998). In addition, evaluation of RBC component therapeutic efficacy is challenging because no single endpoint adequately reflects RBC transfusion efficacy in acute anemia. However, a reasonable approach is to assess a single key organ system such as renal as the primary endpoint. Accordingly, the primary efficacy measure in the proposed study is renal impairment defined by changes in serum creatinine .

Lassnigg et al. (Lassnigg 2004, Lassnigg 2008) found that measuring repeat sCr concentrations within 48 hours of cardiothoracic surgery and determining the ΔsCr from pre-surgery baseline concentrations was the most effective discrimination method to find patients at risk for adverse postoperative outcomes, including mortality by Day 30 post-surgery. In independent studies at two different European institutions that incorporated all cardiac surgery patients who survived at least 48 hours post-surgery, they found that ΔsCr concentrations declined in the majority of patients and was associated with the lowest mortality (1.8%). Minimal increases [0-0.5 mg/dL were associated with a more than doubled mortality in both centers (5%/6%). Used as a sole criterion, ΔsCr within 48 hours of surgery was more sensitive than the RIFLE (Mehta 2007) and AKIN (Bellomo 2004) definitions of Acute Kidney Injury (AKI) as a correlate of poor outcomes. The most important findings of these studies were that 1) even a small absolute increase in sCr in the post-cardiac surgery setting confers an adverse prognosis and increases the risk of death; 2) a window of 48 hours following cardiac surgery was able to classify the risk groups; and 3) ease of use and early prediction ability of absolute sCr changes alone challenge the RIFLE and AKIN classifications in these patients.

Historically acute kidney injury (AKI) is known to complicate recovery from cardiac surgery in up to 30% of patients, and places patients at a 5-fold increased risk of death during hospitalization (O'Neal et al. 2016).

AKI has been validated as a predictor of adverse outcomes after cardiac surgery based on sCr assessment alone. Many analyses do not incorporate urinary output (UO) as a component of the AKI measure, especially in cardiac surgery patients. For example:

- Hobson et al. (Hobson 2009) describe 2973 cardiac surgery patients between 1992 and 2002 and define AKI as a ≥50% increase in sCr from pre-surgery baseline. Survival was worse among patients with AKI and was proportional to its severity, with an adjusted hazard ratio of 1.23 (95% CI 1.06 to 1.42).
- Loef et al. (Loef 2005) describe an association of in-hospital and long term mortality with post-operative sCr levels only, in 843 cardiac surgery patients in 1991 (hazard ratio of death 1.83;95% confidence interval 1.38 to 3.20).
- More recently, Zhou et al. (Zhou 2016) confirmed the association of AKI based only on sCr criteria, with higher mortality and longer length of stay in 1036 critically ill ICU patients.

AKI that requires renal replacement therapy occurs in 2–5 % of patients following cardiac surgery and is associated with 50 % mortality (O'Neal 2016). For those who recover from renal replacement therapy or even mild AKI, progression to chronic kidney disease in the ensuing months and years is more likely than for those who do not develop AKI. Renal ischemia, reperfusion, inflammation, hemolysis, oxidative stress, cholesterol emboli, and toxins are known to contribute to the development and progression of AKI. Transfusion with RBC may prevent AKI by ensuring tissue oxygenation during and after surgery, but is also hypothesized to exacerbate AKI by the release of non-transferrin bound iron, promotion of a pro-inflammatory state, impairment of tissue oxygen delivery, and exacerbation of tissue oxidative stress (Karkouti 2012). A comparison of AKI incidence using conventional and INTERCEPT-treated RBC in cardiac surgery therefore offers a sensitive predictive measure of the equivalence of long-term outcomes following acute RBC transfusion for both benefits and potential harms.

Lassnigg et al. (Lassnigg 2004, Lassnigg 2008) found an association of small changes in serum creatinine (ΔsCr) in the first 48 hours after surgery with mortality by day 30, and an independent association of transfusion with adverse outcomes. In the ReCePI study we will enroll cardiac patients that are likely to require RBC transfusions using the Transfusion Risk Understanding Screening Tool (TRUST) Score (Alghamdi 2006), and these patients are more likely to suffer post-surgery renal impairment than patients who are less likely to require transfusion.

Cerus has completed two studies in cardiac surgery in patient populations similar to that proposed in ReCePI, and these data have been submitted to the FDA: RBC3A01, "*S-303 Treated Red Blood Cell Use in Patients Requiring Acute Transfusion Support*,"(Benjamin et al. 2005) (submitted to the FDA on March 30, 2005 under IDE 7750/91) and CLI 00070, "*A Randomized Controlled Double-Blind Phase 3*

Study to Assess Characteristics of S-303 Treated RBC Components and Evaluate Safety and Efficacy in Patients Requiring Transfusion Support of Acute Anemia," (submitted to the FDA on 30 September 2016 [Reference IDE 13803/65]).

The above studies inform the selection of the proportion of patients that are likely to meet the criterion of raised ΔsCr within 48 hours post the completion of cardiac surgery. A summary table (**Table 2.2**) provides the data from our analysis of studies RBC 3A01 and CLI 00070 that shows that the proportions of Control patients had ΔsCr values within 48 hours of surgery completion as follows: ≥0.1mg/dL = 55%; ≥0.2 mg/dL = 45%; and ≥0.3 mg/dL = 30%.

Table 2.2 Reanalysis of Cerus Studies RBC 3A01 and CLI 00070 Using Renal Impairment Based on Change in Serum Creatinine Levels within 48 hours of Cardiac Surgery

	Valve Only		CABG Only		Valve and CABG		All Patients		
CLI 00070	**Test**	**Control**	**Test**	**Control**	**Test**	**Control**	**Test**	**Control**	**Total**
	(N=10)	**(N=8)**	**(N=12)**	**(N=13)**	**(N=3)**	**(N=5)**	**(N=25)**	**(N=26)**	**(N=51)**
Cr Increase ≥0.1 mg/dL	7 (70.0%)	5 (62.5%)	5 (41.7%)	3 (23.1%)	3 (100%)	4 (80.0%)	15 (60.0%)	12 (46.2%)	27 (52.9%)
Cr Increase ≥0.2 mg/dL	6 (60.0%)	3 (37.5%)	2 (16.7%)	3 (23.1%)	3 (100%)	4 (80.0%)	11 (44.0%)	10 (38.5%)	21 (41.2%)
Cr Increase ≥0.3 mg/dL	5 (50.0%)	2 (25.0%)	0	1 (7.7%)	1 (33.3%)	2 (40.0%)	6 (24.0%)	5 (19.2%)	11 (21.6%)

	Valve Only		CABG Only		Valve and CABG		All Patients *		
RBC 3A	**Test**	**Control**	**Test**	**Control**	**Test**	**Control**	**Test**	**Control**	**Total**
	(N=31)	**(N=28)**	**(N=4)**	**(N=10)**	**(N=36)**	**(N=34)**	**(N=74)**	**(N=74)**	**(N=148)**
Cr Increase ≥0.1 mg/dL	16 (51.6%)	14 (50.0%)	3 (75.0%)	6 (60.0%)	24 (66.7%)	21 (61.8%)	45 (60.8%)	43 (58.1%)	88 (59.5%)
Cr Increase ≥0.2 mg/dL	10 (32.3%)	12 (42.9%)	3 (75.0%)	4 (40.0%)	15 (41.7%)	17 (50.0%)	29 (39.2%)	35 (47.3%)	64 (43.2%)
Cr Increase ≥0.3 mg/dL	7 (22.6%)	10 (35.7%)	2 (50.0%)	3 (30.0%)	10 (27.8%)	10 (29.4%)	20 (27.0%)	25 (33.8%)	45 (30.4%)

	Valve Only		CABG Only		Valve and CABG		All Patients		
CLI 00070 and RBC 3A	**Test**	**Control**	**Test**	**Control**	**Test**	**Control**	**Test**	**Control**	**Total**
	(N=41)	**(N=36)**	**(N=16)**	**(N=23)**	**(N=39)**	**(N=39)**	**(N=99)**	**(N=100)**	**(N=199)**
Cr Increase ≥0.1 mg/dL	23 (56.1%)	19 (52.8%)	8 (50.0%)	9 (39.1%)	27 (69.2%)	25 (64.1%)	60 (60.6%)	55 (55.0%)	115 (57.8%)
Cr Increase ≥0.2 mg/dL	16 (39.0%)	15 (41.7%)	5 (31.3%)	7 (30.4%)	18 (46.2%)	21 (53.8%)	40 (40.4%)	45 (45.0%)	85 (42.7%)
Cr Increase ≥0.3 mg/dL	12 (29.3%)	12 (33.3%)	2 (12.5%)	4 (17.4%)	11 (28.2%)	12 (30.8%)	26 (26.3%)	30 (30.0%)	56 (28.1%)

Notes:
* Included patients with "Other" type of surgery.

Based on these data, Cerus proposed a non-inferiority design in ReCePI to rule out an increase of ΔsCr ≥0.3mg/dL more than 50% from the Control rate with approximately 80% power and one-sided alpha of 2.5%. This is based on a Control rate of ΔsCr ≥0.3 mg/dL of 30%. At least 292 subjects will be randomized and transfused. Randomization (in 1:1 ratio for Test:Control) stratified by site, pre-existing renal impairment (stratum with either sCr ≥1.2mg/dL or sCr<1.2 mg/dL at baseline), and cardiac surgery risk level (high or low risk stratum group 1 or 2, respectively) will be employed.

As per Lassnigg et al (2004 and 2008) patients who die within 48 hours of the end of surgery and have received at least one study transfusion will be included in the modified intent-to-treat (mITT) analysis but excluded from the per protocol analysis. Patients who have not received a study transfusion within 48 hours of surgery will be excluded from the analysis and replaced.

Additional endpoints will include mortality or the need for RRT (defined as hemodialysis or peritoneal dialysis) by Day 30 post-surgery; and AKI as defined by modified Kidney Disease Improving Global Outcomes (KDIGO) criteria. Any RRT that is provided prophylactically during surgery while patient is on a bypass machine does not meet this endpoint. The vital status and RRT assessment on Day 30 after surgery can be performed either from the medical records, from a phone call to the subject or family, or during the visit 28 +/- 3 days after the last study transfusion if the window covers 30 days after surgery time point.

3 STUDY OBJECTIVES

The objective of this study is to evaluate the efficacy and safety of RBC transfusion for support of acute anemia in cardiovascular surgery patients based on the clinical outcome of renal impairment following transfusion of RBCs treated with the INTERCEPT Blood System for Red Blood Cells compared to patients transfused with conventional RBCs.

4 INVESTIGATIONAL PLAN

4.1 ENDPOINTS

4.1.1 Primary Endpoints

The primary efficacy endpoint is the proportion of patients, who have received at least one study transfusion with a diagnosis of renal impairment defined as:

- Any raised sCr level, occurring after transfusion of a study RBC, of ≥0.3 mg/dL (or 26.5 μmol/L) from the pre-surgery baseline within 48±4 hours of the end of surgery.

If any subject meets this criterion before receiving a study transfusion, that particular event will not be included in the primary endpoint analysis. The treatment comparison for the primary efficacy endpoint will be assessed by a non-inferiority test (Test–Control) with a non-inferiority margin of 50% increase from the Control rate and two-sided 0.05 alpha level. Patients who receive a study transfusion but die within 48 hours after surgery will be included in the mITT analysis but excluded from the per protocol analysis.

The primary safety endpoints are:

- Proportion of patients with any treatment-emergent adverse events (TEAEs) possibly, probably or definitely related to study RBC transfusion through 28 days after the last study transfusion; and
- Proportion of patients with treatment-emergent antibodies with confirmed specificity to INTERCEPT RBCs by end of study (i.e., 75±15 days after the last study transfusion).

TEAEs by definition will comprise all untoward medical events occurring after the start of the first study RBC transfusion and during the study (i.e., adverse events, serious adverse events, unanticipated adverse device effects, TRs and within 28 days post last study RBC transfusion). The primary safety endpoint is focused on possibly, probably or definitely related adverse events to the study RBC transfusion, because these patients have many adverse events which are unrelated to study RBC transfusion.

4.1.2 Secondary Endpoints

- Efficacy: Secondary efficacy endpoints include:
  - The proportion of patients with a diagnosis of stage I, II or III Acute Kidney Injury (KDIGO 2012) based on changes in sCr levels from pre-surgery baseline and the need for renal replacement therapy (RRT) post-surgery.
  - Mortality or the need for RRT by 30 days post completion of surgery.

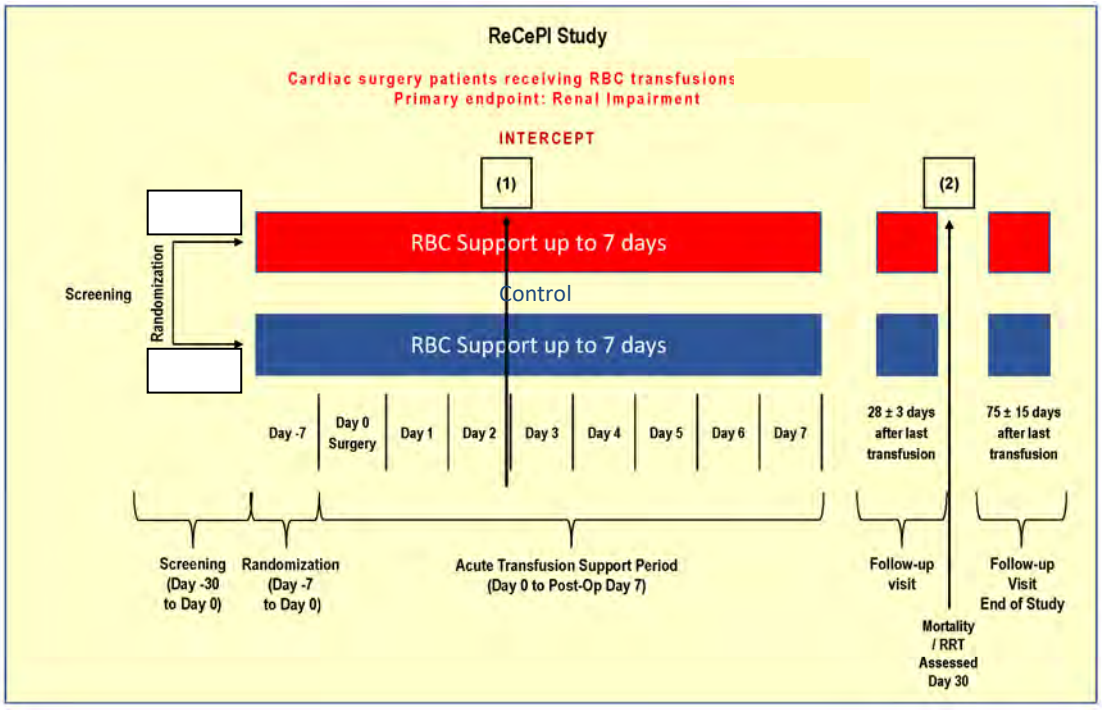
Safety: Assessment of additional safety parameters in post-surgical subjects transfused with INTERCEPT RBCs compared with subjects transfused with conventional RBCs, include:

- Treatment-emergent AEs through 28 days after the last study transfusion.
- Treatment-emergent SAEs through 28 days after the last study transfusion.
- Transfusion reactions (as defined by the CDC National Healthcare Safety Network [NHSN] Hemovigilance Module protocol) through 28 days after last study transfusion.
- Treatment-emergent immunization to RBC allo-antigens through 28 ±3 days after the last study transfusion.
- Treatment-emergent immunization to HLA allo-antigens through 28±3 days after the last study transfusion.

4.2 STUDY DESIGN

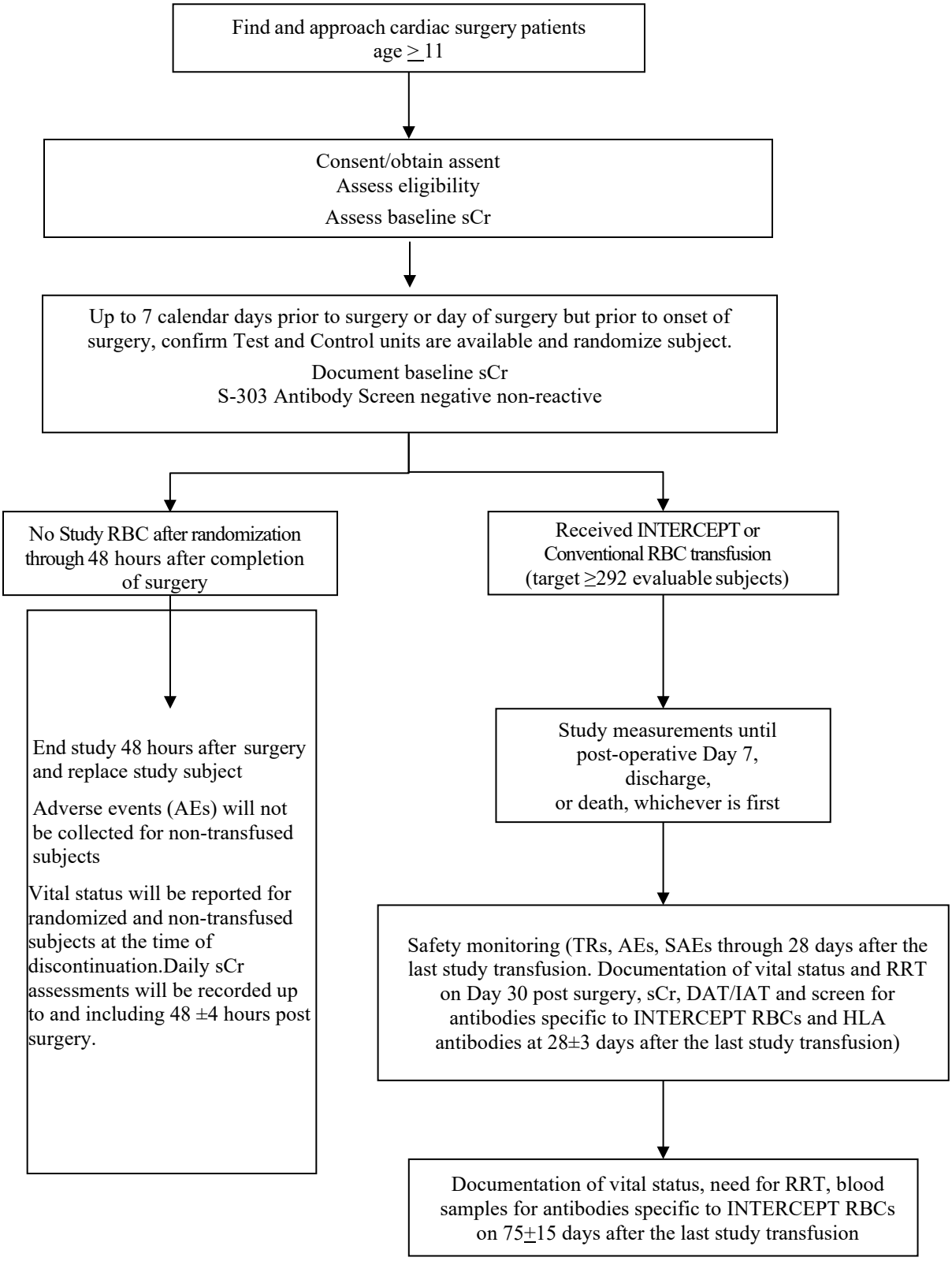
The study is a prospective, multicenter, randomized, double-blinded, active controlled, parallel-design, non-inferiority study. **Figure 4.1** shows the study design and **Figure 4.2** shows the clinical study flowchart.

Figure 4.1 Study Design Schematic



(1) Primary efficacy endpoint ΔsCr ≥0.3 mg/dL from baseline assessed within 48±4 hours of the end of surgery.
(2) Secondary efficacy endpoint of mortality or need for RRT assessed on Day 30 post-surgery

Figure 4.2 Study Flowchart



4.3 RANDOMIZATION AND BLINDING

Potentially eligible subjects will be screened and will be considered for randomization. If a subject is screened and receives a RBC transfusion prior to randomization, that subject will no longer be considered for randomization, and their participation in the study will end. Patients may be rescreened for eligibility closer to the time of surgery. An Interactive Web Response System (IWRS) will be used for electronic randomization of eligible patients. Following screening and prior to surgery (up to 7 days before surgery or day of surgery but before start of surgical procedure), the subject's eligibility status will be re-checked and entered in the eCRF. If eligible, the subject will be randomized with a 1:1 ratio for Test:Control within his/her randomization stratum. Randomization will be stratified by site, pre-existing renal impairment (sCr ≥1.2 mg/dL vs. < 1.2 mg/dL), and surgery group based on less (# 1-3 below) vs. more (#4-7 below) risk for renal complications (based on Mehta 2006 and expert opinion).

Less Risk

1. Single Vessel Coronary Artery Bypass Graft, first or repeat procedure
2. Multiple Coronary Artery Bypass Grafts, first or repeat procedure
3. Single Valve Repair or Replacement, first or repeat procedure

More Risk

4. Multiple Valve Repair or Replacement, first or repeat procedure
5. Surgery involving both Coronary Artery Bypass Graft(s) and Valve Repair(s), first or repeat procedure
6. One or more of the following procedures, with or without Coronary Bypass Graft(s):
   - Left ventricular aneurysm repair,
   - Ventricular and/or atrial septal defect repairs,
   - Batista procedure (surgical ventricular remodeling),
   - Surgical ventricular restoration,
   - Congenital cardiac defect repair,
   - Aortic procedures,
7. Other complex cardiac surgery or thoracic aorta surgery procedures not listed above

Patients undergoing urgent or emergent cardiac surgery are eligible for the study, subject to institutional review board (IRB) approval of an appropriate informed consent process.

Randomized subjects who do not receive any study RBC transfusions within the first 48 hours after completion of surgery will be discontinued from study and replaced. Serum Creatinine up to and including 48 ±4 hours post-surgery will be collected.

Other post baseline laboratory parameters and Adverse events (AEs) will not be collected for non-transfused subjects. Vital status will be reported for randomized and non-transfused subjects at the time of discontinuation.

Only appropriate blood bank staff and unblinded delegates who monitor the production of the RBC components will be able to access the treatment arm assignment. Selected Blood Center staff will not be blinded due to their role required for collection, preparation, and releasing of Test and Control RBC components for transfusion to study subjects. An unblinded study monitor will review and verify source data collected at the blood banks. Operating room staff, surgical staff, ICU staff and others caring for participating patients, as well as the sponsor (and delegates) will be blinded to treatment assignment. Study RBC components will be labeled in a manner to maintain the blind. In order to protect the blind, on the day of planned transfusion, the final product (test and control) will be transferred by the Blood Bank unblinded personnel into a commercially available RBC storage container (Fenwal™ Transfer Pack™ Container – 600mL, product code 4R2023) using a sterile docking technique. Blood transferred into an ancillary container should be stored at 1°C to 6°C and transfused within 7 days of transfer.

4.4 TREATMENT

Eligible subjects will be consented/provide assent and randomized to receive either INTERCEPT RBCs (Test) or conventional RBCs (Control) which will be transfused as needed starting from surgery at Day 0 until study post-operative Day 7, hospital discharge or death, whichever is first.

Treatment assessments will be divided into an acute transfusion support period starting on the day of surgery (Day 0) until post-operative Day 7, hospital discharge, or death, whichever is first, and a post-surgical follow-up visit (28±3 days) after the last study transfusion to collect additional safety data. A sample for sCr determination will be taken at 48±4 hours after the end of surgery to document the primary efficacy endpoint. For non-transfused subjects, a blood sample for sCr will be drawn at 48 ± 4 hours post-surgery. Patient status with regard to mortality and RRT on Day 30 post surgery will be documented. Anesthesia and surgical procedures will be performed according to the local standards of the institution.

Study RBC components will be ordered and administered to study subjects by treating physicians, according to the local standards of care. Following the post-surgery 7-day acute transfusion support period, subjects will receive conventional RBC components if additional transfusions are needed, as indicated by their treating physician.

4.4.1 Test Product

The INTERCEPT treatment will be performed on leukoreduced RBC components prepared from citrate phosphate dextrose (CPD) anticoagulated whole blood and suspended in AS-5 additive solution (input) within 24 hours of collection. The test component is allogeneic INTERCEPT treated RBC components prepared following the Instructions for Use for the INTECEPT Blood System for RBCs (SPC-EN 00581-AW) and stored in SAG-M at 1°C to 6°C for up to 35 days post-donation and administered intravenously. Test RBC components will be released to clinical inventory after review of the batch production record associated with the INTERCEPT treatment process.

4.4.2 Control (reference) Product

The Control transfusion component is CPD or citrate phosphate double dextrose (CP2D) anticoagulated whole blood derived conventional leukoreduced RBC components suspended in an FDA approved additive solution (e.g., AS-1, AS-3 or AS-5) and stored at 1°C to 6°C for up to 35 days post-donation and administered intravenously. The Control RBC components will be handled and labeled in a manner to maintain blinding. Control RBC components will be released to clinical inventory after review of the batch production record associated with the trial.

4.5 SUBJECT DISCONTINUATION

The following groups of subjects will not be eligible for study enrollment or will be discontinued from the study and may be replaced.

- Screened subjects who receive an RBC transfusion before undergoing randomization will not be eligible for study enrollment.
- Screened subjects who are not randomized before their surgery begins will not be eligible for enrollment.
- Randomized subjects who do not undergo surgery within 7 days of randomization, will be discontinued 7 days after randomization. Patients may be re-screened for eligibility and randomization closer to the time of surgery.

Randomized subjects who do not receive a study RBC transfusion within the first 48 ±4 hours after surgery will be discontinued and replaced and will not be followed any longer. For non-transfused subjects, a blood sample for sCr will be drawn at 48 ± 4 hours. Daily sCr assessments will be recorded up to and including 48 ±4 hours post surgery. Other post baseline laboratory parameters and Adverse events (AEs) will not be collected for non-transfused subjects. Vital status will be recorded at the time of discontinuation.

- Enrollment Pause and Stopping Rules

4.5.1 Definitions

4.5.1.1 Enrollment Pause

"Enrollment Pause" means that new patients will not be consented or provide assent for the study and subjects already screened will not be randomized. Subjects already randomized and receiving study RBC transfusions will continue to receive study transfusions with IAT crossmatch with each RBC component and a new screen for antibodies specific to INTERCEPT RBCs every third day to optimize protection of enrolled recipients. The FDA will be notified of all DSTRs specific to INTERCEPT RBCs.

4.5.1.2 Clinical Stop

"Clinical Stop" means complete cessation of recruitment activities and all study transfusions, thus stopping the active study transfusion phase of the study. Study participants will continue receiving non-study conventional transfusions as needed. All safety monitoring tasks will continue as per protocol.

4.5.1.3 Rules

The study may be temporarily paused or definitively stopped based on, but not limited to, the following rules/considerations:

- Poor/slow accrual: The goal is to recruit at least 292 patients in the study. The study may be stopped by the Sponsor if enrollment rates are not deemed acceptable or financially sustainable.
- Safety
- The DSMB will review safety data and make recommendations as per the current version of the DSMB Charter including interpretation of the stopping rules.

- The major safety concern in this trial is the possible development of antibodies specific to INTERCEPT RBCs that causes accelerated RBC clearance, as evidence of an acute or delayed hemolytic transfusion reaction (AHTR or DHTR). The study will be stopped if one subject who has been exposed to INTERCEPT RBC demonstrates a confirmed antibody with specificity to INTERCEPT RBCs and experiences a clinically significant HTR with overt intravascular or extravascular hemolysis as assessed by the Investigator and reviewed by the DSMB.

Stopping rules due to the occurrence of INTERCEPT RBC-specific DSTRs, DHTRs, AHTRs or hyperhemolysis syndrome are followed after discussion with Sponsor in the event of a positive antibody specific for INTERCEPT RBCs.

Table 4.1 Stopping Rules for INTERCEPT RBC-specific antibodies

	Trigger	Sponsor Action	Notify			Enrollment	On Study Patients	Continuation	Additional actions
	For INTERCEPT RBC- Specific Abs		**IRB**	**FDA**	**DSMB**			-	
1	INTERCEPT RBC-Specific DSTR with no evidence of hemolysis	Patient Withdrawal	X	X	X	Continue	Continue[1]	-	Sponsor will notify DSMB and FDA of each INTERCEPT RBC-Specific Ab[2]. Investigation may include unblinding the treatment assignment
2	INTERCEPT RBC-Specific DHTR (x1)	Clinical Stop	X	X	X	Stop	Stop	After Investigation & discussion with FDA & DSMB	Investigate full hemolytic potential. Continuation contingent on outcome of investigation, including confirmation that the subject has been exposed to INTERCEPT (Test) RBCs, and on FDA agreement on resumption.
3	INTERCEPT RBC-Specific AHTR (x1)	Clinical Stop	X	X	X	Stop	Stop	After Investigation & discussion with FDA & DSMB	Stop study for an INTERCEPT RBC-specific single acute hemolytic reaction. Continuation contingent on outcome of investigation, including confirmation that the subject has been exposed to INTERCEPT (Test) RBC, and on FDA agreement on resumption.

	Trigger	Sponsor Action	Notify			Enrollment	On Study Patients	Continuation	Additional actions
	For INTERCEPT RBC- Specific Abs		**IRB**	**FDA**	**DSMB**			-	
4	INTERCEPT RBC-Specific Hyper-hemolysis Syndrome (x1)	Clinical Stop	X	X	X	Stop	Stop	With FDA release	Investigation may include unblinding the treatment assignment

[1] The DSMB would make a decision on whether or not to pause the study each time a DSTR occurs with INTERCEPT RBC specificity.
[2] Applies to all INTERCEPT RBC-specific antibody examples shown in rows 1-4.

4.6 ACCOUNTABILITY OF STUDY PRODUCT

The Investigational Product includes both the INTERCEPT Blood System for RBCs, a medical device used to prepare pathogen inactivated RBC components for transfusion, and the investigational biological product, INTERCEPT RBCs in SAG-M.

The investigational device accountability will be verified by the unblinded study monitors throughout the duration of study. They will assure that the device components are under control at all times inclusive of shipment, storage, usage, and disposition.

The investigational biologic product will be produced by each Blood Center according to the Study RBC Processing Procedures and accountability will be tracked using the Blood Center's electronic data management system.

Both Test and Control RBC components are for the sole use of study participants. They may not be crossed back into general inventory at a blood center or clinical site. The disposition of all components prepared for the study (transfused, discarded or expired) will be recorded. The investigational biologic product accountability will be verified by the unblinded study monitors throughout the duration of study.

4.7 SOURCE DATA

The subjects' medical records are the source data; the study data will be recorded in an EDC system using eCRFs. Data worksheets used during the preparation of study RBC components are considered the source data for processing study RBC components.

5 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 SUBJECT INCLUSION CRITERIA

The following conditions must be met before a subject may be randomized into the study.

1. Age ≥ 11 years old
2. Weight ≥ 40 kg
3. Scheduled complex cardiac surgery or thoracic aorta surgery. The procedure may be performed either on or off cardiopulmonary bypass machine (CPB or "pump"). For the purposes of this protocol "Repeat procedure" means that the subject had a previous cardiac surgery. Procedures that qualify as complex cardiac surgery include but are not limited to the following:

- Single Vessel Coronary Artery Bypass Graft, first or repeat procedure
- Multiple Coronary Artery Bypass Grafts, first or repeat procedure
- Single Valve Repair or Replacement, first or repeat procedure
- Multiple Valve Repair or Replacement, first or repeat procedure
- Surgery involving both Coronary Artery Bypass Graft(s) and Valve Repair(s), first or repeat procedure
- One or more of the following procedures, with or without Coronary Bypass Graft(s):
    - left ventricular aneurysm repair,
    - ventricular and/or atrial septal defect repairs,
    - Batista procedure (surgical ventricular remodeling),
    - surgical ventricular restoration,
    - congenital cardiac defect repair
    - aortic procedures
    - other cardiac surgery or thoracic aorta surgery types with a high probability of bleeding.

4. TRUST probability score (Alghamdi, Davis et al. 2006) ≥ 3, or currently on regimen of aspirin (any dose), clopidogrel (or analogs) and/or GPIIb/IIIa inhibitors, or at a high probability for need of a transfusion during or after surgery at the discretion of the Investigator.

5. Female subjects of child-bearing potential who meet the 2 criteria below at screening:
    - A negative urine or serum pregnancy test
    - Use at least one method of birth control that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized partner.
6. Signed and dated informed consent/assent form.

5.2 SUBJECT EXCLUSION CRITERIA

Patients will be excluded from this study if they meet any of the following criteria:

1. Confirmed positive baseline serum/plasma antibody specific to INTERCEPT RBCs (S-303 specific antibody) screening panel prior to randomization.
2. Pregnant or breast feeding.
3. Refusal of blood products or other inability to comply with the protocol in the opinion of the Investigator or the treating physician.
4. Treatment with any medication that is known to adversely affect RBC viability, such as, but not limited to dapsone, levodopa, methyldopa, nitrofurantoin, and its derivatives, phenazopyridine and quinidine.
5. Planned cardiac transplantation.
6. Active autoimmune hemolytic anemia.
7. Left ventricular assist device (LVAD) or extracorporeal membrane oxygenation (ECMO) support pre-operatively or planned need post-operatively.
8. Cardiogenic shock requiring pre-operative placement of an intra-aortic balloon pump (IABP) (NOTE: IABP done for unstable angina or prophylactically for low ejection fraction is not excluded).
9. Planned use of autologous or directed donations.
10. RBC transfusion during current hospitalization prior to enrollment and randomization (within 7 days).
11. Participation in an interventional clinical study concurrently or within the previous 28 days. This includes investigational blood products, pharmacologic agents, imaging materials (including dyes), surgical techniques, or devices. Observational studies of FDA cleared or approved products or nutrition, psychology, or socioeconomic issues are not grounds for exclusion.

12. Patients with a current diagnosis of either chronic kidney disease or acute kidney injury and with sCr ≥1.8 mg/dL at screening and patients requiring RRT. (NOTE: If sCr at screening is <1.8 mg/dL, a patient with a diagnosis of chronic or acute kidney injury alone is not excluded).
13. Patients with a current diagnosis of either chronic or acute hepatic insufficiency and with a total serum bilirubin ≥ 2.0 mg/dL (≥34.2 µmol/L). (NOTE: If total serum bilirubin at screening is <2.0 mg/dL, a patient with a diagnosis of chronic or acute hepatic failure alone is not excluded).
14. Pre-existing RBC antibody that may make the provision of compatible study RBC components difficult.
15. History of TRs requiring washed RBCs, volume reduced RBCs, or RBCs with additive solution removed.
16. Patients with documented IgA deficiency or a history of severe allergic reactions to blood products.
17. Patients who require gamma-irradiated RBC blood components.
18. Positive DAT as defined below:
    A polyspecific DAT reaction strength > 2+, or
    A polyspecific DAT (any strength) in conjunction with pan-reactivity with a commercial IAT antibody screening panel that precludes the identification of underlying alloantibodies or indicates the presence of autoantibody.

5.3 SUBJECT WITHDRAWAL CRITERIA

Study subjects are free to withdraw consent/assent or discontinue participation in the study at any time, without prejudice to further treatment. A patient's participation in the study may be terminated at any time at the discretion of the investigator if he/she feels it is in the patient's best interest. Randomized subjects who do not receive any study RBC transfusions from randomization to within the first 48 hours after surgery will be replaced.

5.3.1 Discontinuation from study RBC transfusions

Study RBC transfusions will be discontinued if the subject:

- Becomes pregnant.
- Is treated with a concurrent prescribed medication demonstrated to have caused hemolysis while on study.
- Develops an antibody with presumed or documented INTERCEPT RBC specificity and cannot be transfused further with INTERCEPT RBCs.

- If INTERCEPT RBC-specific antibodies cannot formally be ruled out, or agglutination is visible for all the untreated RBC cells in the panel, (i.e., "pan-reactive").

If the subject is discontinued from study transfusions due to development of INTERCEPT RBC-specific antibody after receiving one or more study RBC transfusions, the subject should continue on study receiving only non-study RBC transfusions if needed and should complete all safety assessments, including the study 75 ±15 days post last transfusion follow-up visit. REF 01606 (S-303 Reactive Samples: Management of Patients and Samples) should be followed immediately after the INTERCEPT RBC-specific antibodies are identified. A specific data entry guidance is provided in CRF Completion Guidelines (CCGs) for the INTERCEPT RBC-specific antibody reactive test results.

5.3.2 Early termination from Study

Upon early termination from study the tests required of the termination visit will be performed. If the subject is terminated from study (for any reason) before transfusion of any study RBC product, the subject will be replaced and no further follow up is required. For non-transfused subjects, a blood sample for sCr will be drawn at 48 ± 4 hours. Daily sCr assessments will be recorded up to and including 48 ±4 hours post surgery. Other post baseline laboratory parameters and Adverse events (AEs) will not be collected for non-transfused subjects. Vital status will be recorded at the time of discontinuation. If the subject has received any study RBC product and it is possible, a physical examination, including general neurological examination, should be performed, concomitant medications and adverse events should be recorded, standard laboratory tests should be collected, and other blood samples should be obtained on day 28 ±3 and day 75 ±15 as described in the protocol.

If consent/assent for further follow-up is withdrawn, the subject should, at minimum, be asked to provide a blood sample at the time of withdrawal for sCr, DAT, IAT and INTERCEPT RBC-specific antibody screen.

6 TREATMENT OF SUBJECTS

6.1 TREATMENT PLAN

6.1.1 Screening/Randomization (Day -30 to Day 0 Pre-Surgery)

Patients will be identified through pre-operative scheduling procedures in advance of their complex cardiac surgery. Patients already hospitalized may be included.

Patients undergoing urgent or emergent cardiac surgery are eligible for the study, subject to institutional review board (IRB) approval of an appropriate informed consent process.

In order to minimize the number of patients who enroll in the study but do not require RBC transfusion, only patients with a relatively high likelihood to receive a transfusion as determined by the Investigator (e.g., patients currently on regimen of aspirin, clopidogrel (or analogs) and/or GPIIb/IIIa inhibitors), or patients with a TRUST score of ≥3 will be eligible for enrollment. A TRUST score of ≥3 corresponds to a high likelihood of requiring red cell transfusion within 96 hours of surgery. Study consent/assent will be sought in these eligible subjects within 30 days of their surgical procedure. Subjects who consent/assent to the study will be assigned a subject identification (ID) number and undergo screening.

The complete list of screening assessments are outlined in Table 7.1a. Data may be derived from the medical record where performed within 30 days prior to their surgical procedure. Blood samples for determination of HLA antibodies will also be collected at the screening visit and sent for testing at a specialty central laboratory. In certain situations, it is possible for a mobile medical professional, authorized by the sponsor and requested by site personnel, to conduct a home health service visit at a subject's home to collect screening assessments. Patients who fail eligibility for any or multiple inclusion/exclusion criteria may be rescreened for eligibility closer to the time of surgery.

All available components of the TRUST score (age, sex, Hb, weight, type of surgery, serum creatinine, surgical history and surgical task) will be collected on the case report form. The TRUST score (or the minimum and maximum possible TRUST scores, if there are any missing components) will be calculated according to the published algorithm (APPENDIX 1).

Eligible subjects will be randomized up to 7 days before or on the day of surgery, but prior to the start of surgery (i.e., induction of anesthesia). The adverse event collection period will begin at the beginning of surgery or the first study RBC transfusion, whichever is first.

For non-transfused subjects, a blood sample for sCr will be drawn at 48 ± 4 hours. Daily sCr assessments will be recorded up to and including 48 ±4 hours post surgery. Other post baseline laboratory parameters and Adverse events (AEs) will not be collected for non-transfused subjects. Vital status will be recorded at the time of discontinuation.

The complete list of baseline assessments to be performed pre-operatively on the day before or on the day of surgery before surgery commences are outlined in Table 7.1b.

6.1.2 Acute Transfusion Support Period (Surgery [Day 0] to Post-operative Day 7, Hospital Discharge or Death, Whichever is First)

The complete list of assessments to be performed during the acute transfusion support period are outlined in Table 7.1c.

During the acute transfusion support period (Day 0 to Day 7), hospital discharge or death, whichever is first, patients will be transfused with Test or Control RBCs. Induction and end of anesthesia are considered start and stop time of surgery. All transfusions administered through Day 7 will be of the assigned treatment arm as often as feasible without compromising patient care.

A screen for antibodies specific for INTERCEPT RBCs should be performed every time that a routine IAT is performed during the acute 7-day study transfusion period.

A blood sample for sCr will be taken at 48 (±4 hours) after completion of surgery, and sCr will be determined on a daily basis during the acute transfusion support period up to 7 days post-surgery. Other parameters will be collected on eCRFs only when available in the medical record.

Randomized subjects who do not receive an RBC transfusion following randomization within the first 48 hours after surgery will be discontinued from the study and replaced.

For non-transfused subjects, a blood sample for sCr will be drawn at 48 ± 4 hours. Daily sCr assessments will be recorded up to and including 48 ±4 hours post surgery. Other post baseline laboratory parameters and adverse events (AEs)Es) will not be collected for non-transfused subjects. Vital status will be recorded at the time of discontinuation.

Once a subject is randomized, in rare exceptions where study RBCs are unavailable or a subject's need for RBC transfusions exceeds the quantities of the prepared study RBCs (e.g., during a Massive Transfusion Protocol), non-study RBC (conventional) transfusion may be given to provide the subject with an appropriate and necessary treatment. Non-study RBC transfusion data is captured in the eCRF. In this case, a protocol deviation should be noted. Transfusions will be administered according to

local institutional policy and safety standards as ordered by the medical team for patient care needs. Anesthesia and surgical procedures will be performed according to the local standards of the institution.

Hemodynamic and laboratory results will be recorded daily from post-surgery through post-operative Day 7, hospital discharge or death, whichever occurs first. If an assessment is performed more than once in a day, the first set of results should be entered into the eCRF.

If a subject is discharged prior to the end of the acute transfusion support period (Day 7) but for any reason returns to the study site (e.g., re-hospitalization or standard care) within this acute transfusion support period, lab values routinely collected as standard of care should be recorded in the eCRF.

If multiple assessments (hemodynamic parameters, vital signs, laboratory parameters) are taken in a calendar day, the reported value for first collection of the day should be recorded in the eCRF with the exception of serum creatinine . Serum creatinine will be collected and recorded in the eCRF on a daily basis during the 7 day acute transfusion support period. If serum creatinine is measured multiple times in a day, the worst daily value should be recorded in the eCRF. In addition, a sample to measure sCr will be taken at 48±4 hours after the end of surgery and captured on a specific CRF page for that time-point.

For non-transfused subjects, a blood sample for sCr will be drawn at 48 ± 4 hours hours post-surgery. Serum Creatinine up to and including 48 ±4 hours post-surgery will be collected.

Urine output (mL/kg/hour) will be recorded in the eCRF daily while a urinary catheter is in place.

Other assessments during this trial period include details related to the specific surgical procedure (type of procedure, start and end times, RBC components transfused, all other blood components transfused, estimated blood loss from the surgical procedure, concomitant medications, intraoperative cell recovery and reinfusion, hemodilution, and nadir temperature). Additionally, daily estimated blood loss from chest tube(s) and from other sources, and day of chest tube removal will be recorded. See Table 7.1c for a detailed list of study assessments.

AEs and SAEs, including TRs and protocol-specified AEs (see Section 7.3), will be assessed from the start of surgery or the start of the first study RBC transfusion (whichever is first) on a daily basis and documented in the eCRF through post-operative Day 7. Adverse events (AEs) will not be collected for non-transfused

subjects, but vital status will be recorded at the time of discontinuation. See Table 7.1c for a detailed list of study assessments.

NOTE: The following post-operative assessments apply to randomized transfused subjects only.

6.1.3 Post-operative Period (Day 8 [or Post-discharge, if earlier] through Day 28 After Last Study Transfusion)

The complete list of assessments to be performed during this post-operative period are outlined in Table 7.1d.

Laboratory results recorded in the eCRFs during this period will only be those assessed as clinically significant per the Investigator. Following the post-surgery 7-day acute transfusion support period, the post-operative period starts on Day 8 after surgery and goes through the Day 28±3 visit. Subjects will receive conventional non-study RBC components if additional transfusions are needed, as indicated by their treating physician.

Weekly telephone surveillance calls to the subject will be performed to collect AEs, SAEs and TRs. If a surveillance call falls on the same week as the Day 28±3 follow-up visit, the follow-up visit assessments will take precedent and a surveillance call is not required.

6.1.4 Day 28±3 After Last Study Transfusion or Early Termination

The complete list of assessments to be performed during the Day 28±3 or Early Termination visit are outlined in Table 7.1e.

Subjects should be scheduled for a follow-up visit 28±3 days after the last study transfusion to obtain additional safety information, including subject-reported AEs, SAEs, and laboratory results. This visit may occur either in hospital, clinic visit, or offsite. In certain situations, it is possible for a mobile medical professional, authorized by the Sponsor and requested by site personnel, to conduct a home health service visit at a subject's home to collect these assessments. Blood samples for determination of HLA antibodies will also be collected at the visit and sent for testing at a specialty central laboratory. TRs, AEs and SAEs will be documented for 28 days after the last study transfusion, or earlier if the subject dies prior to Day 28 post last study RBC transfusion. If a subject has been discharged prior to Day 28 post last study RBC transfusion, the vital status, need for RRT and other safety information (e.g., AEs and SAEs) may be obtained through medical records, the subject's physician, or a telephone interview with either the subject or a family member.

6.1.5 Day 30 – After Surgery Assessment

The complete list of assessments to be performed at Day 30 are outlined in Table 7.1e.

All randomized subjects who receive a study RBC transfusion must have their vital status and need for RRT (defined as hemodialysis or peritoneal dialysis) documented at Day 30 after surgery. RRT that is provided prophylactically during surgery while patient is on a bypass machine (the pump) does not meet this endpoint. The vital status and RRT assessment on Day 30 post surgery can be obtained either from the medical records, from a phone call to the subject or family, or during the visit 28±3 days after the last study transfusion (only if the last study transfusion was given at day 2 or later in the acute transfusion support period).

6.1.6 End of Study (75 ±15 Days After Last Study Transfusion)

The complete list of assessments to be performed at the 75 ±15 day study visit are outlined in Table 7.1e.

Subjects should be scheduled for a second follow up visit on Day 75±15 days after the last study transfusion for vital status, need for RRT, and for assessment of INTERCEPT RBC-specific antibodies at end of study, either in hospital, clinic visit or off-site. In certain situations, it is possible for a mobile medical professional, authorized by the Sponsor and requested by site personnel, to conduct a home health service visit at a subject's home to collect these assessments. If the assessment of INTERCEPT RBC-specific antibodies is positive, the positive S-303 specific DSTR should be entered on the Adverse Event eCRF.

6.1.7 Assessments in Follow-up to a Reactive Antibody Test Specific for INTERCEPT RBCs

In the event of detection of treatment-emergent antibodies with specificity to INTERCEPT RBCs, the Investigator shall be instructed about specific laboratory and clinical assessments to be performed. See section 7.3.1.11 Suspected Hemolytic and Serologic TRs after Enrollment and Transfusion with Study RBC Components assessment of immune reactivity of INTERCEPT for more details.

6.2 CONCOMITANT AND EXCLUDED THERAPY

Standard medical care according to local institutional standards will be provided to each subject. The following concomitant (or planned) therapies/procedures will exclude subjects from the current study:

- Left-ventricular assist device (LVAD) or Extracorporeal membrane oxygenation (ECMO) support pre-operatively or planned need post-operatively.
- Cardiogenic shock requiring pre-operative placement of an IABP (Note: IABP done for unstable angina or prophylactically for low ejection fraction is not excluded).
- Treatment with any medication that is known to adversely affect RBC viability, such as but not limited to, dapsone, levodopa, methyldopa, nitrofurantoin, and its derivatives, phenazopyridine and quinidine.
- Planned use of autologous or directed donations
- Patients who have received an RBC transfusion during current hospitalization prior to randomization (within 7 days)
- Subjects who have received investigational products, including investigational blood products, pharmacologic agents or imaging materials, within the prior 28 days will also be excluded.

6.3 TREATMENT COMPLIANCE

Treatment compliance will be overseen by the Investigator and study staff and relevant documentation will be recorded in the eCRF. Compliance will be monitored by the Sponsor and/or Sponsor's representatives by review of source documents. The study RBC components will be labeled and tracked through all stages of processing of Test and Control components, storage, issue, and transfusion.

7 STUDY ASSESSMENTS

7.1 STUDY SCHEDULE OF ASSESSMENTS

A screen for antibodies specific for INTERCEPT RBCs should be performed every time that a routine IAT is performed during the acute 7-day study transfusion period.

A blood sample for sCr will be taken at 48 (±4 hours) after completion of surgery, and sCr will be determined on a daily basis during the acute transfusion support period up to 7 days post-surgery. Other parameters will be collected on eCRFs only when available in the medical record.

For non-transfused subjects, a blood sample for sCr will be drawn at 48 ± 4 hours and daily sCr assessments will be recorded up to and including 48 ±4 hours post surgery. All samples obtained for determination of human leukocyte antigen (HLA) will be stored for up to 1 year after the study has completed.

The study assessments used to evaluate both efficacy and safety are presented in **Table 7.1a**, **Table 7.1b**, **Table 7.1c**, **Table 7.1d, Table 7.1e and 7.2.**

Table 7.1a – Screening/Randomization		
Study Period – Screening Visit (Day -30 to Day 0 pre-surgery)		
Assessment		**Superscripts Defined**
Informed Consent/Assent	X	[1.] For Screening/Randomization purposes, data from medical records within 30 days prior to their surgical procedure may be used. [2.] See **Table** 7.2: Hematology and Chemistry Testing for details on required labs.
Demographics	X	
Indication /Type of scheduled surgery	X	
Medical, surgical, transfusion and medication history including radiographic contrast media within 7 days of surgery/ the need for irradiated RBC products	X	
Number of prior pregnancies (females)	X	
Physical examination including height and weight	X	
Vital signs (HR, BP, RR) [1]	X	
Concomitant medications	X	
EKG [1]	X	
Pregnancy test (if applicable) [1,2]	X	
Hematology panel[1,2]	X	
Blood chemistry[1,2]	X	
Blood type[1]	X	
DAT[1], IAT[1]	X	
INTERCEPT RBC antibody screen (S-303-specific antibody screen)	X	
Sample for HLA antibodies	X	
TRUST score components	X	
Randomization[#]	X	[#] Eligible patients will be randomized up to 7 days before or on the day of surgery, but prior to the start of surgery (i.e., induction of anesthesia).
AEs/SAEs/TRs*	X	*The adverse event, serious adverse event and transfusion reaction collection period will begin at the start of surgery or the first study RBC transfusion, whichever is first. Adverse events (AEs) will not be collected for non-transfused subjects, but vital status will be recorded at the time of discontinuation.

Table 7.1b - Baseline (Pre-Surgery)		
Study Period – Baseline (Day -1 or Day 0 Pre-Surgery)		
Assessment		
Vital signs (HR, BP, RR) [3]	X	[2.] See **Table 7.2**: Hematology and Chemistry Testing for details on required labs.
Concomitant medications[3]	X	[3.]These assessments can be combined with screening assessments if screening visit is also on Day -1 or Day 0 Pre-Surgery.
Pregnancy test (if applicable)[2,3]	X	
Hematology panel[2,3]	X	[4.]Data collected on eCRFs only as available from medical records if performed as Standard of Care.
Blood chemistry[2, 3]	X	
EKG[3]	X[4]	[5.] Hemodynamic Parameters: Peripheral O_2 Saturation, Mean Arterial Pressure, Central Venous Pressure.
Hemodynamic Parameters[5]	X[4]	
Fibrinogen Troponin	X[4]	
AEs/ SAEs/TRs*	X	*The adverse event, serious adverse event and transfusion reaction collection period will begin at the start of surgery or the first study RBC transfusion, whichever is first. Adverse events (AEs) will not be collected for non-transfused subjects but vital status will be recorded at the time of discontinuation.

Table 7.1c – Acute Transfusion Support Period

Study Period - Acute Transfusion Support Period (Surgery [Day 0] to Post-operative Day 7, hospital discharge or death, whichever is first)			
Assessment	**Day 0 Surgery**	**Day 1 - 7**	**Superscripts Defined**
Vital signs (HR, BP, RR)	X	X[6]	[2.] See **Table 7.2**: Hematology and Chemistry Testing for details on required labs. [4.] Data collected on eCRFs only as available from medical records if performed as Standard of Care. [5.] Hemodynamic Parameters, if available- Peripheral O_2 Saturation, Mean Arterial Pressure[4], Central Venous Pressure[4] [6.] These assessments are required to be collected daily on Day 1 through Day 7 post surgery or until discharge. If subject returns after discharge for a postoperative standard of care visit, assessments will be collected in eCRFs on the appropriate study day. [7.] Any drugs given to induce anesthesia or drugs given as a prophylactic in combination with anesthesia prior to surgery do not need to be recorded. Medications given during anesthesia to treat an AE/SAE need to be recorded. [8.] Urine output data collected daily while a urinary catheter is in place. The date entered should reflect the start of the collection and match the visit date. [9.] S-303 screen must be performed whenever a routine RBC alloantibody screen (IAT) is performed during the transfusion period. [10.] For non-transfused subjects, a blood sample for sCr will be drawn at 48 ± 4 hours. Daily sCr
Concomitant medications	X[7]	X[6]	
EKG	X[4]	X[4]	
Hematology panel[2]	X	X[6]	
Blood chemistry[2]	X	X[6]	
Serum Creatinine at 48±4 hours after end of surgery		X[10]	
Hemodynamic Parameters[3]	X[5]	X[6]	
Fibrinogen, Troponin	X[4]	X[4]	
Urine output[8]	X	X[6]	
Procedure details	X		
Study RBC crossmatch and Study RBC transfusion(s)/data	X	X	
DAT, IAT, INTERCEPT RBC antibody screen (S-303-specific antibody screen)[9]	X[4]	X[4]	
All other blood components (including non- study RBCs) transfused, if any	X	X	
Estimated blood loss from surgery	X		
Estimated blood loss from other source including chest tube(s)		X[6]	
AEs/ SAEs/TRs*	X	X[6]	

Table 7.1c – Acute Transfusion Support Period			
Study Period - Acute Transfusion Support Period (Surgery [Day 0] to Post-operative Day 7, hospital discharge or death, whichever is first)			
Assessment	**Day 0 Surgery**	**Day 1 - 7**	**Superscripts Defined**
			assessments will be recorded up to and including 48 ±4 hours post surgery. * The adverse event, serious adverse event and transfusion reaction collection period will begin at the start of surgery or the first study RBC transfusion, whichever is first. AEs including protocol specified AEs, TRs and SAEs (see Section 7.3) are collected through 28 days after the last study transfusion; also collected daily during acute transfusion support period. For non-transfused subjects, adverse events (AEs) will not be collected for non-transfused subjects, but vital status will be recorded at the time of discontinuation.

Table 7.1d – Post-Operative Period		
Study Period- Post-operative Period Day 8 (or Post-discharge, if Earlier) to Day 28 after last study transfusion		
Assessment	**Day 8 through to Day 28 post last study Tx**	**Superscript Defined**
Weekly telephone calls	X	[2.] See Table 7.2: Hematology and Chemistry Testing for details on required labs [4.] Data collected on eCRFs as available from medical records if performed as Standard of Care. [5.] Hemodynamic Parameters, if available- Peripheral O_2 Saturation, Mean Arterial Pressure, Central Venous Pressure [8.] Urine output data collected daily while a urinary catheter is in place. The date entered should reflect the start of the collection and match the visit date. [10.] Laboratory results recorded in the eCRFs during this period will only be those assessed as clinically significant by the Investigator. * The adverse event, serious adverse event and transfusion reaction collection period will begin at the start of surgery or the first study RBC transfusion, whichever is first. AEs including protocol specified AEs, TRs and SAEs (see Section 7.3) are collected through 28 days after the last study transfusion; also collected daily during acute transfusion support period. Adverse events (AEs) will not be collected for non-transfused subjects, but vital status will be recorded at the time of discontinuation.
Concomitant medications	X[4]	
Hematology panel [2, 10]	X[4]	
Blood chemistry [2, 10]	X[4]	
Hemodynamic Parameters[5]	X[4]	
Fibrinogen, Troponin	X[4]	
Urine output[8]	X[4]	
All other blood components (including non- study RBCs) transfused, if any	X[4]	
AEs/ SAEs/TRs*	X	

Table 7.1e - Follow-up Visits (Day 28±3, 30, and 75±15)

Study Period (Day 28±3, 30, and 75±15[End of Study])				
Assessment	**28±3 days After last study transfusion or Early Termination**	**30 days After Surgery**	**End of Study (75±15 Days After Last Study Transfusion)**	**Superscripts Defined**
Vital signs (HR, BP, RR)	X			[2.] See **Table 7.2**: Hematology and Chemistry Testing for details on required labs * The adverse event, serious adverse event and transfusion reaction collection period will begin at the start of surgery or the first study RBC transfusion, whichever is first. AEs including protocol specified AEs, TRs and SAEs (see **Section 7.3**) are collected through 28 days after the last study transfusion; also collected daily during acute transfusion support period. Adverse events (AEs) will not be collected for non-transfused subjects, but vital status will be recorded at the time of discontinuation. [11.] Assess at Day 30 post surgery via clinic visit, medical record or phone call. Any RRT that is provided prophylactically during surgery while the subject is on a bypass machine does not meet this endpoint.
Concomitant medications	X			
Hematology panel[2]	X			
Blood chemistry [2]	X			
DAT, IAT	X			
INTERCEPT RBC antibody screen (S-303-specific antibody screen)	X		X	
Sample for HLA antibodies	X			
All other blood components (including non- study RBCs) transfused, if any	X			
AEs/ SAEs/TRs *	X			
Documentation of vital status and need for RRT	X	X[11]	X	

Table 7.2: Hematology and Chemistry Testing- Required (R) results and Where Available (WA)[a] results

Study Period	Screening / Randomization		Acute Transfusion Support Period (Surgery [Day 0] to Post-operative Day 7, hospital discharge or death, whichever is first)		Post-operative Period	Follow-up Visit
		Baseline (Pre-surgery)				
Window	**Day -30 to Day -1**	**Day -1 or Day 0 pre- surgery[g]**	**Day 0 Surgery**	**Days 1 – 7, hospital discharge or death**	**Days 8 to 28 after last study transfusion / death** Laboratory results recorded in the eCRFs during this period will only be those assessed as clinically significant per the investigator.	**28±3 days after last study transfusion or Premature Discontinuation Visit**
Pregnancy test (if applicable)	R[j]	R[j]				
Hematology (CBC):						
Hematocrit (Hct)	R[b]	WA	R	R[d,e,i]	WA	R
Hemoglobin (Hb)	R[b]	WA	R	R[d,e,i]	WA	R
Platelets (PLT)	R[b]	WA	R	R[d,e,i]	WA	R
RBC Count	R[b]	WA	R	R[d,e,i]	WA	R
WBC Count	R[b]	WA	R	R[d,e,i]	WA	R
Fibrinogen		WA	WA	WA[d]	WA	
Troponin		WA	WA	WA[d]	WA	
Blood chemistry:						
Alkaline Phosphatase (ALP)	WA	WA	WA	WA[d]	WA	WA
Alanine Transaminase (ALT)	WA	WA	WA	WA[d]	WA	WA
Aspartate Aminotransferase (AST)	WA	WA	WA	WA[d]	WA	WA
Bicarbonate (CO_2)	WA	WA	WA	WA[d]	WA	WA
Blood Urea Nitrogen (BUN)	R[b]	R	R[h]	R[d,h,i]	WA	R
Calcium (Ca)	R[b]	WA	R	WA[d]	WA	R
Chloride (Cl)	R[b]	WA	R	WA[d]	WA	R
Creatinine (sCr)	R[b]	R	R[h]	R[c,e,f,h,i]	WA	R
Glucose	R[b]	WA	R	R[d,i]	WA	R
Lactate Dehydrogenase (LDH)	WA	WA	WA	WA[d]	WA	WA
Potassium (K)	R[b]	WA	R	R[d,i]	WA	R
Sodium (Na)	R[b]	WA	R	R[d,i]	WA	R

Study Period	**Screening / Randomization**		**Acute Transfusion Support Period (Surgery [Day 0] to Post-operative Day 7, hospital discharge or death, whichever is first)**		**Post-operative Period**	**Follow-up Visit**
		Baseline (Pre-surgery)				
Window	**Day -30 to Day -1**	**Day -1 or Day 0 pre- surgery[g]**	**Day 0 Surgery**	**Days 1 – 7, hospital discharge or death**	**Days 8 to 28 after last study transfusion / death** Laboratory results recorded in the eCRFs during this period will only be those assessed as clinically significant per the investigator.	**28±3 days after last study transfusion or Premature Discontinuation Visit**
Total Bilirubin	R[b]	R	R	R[d,i]	WA	R

Footnotes:

[a] R= required testing and reporting.
WA=where available. Data collected on eCRFs as available from medical records if performed as Standard of Care.

[b] For Screening/Randomization purposes, data from medical records within 30 days of surgery may be used as long as laboratory tests are performed again prior to surgery in order to establish baseline values and confirm the subject's continued trial eligibility.

[c] A sample to measure sCr will be taken at 48±4 hours after the end of surgery and captured on a specific CRF page for that time-point. For non-transfused subjects, a blood sample for sCr will be drawn at 48 ± 4 hours.

[d] If an assessment is performed more than once in a day, the first set of results should be entered into the eCRF.

[e] If a subject is discharged prior to the end of the acute transfusion support period (Day 7) but for any reason returns to the study site (e.g., re-hospitalization or standard care) within this acute transfusion support period, lab values routinely collected as standard of care should be recorded in the eCRF.

[f] If serum creatinine is measured multiple times in a day, the worst daily value should be recorded in the eCRF.

[g] These assessments can be combined with screening assessments if screening visit is also on Day -1 or Day 0 Pre-Surgery.

[h] Assessments that contribute to the AKI should be measured at approximately the same time every day during the treatment period.

[i] These assessments are required to be collected daily on Day 1 through Day 7 post surgery or until discharge. If subject returns after discharge for a postoperative standard of care visit, assessments will be collected in eCRFs on the appropriate study day.

[j] Negative urine or serum pregnancy test.

7.2 ASSESSMENT OF EFFICACY

7.2.1 Efficacy Parameters

The primary efficacy endpoint is the proportion of patients with a diagnosis of renal impairment defined as any increase in sCr ≥0.3 mg/dL (or 26.5 μmol/L) from the pre-surgery baseline within 48±4 hours after the completion of surgery. If any subject meets this criterion before receiving a study transfusion, that particular event will not be included in this analysis.

Treatment difference (Test−Control) will be compared between the subjects who were randomized to receive INTERCEPT RBCs vs. those randomized to receive conventional RBCs with a non-inferiority margin of 50% increase from the Control rate and two-sided 0.05 alpha level.

Secondary efficacy parameters that will be assessed include:

- The proportion of patients with a diagnosis of stage I, II or III Acute Kidney Injury (KDIGO 2012) based on changes in sCr levels from baseline and the need for renal replacement therapy (RRT) post-surgery.
- Mortality or the need for RRT by Day 30 post-surgery.

7.2.2 Methods and Timing of Efficacy Parameters

Hemodynamic and laboratory measures will be assessed pre-operatively (Day -1 or pre-operatively on the day of surgery) and daily from post-operative Day 1 through post-operative Day 7, hospital discharge or death, whichever occurs first. Serum creatinine will be determined on a daily basis during the acute transfusion support period and, in order to capture the primary efficacy endpoint, a sample for sCr will be taken also at 48±4 hours after the end of surgery.

The rest of the efficacy parameters will be collected only as available in the medical record (refer to Study Schedule of Assessments; Section 7.1).

An end of acute transfusion period a blood sample will be collected at Day 7, hospital discharge, or death, whichever occurs first. If a subject is discharged prior to Day 7 but returns to the study site for a standard of care visit on Day 7, blood samples should be obtained on that day for a complete blood count and sCr determination.

7.3 ASSESSMENT OF SAFETY

7.3.1 Safety Parameters

The primary safety outcome measures are the:

- Proportion of patients with any treatment-emergent adverse events (TEAEs) possibly, probably or definitely related to study RBC transfusion through 28 days after the last study transfusion.
- Proportion of patients with treatment emergent antibodies with confirmed specificity to INTERCEPT RBCs).

Additional safety assessments will include, but are not limited to:

- Treatment-emergent AEs through 28 days after the last study transfusion.
- Treatment-emergent SAEs through 28 days after the last study transfusion.
- Transfusion reactions (as defined by the CDC National Healthcare Safety Network [NHSN] Hemovigilance Module protocol) through 28 days after last study transfusion.
- Treatment-emergent immunization to RBC allo-antigens through 28±3 days after the last study transfusion.
- Treatment-emergent immunization to HLA allo-antigens through 28±3 days after the last study transfusion.

7.3.1.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical (investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product (ICH E2A II/A/1, 21 CFR 312.32).

7.3.1.2 Definition of Serious Adverse Event

A Serious AE (SAE) is any untoward medical occurrence that at any dose results in any of the following outcomes:

- Death
- Life-threatening event (results in an immediate risk of death from the reaction as it occurred)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and/or may require intervention to prevent one of the outcomes listed in this definition.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, life-threatening or death according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria). Severity and seriousness need to be assessed for each adverse event recorded on the eCRF.

SAE must be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours) after learning of the event.

7.3.1.3 Unexpected Adverse Event

Any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with (a) the applicable product information (protocol, informed consent/assent, Investigator's Brochure or other product labeling), or (b) the expected natural progression of any underlying disease, disorder or condition of the subject experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

7.3.1.4 Definition of Unanticipated Adverse Device Effects

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or possibly, probably or definitely related to a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or

any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

7.3.1.5 Definition of Renal Impairment

For the purposes of this study, renal impairment is defined as an increase in sCr ≥ 0.3 mg/dL from the pre-surgical baseline concentration.

7.3.1.6 Definition of Acute Kidney Injury (AKI)

For the purposes of this study, a definition of an acute kidney injury during the study is based on the Kidney Disease: Improving Global Outcomes (KDIGO) AKI workgroup definition (KDIGO 2012) criteria as:

- An increase sCr ≥50% of the pre-surgery baseline level within 7 days post-surgery, OR
- An increase in sCr ≥0.3 mg/dL (26.5 µmol/L) from pre-surgery baseline within 48 hours of surgery.

For the purposes of this study, acute kidney injury stages are defined as follows (KDIGO AKI workgroup):

Stage 1	Serum creatinine: 1.5–1.9 times baseline within 7 days after surgery OR ≥0.3 mg/dl (≥26.5 µmol/L) increase within 48 hours of surgery
Stage 2	Serum creatinine: 2.0–2.9 times baseline within 7 days after surgery
Stage 3	Serum creatinine: 3.0 times baseline within 7 days after surgery OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 µmol/L) OR Initiation of renal replacement therapy

If a renal event during the study fulfills KDIGO laboratory criteria as specified above, this may constitute an AE/SAE of AKI as per Investigator's clinical judgement.

7.3.1.7 Renal Replacement Therapy

For the purposes of this study RRT is defined as the institution of hemodialysis or peritoneal dialysis to treat acute or chronic renal failure associated with a decrease in glomerular filtration rate with or without fluid overload, severe acidosis, hyperkalemia or other electrolyte abnormalities. Dialysis performed solely to treat toxin/poisonings or performed preventatively during surgery while on a bypass machine, will not be considered RRT in the terms of meeting a secondary endpoint.

7.3.1.8 Treatment-emergent HLA antibodies

For the purposes of this study, HLA Class I and II antibody testing will be performed in a central laboratory according to the method described by Triulzi et al. (Triulzi 2009). Screening tests for anti-HLA Class I and II will be performed with multi-antigen bead kits (LabScreen LSM12, LabScreen Mixed, One Lambda, Canoga Park, CA) according to the manufacturer's instructions. Data will be using two different normalized background (NBG) ratio cut-offs. The data will be analyzed using the manufacturer's recommended cutoff of a NBG ratio of 2.2. The data will also be analyzed using NBG ratios of the mean plus three or five standard deviations of a log transformed distribution of values for plasma samples for non-transfused males, as described (Triulzi 2009).

7.3.1.9 Definition of Culture Proven Sepsis/Septic Shock

For the purposes of this study, transfusion related sepsis/septic shock is defined as a positive culture from blood and/or CSF and a study RBC product with matching bacterial strains, with at least 3 of the following signs of septic inflammatory response syndrome (SIRS) (Levy 2003):

- Temperature < 36°C or > 38°C
- Heart rate > 90 bpm
- Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg
- White blood cell count > 12,000 or < 4,000 cells/mm^3 or > 10% bands

7.3.1.10 Definition of Transfusion Reaction

A transfusion reaction is defined as an undesirable response or effect in a patient temporally associated with and possibly, probably or definitely related to the administration of blood or blood components. The current version of the CDC NHSN Hemovigilance Protocol definitions must be used when recording transfusion reaction

terms in this study (APPENDIX 3).

7.3.1.10.1 Clinically Significant Antibodies (Chapman et al. 2004)

Clinically significant antibodies are those that are capable of causing patient morbidity due to accelerated destruction of a significant proportion of transfused red cells.

7.3.1.10.2 Delayed Serological Transfusion Reaction (DSTR) (Ness et al. 1990; Garratty 2012)

The DSTRs are where a particular alloantibody can be shown to be present in the patient's plasma, on the transfused donor RBCs and/or in an eluate from these RBCs, but no clinical or laboratory signs of hemolytic anemia (HA) are present. Regardless of the mechanism, the persistence of a positive DAT does not correlate with the presence or absence of clinical hemolysis (Ness 1990).

The DSTR may be in the form of new antibodies or a rising titer of antibodies in patients with pre-existing antibodies (patients with pre-existing antibodies specific to INTERCEPT RBCs at baseline evaluation will be excluded in ReCePI). DSTR will be categorized as described in the NHSN Hemovigilance Protocol v 2.5.2 (APPENDIX 3).

7.3.1.10.3 Delayed Hemolytic Transfusion Reaction (DHTR) (Ness et al. 1990)

A DHTR is defined as a DSTR that showed clinical and/or laboratory evidence of hemolysis. Table 7.3 shows some differential diagnoses of hemolytic transfusion reactions. DHTR will be categorized as described in the CDC NHSN Hemovigilance Protocol v 2.5.2 (APPENDIX 3).

7.3.1.10.4 Acute Hemolytic Transfusion Reaction (AHTR) (Ness 1990)

An AHTR is defined as the rapid destruction of RBCs during, immediately after, or within 24 hours of cessation of transfusion. Clinical and laboratory signs of hemolysis are present AHTR will be categorized as described in the CDC NHSN Hemovigilance Protocol v 2.5.2 (APPENDIX 3).

7.3.1.10.5 Hyper-hemolysis Syndrome

Hyperhemolysis is characterized by a hemolytic transfusion reaction that leads to a life-threatening anemia, with drops in Hb and Hct to levels markedly lower than those present before transfusion.

Table 7.3 Some Differential Diagnoses of Hemolytic Transfusion Reactions

Immunologically caused hemolysis

Autoimmune hemolytic anemia

'Warm' antibody induced hemolytic anemia
Cold hemagglutinin disease
Paroxysmal cold hemoglobinuria

Drug induced immune hemolytic anemia

Passenger lymphocyte syndrome after stem cell or solid organ transplantation
Hemolytic disease of a newborn

Acute episodes of non-immunologically caused hemolysis

Hereditary erythrocyte defects

Defects of red blood cell (RBC) enzymes (e.g., glucose-6-phosphate dehydrogenase deficiency)
Hemoglobinopathies (e.g., sickle cell disease)
Thalassemia
Defects of RBC membrane
Congenital erythropoietic porphyria

Paroxysmal nocturnal hemoglobinuria

Infections

Bacterial (bartonellosis; hemolytic-uremic syndrome caused by enterohemorrhagic Escherichia coli; severe infections by bacteria producing hemolyzing toxins (e.g., Clostridium perfringens))
Protozoal (malaria, babesiosis)

Mechanical hemolysis by artificial heart valves or by extracorporeal

circulation

Thrombotic-thrombocytopenic purpura (Moschowitz disease)

HELLP syndrome during gravidity

Intoxications

Near drowning

Source: Strobel E. 2008.

7.3.1.11 Suspected Hemolytic and Serologic Transfusion Reactions after Enrollment and Transfusion with Study RBC Components

7.3.1.11.1 Assessment of Immune Reactivity to INTERCEPT RBCs

At the time of RBC crossmatch and at specified times during the study **[**screening (**Table 7.1a**) during the acute transfusion support period (**Table 7.1c**) and at Day 28 (±3 days) and day 75 (± 15 days) (**Table 7.1e**) post first study transfusion;**]**, patient plasma/serum samples are tested for the presence of antibody specific to INTERCEPT RBCs. The RBC screening panel uses a gel card agglutination format and has been validated at the Blood Center of Wisconsin for this purpose. The primary RBC screening panel is composed of reagent RBCs from 3 blood group O donors and is analogous to routine screening panels used in regular blood banking practice. The secondary RBC screening panel is composed of reagent RBCs from 6 different blood group O donors and is analogous to secondary panels used in routine practice to identify antibody specificity for a range of common RBC allo-antigens and is used if reactivity is detected in the primary screening assay. The panel donors were specifically antigen-phenotyped for major blood group systems similar to the commercially available reagent cells panels for antibody identification and differentiation. The primary and secondary RBC screening panel cells have been prepared as both INTERCEPT-treated and untreated RBCs. Each panel has three sets of RBCs made from the identical group O donors: untreated RBC; treated RBCs consisting of cells carrying a “high” level of S-303 (amustaline) adducts (comparable to the INTERCEPT RBCs prepared with the “Original process” and cells carrying a “low” level of S-303 (amustaline) adducts (representative of INTERCEPT RBCs prepared with the “Current process”. The primary screening panel is designed as a sensitive screening test for both common RBC alloantibodies and for INTERCEPT RBC-specific antibodies. The secondary panel is designed to determine the specificity of any antibodies detected in the primary screen and to distinguish common RBC alloantibodies from INTERCEPT RBC-specific antibodies.

By including cells with both low and high acridine adducts there is an increased sensitivity for antibody against acridine adducts and, much in the same way that homozygous donors are used to produce commercially prepared red cells, there is a greater potential for detecting low affinity or low titer (weak) antibodies. Thus, the panels have the capability to detect an antibody specific to INTERCEPT RBCs even in the presence of alloreactivity from an intrinsic antigen.

The patient samples are tested against the screening panel(s) of reagent RBCs to identify an antibody specific to INTERCEPT RBCs. The gel card agglutination test results are scored (0, weak positive, 1+, 2+, 3+, 4+) and the reactivity is classified as follows:

- If the antibody screening score is 0 for all the untreated and INTERCEPT RBCs on the primary RBC screening panel, the sample is considered "non-reactive" with no antibodies (neither an intrinsic alloantibody or INTERCEPT RBC-specific antibody) present in the patient's serum and thus no requirement for antibody identification with the secondary antibody identification panel. Neither the secondary RBC screening panel nor additional tests are required. The patient continues to receive study RBC components according to the protocol. In addition, each unit of study RBC is crossmatched to the patient's plasma using an antiglobulin (AHG) gel card test, providing a further level of protection to detect incompatibility, including that caused by INTERCEPT RBC-specific antibodies.
- If the results of the primary RBC screening panel show concordant 3/3, 2/3, or 1/3 reactive with BOTH the INTERCEPT treated reagent RBCs and the corresponding Control untreated RBCs, the sample will be considered "presumed allo-reactive" antibody to an intrinsic red cell antigen. The sample is tested against the secondary RBC screening panel to identify and confirm the specificity of the allo-antibody producing the reaction according to standard blood banking rules (reactivity with three RBC cells bearing the RBC antigen, and non-reactivity with three RBC that lack the antigen). If the antibody that is causing the agglutination is identified and confirmed, then the sample is considered "allo-reactive" for that RBC alloantigen. In this setting, lack of reactivity with all (at least three) INTERCEPT treated RBC cells that lack the RBC alloantigen, will rule out INTERCEPT RBC antibody specificity. The patient continues on study and will receive compatible (cross matched) study RBC components.
- If INTERCEPT RBC-specific antibodies cannot be ruled out, or agglutination is visible for all the untreated RBC cells in the panel, (i.e., "pan-reactive"), the patient will be discontinued from the study transfusions and followed up at planned visits for safety until study completion.
- If the primary RBC screening panel score is positive with 2/3 or 3/3 of the INTERCEPT RBCs carrying S-303 (amustaline) adducts at either 'high" and/or "low" level AND 0/3 with the corresponding Control untreated RBCs which lack S-303 adducts, the sample is classified as "reactive for -INTERCEPT RBC-specific antibodies" and the sample will be sent to the central testing lab for further characterization of specificity.

Weak false positive reactions occur with serological tests due to variation in performance of the test and manual interpretation of the results (Aubuchon 2008). The provisos below are put in place to ensure that patients are not inappropriately withdrawn from the study and are in keeping with the current blood bank policies that repeat reactive results with a minimum of two tests are required for a positive test in serological viral marker assays.

- Should only 1/3 INTERCEPT RBC cells in the primary panel test **reactive** for the S-303 labeled cells without reactivity for the untreated RBCs, that INTERCEPT RBC cell (at both high and low levels of surface bound acridine) and its untreated control will be considered "**initially reactive**" and the test will be **repeated in duplicate on that cell only** (of the three cells in the primary panel), **and the secondary panel will also be tested**. In this setting the secondary panel serves to increase the sensitivity for INTERCEPT RBC- specific antibodies by testing a larger number of INTERCEPT RBC cells. Negative reactivity to both repeat tests of the primary panel cell and negativity with the secondary panel will be considered a negative test. Reactivity in at least one of two repeat primary panel cells INTERCEPT RBC cells or any INTERCEPT RBC cell in the secondary panel without reactivity with the corresponding untreated RBC will be a considered positive test for INTERCEPT RBC reactivity. The sample will be sent for additional characterization at the Central immunohematology reference laboratory to include inhibition studies to determine specificity of observed reactivity. (see APPENDIX 2 for a Characterization plan for potential antibody to INTERCEPT RBCs- Addendum to the CLI 00125 Protocol).

The above-mentioned Central Laboratory protocol will ensure that the minimum criteria for discontinuation of a patient from study transfusions requires reactivity with at least two INTERCEPT RBC cells in the panel with no reactivity with the corresponding untreated control, or repeat reactivity with a single INTERCEPT RBC cell with an unreactive determination with its untreated control.

The patient will be followed up until completion of all study visits, and, if transfused with study RBCs, and evidence for clinical hemolysis will be investigated. A procedure, for patient and laboratory sample management for studies involving INTERCEPT Blood System for RBCs when a reactive S-303 result is obtained (S-303 Reactive Samples: Management of Patients and Samples; REF 01606), will be followed.

To discriminate whether an antibody with specificity for INTERCEPT RBCs is physiologically active or clinically significant, any one of the following criteria indicative of accelerated RBC clearance in the absence of active bleeding, organ-mediated RBC sequestration, severe erythroid hypoplasia or other concurrent medical

cause for acute anemia not associated with transfusion, should be present:

a. During the first 7 days following transfusion, the patient's hemoglobin level has returned to the pre-transfusion level.

b. During Days 8-14 following transfusion, patient's hemoglobin level has declined below the pre-transfusion hemoglobin level for this transfusion.

Beyond Day 14 post-transfusion, the assessment of a clinically significant change in the patient's post-transfusion hemoglobin level compared with prior responses for comparable hemoglobin doses transfused as judged by the Investigator.

Other clinical signs and symptoms that may be considered by the Investigator to judge whether accelerated RBC clearance is occurring, include:

Extravascular hemolysis

- falling hematocrit
- increased unconjugated bilirubin (≥1.5-fold higher than the upper limit of normal)
- fever
- positive DAT
- micro-spherocytes on peripheral smear
- decreased or absent haptoglobin levels
- elevated reticulocyte count

Intravascular hemolysis

- shock syndrome
- hypotension (BP lower than 90/60 mmHg)
- back pain
- plasma free hemoglobin increased
- increase in lactate dehydrogenase (LDH) ≥1.5-fold higher than the upper limit of normal (LDH ≥1.5×ULN)
- urine hemoglobin (hemoglobinuria)
- urine hemosiderin (hemosiderinuria)
- decreased or absent haptoglobin levels

- elevated reticulocyte count
- fragmented RBC on peripheral smear
- DAT may be positive

Plasma/serum samples for patients with confirmed antibodies specific to INTERCEPT RBCs (i.e., a DSTR, DHTR or any ATR) will be assessed for hemolytic potential according to a defined Central Laboratory protocol, provided to the sites and filed in the Investigator Site File (see APPENDIX 2) to define physiologic significance. For the purposes of this protocol, the development of a new antibody specific to INTERCEPT RBCs in the patient and with evidence of accelerated RBC clearance, in the absence of clinical alternative explanations (e.g., concomitant RBC alloantibodies, sickle cell disease, etc.) will be classified as a hemolytic transfusion reaction. All INTERCEPT RBC-specific antibodies and all hemolytic TRs will be reported to the FDA and DSMB.

7.3.1.11.2 Investigation of Hemolytic Potential

Investigation of the hemolytic potential of any INTERCEPT RBC-specific antibodies found in the ReCePI study will be conducted by a Central Laboratory according to the document titled "Evaluation of Reactivity with INTERCEPT RBC" provided to the sites and filed in the Investigator Site File and the protocol in APPENDIX 2. Patient samples will be managed using the supplemental instructions for patient and laboratory sample management for studies involving INTERCEPT Blood System for RBCs when a reactive S-303 result is obtained (S-303 Reactive Samples: Management of Patients and Samples; REF 01606) Possible studies may include:

- Antibody specificity via inhibition studies (inhibited by soluble acridine or not)
- Antibody characterization:
- Immunoglobulin isotype and IgG subclass (IgM, $IgG_{1, 2, 3 \text{ or } 4}$)
- Antibody titer
- Persistence and titer over time
- Thermal spectrum and phase of reaction
- Complement-mediated in vitro hemolysis
- Investigation of concurrent antibodies to intrinsic RBC allo-antigens
- Monocyte Monolayer Assay for clinical significance (Arndt and Garratty 2004)

7.3.1.12 Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in trial dosing or discontinuation from the study participation, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the Investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

7.3.2 Methods and Timing of Safety Parameters

The use of intravenous radiographic contrast media will be documented starting 7 days prior to surgery, as will details related to the specific surgical procedure (type of procedure, start and end times), RBC components transfused, all other blood components transfused, estimated blood loss from the surgical procedure, concomitant medications, intraoperative cell recovery and reinfusion, hemodilution, and nadir temperature. Additionally, daily estimated blood loss from chest tube(s) and from other sources, and day of chest tube removal will be recorded. Safety events (TRs, AEs and SAEs) will be documented on a daily basis during the acute transfusion support period (through Day 7).

Subjects will continue to be monitored through a post-surgical follow-up period for up to 28 days after the last study transfusion, or death, whichever occurs first. During this period, subjects will be monitored for safety events. Blood samples for laboratory studies, DAT/IAT and for antibodies specific to INTERCEPT RBC- associated antigens will be obtained at 28±3 days after the last study transfusion and at end of study.

All samples obtained for determination of human leukocyte antigen (HLA) will be stored for up to 1 year after the study has completed.

7.4 REPORTING PERIOD

All safety events will be collected from the start of surgery or the start of the first study transfusion (whichever is first) through 28 days after the last study transfusion or death, whichever is first.

Vital status and need for RRT of all subjects will be collected at 30 days after the end of surgery and at the end of study visit (Day 75 ±15 days).

Blood sample for assessment of sCr will be collected on post-operative day 2 (at 48 ± 4 hours post end of surgery) for the primary endpoint. For non-transfused subjects, a blood sample for sCr will be drawn at 48 ± 4 hours post-surgery.

Blood samples for assessment of INTERCEPT RBC-specific antibody, HLA antibodies and chemistry and hematology laboratory studies at 28±3 days after the last study transfusion.

Blood samples for assessment of INTERCEPT RBC-specific antibody will also be obtained 75 ±15 days after the last study transfusion.

7.5 RECORDING AND REPORTING ADVERSE EVENTS

7.5.1 Assessing Severity of an Adverse Event

The Investigator will assess the severity of each adverse event based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) (APPENDIX 4) and summarized in **Table 7.4**.

Table 7.4 Severity Assessment of Adverse Events

Grade 1: Mild asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.

Link to NCI CTCAE 5.0:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf (APPENDIX 4)

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events. Consistency between severity and seriousness assessments should be ensured by the Investigator.

7.5.2 Assessing Seriousness of an Adverse Event

The Investigator will assess if an AE resulted in any one or more of the following outcomes that result in classification of the event as an SAE: death, a life-threatening event (results in an immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or another important medical event (Section 7.3.1.2).

7.5.3 Assessing Causality of an Adverse Event

The Investigator's assessment of causality must be provided for all adverse events (serious and non-serious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the Investigator does not know whether or not investigational product caused the event, then the event will be handled as "possibly related to investigational product" for reporting purposes.

Adverse events assessed by the Investigator to be related (possible, likely/probable) to the investigational product also must be evaluated as a Transfusion Reaction and classified per the CDC NHSN Hemovigilance Protocol (APPENDIX 3).

The standard nomenclature for defining the causal relationship between an AE and the

blinded study product transfused is listed in **Table 7.5**.

Table 7.5 Relationship between Investigational Product and Adverse Events

Imputability Level	Explanation
Excluded	When there is conclusive evidence beyond reasonable doubt that the adverse event can be attributed to alternative causes
Unlikely	When the evidence is clearly in favor of attributing the adverse event to causes other than the study transfusion
Possible	When the evidence is indeterminate for attributing the adverse event to the study transfusion or an alternate cause
Likely/Probable	When the evidence is clearly in favor of attributing the adverse event to the study transfusion
Certain/Definite	When there is conclusive evidence beyond reasonable doubt that the adverse event can be attributed to the study transfusion

7.5.4 Assessing Relationship to the INTERCEPT Blood System Device

The Clinical Investigator in collaboration with the blood transfusion service staff will assess whether there is a reasonable possibility that the INTERCEPT Blood System for Red Blood Cells medical device used for preparation and or processing of the blood component caused or contributed to an AE. Determination of whether there is a reasonable possibility that an INTERCEPT component caused or contributed to an AE includes assessing whether a device malfunction occurred during the preparation of the blinded study RBC component.

7.5.5 Reporting Requirements

The AE, SAE, and TR collection period will begin at the start of surgery or the first study RBC transfusion, whichever is first. AEs including protocol specified AEs, TRs, and SAEs (see Section 7.3) are collected daily during the acute transfusion support period and as reported through 28 days after the last study transfusion. Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow regional and international regulations, as appropriate. Adverse events (AEs) will not be collected for non-transfused subjects. Vital status will be reported for randomized and non-transfused subjects at the time of discontinuation.

If an SAE occurs, the Investigator must notify Cerus or its designated safety representative within 24 hours after becoming aware of the event by entering in the eCRF. When reporting SAEs to Cerus, the Investigator will ensure the report includes the severity, seriousness criteria or criterion, and causality assessments as detailed in section 7.5.

Recording the data directly into the eCRF is the preferred method to send this information to the

project contact for SAE receipt. In circumstances where the Investigator is unable to record the data on the eCRF, the Investigator must notify Cerus Product Safety via e-mail or the PPD Hotline within 24 hours of the site's awareness. Sponsor and Contract Research Organization (CRO) contact information is provided in **Table 7.6**.

Table 7.6 Cerus Product Safety Contact Information

Name, Title (Study Role)	Phone	Address
ePIP (protocol inquiries)	N/A	No longer used
PPD Safety Hotline (SAE reporting if Medidata Rave is unavailable)	800-201-8725	N/A
Cerus Product Safety Team	N/A	ReCePISafety@cerus.com
Christine Ernst, MD, PhD Sr. Director, Clinical Research & Medical Affairs (Medical Monitor)	925-288-6259	cernst@cerus.com
Richard Benjamin, MD, PhD Chief Medical Officer (Back-up Medical Monitor)	925 288-6020	rbenjamin@cerus.com

Investigators must also comply with local requirements for reporting SAEs to the Institutional Review Board/Ethics Committee (IRB/EC).

For all SAEs, the Investigator is obligated to pursue and provide information to Cerus or its representative in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by Cerus or its designee to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be sent as soon as possible to Cerus or its designated representative.

7.5.6 Reporting Device Malfunctions

Blood centers are required to report any malfunctions of the INTERCEPT Blood System for RBCs medical device on the eCRFs. If a device malfunction impacts the

health of a person (patient, user or other) during the study, it may also be considered an AE/SAE. The Investigator must notify Cerus Product Safety. Sponsor contact information is provided in **Table 7.6**. If a device malfunction occurs at the participating hospitals sites, the site will complete a Device Malfunction Form.

7.6 DATA AND SAFETY MONITORING BOARD (DSMB) AND INTERIM ANALYSIS

The study data and safety will be monitored on a regular basis by an independent Data and Safety Monitoring Board (DSMB). The primary responsibility of the DSMB is to ensure patient safety and review protocol compliance for data collection. The DSMB will be assembled by the Sponsor and composed of transfusion medicine experts, surgeon(s) and a statistician. DSMB members will be independent of the Sponsor. The DSMB will review safety data and make recommendations according to the current DSMB charter.

Aside from the blinded interim analysis for sample size re-estimation performed in October 2021 that resulted in the reduction in study size from 600 to ≥292 patients, no other interim analysis is planned for this study to compare treatment differences with respect to efficacy or safety at any time prior to the completion of the study. Specific stopping rules, developed for safety considerations, are defined in Section 4.6.

8 STATISTICS

8.1 STATISTICAL METHODS

8.1.1 Efficacy Analysis

For the primary efficacy endpoint, the treatment difference (Test – Control) and its two-sided 95% confidence interval (CI) will be estimated from Cochran-Mantel-Haenszel (CMH) test stratified by baseline sCr (sCr ≥1.2 mg/dL vs. < 1.2 mg/dL) and cardiac surgery group (more at risk for renal complications vs. less at risk) performed. The upper bound of the two-sided 95% CI will be compared with the 50% of the observed Control rate. Non-inferiority will be achieved if the upper bound is less than the 50% of the observed Control rate. For the non-inferiority test, the null and alternative hypotheses (H0 and H1, respectively) will be formulated as follows:

$$H_0: P_{Test} - P_{Control} \geq 50\% \times \hat{P}_{Control} \quad vs. \quad H_1: P_{Test} - P_{Control} < 50\% \times \hat{P}_{Control},$$

where P_{Test} and $P_{Control}$ are the event rates for Test (INTERCEPT) and Control groups, respectively, and $\hat{P}_{Control}$ is the observed Control rate.

Same CMH test will be used for assessment of treatment differences for the secondary efficacy endpoints. As a sensitivity analysis, logistic regression will be utilized to estimate the treatment differences after controlling for baseline sCr, cardiac surgery group performed and other covariates to be detailed in the statistical analysis plan (SAP).

8.1.2 Safety Analyses

Treatment- emergent AEs (defined as AEs with an onset date/time that is on or after the start date/time of the first study transfusion) will be summarized by treatment group, system organ class (SOC), and preferred term. Descriptive summaries of safety measures will be based on observed data. No imputation of missing scores will be implemented.

8.1.3 Subgroup Analyses

Subgroup analysis by the randomization stratification variables (clinical site, pre-surgery renal impairment, and cardiac surgery group) and by demographic variables such as age group (≤18, 19 to 65, and >65 years old), sex, and race will be presented for primary and secondary efficacy endpoints.

Additional subgroup analysis may also be presented as suggested by the data.

8.2 DETERMINATION OF SAMPLE SIZE

A total of at least 292 transfused subjects, approximately 146 per arm, are planned to generate sufficient efficacy and safety data for the Test and Control components in patients undergoing cardiac surgery procedures.

For the primary efficacy endpoint, a non-inferiority test will be conducted to assess for treatment difference (Test – Control). By assuming the proportion of patients with ΔsCr $\geq$0.3mg/dL to be 30% in the Control arm and no more than 50% increase from the Control rate as the non-inferiority margin, a sample size of 292 patients (146 per arm) will provide approximately 80% power to declare non-inferiority at the two-sided 0.05 alpha level, assuming the true treatment difference is zero.

8.3 CRITERIA FOR TERMINATION OF THE STUDY

No statistical stopping rules for efficacy will be carried out for this trial. However, specific stopping rules for safety considerations based on development of specific immune reactivity to INTERCEPT RBCs and life-threatening or fatal adverse events will be implemented as described in **Section 4.6**.

The Sponsor may stop the trial for any reason; the reason for trial cessation will be documented.

8.4 HANDLING OF DROPOUTS OR MISSING DATA

For the primary analysis of the primary efficacy endpoint, missing data will be noted as such without imputation. Multiple imputation may be explored as an additional analysis.

8.5 DEVIATIONS FROM THE STATISTICAL PLAN

Any changes in the planned analyses specified in this protocol will be documented. The reasons for the modifications and when the changes were made will also be documented.

8.6 SELECTION OF SUBJECTS TO BE ANALYZED

The primary efficacy analysis group will be based on the modified intent-to-treat (mITT) population, including all randomized subjects who undergo cardiac surgery and receive one or more study RBC transfusions from randomization to within the first 48 hours post-surgery, hospital discharge, or death, whichever occurs first, and summarized under their assigned treatment group, regardless of the type of RBC components transfused.

The safety analysis group will be based on the safety population and include all randomized subjects who have received any study transfusions during the study. Safety analyses will be performed using the Safety Population and summarizing by actual treatment group received.

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Prior to participating in the study, the Investigator agrees to provide Cerus representatives or their designees direct access to source documents for trial-related monitoring and auditing. The quality representative(s) of the Sponsor may visit a clinical facility or blood center to ensure proper conduct of the protocol, recording of data, and maintenance of records.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 MONITORING

During trial conduct, Cerus or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on eCRFs are accurate. The Investigator and institution will allow Cerus monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The trial site may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), and/or to quality assurance audits performed by Cerus and/or to inspection by appropriate regulatory authorities.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

10.2 INVESTIGATIONAL PRODUCT

Each red cell collection center and each processing center will be accountable for receipt and disposition of all investigational device inventory shipped to the site. All investigational devices used to manufacture the study RBC will be stored at the Blood Centers, in a secure area with access limited to authorized study personnel. Inventory records will be maintained and reviewed according to monitoring procedures.

An investigational device receiving, and dispensing record will be maintained by the Blood Centers to maintain control of investigational devices used during the study. Unused Investigational Product (IP), study RBC units, should not be returned to the Blood Center, but must be destroyed by the Hospital or Clinic Blood Bank according to the Hospital/Institution's Standard Operating Procedure (SOP). Destruction of any IP must be properly documented on the IP Accountability log.

Any device malfunction will be documented on the eCRFs. If an investigational device fails to perform in the expected manner, the Sponsor will be notified, and the event will be appropriately reported. If requested, defective devices will be returned to the Sponsor for inspection and analysis according to procedures.

11 ETHICS

11.1 CONDUCT OF THE TRIAL

The trial will be conducted according to the protocol, the International Council on Harmonization E6 Good Clinical Practice (GCP), and applicable local/national regulatory requirements and laws.

11.2 PATIENT INFORMATION AND CONSENT

The informed consent/assent form must be agreed to by Cerus and the IRB/IEC and must be in compliance with ICH GCP, regional regulatory requirements, and legal requirements.

The Investigator must ensure that each trial patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with participation. The Investigator will obtain written informed consent/assent from each patient or the patient's legally acceptable representative before any trial-specific activity is performed. The informed consent/assent form used in this trial, and any changes made during the course of the trial, must be prospectively approved by both the IRB/IEC and Cerus before use. The investigator will retain the original of each patient's signed consent/assent form.

11.3 INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC)

This protocol will be submitted to an appropriate central or local IRB/EC and its written unconditional approval obtained and submitted to Cerus or its designee before enrollment of the first subject.

Cerus will supply relevant data for Investigators to submit to the IRB/EC for the protocol's review and approval. Written verification of IRB/EC unconditional approval of the protocol and the subject Informed Consent Form (ICF)/assent form will be transmitted to Cerus or its designee prior to enrolling any subjects in the study. This approval must refer to the study by exact protocol title and number (including version), identify documents reviewed, and state the date of approval.

The Investigator must promptly report to the IRB/EC all changes in the research activity and all unanticipated problems involving risk to human subjects or others. This includes all SAEs that have resulted in an expedited safety report to the regulatory authorities (serious, unexpected AEs possibly related to investigational product). Concurrently, the Investigator must send the study Sponsor documentation of such IRB/EC notification. The Investigator must not make any changes in the research without IRB/EC approval

and Cerus approval, except where necessary to eliminate apparent immediate hazards to human subjects.

11.4 CONFIDENTIALITY

Individual subject medical information obtained as a result of this study is considered confidential, and disclosure to third parties other than those noted below is prohibited. Subject confidentiality will be further assured by utilizing subject identification code numbers to correspond to treatment data in the computer files.

However, such medical information may be given to the subject's personal physician, or to other appropriate medical personnel responsible for the subject's welfare.

In addition, data generated as a result of this study are to be available for inspection upon request by local health authority auditors, the Sponsor (including any person or companies that are working for or with or owned by the Sponsor [including monitors and auditors]), or by the IRB/EC. Therefore, absolute confidentiality cannot be guaranteed.

12 DATA HANDLING AND RECORD KEEPING

12.1 CASE REPORT FORMS

An eCRF is required and should be completed for each included patient. The completed original eCRFs are the sole property of Cerus and should not be made available in any form to third parties, except for authorized representatives of Cerus or appropriate regulatory authorities, without written permission from Cerus.

It is the investigator's responsibility to ensure completion of, to review, and to approve all eCRFs. The eCRFs must be signed by the Investigator or by an authorized staff member. These signatures serve to attest that the information contained on the eCRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the eCRFs. Patient source documents are the physician's patient records maintained at the trial site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital or the physician's chart, the information entered on the eCRFs must match those charts.

In some cases, the eCRF may also serve as the source document. In these cases, Cerus and the Investigator must prospectively document which items will be recorded in the source documents and for which items the eCRF will stand as the source document.

12.2 RECORD RETENTION

Investigators/institutions and the Sponsor shall maintain all study records required (by subpart 21CFR 812.140) during the investigation and for a period of 2 years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. Investigator/institution shall not destroy any such records prior to obtaining written permission from Cerus.

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14 APPENDICES

APPENDIX 1: Transfusion Risk Understanding Scoring Tool (TRUST)

(Alghamdi AA, Davis A, Brister S, Corey P, Logan A. Development and validation of Transfusion Risk Understanding Scoring Tool (TRUST) to stratify cardiac surgery patients according to their blood transfusion needs. Transfusion 2006; 46:1120-1129.)

Parameter	Finding	Points
Age of the patient in years	≤ 65 years	0
	> 65 years	1
Sex	male	0
	female	1
hemoglobin	≥ 13.5 g/dL	0
	< 13.5 g/dL	1
body weight in kilograms	≥77 kilograms	0
	< 77 kilograms	1
elective surgery	yes	0
	no (non-elective)	1
serum creatinine	≤ 1.36 mg/dL (120 µmol/L)	0
	> 1.36 mg/dL (120 µmol/L)	1
history of previous cardiac surgery	no	0
	yes	1
surgical task	isolated	0
	Non-isolated (CABG + valve replacement, etc.)	1

Total TRUST Score = SUM (points for all 8 parameters)

Interpretation:

minimum score: 0
maximum score: 8

The higher the score the greater the probability of requiring a blood transfusion.

Total Score	Risk Group	Probability of Transfusion
0	baseline risk	< 20%
1	low risk	20 - 39%
2	intermediate risk	40 - 59%
3	high risk	60 - 79%
4 to 8	very high risk	80 - 100%

X = (0.8377 * (total score)) - 1.9503
Probability of blood transfusion = 1 / (1 + EXP((-1) * X))

APPENDIX 2: Evaluation of Reactivity with INTERCEPT RBCs

CHARACTERIZATION PLAN FOR POTENTIAL ANTIBODY TO INTERCEPT RBCs

PROTOCOL
Version 2
Addendum to CLI 00125

STUDY TITLE

EVALUATION OF REACTIVITY WITH IBS RBC

SPONSOR

Cerus Corporation
2550 Stanwell Drive
Concord, CA 94520, USA

TEST SITE

Gregory A. Denomme, PhD, FCSMLS(D)
Director of Immunohematology &
Transfusion Services
BloodCenter of Wisconsin
638 N. 18th Street
Milwaukee, WI 53201-2178

PROTOCOL **CLI 00125**

CHARACTERIZATION PLAN FOR POTENTIAL ANTIBODY TO INTERCEPT RBCs

1.0 INTRODUCTION

The INTERCEPT Blood System for RBC uses the small molecule Amustaline to form covalent crosslinks within nucleic acids of contaminating pathogens and residual leukocytes, preventing their replication. Amustaline (also referred to as S-303) is a modular compound that decomposes by hydrolysis to the non-reactive compound S-300. Glutathione (GSH), a natural antioxidant, is included in the treatment process to quench unreacted S-303.

Clinical development of the INTERCEPT System for RBC initially involved a previous formulation and processing system (First Generation Process). During two Phase 3 studies (patients with acute anemia secondary to cardiovascular surgery (RBC 3A01) and patients with chronic anemia due to thalassemia or sickle cell disease (RBC 3B01) an unexpected cross-match reactivity specific to INTERCEPT RBCs was found in 2 patients in the chronic anemia study. The antibodies were low-titer (which declined to undetectable levels over 11 months) and were specific for the acridine moiety in S-303. Neither patient had demonstrable clinical evidence of accelerated red cell destruction in association with these antibodies (Benjamin et al, 2005). Follow-up evaluation demonstrated no adverse health effects and the potential for physiologic activity of the anti-acridine antibody evaluated by a monocyte monolayer phagocytosis assay (Nance, et al. 1987; Arndt and Garratty 2004) indicated that these antibodies were unlikely to cause a hemolytic transfusion event. A Second Generation System was subsequently developed to reduce the density of INTERCEPT treatment-related membrane bound acridine adducts by increasing the concentration of the GSH quencher by 10-fold to 20 mM.

Using established routine methods, this document outlines the procedure for characterization of to any treatment-emergent antibody with confirmed specificity to IBS RBCs associated with clinically significant hemolysis.

At study entry and at specific times during the study, subject plasma/serum samples are tested for the presence of antibody against INTERCEPT RBC. The initial testing will be performed at the site with patient plasma or serum and Cerus Frozen Reagent RBCs using a commercial gel card IAT assay.

PROTOCOL **CLI 00125**

CHARACTERIZATION PLAN FOR POTENTIAL ANTIBODY TO INTERCEPT RBCs

If a study site experiences positive reactivity/agglutination with patient plasma and INTERCEPT RBCs, an additional sample of plasma or serum will be sent to the central testing lab (BCW) for characterization.

1.1 RESPONSIBILITIES

Clinical department management or a designated alternate at the hospital blood center and the Central Testing Laboratory at Blood Center of Wisconsin are responsible for implementing this procedure and revising it whenever necessary.

All trained personnel are responsible for performing this procedure to assure that quality standards are met.

1.2 SCOPE AND OBJECTIVE

This document contains the procedure for characterization of positive reactivity with specificity (presumed or confirmed) against INTERCEPT treated RBC at any time during the study.

If a patient develops an antibody, the Investigator will collect patient samples (if possible, EDTA plasma and serum) and send them, along with the Patient Information form (FRM 00782) to the Blood Center of Wisconsin (BCW) who will act as the Central Testing Laboratory for antibody evaluation.

2.0 MATERIALS AND METHOD

Lot numbers, serial numbers, and expiration dates will be recorded for all materials identified in this protocol.

- 10 x 75 mm borosilicate glass tubes (Kimble-Chase, Vineland, NJ)
- IgG gel cards, MDP081, Ortho Diagnostics, Raritan, NJ
- ID-Diluent 2, Ortho Diagnostics, Catalog number MTS9230
- Isotonic (0.85%) NaCl, EK Industries, Joliet, IL Product code 12441
- 9% w/v NaCl in H_2O
- 2.5% w/v NaCl in H_20, lot numbers referenced in each appropriate section
- MLB2 Modified LISS, BioRad, Hercules, CA Reference number 8236100

- Human Serum Albumin (HSA), Millipore, Kankakee, Illinois
- Frozen Reagent RBC panels (Primary and Secondary panels)
- Monoclonal anti-acridine antibody positive control (2S-197-2M1, Antibody Solutions, Sunnyvale, CA. SPC-COA 00035)
- 2-mercapto ethanol (Sigma Aldrich, M6250)

For specificity determinations

- Cerus acridine compound S-300 (Lot number of compound will be recorded with the procedure)
- GSH (Identity/Code P/N 271) (Cerus SPC 00271)

Equipment

- Ortho gel card incubator (Ortho Clinical; MTS9680) or equivalent
- Ortho Gel card centrifuge (Ortho Clinical; MTS5160) or equivalent

3.0 REAGENT RBC PANELS

Reagent RBC panels have been prepared under contract from Cerus corp. from RBC components collected from different blood group O donors with defined red cell antigenic composition representative of the types of RBC antigens associated with clinically relevant immunologic reactions.

For the Primary "antibody detection" or "screening" panel, RBCs from 3 different donors were used and together, these 3 donor RBC components provided a reagent cell panel with a combination of intrinsic RBC antigens able to detect most clinically significant antibodies.

In addition to the "Primary 3 cell screening panel", a 6 donor RBC cell "Secondary identification panel" has been produced to aid identification of antibody should results from the Primary panel be equivocal or indeterminate. For the Secondary "antibody identification" panel, an additional 6 different donors were used, each again with specific antigen phenotypes to allow characterization of any positive response from the primary panel.

Thawing and use of Reagent frozen RBC is detailed in Cerus document INS 00593.

4.0 MOUSE MONOCLONAL ANTI-ACRIDINE ANTIBODY (POSITIVE CONTROL)

For each antibody analysis, a monoclonal anti-acridine antibody will be used as a positive control to demonstrate the detection of acridine on the surface of the frozen S-303 RBC panel cells. The monoclonal antibody was produced from a hybridoma obtained from a mouse immunized with KLH-conjugated S-197, a stable non-hydrolysable acridine analog of amustaline and specificity and sensitivity for acridine on the red cell surface has been extensively characterized (SUD 00734) The monoclonal antibody reacts with High and Low S303 treated RBC and fails to react with RBCs that had not been treated with INTERCEPT.

5.0 PATIENT INFORMATION FORM

This information must be sent with the patient samples to the Central Testing Laboratory and include the following information:

- **Patient identifier (patient ID number)**
- **Patient date of birth**
- **Patient Blood Group, including ABO and D (if available)**
- **Type of anticoagulant used and date of blood collection into anticoagulant**
- **IAT and DAT testing result**
- **Presence and identity of preexisting or newly acquired alloantibody against intrinsic red cell antigens**
- **Copies of laboratory worksheets of the tests performed identifying allo- or S-303 antibodies**

Any additional comments which may be useful to the Central Laboratory can be added to the last section of the form

6.0 SAMPLES FOR ANALYSIS

Plasma or serum samples for antibody characterization will be prepared per Cerus INS 00733. The samples will be frozen and shipped to BCW (FRM 00781).

Gregory A. Denomme, PhD, FCSMLS(D)
Director of Immunohematology & Transfusion Services
Blood Center of Wisconsin
638 N. 18th Street, Milwaukee, WI 53201-2178

Notify the Central testing laboratory (BCW) that there is a World Courier delivery on the way by sending a copy of the Shipping Invoice by email or by FAX.

7.0 SAMPLE ANAYSIS AT BCW

On arrival at BCW the plasma/serum sample will undergo extensive characterization to include confirmation of reactivity identified at the clinical site, characterization of antibody specificity, antibody titer, antibody type and subtype, and thermal amplitude. Allo-adsorption may be performed in cases with potential autoantibody and complement activations may be performed to characterize the hemolytic potential of IgM antibodies

All of the tests performed at BCW will be carried out according to their SOPs.

7.1 CONFIRMATION OF INTERCEPT RBC REACTIVITY WITH FROZEN RBC PANEL CELLS

The gel column agglutination technique developed and validated for use with human serum to detect antibodies to INTERCEPT RBC will be used in this characterization (VAL 00257).

As per manufacturer's recommendation, 50 µL of Cerus Reagent RBC Primary panel cells at 0.8% hematocrit in ID-Diluent 2 (INS 00593) will be added to a

column in the gel card followed by 25 µL of patient plasma or serum and gel cards incubated at 37°C for 15 minutes in the gel card incubator (Ortho Clinical MTS 9680). After incubation, the gel cards are centrifuged with a speed of ~1000 rpm for 10 minutes (Ortho Clinical MTS 9650), the hemagglutination score will be noted as an indication of antibody bound to the RBCs (INS 00625).
Using (i) High acridine, (ii) Low acridine, and (iii) untreated RBCs in a 3-cell screening procedure, reactivity to the INTERCEPT treated RBCs with no reactivity with corresponding untreated control cells is an indication that antibodies specific to S-303 RBC are present.
Reactivity will also be confirmed by traditional LISS tube agglutination with and without AHG.

7.2 ANTIBODY CHARACTERIZATION

7.2.1 ANTIBODY TITER

Serial doubling dilutions of patient sample will be made using 6% albumin in saline as diluent to determine the positive reaction limit of the gel column agglutination assay using RBCs carrying both High and Low acridine adducts. The titer will be recorded as the inverse of the highest dilution that gave an observable, reproducible positive agglutination result with INTERCEPT treated RBCs. The accepted variation in strength of agglutination, particularly with weak reactivity, is +/- 1 doubling dilution (VAL 00257).

In conjunction, a series of doubling dilution will also be made of the murine monoclonal anti-S197 antibody as positive control using 6% albumin in saline as diluent.

7.2.2 ANTIBODY SPECIFICITY BY HEMAGGLUTINATION INHIBITION

To establish specificity of patient sample reactivity, an acridine competition assay using agglutination inhibition (neutralization) with S-300 in solution (S-300 is the major acridine degradation product of INTERCEPT treated RBC) will be used (INS 00732).

Patient plasma/serum (25 µL) will be incubated with increasing concentrations of S-300 in 1.5 mL microcentrifuge tubes (5 µL per tube) and incubated for 15 minutes at 37°C. During this time, 50 µL of 0.8% INTERCEPT RBC (INS 00593) with high levels of acridine will be added to the upper well of the gel column. At the end of the incubation time (during which anybody in patient sample will bind to the free acridine), 25 µL of the incubated plasma/S-300 mixture will be added to the INTERCEPT RBC in the gel card and incubated and centrifuged according to standard practice.

If the agglutination is reduced in an acridine dose-dependent manner this indicates that the antibody in the sample had specificity for acridine (S-300). As a positive control in each determination of specificity, incubation of compound with the monoclonal anti-S197 antibody will be included.

7.2.3 IMMUNOGLOBULIN ISOTYPE

Gel column agglutination will be performed with monoclonal anti-IgG_1 & IgG_3 reagent in the gel cards. Reactivity in this card indicates the presence of an IgG_1, IgG_3 or an IgM antibody. Absence of reactivity in samples that have previous reacted in anti IgG Gel cards, suggests the presence of an IgG2 or IgG4 subtype antibody. In order to exclude an IgM antibody, the procedure is performed with 'blank' or buffer only gel cards. Hemagglutination in a blank card (no anti-IgG, IgG1 or IgG3 reagent) is an indication that an IgM isotype antibody is present.

If an IgM antibody is suggested by the agglutination pattern in the buffer card, plasma will be treated with 2-Mercaptoenthanol (2-ME) to destroy the J-chain of IgM molecules. 2-ME treatment essentially destroys the ability of IgM to cause direct hemagglutination and will be used to further confirm the presence of IgM anti-S-303 in standard clinical tube test method. Both IgG_1 and IgG_3 isotype subclasses have the potential to activate complement and therefore the potential for causing hemolysis in vivo.

7.2.4 THERMAL AMPLITUDE TEST

An anti-S-303 antibody will be evaluated at different temperatures to determine the temperature range of reactivity. Standard tube tests will be performed at Room Temperature (RT) and at (or near) 37°C to determine the temperature range of reactivity. Antibodies that react at RT only are considered clinically insignificant. Antibodies that react at or near 37°C indicate the potential for binding at body temperature. Binding of antibodies at body temperature in vivo can result in their intra- or extravascular destruction, i.e. the potential for hemolysis.

7.2.5 COMPLEMENT ACTIVATION

Some IgG antibodies may activate complement due to the initial binding to the RBCs, which can lead to hemolysis if this occurs in vivo. Tube tests can be performed to combine RBCs and serum at 37°C to determine if anti-S-303 antibodies can activate complement. These assays rely on an anti-globulin reagent that contains anti-C3b antibodies.

7.2.6 COMPLEMENT-MEDIATED IN VITRO HEMOLYSIS

A bioassay can assess the direct potential for anti-S-303 to activate complement that proceeds to completion with an endpoint of hemolysis (Cunnion et al., 2016). In brief, serum or plasma are added in a calcium/magnesium buffer that facilitates complement activation through to C9 (complete hemolysis). The combined RBCs and serum are incubated at 37°C. Hemolysis is measured by optical density reading at 412nm. This in vitro hemolysis assay is a direct measure of the potential for hemolysis in vivo.

7.2.7 MONOCYTE MONONUCLEAR ASSAY

The MMA is a sensitive and sophisticated in vitro measure of the clinical significance of antibodies to RBC. The MMA will be used to evaluate the hemolytic potential of antibodies with specificity for INTERCEPT RBCs identified in the clinical trial. MMA results, in some instances may prove inconclusive: Arndt and Garratty (2004) reported that "No patients with MMA

results less than or equal to 5 percent had clinical signs of a reaction; one-third of patients with MMA results 5.1 to 20 percent versus two thirds with results greater than 20 percent had clinical signs of a Hemolytic Transfusion Reaction (HTR) after transfusion of incompatible blood." Based on these findings, Cerus will interpret the MMA results in the following way:

- INTERCEPT-RBC specific antibodies with an MMA of <5% will be declared "not clinically significant".
- INTERCEPT-RBC specific antibodies with an MMA of >20% will be declared "clinically significant".
- Should an emergent S-303 specific antibody prove to have an MMA result of 5.1-20 percent reactivity, indicative of a 30% of probability of clinical significance, Cerus will request a second patient sample taken at a later time point to seek further collaborative evidence of clinical significance, such as a rising titer, isotype class switch or increasing MMA reactivity.

8.0 DEVIATIONS

Any deviations to the protocol or standard operating procedures during the performance of this study will be documented and included in the final report.

9.0 DOCUMENTATION AND REPORT

Each run will be documented. Sampling and sample preparation will be recorded on data capture sheets. Upon completion of this protocol, a report for this study will be prepared.

10.0 DATA RETENTION

All raw data will be retained by BCW and copies will be provided to Cerus and retained in the Cerus Corporation archives, managed from 2550 Stanwell Drive, Concord, CA 94520.

11.0 COMPLIANCE

Unless otherwise stated, all procedures will be performed according to Cerus or BCW operating procedures.

REFERENCES

- Benjamin et al. 2005. "Therapeutic efficacy and safety of red blood cells treated with a chemical process (S-303) for pathogen inactivation: a Phase III clinical trial in cardiac surgery patients." Transfusion. 2005 Nov;45(11):1739-49.
- Nance, et al. 1987 "Predicting the clinical significance of red cell alloantibodies using a monocyte monolayer assay". TRANSFUSION 1987;27:449-452.
- Arndt and Garratty 2004. A retrospective analysis of the value of monocyte monolayerassay results for predicting the clinical significance of blood group alloantibodies. Transfusion Volume 44, September 2004Cunnion et al, Transfusion 2016;56:1845-8.

PROTOCOL **CLI 00125**

CHARACTERIZATION PLAN FOR POTENTIAL ANTIBODY TO INTERCEPT RBCs

APPENDIX 1 CERUS REFS

CLI 00033; RBC3A01

FRM 00782; "CLI 00126, PATIENT INORMATION TO ACCOMPANY SAMPLES FOR ANTIBODY INVESTIGATION AT CENTRAL TESTING LABORATORY

INS 00593; FREEZİNG AND THAWİNG OF RED BLOOD CELL SAMPLES

INS 00625; READİNG AND GRADİNG GEL CARD HEMAGGLTUİNATİON REACTİON WİTH CERUS FROZEN RED CELL PANELS

INS 00732 " AGGLUTINATION INHIBITION TO DETERMINE SPECIFICITY OF A POSITIVE REACTIVITY TO INTERCEPT TREATED RBCS IN CLI 00126"

INS 00733; PREPARATION OF SAMPLES FOR ANTIBODY CHARACTERIZATION AT A REFERENCE LABORATORY, CLI 00126"

FRM 00781 for "SHIPPING INVOICE FOR ANTIBODY TESTING SAMPLES FOR CLI 00126"

SPC-COA 00035; MOUSE MONOCLONAL ANTİBODY AGAİNST THE S-303 ANALOG, S-197 (2S197-2M1)

SUD 00734; INHİBİTİON OF AGGLUTİNATİON WİTH S-300 TO DETERMİNE ACRİDİNE SPECİFİCİTY OF A POSİTİVE REACTİON TO INTERCEPT TREATED RBCS

VAL 00257; A VALIDATION STUDY FOR THE USE OF GEL COLUMN AGGLUTINATION TECHNOLOGY IN THE DETECTION OF IGG AND IGM SERUM AND PLASMA ANTIBODY TO S-303-TREATED RBCS

APPENDIX 3 CDC National Healthcare Safety Network Biovigilance Component Hemovigilance Module Surveillance Protocol v2.5.2

National Healthcare Safety Network Biovigilance Component Hemovigilance Module Surveillance Protocol

Division of Healthcare Quality Promotion
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, GA, USA

Version History

Version	Release Date	Summary of Revisions
1.0	March 2009	First version publicly released.
1.1	June 2010	Revised background and text in main body of document.
		Revised case definition criterion based on WG recommendations, pilot responses, and CDC recommendations.
		Updated FNHTR definition to allow reaction without documented fever.
		Defined hypotension for infants and small children.
		Clarified TAGVHD probable and possible criteria.
1.2	July 2010	Corrected definition of hypoxemia in glossary of terms.
1.3	June 2011	Added version number and version history summary.
		Summarized introduction and background sections for brevity.
		Reorganized surveillance methods section for ease of use.
		Clarified reporting of "approved deviation" incidents.
		Clarified use of "other" in adverse reaction reporting.
		Clarified use of "doubtful" or "ruled out" in adverse reaction reporting.
		Added denominator summary options to list of available analysis reports.
		Replaced < and > signs with appropriate text for.
		Added "cessation of" to time frame requirements in case definitions.
		NEW probable case definition category for allergic reaction reporting.
		Updated adult hypotensive reaction case definition to align with updated ISBT definition.
		NEW possible imputability category for DHTR.
		DELETED possible case definition category for hypotensive reaction.
		NEW probable imputability category for PTP reaction.
		Updated and clarified imputability categories for TAGVHD reaction.
		DELETED possible case definition category for TRALI.
		Simplified imputability criteria for TTI.
		Clarified case definition and imputability criteria for all adverse reactions.
2.0	January 2013	Complete revision of organization and presentation of information
		Major change in incident reporting requirements. With this release, only incidents that relate to an adverse patient reaction are required for participation.
		Major change in adverse reaction reporting requirements. With this release, minor allergic reactions are no longer required for participation.
		Combined the signs/symptoms with laboratory/radiology columns in case definition tables for clarity. Listed criteria in alphabetical order where possible for consistency and clarity. Moved general severity requirements from the appendix to the criteria tables where they were previously missing.
		Re-ordered adverse reaction tables to put respiratory reactions first.
		Added Imputability criteria of Doubtful, Ruled Out, and Not Determined to the case definition tables as OPTIONAL reporting categories. The reporting is not a change, but including them in the table is new. They were added for clarity.
		Added specific AHTR criteria to allow for reporting of non-immune mediated reactions.
		Added a separate case definition table for Other and Unknown reactions. These categories are available for OPTONAL use.
		Removed redundant and unnecessary appendices.
2.1	August 2013	Minor revisions to verbiage throughout for clarity.
		Added definitions and illustration of surveillance key terms in Section 1.
		Added clarification of surveillance vs. clinical definitions in Section 1.
		Added less-specific case definition categories for OPTIONAL reporting of cases that do not fully meet CDC case criteria for the following reactions: hypotension, febrile non-hemolytic, acute hemolytic and delayed hemolytic.

Version	Release Date	Summary of Revisions
		Added a possible case definition category for TTI for OPTIONAL reporting of syndromic cases that are not laboratory confirmed.
2.1.1	September 2013	Updated diagram in Section 1 and added version history for v2.0 and v2.1.
2.1.2	January 2014	Updated the incident codes in Section 4 and included required reporting of discards and total crossmatch procedures on the Monthly Reporting Denominators form in Section 5.
2.1.3	August 2014	Added a suggested citation for the surveillance protocol in Section 1. Updated the acute hemolytic case definition in Section 3 for clarity. Updated the reporting requirements in Section 5 for clarity.
2.2	January 2016	Updated contact instructions for consistency in Section 1: User support
		Updated version number in Section 1: Suggested Citation
		Remove Root Cause Analysis Result from Section 4: Incident Glossary
		Updated denominator report description to include Pathogen-reduced products in Section 5: Required Reporting
2.3	June 2016	Updated denominator report description to include Table 3 description.
2.4	January 2017	Section 1: Setting – Added additional Annual Facility form for Non-Acute Care Facilities to report.
		Section 2: Annual Facility Survey – Added information about Non-Acute Care Facility Annual Facility Survey, Added links to the Annual Facility Survey – Non-Acute Care Facility form and table of instructions for clarity.
2.5	January 2018	Section 1: Training, User Support, Data Reporting – Minor language changes for clarification
		Section 3: Adverse Reaction Classification – Added information about module-generated classification designations.
		Adverse Reaction Glossary: Updated the definition of fever to be consistent with FNHTR criteria.
2.5.2	April 2018	Section 4: Incident codes - UT 06 – "incompatible" replaced with "unapproved"

Table of Contents

Section 1. Hemovigilance Module Surveillance Overview

Purpose
The National Healthcare Safety Network (NHSN) Hemovigilance (HV) Module was created to implement national surveillance of transfusion-associated adverse events aimed at improving patient safety, minimizing morbidity and mortality of transfusion recipients, and identifying emerging complications and pathogens associated with blood transfusion.

Settings
The Hemovigilance Module may be used by any U.S. healthcare facility where blood components and manufactured blood products are transfused (e.g., adult or pediatric facilities, acute or non-acute care facilities). Surveillance must be performed facility-wide, including patient care areas for emergency, general medical, and surgical patients; obstetrics and gynecology; orthopedics, oncology, and other chronic diseases; and any other facility location where transfusions are administered.

Methods
The NHSN Hemovigilance Module requires comprehensive surveillance of patients and blood components throughout the transfusion process, from product receipt to administration to the patient. Participation in the NHSN Hemovigilance Module requires reporting of all adverse transfusion reactions and reaction-associated incidents that occur **for patients transfused at or by your facility** as well as a monthly summary of components transfused or discarded and patient samples collected for type and screen or crossmatch.

Data Collection
NHSN is a web-based application used by healthcare facilities to report surveillance data. Paper versions of all forms are used to collect data prior to data entry in the NHSN Hemovigilance Module. The paper forms are available on the NHSN Blood Safety Surveillance website. A link to the appropriate form(s) and their instructions is provided in the following sections for your convenience.

Training
Training presentations are available on the NHSN Blood Safety Surveillance website for self-paced training and must be reviewed prior to participating in the Hemovigilance Module. CDC also provides webinar and in-person training opportunities for current NHSN participants. These opportunities are communicated through the NHSN quarterly newsletter and emails from the Hemovigilance Team.

User Support
CDC is available to answer your questions about the Surveillance Protocol and to help navigate the NHSN web application. Please contact us at nhsn@cdc.gov. Type **HEMOVIGILANCE** in the subject line for quickest routing to the Hemovigilance Team.

Suggested Citation for the Hemovigilance Module Surveillance Protocol
U.S. Centers for Disease Control and Prevention. The National Healthcare Safety Network (NHSN) Manual: Biovigilance Component v2.5. Atlanta, GA: Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases. Available at: http://www.cdc.gov/nhsn/PDFs/Biovigilance/BV-HV-protocol-current.pdf. Accessed [enter date].

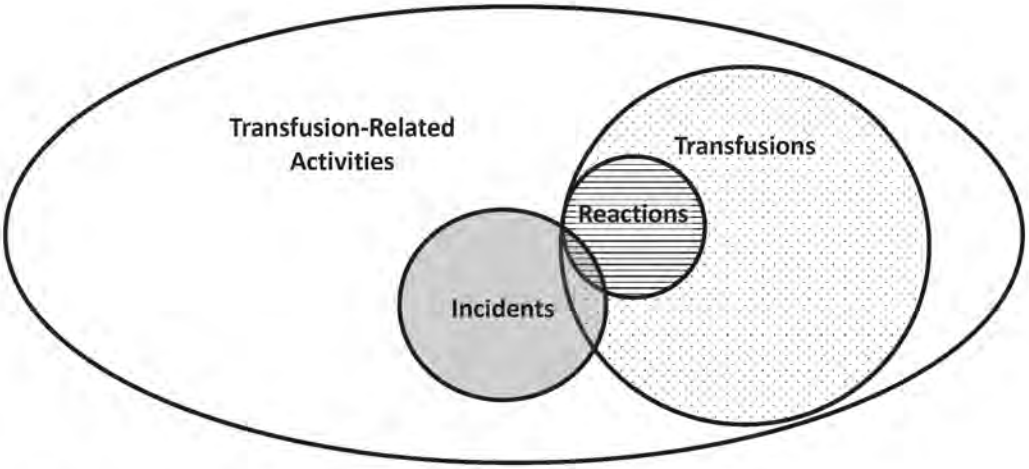
Key Terms (see Fig. 1)

- **Adverse event:** An unintended and undesirable occurrence before, during or after transfusion of blood or blood components. Adverse events include both incidents and adverse reactions.
- **Adverse reaction:** An undesirable response or effect in a patient temporally associated with the administration of blood or blood components. It may or may not be the result of an incident.
- **Incident:** Any error or accident that could affect the quality or efficacy of blood, blood components, or patient transfusions. It may or may not result in an adverse reaction in a transfusion recipient.
- **Near miss:** A subset of incidents that are discovered before the start of a transfusion that *could* have led to a wrongful transfusion or an adverse reaction in a transfusion recipient.

Data Reporting (See Fig. 1)

- An annual facility demographic and practice survey for each **calendar** year of participation
- ALL adverse reactions defined in this protocol that follow transfusion **at or by your facility**
- ALL incidents (i.e., errors or accidents) associated with an adverse reaction
- The number of blood components transfused or discarded and patient samples collected for type and screen or crossmatch each month

Figure 1. Venn diagram of NHSN Hemovigilance Module surveillance terms.



Transfusion-Related Activities
- Patient Sample Collection
- Sample Handling and Testing
- Inventory Management
- Patient Monitoring

Transfusion
- Number of Components
- Number of Patients

Adverse Events

Reactions

Incidents

Near Miss Incidents

Incidents Related to Transfusion (No Adverse Reaction)

Incidents Related to Transfusion and Adverse Reaction

NHSN National Healthcare Safety Network

Section 2. Hemovigilance Module Annual Facility Survey

Required Reporting
Participating facilities must enter the Hemovigilance Module Annual Facility Survey at the time that they enroll or activate the Biovigilance Component and at the beginning of each calendar year thereafter. The survey is used by CDC to classify facilities for appropriate comparisons in aggregate data analyses and to learn more about common practices among transfusion services. The data collected in the survey covers the previous **calendar** year. For example, if the facility is enrolling in NHSN for the first time in October of 2013, report information for January 2012-December 2012 on the first Hemovigilance Module Annual Facility Survey. In January 2014, complete a new survey with data from January 2013-December 2013. CDC recommends collecting all survey information on a paper form before attempting to enter data into the web application.

As of January 2017, non-acute care facilities are able to report hemovigilance data to NHSN. Non-acute care facilities should complete Annual Facility Survey for Non-acute care facility 57.306. This form contains questions tailored to non-acute care facilities. Users may refer to the Non-Acute Care Facility Table of Instructions form 57.306 for detailed instruction about data collection.

Form
CDC 57.300 Hemovigilance Module Annual Facility Survey - Acute Care Facility

CDC 57.306 Hemovigilance Module Annual Facility Survey - Non-Acute Care Facility

Form Instructions
CDC 57.300 Hemovigilance Module Annual Facility Survey - Acute Care Facility Table of Instructions

CDC 57.306 Hemovigilance Module Annual Facility Survey - Non-Acute Care Facility Table of Instructions

Section 3: Hemovigilance Module Adverse Reactions

Required Reporting
All CDC-defined transfusion-associated adverse reactions that are possibly, probably, or definitely related to a **transfusion performed by the participating facility** must be reported to NHSN. If a patient experiences more than one adverse reaction during or following the same transfusion episode, complete a separate form for each reaction. Adverse reaction reports should be entered into NHSN after an investigation of the reaction has been completed and imputability has been determined to the extent possible. Reports should be entered within 30 days of the month that the reaction occurred or when the investigation is completed.

Optional Reporting
Reporting suspected adverse reactions where imputability is determined to be doubtful or ruled out is not required. A facility may report reactions determined to be doubtful or ruled out in order to use NHSN to document transfusion reaction investigations each month. Adverse reactions that are not defined in the surveillance protocol may also be reported using the 'Other' and 'Unknown' adverse reaction categories; standard severity and imputability criteria are provided for that purpose.

Adverse Reaction Classification
Each CDC-defined transfusion-associated adverse reaction **must** be classified according to the reaction-specific case definition, severity, and imputability criteria printed in the protocol. It is imperative that every facility classify adverse reactions according to protocol definitions. Accurate classification will usually require a detailed review of the patient record.

To assist in classification, the Module will generate and assign designations for case definition, severity, and imputability based on signs, symptoms, and lab results entered in the investigation results section of the adverse reaction form.

Surveillance definitions are distinctly different from clinical definitions. Surveillance definitions are designed to capture data consistently and reliably in order to identify trends and inform quality improvement practices. The surveillance definitions are not intended as clinical diagnostic criteria or to provide treatment guidance.

Defined Adverse Reactions
- Transfusion-associated circulatory overload (TACO)
- Transfusion-related acute lung injury (TRALI)
- Transfusion-associated dyspnea (TAD)
- Allergic reaction (where severity is severe, life threatening, or death)
- Hypotensive transfusion reaction
- Febrile non-hemolytic transfusion reaction (FNHTR)
- Acute hemolytic transfusion reaction (AHTR)
- Delayed hemolytic transfusion reaction (DHTR)
- Delayed serologic transfusion reaction (DSTR)
- Transfusion-associated graft vs. host disease (TAGVHD)
- Post-transfusion purpura (PTP)
- Transfusion-transmitted infection (TTI)

Form
Adverse reaction forms are available at the NHSN Blood Safety Surveillance website.

Form Instructions
Adverse Reaction forms' Table of Instructions are available at the NHSN Blood Safety Surveillance website.

Adverse Reaction Case Classification Criteria Tables

Transfusion-associated circulatory overload (TACO)

Case Definition	Severity	Imputability
Definitive: New onset or exacerbation of 3 or more of the following within 6 hours of cessation of transfusion. • Acute respiratory distress (dyspnea, orthopnea, cough) • Elevated brain natriuretic peptide (BNP) • Elevated central venous pressure (CVP) • Evidence of left heart failure • Evidence of positive fluid balance • Radiographic evidence of pulmonary edema **Probable:** N/A **Possible:** N/A	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction**. **Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** No other explanations for circulatory overload are possible. **Probable:** Transfusion is a likely contributor to circulatory overload **AND EITHER** The patient received other fluids as well **OR** The patient has a history of cardiac insufficiency that could explain the circulatory overload, but transfusion is just as likely to have caused the circulatory overload. **Possible:** The patient has a history of pre-existing cardiac insufficiency that most likely explains circulatory overload. **OPTIONAL** **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Transfusion-related acute lung injury (TRALI)

Case Definition	Severity	Imputability
Definitive: NO evidence of acute lung injury (ALI) prior to transfusion **AND** ALI onset during or within 6 hours of cessation of transfusion **AND** Hypoxemia defined by any of these methods: • PaO2/FiO2 less than or equal to 300 mm Hg • Oxygen saturation less than 90% on room air • Other clinical evidence **AND** Radiographic evidence of bilateral infiltrates **AND** No evidence of left atrial hypertension (i.e., circulatory overload) **Probable:** N/A **Possible:** N/A	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction**. **Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** There are no alternative risk factors for ALI present. **Probable:** N/A **Possible:** There is evidence of other causes for acute lung injury such as: Direct Lung Injury • Aspiration • Pneumonia • Toxic inhalation • Lung contusion • Near drowning Indirect Lung Injury • Severe sepsis • Shock • Multiple trauma • Burn injury • Acute pancreatitis • Cardiopulmonary bypass • Drug overdose **OPTIONAL** **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Transfusion-associated dyspnea (TAD)

Case Definition	Severity	Imputability
Definitive: Acute respiratory distress occurring within 24 hours of cessation of transfusion **AND** Allergic reaction, TACO, and TRALI definitions are not applicable. **Probable:** N/A **Possible:** N/A	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** Patient has no other conditions that could explain symptoms. **Probable:** There are other potential causes that could explain symptoms, but transfusion is the most likely cause. **Possible:** Other present causes are most likely, but transfusion cannot be ruled out. **OPTIONAL** **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Allergic reaction

Note: Minor allergic reactions (Non-severe) do not have to be reported to NHSN.

Case Definition	Severity	Imputability
Definitive: **2 or more** of the following occurring during or within 4 hours of cessation of transfusion: • Conjunctival edema • Edema of lips, tongue and uvula • Erythema and edema of the periorbital area • Generalized flushing • Hypotension • Localized angioedema • Maculopapular rash • Pruritus (itching) • Respiratory distress; bronchospasm • Urticaria (hives) **Probable:** **ANY 1** of the following occurring during or within 4 hours of cessation of transfusion: • Conjunctival edema • Edema of lips, tongue and uvula • Erythema and edema of the periorbital area • Localized angioedema • Maculopapular rash • Pruritus (itching) • Urticaria (hives)	**Severe, Life-threatening, Death:** Involves respiratory and/or cardiovascular systems and presents like an anaphylactic reaction. There is anaphylaxis when, in addition to mucocutaneous symptoms, there are airway symptoms, hypotension, or associated symptoms like hypotonia and syncope. The respiratory signs and symptoms may be laryngeal (tightness in the throat, dysphagia, dysphonia, hoarseness, stridor) or pulmonary (dyspnea, cough, wheezing, bronchospasm, hypoxemia). Such a reaction usually occurs during or shortly after cessation of transfusion. **Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** Occurs during or within 2 hours of cessation of transfusion **AND** No other evidence of environmental, drug or dietary risks. **Probable:** Occurs during or within 2 hours of cessation of transfusion **AND** There are other potential causes present that could explain symptoms, but transfusion is the most likely cause. **Possible:** Occurs 2 - 4 hours after cessation of transfusion **OR** Other present causes are most likely, but transfusion cannot be ruled out.
OPTIONAL	**OPTIONAL**	**OPTIONAL**
Possible: N/A	**Non-severe:** There is no immediate risk to the life of the patient, and the patient responds quickly to symptomatic treatment.	**Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Hypotensive transfusion reaction

Case Definition	Severity	Imputability
Definitive: All other adverse reactions presenting with hypotension are excluded **AND** Hypotension occurs during or within 1 hour after cessation of transfusion. • **Adults (18 years and older):** Drop in systolic BP of greater than or equal to 30 mmHg and systolic BP less than or equal to 80 mmHg. • **Infants, children and adolescents (1 year to less than 18 years old):** Greater than 25% drop in systolic BP from baseline (e.g., drop in systolic BP of 120mmHg to below 90mmHg). • **Neonates and small infants (less than 1 year old OR any age and less than 12 kg body weight):** Greater than 25% drop in baseline value using whichever measurement is being recorded (e.g., mean BP). **Probable:** N/A	**Non-severe:** The recipient required no more than discontinuation of transfusion and symptom management and no long-term morbidity resulted from the reaction. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to hypotension, or hypotension led directly to long-term morbidity (e.g., brain damage) **AND** Vasopressors were not required. **Life-threatening:** The recipient required vasopressors. **Death:** The recipient died **as a result of the adverse transfusion reaction**. **Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** Occurs less than 15 minutes after the start of the transfusion **AND** Responds rapidly (i.e., within 10 minutes) to cessation of transfusion and supportive treatment **AND** The patient has no other conditions that could explain hypotension. **Probable:** Onset is between 15 minutes after start and 1 hour after cessation of transfusion **OR** The patient does not respond rapidly to cessation of transfusion and supportive treatment **OR** There are other potential causes present that could explain hypotension, but transfusion is the most likely cause. **Possible:** Other conditions that could readily explain hypotension are present.
OPTIONAL		**OPTIONAL**
Possible: Hypotension occurs, does not meet the criteria above. Other, more specific reaction definitions do not apply.		**Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Febrile non-hemolytic transfusion reaction (FNHTR)
Note: Reactions may be classified as FNHTRs in the absence of fever if chills or rigors occur.

Case Definition	Severity	Imputability
Definitive: Occurs during or within 4 hours of cessation of transfusion **AND EITHER** Fever (greater than or equal to 38°C/100.4°F oral and a change of at least 1°C/1.8°F) from pre-transfusion value **OR** Chills/rigors are present. **Probable:** N/A	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction**. **Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** Patient has no other conditions that could explain signs/symptoms. **Probable:** There are other potential causes present that could explain signs/symptoms, but transfusion is the most likely cause. **Possible:** Other present causes are most likely, but transfusion cannot be ruled out.
OPTIONAL		**OPTIONAL**
Possible: FNHTR is suspected, but reported symptoms and/or available information are not sufficient to meet the criteria defined above. Other, more specific adverse reaction definitions do not apply.		**Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Acute hemolytic transfusion reaction (AHTR)

Note: Report hemolytic reactions resulting from immune or non-immune causes, including when the recipient is **intentionally** transfused with incompatible blood components.

Case Definition	Severity	Imputability
Definitive: Occurs during, or within 24 hours of cessation of transfusion with new onset of **ANY** of the following signs/symptoms: • Back/flank pain • Chills/rigors • Disseminated intravascular coagulation (DIC) • Epistaxis • Fever • Hematuria (gross visual hemolysis) • Hypotension • Oliguria/anuria • Pain and/or oozing at IV site • Renal failure **AND** **2** or more of the following: • Decreased fibrinogen • Decreased haptoglobin • Elevated bilirubin • Elevated LDH • Hemoglobinemia • Hemoglobinuria • Plasma discoloration c/w hemolysis • Spherocytes on blood film **AND EITHER** **(IMMUNE-MEDIATED)** Positive direct antiglobulin test (DAT) for anti-IgG or anti-C3 **AND** Positive elution test with alloantibody present on the transfused red blood cells **OR** **(NON-IMMUNE MEDIATED)** Serologic testing is negative, and physical cause (e.g., thermal, osmotic, mechanical, chemical) is confirmed. **Probable:** Meets signs and symptoms criteria for acute hemolysis **AND EITHER** **(IMMUNE MEDIATED)** Physical cause is excluded but serologic evidence is not sufficient to meet definitive criteria **OR** **(NON-IMMUNE MEDIATED)** Physical cause is suspected and serologic testing is negative. **OPTIONAL** **Possible:** AHTR is suspected within 24 hours of cessation of transfusion, but symptoms, test results, and/or information are not sufficient to meet the criteria defined above. Other, more specific adverse definitions do not apply.	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** ABO or other allotypic RBC antigen incompatibility is known **OR** Only transfusion-related (i.e., immune or non-immune) cause of acute hemolysis is present. **Probable:** There are other potential causes present that could explain acute hemolysis, but transfusion is the most likely cause. **Possible:** Other causes of acute hemolysis are more likely, but transfusion cannot be ruled out. **OPTIONAL** **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Delayed hemolytic transfusion reaction (DHTR)
Note: Report all hemolytic reactions, including when the recipient is **intentionally** transfused with incompatible blood components.

Case Definition	Severity	Imputability
Definitive: Positive direct antiglobulin test (DAT) for antibodies developed between 24 hours and 28 days after cessation of transfusion **AND EITHER** Positive elution test with alloantibody present on the transfused red blood cells **OR** Newly-identified red blood cell alloantibody in recipient serum **AND EITHER** Inadequate rise of post-transfusion hemoglobin level or rapid fall in hemoglobin back to pre-transfusion levels **OR** Otherwise unexplained appearance of spherocytes.	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** No other explanation for symptoms or newly-identified antibody is present. **Probable:** An alternate explanation for symptoms or newly-identified antibody is present, but transfusion is the most likely cause. **Possible:** Other explanations for symptoms or newly-identified antibody are more likely, but transfusion cannot be ruled out.
Probable: Newly-identified red blood cell alloantibody demonstrated between 24 hours and 28 days after cessation of transfusion **BUT** Incomplete laboratory evidence to meet definitive case definition criteria. **NOTE:** Patient may be asymptomatic or have symptoms that are similar to but milder than AHTR; symptoms are not required to meet case definition criteria.		
OPTIONAL		**OPTIONAL**
Possible: DHTR is suspected, but reported symptoms, test results, and/or available information are not sufficient to meet the criteria defined above. Other, more specific adverse reaction definitions do not apply.		**Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Delayed serologic transfusion reaction (DSTR)
Note: Delayed serologic reactions should only be reported for patients **transfused by your facility**.

Case Definition	Severity	Imputability
Definitive: Absence of clinical signs of hemolysis **AND** Demonstration of new, clinically-significant antibodies against red blood cells **BY EITHER** Positive direct antiglobulin test (DAT) **OR** Positive antibody screen with newly identified RBC alloantibody. **Probable:** N/A **Possible:** N/A	**Not Determined:** Since this is by definition a reaction with no clinical symptoms, severity of the reaction cannot be graded.	**Definite:** New alloantibody is identified between 24 hours and 28 days after cessation of transfusion **AND** Transfusion performed by your facility is the only possible cause for seroconversion. **Probable:** New alloantibody is identified between 24 hours and 28 days after cessation of transfusion **AND** The patient has other exposures (e.g. transfusion by another facility or pregnancy) that could explain seroconversion, but transfusion by your facility is the most likely cause. **Possible:** New alloantibody is identified between 24 hours and 28 days after cessation of transfusion **AND** The patient was transfused by your facility, but other exposures are present that most likely explain seroconversion. **OPTIONAL** **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Transfusion-associated graft vs. host disease (TAGVHD)

Case Definition	Severity	Imputability
Definitive: A clinical syndrome occurring from 2 days to 6 weeks after cessation of transfusion characterized by: • Characteristic rash: erythematous, maculopapular eruption centrally that spreads to extremities and may, in severe cases, progress to generalized erythroderma and hemorrhagic bullous formation. • Diarrhea • Fever • Hepatomegaly • Liver dysfunction (i.e., elevated ALT, AST, Alkaline phosphatase, and bilirubin) • Marrow aplasia • Pancytopenia **AND** Characteristic histological appearance of skin or liver biopsy. **Probable:** Meets definitive criteria **EXCEPT** Biopsy negative or not done. **Possible:** N/A	**Non-severe:** N/A **Severe:** Patient had marked symptoms and responded to treatment. **Life-threatening:** Patient had severe symptoms and required life-saving treatment (e.g., immunosuppression). **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** WBC chimerism present in the absence of alternative diagnoses. **Probable:** WBC chimerism present **BUT** Other potential causes are present (e.g., stem cell transplantation). **Possible:** WBC chimerism not present or not done **OR** Alternative explanations are more likely (e.g., solid organ transplantation). **OPTIONAL** **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Post transfusion purpura (PTP)

Case Definition	Severity	Imputability
Definitive: Alloantibodies in the patient directed against HPA or other platelet specific antigen detected at or after development of thrombocytopenia **AND** Thrombocytopenia (i.e., decrease in platelets to less than 20% of pre-transfusion count). **Probable:** Alloantibodies in the patient directed against HPA or other platelet specific antigen detected at or after development of thrombocytopenia. **AND** Decrease in platelets to levels between 20% and 80% of pre-transfusion count.	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly, probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** Occurs 5-12 days post-transfusion **AND** Patient has no other conditions to explain thrombocytopenia. **Probable:** Occurs less than 5 or more than 12 days post-transfusion **OR** There are other potential causes present that could explain thrombocytopenia, but transfusion is the most likely cause. **Possible:** Alternate explanations for thrombocytopenia are more likely, but transfusion cannot be ruled out.
OPTIONAL		**OPTIONAL**
Possible: PTP is suspected, but laboratory findings and/or information are not sufficient to meet defined criteria above. For example, the patient has a drop in platelet count to less than 80% of pre-transfusion count but HPA antibodies were not tested or were negative. Other, more specific adverse reaction definitions do not apply.		**Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Transfusion-transmitted infection (TTI)

Case Definition	Severity	Imputability
Definitive: Laboratory evidence of a pathogen in the transfusion recipient. **Probable:** N/A	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function.	**Definite:** **ONE or more of the following:** • Evidence of the pathogen in the transfused component • Evidence of the pathogen in the donor at the time of donation • Evidence of the pathogen in an additional component from the same donation • Evidence of the pathogen in an additional recipient of a component from the same donation **AND** No other potential exposures to the pathogen could be identified in the recipient. **AND EITHER** Evidence that the recipient was not infected with the pathogen prior to transfusion **OR** Evidence that the identified pathogen strains are related by molecular or extended phenotypic comparison testing with statistical confidence ($p<0.05$). **Probable:** **ONE or more of the following:** • Evidence of the pathogen in the transfused component • Evidence of the pathogen in the donor at the time of donation • Evidence of the pathogen in an additional component from the same donation • Evidence of the pathogen in an additional recipient of a component from the same donation. **AND EITHER:** Evidence that the recipient was not infected with this pathogen prior to transfusion **OR** No other potential exposures to the pathogen could be identified in the recipient. **Possible:** Case fails to meet definite, probable, doubtful, or ruled out imputability criteria.
OPTIONAL		**OPTIONAL**
Possible: Temporally associated unexplained clinical **illness** consistent with infection, but no pathogen is detected in the recipient. Other, more specific adverse reactions are ruled out. **Note:** Possible cases cannot meet the **definite** or **probable** imputability criteria.	**Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction**. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Doubtful:** Laboratory evidence that the recipient was infected with this pathogen prior to transfusion **OR** Evidence is clearly in favor of a cause other than transfusion, but transfusion cannot be excluded. **Ruled Out:** **ALL** of the following (where applicable): • Evidence that the transfused component was negative for this pathogen at the time of transfusion • Evidence that the donor was negative for this pathogen at the time of donation • Evidence that additional components from the same donation were negative for this pathogen **OR** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Transfusion-transmitted infection (TTI)
(continued)

Pathogens of well-documented importance in blood safety.

These pathogens have public health significance for hemovigilance, are well-documented blood stream pathogens, and/or are routinely screened for in blood donors. A full list of potentially infectious organisms is available in the drop-down pathogen list in NHSN.

Bacterial	Viral	Parasitic	Other
Enterobacter cloacae *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Pseudomonas aeruginosa* *Serratia marcescens* *Staphylococcus aureus* *Staphylococcus epidermidis* *Staphylococcus lugdunensis* Syphilis (*Treponema pallidum*) *Yersinia enterocolitica*	Cytomegalovirus (CMV) *Enterovirus spp.* Epstein Barr (EBV) Hepatitis A Hepatitis B Hepatitis C Human Immunodeficiency Virus 1 (HIV-1) Human Immunodeficiency Virus 2 (HIV-2) Human Parvovirus B-19 Human T-Cell Lymphotropic Virus-1 (HTLV-1) Human T-Cell Lymphotropic Virus-2 (HTLV-2) West Nile Virus (WNV) Zika Virus (ZIKAV)	Babesiosis (*Babesia spp.*) Chagas disease (*Trypanosoma cruzi*) Malaria (*Plasmodium spp.*)	Creutzfeldt-Jakob Disease, Variant (vCJD)

Investigation triggers for potential transfusion-transmitted infections:

1. Identification by testing (e.g., gram stain, other smear/staining, culture, or other method) of a bacterial, mycobacterial, or fungal pathogen in a recipient within the time period from exposure (i.e., transfusion) to onset of infection appropriate for the suspected pathogen.

2. Identification of an unexpected virus in the transfusion recipient by testing (e.g., culture, direct fluorescent antibody, or polymerase chain reaction) within the time period from exposure (i.e., transfusion) to onset of infection appropriate for the suspected virus.

3. Identification of an unexpected parasite in the recipient by testing (e.g., blood smear, histopathology, serologic testing, or polymerase chain reaction) within the time period from exposure (i.e., transfusion) to onset of infection appropriate for the suspected parasite.

4. Any of the above laboratory findings in the recipient unit upon residual testing.

5. Unexplained clinical events occurring after transfusion that are consistent with transfusion-transmitted infection, such as:
   a. Encephalitis, meningitis, or other unexplained central nervous system abnormalities.
   b. Sepsis with or without multi-organ system dysfunction.
   c. Hemolytic anemia and/or fever (e.g., in cases of transfusion-associated babesiosis or malaria).
   d. Recipient death.

6. For pathogens routinely screened in the blood donor, any infection in the recipient occurring within 6 months after transfusion if:
   a. The index donation testing was negative but
   b. The donor was subsequently found to be infected, and
   c. The recipient had no pre-transfusion history of the same infection.

Other or Unknown

Other: Use this option if the recipient experienced an adverse reaction that is not defined in the Hemovigilance Module surveillance protocol (e.g., transfusion-associated acute gut injury (TRAGI), transfusion-associated immunomodulation (TRIM), iron overload, microchimerism, hyperkalemia, thrombosis).

Unknown: Use this category if the patient experienced transfusion-related symptoms, but the medical event that caused those symptoms could not be classified.

Note: Reporting 'Other' and 'Unknown' reactions is not required by CDC.

REPORTING OPTIONAL		
Case Definition	**Severity**	**Imputability**
Not Applicable: CDC does not specifically define the 'Other' or 'Unknown' adverse reaction categories, therefore the case definition criteria may only be reported as N/A.	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** Conclusive evidence exists that the adverse reaction can be attributed to the transfusion. **Probable:** Evidence is clearly in favor of attributing the adverse reaction to the transfusion. **Possible:** Evidence is indeterminate for attributing the adverse reaction to the transfusion or an alternate cause. **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

Adverse Reaction Glossary

Antibodies often associated with AHTR, DHTR, DSTR:

Anti-A	Anti-B	Anti-A,B	Anti-C	Anti-c	Anti-D	Anti-E	Anti-e	Anti-Fy[a]
Anti-Fy[b]	Anti-Jk[a]	Anti-Jk[b]	Anti-K	Anti-k	Anti-M	Anti-S	Other	

Bronchospasm (wheezing): A contraction of smooth muscle in the walls of the bronchi and bronchioles, causing acute narrowing and obstruction of the respiratory airway. This constriction can result in a rasp or whistling sound while breathing.

Chills/rigors: A feeling of cold with shivering or shaking and pallor.

Disseminated intravascular coagulation (DIC): Bleeding disorder characterized by reduction in the factors involved in blood clotting due to their use in widespread clotting within the vessels. The intravascular clotting ultimately produces hemorrhage because of rapid consumption of clotting factors.

Edema: Swelling of soft tissues as a result of excessive fluid accumulation.

Epistaxis: Bleeding from the nose.

Fever: For the purposes of hemovigilance, greater than or equal to 38°C/100.4°F oral and a change of at least 1°C/1.8°F from pre-transfusion value.

Hematuria: Presence of blood or red blood cells in the urine.

Hemoglobinemia: The presence of free hemoglobin in the blood plasma.

Hemoglobinuria: Presence of free hemoglobin in the urine.

Hypoxemia: Abnormal deficiency in the concentration of oxygen in arterial blood. PaO2 / FiO2 less than or equal to 300 mm Hg OR oxygen saturation is less than 90% on room air.

Jaundice: New onset or worsening of yellow discoloration (icterus) of the skin or sclera (scleral icterus) secondary to an increased level of bilirubin.

Oliguria: New onset of decreased urinary output (less than 500cc output per 24 hours).

Other rash: Non-urticarial skin rash.

Pruritus: Itching.

Shock: A drop in blood pressure accompanied by a drop in cardiac output including rapid heart rate (increase to 100 beats per minute or more), rapid breathing, cutaneous vasoconstriction, pallor, sweating, decreased or scanty urine production, agitation and/or loss of consciousness that required fluid resuscitation, with or without inotropic support.

Shortness of breath (dyspnea): New onset or significant worsening of shortness of breath; or a significant increase in respiratory rate (with or without hypoxemia).

Urticaria (hives): Raised wheals on the skin.

Section 4. Hemovigilance Module Incidents

Required Reporting
All incidents (i.e., accidents or errors) that are **associated with a reported adverse reaction** must be reported to NHSN using a detailed Incident form (CDC 57.305). If multiple incidents occur in association with an adverse reaction then report all. Incidents may occur before (e.g., wrong product released) or after (e.g., failure to report adverse reaction to blood bank) an adverse reaction. Each reaction must be reported using the detailed incident form; the incident result must be coded as 'Product transfused, reaction' to enter the associated patient identifier on the form. After the incident record is entered, the adverse reaction record must be linked to the incident record in the NHSN web application.

Incident Classification
Use the incident codes provided at the end of this section to classify incidents. If there is uncertainty then please contact NHSN User Support.

Optional Reporting
Any incident may be optionally reported to NHSN using the detailed Incident form (57.305) or the Monthly Incident Summary form (57.302). Approved deviations from standard operating procedure are not considered incidents because they did not occur by accident or in error. However, approved deviations may be optionally reported for a facility's use. Incidents that are optionally reported will not be aggregated or analyzed by CDC.

Form
CDC 57.305 Hemovigilance Module Incident

Form Instructions
CDC 57.305 Hemovigilance Module Incident Table of Instructions

Summary Form (Optional)
CDC 57.302 Hemovigilance Module Monthly Incident Summary

Summary Form Instructions (Optional)
CDC 57.302 Hemovigilance Module Monthly Incident Summary Table of Instructions

Incident Codes

Note: Incident codes are based on MERS TM (US) and TESS (Canada) incident classification schemes.

Product Check-In
(Transfusion Service)
Events that occur during the shipment and receipt of products into the transfusion service from the supplier, another hospital site, satellite storage, or clinical area.
- PC 00 Detail not specified
- PC 01 Data entry incomplete/incorrect/not performed
- PC 02 Shipment incomplete/incorrect
- PC 03 Products and paperwork do not match
- PC 04 Shipped/transported under inappropriate conditions
- PC 05 Inappropriate return to inventory
- PC 06 Product confirmation incorrect/not performed
- PC 07 Administrative check not incorrect/not performed (record review/audit)
- PC 08 Product label incorrect/missing

Product Storage
(Transfusion Service)
Events that occur during product storage by the transfusion service.
- US 00 Detail not specified
- US 01 Incorrect storage conditions
- US 03 Inappropriate monitoring of storage device
- US 04 Unit stored on incorrect shelf (e.g., ABO/autologous s/directed)
- US 05 Incorrect storage location

Inventory Management
(Transfusion Service)
Events that involve quality management of the blood product inventory.
- IM 00 Detail not specified
- IM 01 Inventory audit incorrect/not performed
- IM 02 Product status incorrectly/not updated online (e.g., available/discarded)
- IM 03 Supplier recall/traceback not appropriately addressed/not performed
- IM 04 Product order incorrectly/not submitted to supplier
- IM 05 Outdated product in available inventory
- IM 06 Recalled/quarantined product in available inventory

Product/Test Request
(Clinical Service)
Events that occur when the clinical service orders patient tests or blood products for transfusion.
- PR 00 Detail not specified
- PR 01 Order for wrong patient
- PR 02 Order incompletely/incorrectly ordered (online order entry)
- PR 03 Special processing needs not indicated (e.g., CMV negative, autologous)
- PR 04 Order not done
- PR 05 Inappropriate/unnecessary (intended) test ordered
- PR 06 Inappropriate/unnecessary (intended) blood product ordered
- PR 07 Incorrect (unintended) test ordered
- PR 08 Incorrect (unintended) blood product ordered

Product/Test Order Entry
(Transfusion Service)
Events that occur when the transfusion service receives a patient order. This process may be excluded if clinical service uses online ordering.
- OE 00 Detail not specified
- OE 01 Order entered for wrong patient
- OE 02 Order incompletely/incorrectly entered online
- OE 03 Special processing needs not entered (e.g., CMV-, autologous)
- OE 04 Order entry not done
- OE 05 Inappropriate/unnecessary (intended) test order entered
- OE 06 Inappropriate/unnecessary (intended) blood product order entered
- OE 07 Incorrect (unintended) test ordered
- OE 08 Incorrect (unintended) blood product ordered

Sample Collection
(Service collecting the samples)
Events that occur during patient sample collection.
- SC 00 Detail not specified
- SC 01 Sample labeled with incorrect patient name
- SC 02 Not labeled
- SC 03 Wrong patient collected
- SC 04 Collected in wrong tube type
- SC 05 Sample QNS
- SC 06 Sample hemolyzed
- SC 07 Label incomplete/illegible/incorrect (other than patient name)
- SC 08 Sample collected in error
- SC 09 Requisition arrived without samples
- SC 10 Wristband incorrect/not available
- SC 11 Sample contaminated

Incident Codes

(continued)

Note: Incident codes are based on MERS TM (US) and TESS (Canada) incident classification schemes.

Sample Handling
(Service collecting the samples)
Events that occur when a patient sample is sent for testing.
- SH 00 Detail not specified
- SH 01 Sample sent without requisition
- SH 02 Requisition and sample label don't match
- SH 03 Patient ID incomplete/illegible on requisition
- SH 04 No Patient ID on requisition
- SH 05 No phlebotomist/witness identification
- SH 06 Sample sent with incorrect requisition type
- SH 07 Patient information (other than ID) missing/incorrect on requisition
- SH 08 Requisition sent without sample
- SH 09 Data entry incorrect/incomplete/not performed
- SH 10 Sample transport issue (e.g., sample broken/inappropriate conditions)
- SH 11 Duplicate sample sent in error

Sample Receipt
(Transfusion Service)
Events that occur when a sample is received by the transfusion service.
- SR 00 Detail not specified
- SR 01 Sample accepted in error
- SR 02 Historical review incorrect/not performed
- SR 03 Demographic review/ data entry incorrect/not performed
- SR 04 Sample incorrectly accessioned

Sample Testing
(Transfusion Service)
*Events that occur during **patient sample** testing by the transfusion service.*
- ST 00 Detail not specified
- ST 01 Data entry incomplete/incorrect/not performed
- ST 02 Appropriate sample checks incomplete/incorrect/not performed
- ST 03 Computer warning overridden in error or outside SOP
- ST 05 Sample test tube incorrectly accessioned
- ST 07 Sample test tubes mixed up
- ST 09 Sample test tube mislabeled (wrong patient identifiers)
- ST 10 Equipment problem/failure/not properly QC'd
- ST 12 Sample testing not performed
- ST 13 Incorrect sample testing method chosen
- ST 14 Sample testing performed incorrectly
- ST 15 Sample test result misinterpreted

Sample Testing (continued)
- ST 16 Reagents used were incorrect/inappropriate/expired/not properly QC'd
- ST 17 ABO/Rh error caught on final check
- ST 18 Current/historical ABO/Rh mismatch
- ST 19 Additional testing not performed
- ST 20 Confirmatory check incorrect/not performed (at time work performed)
- ST 21 Administrative check incorrect/not performed (record review/audit)
- ST 22 Sample storage incorrect/inappropriate

Product Manipulation/Processing/Testing
(Transfusion Service)
Events that occur while testing, manipulating (e.g., pooling, washing, aliquoting, irradiating), processing, or labeling blood products.
- UM 00 Detail not specified
- UM 01 Data entry incomplete/incorrect/not performed
- UM 02 Record review incomplete/incorrect/not performed
- UM 03 Incorrect product (type) selected
- UM 04 Incorrect product (patient) selected
- UM 05 Product labeled incorrectly (new/updated)
- UM 06 Computer warning overridden in error or outside SOP
- UM 07 Special processing needs not checked
- UM 08 Special processing needs misunderstood or misinterpreted
- UM 09 Special processing needs performed incorrectly
- UM 10 Special processing needs not performed
- UM 11 Equipment problem/failure/not properly QC'd
- UM 12 Reagents used were incorrect/inappropriate/expired/not properly QC'd
- UM 13 Confirmatory check incorrect/not performed (at time work performed)
- UM 14 Administrative check incorrect/not performed (record review/audit)

Incident Codes

(continued)

Note: Incident codes are based on MERS TM (US) and TESS (Canada) incident classification schemes.

Request for Pick-up
(Clinical Service)
Events that occur when the clinical service requests pick-up of a blood product from the transfusion service.
- RP 00 Detail not specified
- RP 01 Request for pick-up on wrong patient
- RP 02 Incorrect product requested for pick-up
- RP 03 Product requested prior to obtaining consent
- RP 04 Product requested for pick-up, but patient not available
- RP 05 Product requested for pick-up, but IV not ready
- RP 06 Request for pick-up incomplete (e.g., patient ID/product type missing)
- RP 07 Pick-up slip did not match patient information on product

Product Issue
(Transfusion Service)
Events that occur when the transfusion service issues blood product to the clinical service.
- UI 00 Detail not specified
- UI 01 Data entry incomplete/incorrect/not performed
- UI 02 Record review incomplete/incorrect/not performed
- UI 03 Product issued for wrong patient
- UI 04 Product issued out of order
- UI 05 Product issue delayed
- UI 06 LIS warning overridden in error or outside SOP
- UI 07 Computer issue not completed
- UI 08 Issued visibly defective product (e.g., clots/aggregates/particulate matter)
- UI 09 Not/incorrect checking of unit and/or patient information
- UI 10 Product transport issues (e.g., delayed) by transfusion service
- UI 11 Unit delivered to incorrect location by transfusion service
- UI 12 Product transport issue (from transfusion service to clinical area)
- UI 18 Wrong product issued for intended patient (e.g., incompatible)
- UI 19 Inappropriate product issued for patient (e.g., not irradiated, CMV+)
- UI 20 Confirmatory check incorrect/not performed (at time work performed)
- UI 21 Administrative check incorrect/not performed (record review/audit)
- UI 22 Issue approval not obtained/documented
- UI 23 Receipt verification not performed (pneumatic tube issue)

Satellite Storage
(Clinical Service)
Events that occur while product is stored and handled by the clinical service.
- CS 00 Detail not specified
- CS 01 Incorrect storage conditions of product in clinical area
- CS 02 Incorrect storage location in the clinical area
- CS 03 Labeling issue (by clinical staff)
- CS 04 Floor/clinic did not check for existing products in their area
- CS 05 Product transport issues (to or between clinical areas)
- CS 06 Monitoring of satellite storage incorrect/incomplete/not performed
- CS 07 Storage tracking/documentation incorrect/incomplete/not performed

Product Administration
(Clinical Service)
Events that occur during the administration of blood products.
- UT 00 Detail not specified
- UT 01 Administered intended product to wrong patient
- UT 02 Administered wrong product to intended patient
- UT 03 Transfusion not performed in error
- UT 05 Bedside check (patient ID confirmation) incomplete/not performed
- UT 06 Transfused product with unapproved IV fluid
- UT 07 Transfusion delayed beyond pre-approved timeframe
- UT 09 Transfused unsuitable product (e.g., outdated/inappropriately stored)
- UT 10 Administered components in wrong order
- UT 11 Appropriate monitoring of patient not performed
- UT 14 Transfusion volume too low (per order or SOP)
- UT 15 Transfusion volume too high (per order or SOP)
- UT 16 Transfusion rate too slow (per order or SOP)
- UT 17 Transfusion rate too fast (per order or SOP)
- UT 18 Inappropriate preparation of product
- UT 19 Transfusion protocol not followed (not otherwise specified)
- UT 22 Order/consent check incorrect/not performed
- UT 23 Transfusion documentation incorrect/incomplete/not performed
- UT 24 Transfusion documentation not returned to transfusion service
- UT 26 Transfusion reaction protocol not followed

Other
- MS 99 Other

Occupation Codes

Laboratory		Additional Occupation Types	
IVT	IVT Team Staff	ATT	Attendant/Orderly
MLT	Medical Laboratory Technician	CSS	Central Supply
MTE	Medical Technologist	CSW	Counselor/Social Worker
PHL	Phlebotomist/IV Team	DIT	Dietician
Nursing		DNA	Dental Assistant/Technician
LPN	Licensed Practical Nurse	DNH	Dental Hygienist
CNA	Nurse Anesthetist	DNO	Other Dental Worker
CNM	Certified Nurse Midwife	DNT	Dentist
NUA	Nursing Assistant	DST	Dental Student
NUP	Nurse Practitioner	FOS	Food Service
RNU	Registered Nurse	HSK	Housekeeper
Physician		ICP	Infection Control Professional
FEL	Fellow	LAU	Laundry Staff
MST	Medical Student	MNT	Maintenance/Engineering
PHY	Attending/Staff Physician	MOR	Morgue Technician
RES	Intern/Resident	OAS	Other Ancillary Staff
Technicians		OFR	Other First Responder
EMT	EMT/Paramedic	OH	Occupational Health Professional
HEM	Hemodialysis Technician	OMS	Other Medical Staff
ORS	OR/Surgery Technician	OTH	Other
PCT	Patient Care Technician	OTT	Other Technician/Therapist
Other Personnel		PAS	Physician Assistant
CLA	Clerical/Administrative	PHA	Pharmacist
TRA	Transport/Messenger/Porter	PHW	Public Health Worker
		PLT	Physical Therapist
		PSY	Psychiatric Technician
		RCH	Researcher
		RDT	Radiologic Technologist
		RTT	Respiratory Therapist/Technician
		STU	Other Student
		VOL	Volunteer

Incident Glossary

Incident Result

Product transfused; reaction (No recovery; harm):
A product related to this incident was transfused; the patient experienced an adverse reaction.

Product transfused; no reaction (No recovery; no harm):
A product related to this incident was transfused; the patient did not experience an adverse reaction.

No product transfused; unplanned recovery (Near miss; unplanned recovery):
No product related to this incident was transfused; the incident was discovered ad hoc, by accident, by human lucky catch, etc.

No product transfused; planned recovery (Near miss; planned recovery):
No product related to this incident was transfused; the incident was discovered through a standardized process or barrier designed to prevent errors.

Section 5. Hemovigilance Module Denominators

Required Reporting
Facilities must report the total number of units and aliquots of specified blood components transfused and total number of discards each month. When reporting aliquots, the units from which they are made should **NOT** be counted as a transfused unit. The components transfused count should include autologous units. The total number of patient samples collected and total crossmatch procedures must also be reported. This form must be completed each month that surveillance is conducted and data can only be entered once the calendar month is over. For instance, February data must be entered after March 1st. Additionally, data cannot be entered for upcoming months.

Pathogen Reduced Blood Products
The total number of transfused units of blood components which are produced with pathogen-reduction technology (PRT) should be reported each month, if applicable. These PRT units are reported in Table 2 and are a subset of total number of units and aliquots transfused that are reported in Table 1. Table 3 relates to pathogen reduced apheresis platelets, if reported in table 2. For more guidance please refer to the Denominator QuickLearn on the NHSN Blood Safety Surveillance website.

Electronic Reporting
In January 2017, the NHSN Hemovigilance Module can accept electronically reported denominator data via clinical documentation architecture (CDA). Compared to manual reporting, electronic reporting will decrease the time required for data collection and reporting, reduce data entry errors, and increase data granularity. In order to electronically report data, facilities' software system must have CDA functionality. For more information about electronic reporting and CDA, review CDA Frequently Asked Questions on the NHSN Blood Safety Surveillance website.

Form
CDC 57.303 Hemovigilance Module Monthly Reporting Denominators

Form Instructions
CDC 57.303 Hemovigilance Module Monthly Reporting Denominators Tables of Instructions

APPENDIX 4: Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: November 27, 2017

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

Published: November 27, 2017

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Publish Date: November 27, 2017

Introduction
The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

SOC
System Organ Class (SOC), the highest level of the MedDRA[1] hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms
An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Grades
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5
Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Definitions
A brief Definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a Definition is not available.

Navigational Notes
A Navigational Note is used to assist the reporter in choosing a correct AE. It may list other AEs that should be considered in addition to or in place of the AE in question. A single dash (-) indicates a Navigational Note has not been defined for the AE term.

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

[1] CTCAE v5.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (https://www.meddra.org/).

Table of Contents

Blood and lymphatic system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability. **Navigational Note:** -					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements. **Navigational Note:** -					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors. **Navigational Note:** -					
Eosinophilia	>ULN and >Baseline	-	Steroids initiated	-	-
Definition: A disorder characterized by laboratory test results that indicate an increased number of eosinophils in the blood. **Navigational Note:** -					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour. **Navigational Note:** -					
Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 g decrease in hemoglobin	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction. **Navigational Note:** -					

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Blood and lymphatic system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hemolytic uremic syndrome	-	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia. **Navigational Note:** -					
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood. **Navigational Note:** -					
Lymph node pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a lymph node. **Navigational Note:** -					
Methemoglobinemia	-	>ULN	Requiring urgent intervention	Life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate increased methemoglobin in the blood. **Navigational Note:** -					
Thrombotic thrombocytopenic purpura	-	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition. **Navigational Note:** -					
Blood and lymphatic system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Aortic valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in aortic valve function or structure. **Navigational Note:** -					
Asystole	Periods of asystole; non-urgent medical management indicated	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without cardiac electrical activity. Typically, this is accompanied by cessation of the pumping function of the heart. **Navigational Note:** -					
Atrial fibrillation	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated; device (e.g., pacemaker); ablation; new onset	Life-threatening consequences; embolus requiring urgent intervention	Death
Definition: A disorder characterized by a dysrhythmia without discernible P waves and an irregular ventricular response due to multiple reentry circuits. The rhythm disturbance originates above the ventricles. **Navigational Note:** -					
Atrial flutter	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated; device (e.g., pacemaker); ablation	Life-threatening consequences; embolus requiring urgent intervention	Death
Definition: A disorder characterized by a dysrhythmia with organized rhythmic atrial contractions with a rate of 200-300 beats per minute. The rhythm disturbance originates in the atria. **Navigational Note:** -					
Atrioventricular block complete	-	Non-urgent intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker); new onset	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with complete failure of atrial electrical impulse conduction through the AV node to the ventricles. **Navigational Note:** -					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Atrioventricular block first degree	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	-	-	-
Definition: A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds. **Navigational Note:** -					
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by cessation of the pumping function of the heart. **Navigational Note:** -					
Chest pain - cardiac	Mild pain	Moderate pain; pain on exertion; limiting instrumental ADL; hemodynamically stable	Pain at rest; limiting self care ADL; cardiac catheterization; new onset cardiac chest pain; unstable angina	-	-
Definition: A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation e.g., angina pectoris. **Navigational Note:** Also consider Cardiac disorders: Myocardial infarction.					
Conduction disorder	Mild symptoms; intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences	Death
Definition: A disorder characterized by pathological irregularities in the cardiac conduction system. **Navigational Note:** -					
Cyanosis	-	Present	-	-	-
Definition: A disorder characterized by a bluish discoloration of the skin and/or mucous membranes. **Navigational Note:** -					
Heart failure	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with moderate activity or exertion	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure. **Navigational Note:** If left sided use Cardiac disorders: Left ventricular systolic dysfunction; also consider Cardiac disorders: Restrictive cardiomyopathy, Investigations: Ejection fraction decreased.					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Left ventricular systolic dysfunction	-	-	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death
Definition: A disorder characterized by failure of the left ventricle to produce adequate output. **Navigational Note:** Also consider Investigations: Ejection fraction decreased.					
Mitral valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in mitral valve function or structure. **Navigational Note:** -					
Mobitz (type) II atrioventricular block	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker); new onset	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with relatively constant PR interval prior to the block of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles. **Navigational Note:** -					
Mobitz type I	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a progressively lengthening PR interval prior to the blocking of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles. **Navigational Note:** -					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death
Definition: A disorder characterized by gross necrosis of the myocardium; this is due to an interruption of blood supply to the area. **Navigational Note:** -					
Myocarditis	-	Symptoms with moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by inflammation of the muscle tissue of the heart. **Navigational Note:** -					
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Definition: A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of the heart. **Navigational Note:** -					
Paroxysmal atrial tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated; ablation	Life-threatening consequences; incompletely controlled medically; cardioversion indicated	Death
Definition: A disorder characterized by a dysrhythmia with abrupt onset and sudden termination of atrial contractions with a rate of 150-250 beats per minute. The rhythm disturbance originates in the atria. **Navigational Note:** -					
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation. **Navigational Note:** -					
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium. **Navigational Note:** -					

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Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pericarditis	Asymptomatic, ECG or physical findings (e.g., rub) consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irritation to the layers of the pericardium (the protective sac around the heart). **Navigational Note:** -					
Pulmonary valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in pulmonary valve function or structure. **Navigational Note:** -					
Restrictive cardiomyopathy	Imaging findings only	Symptomatic without signs of heart failure	Symptomatic heart failure or other cardiac symptoms, responsive to intervention; new onset of symptoms	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Definition: A disorder characterized by an inability of the ventricles to fill with blood because the myocardium (heart muscle) stiffens and loses its flexibility. **Navigational Note:** -					
Right ventricular dysfunction	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with moderate activity or exertion	Severe symptoms, associated with hypoxia, right heart failure; oxygen indicated	Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated	Death
Definition: A disorder characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility of the right ventricular wall. **Navigational Note:** -					
Sick sinus syndrome	Asymptomatic, intervention not indicated	Symptomatic, intervention not indicated; change in medication initiated	Symptomatic, intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with alternating periods of bradycardia and atrial tachycardia accompanied by syncope, fatigue and dizziness. **Navigational Note:** -					
Sinus bradycardia	Asymptomatic, intervention not indicated	Symptomatic, intervention not indicated; change in medication initiated	Symptomatic, intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node. **Navigational Note:** -					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	-	-
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node. **Navigational Note:** -					
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates above the ventricles. **Navigational Note:** -					
Tricuspid valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in tricuspid valve function or structure. **Navigational Note:** -					
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Urgent intervention indicated	Life-threatening consequences; hemodynamic compromise	Death
Definition: A disorder characterized by a dysrhythmia that originates in the ventricles. **Navigational Note:** -					
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise	Death
Definition: A disorder characterized by a dysrhythmia without discernible QRS complexes due to rapid repetitive excitation of myocardial fibers without coordinated contraction of the ventricles. **Navigational Note:** -					
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences; hemodynamic compromise	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates distal to the bundle of His. **Navigational Note:** -					
Cardiac disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

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Congenital, familial and genetic disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Congenital, familial and genetic disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: -					
Navigational Note: -					

Ear and labyrinth disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the ear. **Navigational Note:** -					
External ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the external ear region. **Navigational Note:** -					
Hearing impaired	**Adults** enrolled on a Monitoring Program (on a 1, 2, 4, 3, 6, and 8 kHz audiogram): Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear; **Adults** not enrolled on a Monitoring Program: Subjective change in hearing in the absence of documented hearing loss; **Pediatric** (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift >20 dB hearing loss (HL) (i.e., 25 dB HL or greater); sensorineural hearing loss (SNHL) above 4 kHz (i.e., 6 or 8 kHz) in at least one ear	**Adults** enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear; **Adults** not enrolled on a Monitoring Program: Hearing loss with hearing aid or intervention not indicated; limiting instrumental ADL; **Pediatric** (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift >20 dB at 4 kHz in at least one ear	**Adults** enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated; **Adults** not enrolled on a Monitoring Program: Hearing loss with hearing aid or intervention indicated; limiting self care ADL; **Pediatric** (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Hearing loss sufficient to indicate therapeutic intervention, including hearing aids; threshold shift >20 dB at 2 to < 4 kHz in at least one ear	**Adults:** Decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above); nonservicable hearing **Pediatric:** Audiologic indication for cochlear implant; > 40 dB HL (i.e., 45 dB HL or more); SNHL at 2 kHz and above	-
Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures. **Navigational Note:** -					

Ear and labyrinth disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Middle ear inflammation	Serous otitis	Serous otitis, medical intervention indicated	Mastoiditis; necrosis of canal soft tissue or bone	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation (physiologic response to irritation), swelling and redness to the middle ear. **Navigational Note:** -					
Tinnitus	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking. **Navigational Note:** -					
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo). **Navigational Note:** -					
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dizziness, imbalance, nausea, and vision problems. **Navigational Note:** -					
Ear and labyrinth disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Endocrine disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the adrenal cortex not producing enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency.					
Navigational Note: -					
Cushingoid	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms, medical intervention or hospitalization indicated	-	-
Definition: A disorder characterized by signs and symptoms that resemble Cushing's disease or syndrome: buffalo hump obesity, striations, adiposity, hypertension, diabetes, and osteoporosis, usually due to exogenous corticosteroids.					
Navigational Note: -					
Delayed puberty	-	No breast development by age 13 yrs for females; testes volume of <3 cc or no Tanner Stage 2 development by age 14.5 yrs for males	No breast development by age 14 yrs for females; no increase in testes volume or no Tanner Stage 2 by age 16 yrs for males; hormone replacement indicated	-	-
Definition: A disorder characterized by unusually late sexual maturity.					
Navigational Note: -					
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-
Definition: A disorder characterized by greater growth than expected for age.					
Navigational Note: -					
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an increase in production of parathyroid hormone by the parathyroid glands. This results in hypercalcemia (abnormally high levels of calcium in the blood).					
Navigational Note: -					
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose.					
Navigational Note: -					

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Endocrine disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypoparathyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; medical intervention or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of parathyroid hormone by the parathyroid glands.					
Navigational Note: -					
Hypophysitis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation and cellular infiltration of the pituitary gland.					
Navigational Note: -					
Hypopituitarism	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of hormones from the pituitary gland.					
Navigational Note: -					
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of thyroid hormone by the thyroid gland.					
Navigational Note: -					
Precocious puberty	Physical signs of puberty with no biochemical markers for females <8 years and males <9 years	Physical signs and biochemical markers of puberty for females <8 years and males <9 years	-	-	-
Definition: A disorder characterized by unusually early development of secondary sexual features; the onset of sexual maturation begins usually before age 8 for girls and before age 9 for boys.					
Navigational Note: -					

Endocrine disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Testosterone deficiency	Asymptomatic; mild symptoms with no intervention indicated	Replacement therapy initiated	-	-	-
Definition: A disorder characterized by low testosterone. **Navigational Note:** -					
Virilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by inappropriate masculinization occurring in a female or prepubertal male. **Navigational Note:** -					
Endocrine disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Blurred vision	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by visual perception of unclear or fuzzy images. **Navigational Note:** -					
Cataract	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); glare symptoms affecting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated. **Navigational Note:** -					
Corneal ulcer	-	-	Corneal ulcer without perforation in the affected eye	Perforation in the affected eye	-
Definition: A disorder characterized by an area of epithelial tissue loss on the surface of the cornea. It is associated with inflammatory cells in the cornea and anterior chamber. **Navigational Note:** -					
Dry eye	Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	-	-
Definition: A disorder characterized by dryness of the cornea and conjunctiva. **Navigational Note:** If corneal ulcer is present, grade under Eye disorders: Corneal ulcer.					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Extraocular muscle paresis	Asymptomatic; clinical or diagnostic observations only	Unilateral paresis without double vision	Bilateral paresis or unilateral paresis causing double vision in peripheral gaze, but not in central gaze	Bilateral paresis requiring head turning to see beyond central 60 degrees or double vision in central gaze	-
Definition: A disorder characterized by incomplete paralysis of an extraocular muscle. **Navigational Note:** -					
Eye pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the eye. **Navigational Note:** -					
Eyelid function disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; nonoperative intervention indicated; limiting instrumental ADL	Limiting self care ADL; operative intervention indicated	-	-
Definition: A disorder characterized by impaired eyelid function. **Navigational Note:** -					
Flashing lights	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a sudden or brief burst of light. **Navigational Note:** Also consider Eye disorders: Retinal tear or Retinal detachment					
Floaters	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by an individual seeing spots before their eyes. The spots are shadows of opaque cell fragments in the vitreous humor or lens. **Navigational Note:** Also consider Eye disorders: Retinal tear or Retinal detachment					
Glaucoma	Less than 8 mmHg of elevated intraocular pressure (EIOP); no visual field deficit	EIOP which can be reduced to 21 mmHg or under with topical medications and no visual field deficit	EIOP causing visual field deficits	Visual field deficit within the central 10 degrees of the visual field in the affected eye	-
Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow. **Navigational Note:** -					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Keratitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); corneal ulcer; limiting self care ADL	Perforation; best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by inflammation to the cornea of the eye. **Navigational Note:** Also consider Eye disorders: Corneal ulcer					
Night blindness	Symptomatic but not limiting ADL	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by an inability to see clearly in dim light. **Navigational Note:** -					
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by involvement of the optic nerve (second cranial nerve). **Navigational Note:** -					
Papilledema	Asymptomatic; no visual field deficit	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by swelling around the optic disc. **Navigational Note:** -					

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Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid around the orbits of the face. **Navigational Note:** -					
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by fear and avoidance of light. **Navigational Note:** -					
Retinal detachment	-	-	Macular sparing rhegmatogenous detachment	Macula-off rhegmatogenous retinal detachment	-
Definition: A disorder characterized by the separation of the inner retina layers from the underlying pigment epithelium. **Navigational Note:** -					
Retinal tear	No retinal detachment and treatment not indicated	No retinal detachment and treatment indicated	-	-	-
Definition: A disorder characterized by a small laceration of the retina, this occurs when the vitreous separates from the retina. Symptoms include flashes and floaters. **Navigational Note:** If retinal detachment is present, grade under Eye disorders: Retinal detachment					
Retinal vascular disorder	-	Retinal vascular disorder without neovascularization	Retinal vascular disorder with neovascularization	-	-
Definition: A disorder characterized by pathological retinal blood vessels that adversely affects vision. **Navigational Note:** If vitreous hemorrhage is present, report under Eye disorders: Vitreous hemorrhage.					
Retinopathy	Asymptomatic; clinical or diagnostic observations only	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder involving the retina. **Navigational Note:** If vitreous hemorrhage is present, report under Eye disorders: Vitreous hemorrhage.					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Scleral disorder	No change in vision from baseline	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by involvement of the sclera of the eye. **Navigational Note:** -					
Uveitis	Anterior uveitis with trace cells	Anterior uveitis with 1+ or 2+ cells	Anterior uveitis with 3+ or greater cells; intermediate posterior or pan-uveitis	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by inflammation to the uvea of the eye. **Navigational Note:** -					
Vision decreased	-	Moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by a decrease in visual acuity. **Navigational Note:** If etiology is known, use a more specific CTCAE term.					
Vitreous hemorrhage	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL; vitrectomy indicated	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by bleeding into the vitreous humor. **Navigational Note:** -					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Watering eyes	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by excessive tearing in the eyes; it can be caused by overproduction of tears or impaired drainage of the tear duct. **Navigational Note:** -					
Eye disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; no change in vision	Moderate; minimal, local or noninvasive intervention indicated; limiting instrumental ADL; best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline	Severe or medically significant but not immediately sight-threatening; limiting self care ADL; decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Sight-threatening consequences; urgent intervention indicated; best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: - **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Abdominal distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-
Definition: A disorder characterized by swelling of the abdomen. **Navigational Note:** -					
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the abdominal region. **Navigational Note:** -					
Anal fissure	Asymptomatic	Symptomatic	Invasive intervention indicated	-	-
Definition: A disorder characterized by a tear in the lining of the anus. **Navigational Note:** -					
Anal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the opening in the anal canal to the perianal skin. **Navigational Note:** -					
Anal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the anal region. **Navigational Note:** -					
Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by ulceration or inflammation of the mucous membrane of the anus. **Navigational Note:** Report Grade 4 and 5 as Gastrointestinal disorders: Anal ulcer					
Anal necrosis	-	-	TPN or hospitalization indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the anal region. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the anal region. **Navigational Note:** -					
Anal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; non-emergent operative intervention indicated; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the anal canal. **Navigational Note:** -					
Anal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the anal canal. **Navigational Note:** -					
Ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of serous or hemorrhagic fluid in the peritoneal cavity. **Navigational Note:** -					
Belching	Increase from baseline	Intervention initiated (including over the counter medications)	-	-	-
Definition: To expel gas noisily from the mouth. **Navigational Note:** Synonym: Burping					
Bloating	No change in bowel function or oral intake	Symptomatic, decreased oral intake; change in bowel function	-	-	-
Definition: A disorder characterized by subject-reported feeling of uncomfortable fullness of the abdomen. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cecal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the cecum. **Navigational Note:** -					
Cheilitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; intervention indicated	-	-
Definition: A disorder characterized by inflammation of the lip. **Navigational Note:** -					
Chylous ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., fat-restricted diet); paracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of milky fluid in the peritoneal cavity. **Navigational Note:** -					
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the colon. **Navigational Note:** -					
Colonic fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the large intestine and another organ or anatomic site. **Navigational Note:** -					
Colonic hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the colon. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Colonic obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the colon. **Navigational Note:** -					
Colonic perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the colonic wall. **Navigational Note:** -					
Colonic stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the colon. **Navigational Note:** -					
Colonic ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the colon. **Navigational Note:** -					
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irregular and infrequent or difficult evacuation of the bowels. **Navigational Note:** -					
Dental caries	One or more dental caries, not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss	-	-
Definition: A disorder characterized by the decay of a tooth, in which it becomes softened, discolored and/or porous. **Navigational Note:** -					

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Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in frequency and/or loose or watery bowel movements. **Navigational Note:** -					
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	-	-
Definition: A disorder characterized by reduced salivary flow in the oral cavity. **Navigational Note:** -					
Duodenal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the duodenum and another organ or anatomic site. **Navigational Note:** -					
Duodenal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the duodenum. **Navigational Note:** -					
Duodenal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of stomach contents through the duodenum. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Duodenal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the duodenal wall. **Navigational Note:** -					
Duodenal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the duodenum. **Navigational Note:** -					
Duodenal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the duodenal wall. **Navigational Note:** -					
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; operative intervention indicated	-	-
Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting. **Navigational Note:** -					
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by difficulty in swallowing. **Navigational Note:** -					
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the small and large intestines. **Navigational Note:** If reporting a known abnormality of the colon, use Gastrointestinal disorders: Colitis. If reporting a documented infection, use Infections and infestations: Enterocolitis infectious.					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Enterovesical fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine. **Navigational Note:** -					
Esophageal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site. **Navigational Note:** -					
Esophageal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the esophagus. **Navigational Note:** -					
Esophageal necrosis	-	-	Inability to aliment adequately by GI tract; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the esophageal wall. **Navigational Note:** -					
Esophageal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents in the esophagus. **Navigational Note:** -					
Esophageal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the esophageal region. **Navigational Note:** -					
Esophageal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the esophagus. **Navigational Note:** -					

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Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Esophageal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the esophagus. **Navigational Note:** -					
Esophageal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the esophageal wall. **Navigational Note:** -					
Esophageal varices hemorrhage	-	Self-limited; intervention not indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from esophageal varices. **Navigational Note:** -					
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the esophageal wall. **Navigational Note:** -					
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by inability to control the escape of stool from the rectum. **Navigational Note:** -					
Flatulence	Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	-
Definition: A disorder characterized by a discharge of excessive gas from the lower GI tract. **Navigational Note:** -					

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Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Gastric fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the stomach and another organ or anatomic site. **Navigational Note:** -					
Gastric hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the gastric wall. **Navigational Note:** -					
Gastric necrosis	-	-	Inability to aliment adequately by GI tract; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gastric wall. **Navigational Note:** -					
Gastric perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the stomach wall. **Navigational Note:** -					
Gastric stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the stomach. **Navigational Note:** -					
Gastric ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the stomach. **Navigational Note:** -					

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Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the stomach. **Navigational Note:** -					
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; operative intervention indicated	-	-
Definition: A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter, and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion. **Navigational Note:** -					
Gastrointestinal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between any part of the gastrointestinal system and another organ or anatomic site. **Navigational Note:** -					
Gastrointestinal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gastrointestinal region. **Navigational Note:** -					
Gastroparesis	Mild nausea, early satiety and bloating, able to maintain caloric intake on regular diet	Moderate symptoms; able to maintain nutrition with dietary and lifestyle modifications; may need pharmacologic intervention	Weight loss >=20% from baseline; tube feeding or TPN indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by an incomplete paralysis of the muscles of the stomach wall resulting in delayed emptying of the gastric contents into the small intestine. **Navigational Note:** -					
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gingival region. **Navigational Note:** -					
Hemorrhoidal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the hemorrhoids. **Navigational Note:** -					

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Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hemorrhoids	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; banding or medical intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by the presence of dilated veins in the rectum and surrounding area. **Navigational Note:** -					
Ileal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the ileum and another organ or anatomic site. **Navigational Note:** -					
Ileal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the ileal wall. **Navigational Note:** -					
Ileal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL; naso-gastric tube indicated	Hospitalization indicated; invasive intervention indicated; limiting self care ADL; long intestinal tube indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the ileum. **Navigational Note:** -					
Ileal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the ileal wall. **Navigational Note:** -					
Ileal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the ileum. **Navigational Note:** -					

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Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ileal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the ileum. **Navigational Note:** -					
Ileus	Asymptomatic and radiologic observations only	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated; tube placement indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by failure of the ileum to transport intestinal contents. **Navigational Note:** -					
Intra-abdominal hemorrhage	-	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding in the abdominal cavity. **Navigational Note:** -					
Jejunal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the jejunum and another organ or anatomic site. **Navigational Note:** -					
Jejunal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the jejunal wall. **Navigational Note:** -					
Jejunal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the jejunum. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Jejunal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the jejunal wall. **Navigational Note:** -					
Jejunal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the jejunum. **Navigational Note:** -					
Jejunal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the jejunum. **Navigational Note:** -					
Lip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort of the lip. **Navigational Note:** -					
Lower gastrointestinal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the lower gastrointestinal tract (small intestine, large intestine, and anus). **Navigational Note:** -					
Malabsorption	-	Altered diet; oral intervention indicated	Inability to aliment adequately; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inadequate absorption of nutrients in the small intestine. Symptoms include abdominal marked discomfort, bloating and diarrhea. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the oral mucosal. **Navigational Note:** -					
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Definition: A disorder characterized by a queasy sensation and/or the urge to vomit. **Navigational Note:** -					
Obstruction gastric	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents in the stomach. **Navigational Note:** -					
Oral cavity fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the oral cavity and another organ or anatomic site. **Navigational Note:** -					
Oral dysesthesia	Mild discomfort; not interfering with oral intake	Moderate pain; interfering with oral intake	Disabling pain; tube feeding or TPN indicated	-	-
Definition: A disorder characterized by a burning or tingling sensation on the lips, tongue or entire mouth. **Navigational Note:** -					
Oral hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the mouth. **Navigational Note:** -					
Oral pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the mouth, tongue or lips. **Navigational Note:** -					

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Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pancreatic duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the pancreatic duct. **Navigational Note:** -					
Pancreatic fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the pancreas and another organ or anatomic site. **Navigational Note:** -					
Pancreatic hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pancreas. **Navigational Note:** -					
Pancreatic necrosis	-	-	Tube feeding or TPN indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the pancreas. **Navigational Note:** -					
Pancreatitis	-	Enzyme elevation; radiologic findings only	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the pancreas with no documented pancreas infection. **Navigational Note:** -					
Periodontal disease	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	-	-
Definition: A disorder in the gingival tissue around the teeth. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Peritoneal necrosis	-	-	Tube feeding or TPN indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the peritoneum. **Navigational Note:** -					
Proctitis	Rectal discomfort, intervention not indicated	Symptomatic (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the rectum. **Navigational Note:** -					
Rectal fissure	Asymptomatic	Symptomatic	Invasive intervention indicated	-	-
Definition: A disorder characterized by a tear in the lining of the rectum. **Navigational Note:** -					
Rectal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the rectum and another organ or anatomic site. **Navigational Note:** -					
Rectal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the rectal wall and discharged from the anus. **Navigational Note:** -					
Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the mucous membrane of the rectum. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Rectal necrosis	-	-	Tube feeding or TPN indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the rectal wall. **Navigational Note:** -					
Rectal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the rectum. **Navigational Note:** -					
Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the rectal region. **Navigational Note:** -					
Rectal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the rectal wall. **Navigational Note:** -					
Rectal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the rectum. **Navigational Note:** -					
Rectal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the rectum. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Retroperitoneal hemorrhage	-	Self-limited; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the retroperitoneal area. **Navigational Note:** -					
Salivary duct inflammation	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms; limiting instrumental ADL	Acute salivary gland necrosis; severe secretion-induced symptoms (e.g., thick saliva/oral secretions or gagging); tube feeding or TPN indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the salivary duct. **Navigational Note:** -					
Salivary gland fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between a salivary gland and another organ or anatomic site. **Navigational Note:** -					
Small intestinal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe pain; interfering with oral intake; tube feeding, TPN or hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the mucous membrane of the small intestine. **Navigational Note:** -					
Small intestinal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents of the small intestine. **Navigational Note:** -					
Small intestinal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the small intestine wall. **Navigational Note:** -					

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Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Small intestinal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the small intestine.					
Navigational Note: -					
Small intestine ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the small intestine.					
Navigational Note: -					
Stomach pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the stomach.					
Navigational Note: -					
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; limiting self care ADL	-	-
Definition: A disorder characterized by a pathological process of the teeth occurring during tooth development.					
Navigational Note: -					
Tooth discoloration	Surface stains	-	-	-	-
Definition: A disorder characterized by a change in tooth hue or tint.					
Navigational Note: -					
Toothache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the tooth.					
Navigational Note: -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Typhlitis	-	-	Symptomatic (e.g., abdominal pain, fever, change in bowel habits with ileus); peritoneal signs	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by necrotizing enterocolitis in neutropenic patients. **Navigational Note:** Also report Investigations: Neutrophil count decreased					
Upper gastrointestinal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, esophagus, and stomach). **Navigational Note:** -					
Visceral arterial ischemia	-	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characterized by a decrease in blood supply due to narrowing or blockage of a visceral (mesenteric) artery. **Navigational Note:** -					
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences	Death
Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth. **Navigational Note:** -					
Gastrointestinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Chills	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	-	-
Definition: A disorder characterized by a sensation of cold that often marks a physiologic response to sweating after a fever.					
Navigational Note: -					
Death neonatal	-	-	-	Neonatal loss of life	-
Definition: Newborn death occurring during the first 28 days after birth.					
Navigational Note: -					
Death NOS	-	-	-	-	Death
Definition: Death that cannot be attributed to a CTCAE term associated with Grade 5.					
Navigational Note: If death is due to an AE (ex., Cardiac disorders: Cardiac arrest), report as a Grade 5 event under that AE.					
Disease progression	-	-	-	-	Death
Definition: Death due to disease progression that cannot be attributed to a CTCAE term associated with Grade 5.					
Navigational Note: If death is due to an AE (ex., Cardiac disorders: Cardiac arrest), report as a Grade 5 event under that AE.					
Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in facial tissues.					
Navigational Note: -					
Edema limbs	5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10 - 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the upper or lower extremities.					
Navigational Note: -					

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Edema trunk	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the trunk area. **Navigational Note:** -					
Facial pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the face. **Navigational Note:** -					
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Definition: A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities. **Navigational Note:** -					
Fever	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death
Definition: A disorder characterized by elevation of the body's temperature above the upper limit of normal. **Navigational Note:** -					
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a group of symptoms similar to those observed in patients with the flu. It includes fever, chills, body aches, malaise, loss of appetite and dry cough. **Navigational Note:** Synonym: Flu, Influenza					
Gait disturbance	Mild change in gait (e.g., wide-based, limping or hobbling)	Moderate change in gait (e.g., wide-based, limping or hobbling); assistive device indicated; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by walking difficulties. **Navigational Note:** -					

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Generalized edema	Noted on exam; 1+ pitting edema	Interfering with instrumental ADLs; oral therapy initiated	Interferes with self care ADL; intravenous therapy indicated; skin breakdown	Life-threatening consequences	-
Definition: A disorder characterized by fluid accumulation in the tissues of the body including the skin. **Navigational Note:** -					
Hypothermia	-	35 - >32 degrees C; 95 - >89.6 degrees F	32 - >28 degrees C; 89.6 - >82.4 degrees F	<=28 degrees C; 82.4 degrees F; life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Definition: A disorder characterized by an abnormally low body temperature. Treatment is required when the body temperature is 35C (95F) or below. **Navigational Note:** -					
Infusion site extravasation	Painless edema	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of the infusion into the surrounding tissue. Signs and symptoms may include induration, erythema, swelling, burning sensation and marked discomfort at the infusion site. **Navigational Note:** -					
Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection. **Navigational Note:** -					
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site. **Navigational Note:** Prior to using this term consider specific edema areas: General disorders and administration site conditions: Edema face, Edema limbs, Edema trunk, or Edema neck; Nervous system disorders: Edema cerebral; Reproductive system and breast disorders: Genital edema; Respiratory, thoracic and mediastinal disorders: Laryngeal edema or Pulmonary edema; Skin and subcutaneous tissue disorders: Periorbital edema; Vascular disorders: Lymphedema					
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being limiting instrumental ADL	Uneasiness or lack of well being limiting self-care ADL	-	-
Definition: A disorder characterized by a feeling of general discomfort or uneasiness, an out-of-sorts feeling. **Navigational Note:** -					

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Multi-organ failure	-	-	Shock with azotemia and acid-base disturbances; significant coagulation abnormalities	Life-threatening consequences (e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	Death
Definition: A disorder characterized by progressive deterioration of the lungs, liver, kidney and clotting mechanisms. **Navigational Note:** -					
Neck edema	Asymptomatic localized neck edema	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	Vascular or respiratory impairment requiring urgent intervention	-
Definition: A disorder characterized by swelling due to an accumulation of excessive fluid in the neck. **Navigational Note:** -					
Non-cardiac chest pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the chest unrelated to a heart disorder. **Navigational Note:** -					
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by the sensation of marked discomfort, distress or agony. **Navigational Note:** Prior to using this term consider using a specific body part pain term found throughout the CTCAE (over 40 different pain terms).					
Sudden death NOS	-	-	-	-	Death
Definition: An unexpected death that cannot be attributed to a CTCAE term associated with Grade 5. **Navigational Note:** If death is due to an AE (ex., Cardiac disorders: Cardiac arrest), report as a Grade 5 event under that AE.					
Vaccination site lymphadenopathy	Local lymph node enlargement	Localized ulceration; generalized lymph node enlargement	-	-	-
Definition: A disorder characterized by lymph node enlargement after vaccination. **Navigational Note:** -					
General disorders and administration site conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

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Hepatobiliary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Bile duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Severely altered GI function; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the bile duct. **Navigational Note:** -					
Biliary fistula	-	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the bile ducts and another organ or anatomic site. **Navigational Note:** -					
Budd-Chiari syndrome	-	Medical management indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; asterixis; mild encephalopathy	Life-threatening consequences; moderate to severe encephalopathy; coma	Death
Definition: A disorder characterized by occlusion of the hepatic veins and typically presents with abdominal pain, ascites and hepatomegaly. **Navigational Note:** -					
Cholecystitis	-	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation involving the gallbladder. It may be associated with the presence of gallstones. **Navigational Note:** -					
Gallbladder fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the gallbladder and another organ or anatomic site. **Navigational Note:** -					
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gallbladder. **Navigational Note:** -					

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Hepatobiliary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Gallbladder obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents of the gallbladder. **Navigational Note:** -					
Gallbladder pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gallbladder region. **Navigational Note:** -					
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the gallbladder wall. **Navigational Note:** -					
Hepatic failure	-	-	Asterixis; mild encephalopathy; drug-induced liver injury (DILI); limiting self care ADL	Life-threatening consequences; moderate to severe encephalopathy; coma	Death
Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, alkaline phosphatase, aminotransferase, and/or prolongation of prothrombin time (INR.) Drug-induced liever injury (DILI) as defined by Hy's Law. **Navigational Note:** -					
Hepatic hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the liver. **Navigational Note:** -					
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma. **Navigational Note:** -					

Hepatobiliary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hepatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the liver region. **Navigational Note:** -					
Perforation bile duct	-	-	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the extrahepatic or intrahepatic bile duct. **Navigational Note:** -					
Portal hypertension	-	Decreased portal vein flow	Reversal/retrograde portal vein flow; associated with varices and/or ascites	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in blood pressure in the portal venous system. **Navigational Note:** -					
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the formation of a thrombus (blood clot) in the portal vein. **Navigational Note:** -					
Sinusoidal obstruction syndrome	-	Blood bilirubin 2-5 mg/dL; minor interventions required (i.e., blood product, diuretic, oxygen)	Blood bilirubin >5 mg/dL; coagulation modifier indicated (e.g., defibrotide); reversal of flow on ultrasound	Life-threatening consequences (e.g., ventilatory support, dialysis, plasmapheresis, peritoneal drainage)	Death
Definition: A disorder characterized by severe hepatic injury as a result of the blood vessels of the liver becoming inflamed and/or blocked. **Navigational Note:** -					
Hepatobiliary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

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Immune system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen. **Navigational Note:** If related to infusion, use Injury, poisoning and procedural complications: Infusion related reaction. Do not report both.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death. **Navigational Note:** -					
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents. **Navigational Note:** Prior to using this term consider specific autoimmune AEs					
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% O2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. **Navigational Note:** Also consider reporting other organ dysfunctions including neurological toxicities such as: Psychiatric disorders: Hallucinations or Confusion; Nervous system disorders: Seizure, Dysphasia, Tremor, or Headache					
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or IV fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately six to twenty-one days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort and dyspnea. **Navigational Note:** -					

Immune system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Immune system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: -					
Navigational Note: -					

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Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Abdominal infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the abdominal cavity. **Navigational Note:** -					
Anorectal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the anal area and the rectum. **Navigational Note:** -					
Appendicitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent. **Navigational Note:** -					
Appendicitis perforated	-	-	Medical intervention indicated; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent with gangrenous changes resulting in the rupture of the appendiceal wall. The appendiceal wall rupture causes the release of inflammatory and bacterial contents from the appendiceal lumen into the abdominal cavity. **Navigational Note:** -					
Arteritis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving an artery. **Navigational Note:** -					
Bacteremia	-	Blood culture positive with no signs or symptoms	-	-	-
Definition: A disorder characterized by the presence of bacteria in the blood stream. **Navigational Note:** Consider Infections and infestations: Sepsis (Grades 3, 4 & 5)					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Biliary tract infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the biliary tract.					
Navigational Note: -					
Bladder infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bladder.					
Navigational Note: -					
Bone infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bones.					
Navigational Note: -					
Breast infection	-	Local infection with moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; severe infection; axillary adenitis	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the breast.					
Navigational Note: -					
Bronchial infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bronchi.					
Navigational Note: -					
Catheter related infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process that arises secondary to catheter use.					
Navigational Note: -					

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Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cecal infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the cecum.					
Navigational Note: -					
Cervicitis infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the uterine cervix.					
Navigational Note: -					
Conjunctivitis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by inflammation, swelling and redness to the conjunctiva of the eye.					
Navigational Note: Consider Infections and infestations: Conjunctivitis infective if caused by infection					
Conjunctivitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by an infectious process involving the conjunctiva. Clinical manifestations include pink or red color in the eyes.					
Navigational Note: -					
Corneal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the cornea.					
Navigational Note: -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cranial nerve infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a cranial nerve. **Navigational Note:** -					
Cytomegalovirus infection reactivation	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated	Life-threatening consequences; urgent intervention indicated; blindness	Death
Definition: A disorder characterized by the reactivation of cytomegalovirus (CMV). **Navigational Note:** Synonym: CMV					
Device related infection	-	Oral intervention indicated (e.g., antibiotic, antifungal)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the use of a medical device. **Navigational Note:** -					
Duodenal infection	-	Moderate symptoms; medical intervention indicated (e.g., oral antibiotics)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the duodenum. **Navigational Note:** -					
Encephalitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; severe changes in mental status; self-limited seizure activity; focal neurologic abnormalities	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the brain tissue. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Encephalomyelitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the brain and spinal cord tissues. **Navigational Note:** -					
Endocarditis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the endocardial layer of the heart. **Navigational Note:** -					
Endophthalmitis	-	Local intervention indicated	Systemic intervention; hospitalization indicated	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by an infectious process involving the internal structures of the eye. **Navigational Note:** -					
Enterocolitis infectious	-	Passage of >3 unformed stools per 24 hrs or duration of illness >48 hrs; moderate abdominal pain; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated; profuse watery diarrhea with signs of hypovolemia; bloody diarrhea; fever; severe abdominal pain; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small and large intestines. **Navigational Note:** Includes Clostridium difficile (c. diff, c. difficile).					
Epstein-Barr virus infection reactivation	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reactivation of Epstein-Barr virus (EBV). **Navigational Note:** Synonym: EBV					

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Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Esophageal infection	-	Local intervention indicated (e.g., oral antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the esophagus. **Navigational Note:** -					
Eye infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated; enucleation	Death
Definition: A disorder characterized by an infectious process involving the eye. **Navigational Note:** -					
Folliculitis	Covering <10% of the body surface area; no intervention indicated	Covering 10-30% of the body surface area; topical intervention initiated	>30% BSA; systemic intervention indicated	-	-
Definition: A disorder characterized by inflammation or infection of the hair follicles. **Navigational Note:** -					
Fungemia	-	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	-	-
Definition: A disorder characterized by the presence of fungus in the blood stream. **Navigational Note:** -					
Gallbladder infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the gallbladder. **Navigational Note:** -					
Gum infection	Local therapy indicated (swish and swallow)	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the gums. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hepatic infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the liver. **Navigational Note:** -					
Hepatitis B reactivation	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated	Life-threatening consequences; urgent intervention indicated; severe decompensated liver function (e.g., coagulopathy, encephalopathy, coma)	Death
Definition: A disorder characterized by the reactivation of hepatitis B virus. **Navigational Note:** -					
Hepatitis viral	Asymptomatic, intervention not indicated	Moderate symptoms; medical intervention indicated	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; severe decompensated liver function (e.g., coagulopathy, encephalopathy, coma)	Death
Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma. **Navigational Note:** -					
Herpes simplex reactivation	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reactivation of Herpes simplex virus. **Navigational Note:** -					
Infective myositis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the skeletal muscles. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Joint infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral); needle aspiration indicated (single or multiple)	Arthroscopic intervention indicated (e.g., drainage) or arthrotomy (e.g., open surgical drainage)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a joint. **Navigational Note:** -					
Kidney infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the kidney. **Navigational Note:** -					
Laryngitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammatory process involving the larynx. **Navigational Note:** For symptoms and no intervention, consider Respiratory, thoracic and mediastinal disorders: Sore throat or Hoarseness.					
Lip infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	-	-
Definition: A disorder characterized by an infectious process involving the lips. **Navigational Note:** -					
Lung infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the lungs, including pneumonia. **Navigational Note:** If infection is due to aspiration, consider reporting Respiratory, thoracic and mediastinal disorders: Apiration					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Lymph gland infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the lymph nodes. **Navigational Note:** -					
Mediastinal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the mediastinum. **Navigational Note:** -					
Meningitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated; focal neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation of the meninges of the brain and/or spinal cord. **Navigational Note:** -					
Mucosal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a mucosal surface. **Navigational Note:** -					
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence. **Navigational Note:** -					
Nail infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	-	-
Definition: A disorder characterized by an infectious process involving the nail. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Otitis externa	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the outer ear and ear canal. Contributory factors include excessive water exposure (swimmer's ear infection) and cuts in the ear canal. Symptoms include fullness, itching, swelling and marked discomfort in the ear and ear drainage. **Navigational Note:** Changes associated with radiation to external ear (pinnae) are graded under Injury, poisoning and procedural complications: Dermatitis radiation					
Otitis media	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the middle ear. **Navigational Note:** -					
Ovarian infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the ovary. **Navigational Note:** -					
Pancreas infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pancreas. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Papulopustular rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; IV antibiotics indicated	Life-threatening consequences	Death
Definition: A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back. Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions. **Navigational Note:** -					
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Operative intervention indicated; IV antibiotics indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an infectious process involving the soft tissues around the nail. **Navigational Note:** -					
Pelvic infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pelvic cavity. **Navigational Note:** -					
Penile infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the penis. **Navigational Note:** -					

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Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Periorbital infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the orbit of the eye. **Navigational Note:** -					
Peripheral nerve infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the peripheral nerves. **Navigational Note:** -					
Peritoneal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the peritoneum. **Navigational Note:** -					
Pharyngitis	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the throat. **Navigational Note:** For Grade 1 Consider Respiratory, thoracic and mediastinal disorders: Sore throat					
Phlebitis infective	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vein. Clinical manifestations include erythema, marked discomfort, swelling, and induration along the course of the infected vein. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pleural infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pleura. **Navigational Note:** -					
Prostate infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the prostate gland. **Navigational Note:** -					
Rash pustular	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	-	-
Definition: A disorder characterized by a circumscribed and elevated skin lesion filled with pus. **Navigational Note:** Synonym: Boil					
Rhinitis infective	-	Localized; local intervention indicated	-	-	-
Definition: A disorder characterized by an infectious process involving the nasal mucosal. **Navigational Note:** -					
Salivary gland infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the salivary gland. **Navigational Note:** -					
Scrotal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the scrotum. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Sepsis	-	-	Blood culture positive with signs or symptoms; treatment indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the presence of pathogenic microorganisms in the blood stream that cause a rapidly progressing systemic reaction that may lead to shock. **Navigational Note:** Includes SIRS. Also consider Infections and infestations: Bacteremia (Grade 2)					
Shingles	Localized, local intervention indicated	Local infection with moderate symptoms; oral intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reactivation of herpes zoster virus. **Navigational Note:** Synonym: Herpes zoster					
Sinusitis	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the mucous membranes of the paranasal sinuses. **Navigational Note:** -					
Skin infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the skin such as cellulitis. **Navigational Note:** -					
Small intestine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small intestine. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Soft tissue infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving soft tissues. **Navigational Note:** -					
Splenic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the spleen. **Navigational Note:** -					
Stoma site infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a stoma (surgically created opening on the surface of the body). **Navigational Note:** -					
Thrush	Asymptomatic; local symptomatic management	Oral intervention indicated (e.g., antifungal)	IV antifungal intervention indicated	-	-
Definition: A disorder characterized by a suspected candidal infection involving an oral mucosal surface. **Navigational Note:** -					
Tooth infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a tooth. **Navigational Note:** -					
Tracheitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the trachea. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Upper respiratory infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea). **Navigational Note:** -					
Urethral infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the urethra. **Navigational Note:** -					
Urinary tract infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the urinary tract, most commonly the bladder and the urethra. **Navigational Note:** -					
Uterine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the endometrium. It may extend to the myometrium and parametrial tissues. **Navigational Note:** -					
Vaginal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vagina. **Navigational Note:** -					
Viremia	-	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	-	-
Definition: A disorder characterized by the presence of a virus in the blood stream. **Navigational Note:** -					

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Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Vulval infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vulva. **Navigational Note:** -					
Wound infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the wound. **Navigational Note:** -					
Infections and infestations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ankle fracture	Mild; non-operative intervention indicated	Limiting instrumental ADL; outpatient operative intervention indicated	Limiting self care ADL; elective operative intervention indicated requiring hospitalization	-	-
Definition: A finding of damage to the ankle joint characterized by a break in the continuity of the ankle bone. Symptoms include marked discomfort, swelling and difficulty moving the affected leg and foot. **Navigational Note:** -					
Aortic injury	-	Operative intervention not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the aorta. **Navigational Note:** -					
Arterial injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to an artery. **Navigational Note:** -					
Biliary anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of bile due to breakdown of a biliary anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Bladder anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of urine due to breakdown of a bladder anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Bruising	Localized or in a dependent area	Generalized	-	-	-
Definition: A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues. **Navigational Note:** -					

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Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
Definition: A finding of impaired integrity to the anatomic site of an adverse thermal reaction. Burns can be caused by exposure to chemicals, direct heat, electricity, flames and radiation. The extent of damage depends on the length and intensity of exposure and time until provision of treatment. **Navigational Note:** -					
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Definition: A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation. **Navigational Note:** Synonym: Radiation induced skin toxicities (CTCAE v3.0)					
Esophageal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an esophageal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Fall	Minor with no resultant injuries; intervention not indicated	Symptomatic; noninvasive intervention indicated	Hospitalization indicated; invasive intervention indicated	-	-
Definition: A finding of sudden movement downward, usually resulting in injury. **Navigational Note:** -					
Fallopian tube anastomotic leak	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a fallopian tube anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Fallopian tube perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated (e.g., organ resection)	Death
Definition: A disorder characterized by a rupture of the fallopian tube wall. **Navigational Note:** -					
Fracture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but non-displaced; immobilization indicated	Severe symptoms; displaced or open wound with bone exposure; limiting self care ADL; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of traumatic injury to the bone in which the continuity of the bone is broken. **Navigational Note:** Prior to using this term consider specific fracture areas: Injury, poisoning and procedural complications: Ankle fracture, Hip fracture, Spinal fracture, or Wrist fracture					
Gastric anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a gastric anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Gastrointestinal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a gastrointestinal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Gastrointestinal stoma necrosis	-	Superficial necrosis; intervention not indicated	Severe symptoms; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gastrointestinal tract stoma. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hip fracture	-	Hairline fracture; mild pain; limiting instrumental ADL; non-operative intervention indicated	Severe pain; hospitalization or intervention indicated for pain control (e.g., traction); operative intervention indicated	Life-threatening consequences; symptoms associated with neurovascular compromise	-
Definition: A finding of traumatic injury to the hip in which the continuity of either the femoral head, femoral neck, intertrochanteric or subtrochanteric regions is broken. **Navigational Note:** -					
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances. **Navigational Note:** -					
Injury to carotid artery	-	Repair or revision not indicated	Severe symptoms; limiting self care ADL (e.g., transient cerebral ischemia); repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the carotid artery. **Navigational Note:** -					
Injury to inferior vena cava	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the inferior vena cava. **Navigational Note:** -					
Injury to jugular vein	-	Repair or revision not indicated	Symptomatic limiting self care ADL; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the jugular vein. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Injury to superior vena cava	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the superior vena cava. **Navigational Note:** -					
Intestinal stoma leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of contents from an intestinal stoma (surgically created opening on the surface of the body). **Navigational Note:** -					
Intestinal stoma obstruction	-	Self-limited; intervention not indicated	Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents of the intestinal stoma. **Navigational Note:** -					
Intestinal stoma site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Transfusion indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the intestinal stoma. **Navigational Note:** -					
Intraoperative arterial injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to an artery during a surgical procedure. **Navigational Note:** -					
Intraoperative breast injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the breast parenchyma during a surgical procedure. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Intraoperative cardiac injury	-	-	Primary repair of injured organ/structure indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the heart during a surgical procedure. **Navigational Note:** -					
Intraoperative ear injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL (e.g., impaired hearing; impaired balance)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the ear during a surgical procedure. **Navigational Note:** -					
Intraoperative endocrine injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the endocrine gland during a surgical procedure. **Navigational Note:** -					
Intraoperative gastrointestinal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the gastrointestinal system during a surgical procedure. **Navigational Note:** -					
Intraoperative head and neck injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the head and neck during a surgical procedure. **Navigational Note:** -					
Intraoperative hemorrhage	-	-	Postoperative invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontrolled bleeding during a surgical procedure. **Navigational Note:** -					

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Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Intraoperative hepatobiliary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the hepatic parenchyma and/or biliary tract during a surgical procedure. **Navigational Note:** -					
Intraoperative musculoskeletal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the musculoskeletal system during a surgical procedure. **Navigational Note:** -					
Intraoperative neurological injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the nervous system during a surgical procedure. **Navigational Note:** -					
Intraoperative ocular injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the eye during a surgical procedure. **Navigational Note:** -					
Intraoperative renal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the kidney during a surgical procedure. **Navigational Note:** -					
Intraoperative reproductive tract injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the reproductive organs during a surgical procedure. **Navigational Note:** -					

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Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Intraoperative respiratory injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the respiratory system during a surgical procedure. **Navigational Note:** -					
Intraoperative splenic injury	-	Primary repair of injured organ/structure indicated	Resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the spleen during a surgical procedure. **Navigational Note:** -					
Intraoperative urinary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the urinary system during a surgical procedure. **Navigational Note:** -					
Intraoperative venous injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to a vein during a surgical procedure. **Navigational Note:** -					
Kidney anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of urine due to breakdown of a kidney anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Large intestinal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the large intestine. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pancreatic anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a pancreatic anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Pharyngeal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a pharyngeal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Postoperative hemorrhage	Mild symptoms; intervention not indicated	Moderate bleeding requiring transfusion < 2 units (10 cc/kg for pediatrics) of pRBCs	Transfusion indicated of >=2 units (10 cc/kg for pediatrics) pRBCs; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding occurring after a surgical procedure. **Navigational Note:** -					
Postoperative thoracic procedure complication	-	Extubated within 24 - 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A finding of a previously undocumented problem that occurs after a thoracic procedure. **Navigational Note:** -					
Prolapse of intestinal stoma	Asymptomatic; reducible	Recurrent after manual reduction; local irritation or stool leakage; difficulty to fit appliance; limiting instrumental ADL	Severe symptoms; elective operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of protrusion of the intestinal stoma (surgically created opening on the surface of the body) above the abdominal surface. **Navigational Note:** -					
Prolapse of urostomy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Local care or maintenance; minor revision indicated	Dysfunctional stoma; elective operative intervention or major stomal revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of displacement of the urostomy. **Navigational Note:** -					

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Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Radiation recall reaction (dermatologic)	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Definition: A finding of acute skin inflammatory reaction caused by drugs, especially chemotherapeutic agents, for weeks or months following radiotherapy. The inflammatory reaction is confined to the previously irradiated skin and the symptoms disappear after the removal of the pharmaceutical agent. **Navigational Note:** -					
Rectal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a rectal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Seroma	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; simple aspiration indicated	Symptomatic, elective invasive intervention indicated	-	-
Definition: A finding of tumor-like collection of serum in the tissues. **Navigational Note:** -					
Small intestinal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the small bowel. **Navigational Note:** -					
Spermatic cord anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a spermatic cord anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Life-threatening consequences; symptoms associated with neurovascular compromise	Death
Definition: A finding of traumatic injury to the spine in which the continuity of a vertebral bone is broken. **Navigational Note:** -					
Stenosis of gastrointestinal stoma	-	Symptomatic; IV fluids indicated <24 hrs; manual dilation at bedside	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of narrowing of the gastrointestinal stoma (surgically created opening on the surface of the body). **Navigational Note:** -					
Stomal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by a circumscribed, erosive lesion on the jejunal mucosal surface close to the anastomosis site following a gastroenterostomy procedure. **Navigational Note:** -					
Tracheal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the trachea. **Navigational Note:** -					
Tracheal obstruction	Partial asymptomatic obstruction on examination (e.g., visual, radiologic or endoscopic)	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Stridor or respiratory distress limiting self care ADL; invasive intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by blockage of the lumen of the trachea. **Navigational Note:** -					
Tracheostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Transfusion indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the tracheostomy site. **Navigational Note:** -					

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Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ureteric anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a ureteral anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Urethral anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a urethral anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Urostomy leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of contents from a urostomy. **Navigational Note:** -					
Urostomy obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; dilation or endoscopic repair or stent placement indicated	Altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the urostomy. **Navigational Note:** -					
Urostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Transfusion indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the urostomy site. **Navigational Note:** -					
Urostomy stenosis	-	Symptomatic but no hydronephrosis, sepsis, or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic (e.g., hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of narrowing of the opening of a urostomy. **Navigational Note:** -					

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Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Uterine anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a uterine anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Uterine perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the uterine wall. **Navigational Note:** -					
Vaccination complication	Mild pain; erythema 2.5-5cm; induration/swelling 2.5-5cm; does not interfere with activity	Moderate pain; Erythema 5.1-10 cm; Induration/swelling 5.1-10 cm; lipodystrophy; limiting instrumental ADL	Severe pain; Erythema > 10 cm; Induration/swelling > 10 cm; necrosis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder that occurs after the injection of a substance with antigenic properties, administered to activate the immune system. **Navigational Note:** For systemic vaccination complications, consider Immune system disorders: Allergic reaction or Anaphylaxis.					
Vaginal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a vaginal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Vas deferens anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a vas deferens anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Vascular access complication	TPA administration into line with no intent for systemic therapy indicated	Device dislodgement, blockage, leak, or malposition; device replacement indicated	Pulmonary embolism, deep vein or cardiac thrombosis; intervention indicated (e.g., anticoagulation, lysis, filter, invasive procedure)	Life-threatening consequences with hemodynamic or neurologic instability	Death
Definition: A finding of a previously undocumented problem related to the vascular access site. **Navigational Note:** -					

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Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Venous injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to a vein. **Navigational Note:** -					
Wound complication	Observation only; topical intervention indicated	Bedside local care indicated	Operative intervention indicated	Life-threatening consequences	Death
Definition: A finding of development of a new problem at the site of an existing wound. **Navigational Note:** Prior to using this term consider Injury, poisoning and procedural complications: Wound dehiscence or Infections and infestations: Wound infection					
Wound dehiscence	Incisional separation, intervention not indicated	Incisional separation, local care (e.g., suturing) or medical intervention indicated (e.g., analgesic)	Fascial disruption or dehiscence without evisceration; revision by operative intervention indicated	Life-threatening consequences; symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
Definition: A finding of separation of the approximated margins of a surgical wound. **Navigational Note:** Also consider Infections and infestations: Wound infection					
Wrist fracture	Mild; non-operative intervention indicated	Limiting instrumental ADL; outpatient operative intervention indicated	Limiting self care ADL; elective operative intervention indicated requiring hospitalization	-	-
Definition: A finding of traumatic injury to the wrist joint in which the continuity of a wrist bone is broken. **Navigational Note:** -					
Injury, poisoning and procedural complications - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding	-	-
Definition: A finding based on laboratory test results in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.					
Navigational Note: -					
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					
Navigational Note: Also consider Hepatobiliary disorders: Hepatic failure					
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.					
Navigational Note: -					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					
Navigational Note: Also consider Hepatobiliary disorders: Hepatic failure					
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of antidiuretic hormone in the blood specimen.					
Navigational Note: -					
Blood bicarbonate decreased	<LLN and no intervention initiated	-	-	-	-
Definition: A finding based on laboratory test results that indicate a decrease in levels of bicarbonate in a venous blood specimen.					
Navigational Note: Also consider Metabolism and nutrition disorders: Acidosis or Alkalosis					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.					
Navigational Note: Also consider Hepatobiliary disorders: Hepatic failure					
Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of corticotrophin in a blood specimen.					
Navigational Note: -					
Blood gonadotrophin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of gonadotrophin hormone in a blood specimen.					
Navigational Note: -					
Blood lactate dehydrogenase increased	>ULN	-	-	-	-
Definition: A finding based on laboratory test results that indicate increased levels of lactate dehydrogenase in the blood specimen.					
Navigational Note: -					
Blood prolactin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of prolactin hormone in a blood specimen.					
Navigational Note: -					
Carbon monoxide diffusing capacity decreased	3 - 5 units below LLN; for follow-up, a decrease of 3 - 5 units (ml/min/mm Hg) below the baseline value; asymptomatic and intervention not indicated	6 - 8 units below LLN; for follow-up, an asymptomatic decrease of >5 - 8 units (ml/min/mm Hg) below the baseline value; symptomatic and intervention not indicated	Asymptomatic decrease of >8 units drop; >5 units drop along with the presence of pulmonary symptoms (e.g., >Grade 2 hypoxia or >Grade 2 dyspnea); intervention indicated	-	-
Definition: A finding based on lung function test results that indicate a decrease in the lung capacity to absorb carbon monoxide.					
Navigational Note: Also consider Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A finding based on laboratory test results that indicate increased levels of cardiac troponin I in a biological specimen. **Navigational Note:** Also consider Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction. Report Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction if same grade event.					
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A finding based on laboratory test results that indicate increased levels of cardiac troponin T in a biological specimen. **Navigational Note:** Also consider Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction. Report Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction if same grade event.					
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of CD4 lymphocytes in a blood specimen. **Navigational Note:** -					
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of cholesterol in a blood specimen. **Navigational Note:** -					
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in levels of creatine phosphokinase in a blood specimen. **Navigational Note:** Also consider Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction. Report Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction if same grade event.					
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Definition: A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen. **Navigational Note:** Also consider Renal and urinary disorders: Acute kidney injury					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >=20% drop from baseline	Resting ejection fraction (EF) <20%	-
Definition: The percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction. **Navigational Note:** Also consider Cardiac disorders: Left ventricular systolic dysfunction. Report Cardiac disorders: Left ventricular systolic dysfunction if same grade event.					
Electrocardiogram QT corrected interval prolonged	Average QTc 450 - 480 ms	Average QTc 481 - 500 ms	Average QTc >= 501 ms; >60 ms change from baseline	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	-
Definition: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval. **Navigational Note:** -					
Electrocardiogram T wave abnormal	T wave flattening	Nonspecific ST segment change	-	-	-
Definition: A disorder characterized by Electrocardiogram T wave amplitude changes. **Navigational Note:** -					
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of fibrinogen in a blood specimen. **Navigational Note:** -					
Forced expiratory volume decreased	FEV1% (percentages of observed FEV1 and FVC related to their respective predicted values) 99 - 70% predicted	FEV1 60 - 69%	50 - 59%	<= 49%	-
Definition: A finding based on test results that indicate a relative decrease in the fraction of the forced vital capacity that is exhaled in a specific number of seconds. **Navigational Note:** Also consider Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea					
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water. **Navigational Note:** -					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen.					
Navigational Note: -					
Haptoglobin decreased	<LLN	-	-	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of haptoglobin in a blood specimen.					
Navigational Note: -					
Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-	-
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin above normal.					
Navigational Note: -					
INR increased	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding	-	-
Definition: A finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood.					
Navigational Note: -					
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-
Definition: A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen.					
Navigational Note: -					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.					
Navigational Note: -					
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.					
Navigational Note: -					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.					
Navigational Note: -					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of pancreatic enzymes in a biological specimen.					
Navigational Note: -					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen. **Navigational Note:** -					
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-
Definition: A finding based on laboratory test results that indicate an increase in the levels of amylase in a serum specimen. **Navigational Note:** -					
Thyroid stimulating hormone increased	TSH increased and no intervention initiated	-	-	-	-
Definition: A disorder characterized by an increase in thyroid stimulating hormone. **Navigational Note:** If intervention initiated or symptomatic, report as Endocrine disorders: Hypothyroidism.					
Urine output decreased	-	-	**Adult:** Oliguria (<80 ml in 8 hr); **Infants:** < 0.5 mL/kg per hour for 24 hours; **Children:** < 500 mL/1.73 m2 body surface area per day	**Adult:** Anuria (<240 ml in 24 hr); **Pediatric:** No urine output over 12 hours	-
Definition: A finding based on test results that indicate urine production is less relative to previous output. **Navigational Note:** -					
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value; limiting instrumental ADL	<50% of predicted value; limiting self care ADL	-	-
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value. **Navigational Note:** Also consider Investigations: Forced Expiratory Volume; Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea					
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterized by an unexpected or abnormal increase in overall body weight; for pediatrics, greater than the baseline growth curve. **Navigational Note:** Do not use Metabolism and nutrition disorders: Obesity, this term is being retired.					
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-
Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve. **Navigational Note:** -					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen. **Navigational Note:** -					
Investigations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Metabolism and nutrition disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high acidity (high hydrogen-ion concentration) of the blood and other body tissues. **Navigational Note:** -					
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity to the adverse effects of alcohol, which can include nasal congestion, skin flushes, heart dysrhythmias, nausea, vomiting, indigestion and headaches. **Navigational Note:** -					
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high alkalinity (low hydrogen-ion concentration) of the blood and other body tissues. **Navigational Note:** -					
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a loss of appetite. **Navigational Note:** -					
Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated	Hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis. **Navigational Note:** -					
Glucose intolerance	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Severe symptoms; insulin indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inability to properly metabolize glucose. **Navigational Note:** -					
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood. **Navigational Note:** -					

Metabolism and nutrition disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hyperglycemia	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance. **Navigational Note:** -					
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs. **Navigational Note:** -					
Hyperlipidemia	Requiring diet changes	Requiring pharmaceutical intervention	Hospitalization; pancreatitis	Life-threatening consequences	-
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of lipids in blood. **Navigational Note:** -					
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood. **Navigational Note:** -					
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood. **Navigational Note:** -					
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; urgent intervention indicated (e.g., dialysis)	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of phosphate in a blood. **Navigational Note:** -					
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood. **Navigational Note:** -					

Metabolism and nutrition disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences	Life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of uric acid. **Navigational Note:** -					
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood. **Navigational Note:** -					
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood. **Navigational Note:** -					
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood. **Navigational Note:** -					
Hypokalemia	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood. **Navigational Note:** -					
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of magnesium in the blood. **Navigational Note:** -					
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood. **Navigational Note:** -					

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Metabolism and nutrition disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of phosphates in the blood. **Navigational Note:** -					
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by accumulation of iron in the tissues. **Navigational Note:** -					
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characterized by having a high amount of body fat. **Navigational Note:** Use term Investigations: Weight gain					
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by metabolic abnormalities that result from a spontaneous or therapy-related cytolysis of tumor cells. **Navigational Note:** -					
Metabolism and nutrition disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Abdominal soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the abdominal wall. **Navigational Note:** -					
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a joint. **Navigational Note:** -					
Arthritis	Mild pain with inflammation, erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; limiting self care ADL	-	-
Definition: A disorder characterized by inflammation involving a joint. **Navigational Note:** -					
Avascular necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure. **Navigational Note:** Use new term: Musculoskeletal and connective tissue disorders: Osteonecrosis					
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the back region. **Navigational Note:** -					
Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the bones. **Navigational Note:** -					
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the buttocks. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Chest wall necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the chest wall including breast. **Navigational Note:** -					
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the chest wall. **Navigational Note:** -					
Exostosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	-	-
Definition: A disorder characterized by non-neoplastic overgrowth of bone. **Navigational Note:** -					
Fibrosis deep connective tissue	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by fibrotic degeneration of the deep connective tissues. **Navigational Note:** -					
Flank pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort on the lateral side of the body in the region below the ribs and above the hip. **Navigational Note:** -					
Generalized muscle weakness	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of muscles in multiple anatomic sites. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Growth suppression	Reduction in growth velocity by 10 - 29% ideally measured over the period of a year	Reduction in growth velocity by 30 - 49% ideally measured over the period of a year or 0 - 49% reduction in growth from the baseline growth curve	Reduction in growth velocity of >=50% ideally measured over the period of a year	-	-
Definition: A disorder characterized by stature that is smaller than normal as expected for age. **Navigational Note:** -					
Head soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the head. **Navigational Note:** -					
Joint effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; invasive intervention indicated	-	-
Definition: A disorder characterized by excessive fluid in a joint, usually as a result of joint inflammation. **Navigational Note:** -					
Joint range of motion decreased	<=25% loss of ROM (range of motion); decreased ROM limiting athletic activity	>25 - 50% decrease in ROM; limiting instrumental ADL	>50% decrease in ROM; limiting self care ADL	-	-
Definition: A disorder characterized by a decrease in joint flexibility of any joint. **Navigational Note:** -					
Joint range of motion decreased cervical spine	Mild restriction of rotation or flexion between 60 - 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	-	-
Definition: A disorder characterized by a decrease in flexibility of a cervical spine joint. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Joint range of motion decreased lumbar spine	Stiffness; difficulty bending to the floor to pick up a very light object but able to do athletic activity	Pain with range of motion (ROM) in lumbar spine; requires a reaching aid to pick up a very light object from the floor	<50% lumbar spine flexion; associated with symptoms of ankylosis or fused over multiple segments with no L-spine flexion (e.g., unable to reach to floor to pick up a very light object)	-	-
Definition: A disorder characterized by a decrease in flexibility of a lumbar spine joint. **Navigational Note:** -					
Kyphosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate accentuation; limiting instrumental ADL	Severe accentuation; operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an abnormal increase in the curvature of the thoracic portion of the spine. **Navigational Note:** -					
Lordosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate accentuation; limiting instrumental ADL	Severe accentuation; operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an abnormal increase in the curvature of the lumbar portion of the spine. **Navigational Note:** -					
Muscle cramp	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked cramping sensation originating from a muscle or group of muscles. **Navigational Note:** Synonym: Muscle spasm					
Muscle weakness lower limb	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the lower limb muscles. **Navigational Note:** -					
Muscle weakness trunk	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the trunk muscles. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Muscle weakness upper limb	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the upper limb muscles. **Navigational Note:** -					
Musculoskeletal deformity	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing; limiting self care ADL	-	-
Definition: A disorder characterized by a malformation of the musculoskeletal system. **Navigational Note:** -					
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation originating from a muscle or group of muscles. **Navigational Note:** -					
Myositis	Mild pain	Moderate pain associated with weakness; pain limiting instrumental ADL	Pain associated with severe weakness; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by inflammation involving the skeletal muscles. **Navigational Note:** -					
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the neck area. **Navigational Note:** -					
Neck soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the neck. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Osteonecrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., analgesics or bisphosphonates); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure. **Navigational Note:** -					
Osteonecrosis of jaw	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the bone of the mandible. **Navigational Note:** -					
Osteoporosis	**Adult:** Radiologic evidence of osteoporosis or Bone Mineral Density (BMD) t-score -1 to -2.5 (osteopenia); **Pediatric:** Radiologic evidence of low BMD with z score of <= -2.0 and no history of significant fractures	**Adult:** BMD t-score < -2.5; loss of height <2 cm; therapy to improve BMD indicated; limiting instrumental ADL; **Pediatric:** Low BMD (z-score <= -2.0) and significant fracture history (defined as a long bone fracture of the lower extremity, vertebral compression, 2 or more long bone fractures of the upper extremities); therapy to improve BMD indicated	**Adult:** Loss of height >=2 cm; hospitalization indicated; limiting self care ADL; **Pediatric:** Limiting self care ADL	-	-
Definition: A disorder characterized by reduced bone mass, with a decrease in cortical thickness and in the number and size of the trabeculae of cancellous bone (but normal chemical composition), resulting in increased fracture incidence. **Navigational Note:** -					
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the upper or lower extremities. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pelvic soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the pelvis. **Navigational Note:** -					
Rhabdomyolysis	Asymptomatic, intervention not indicated; laboratory findings only	Non-urgent intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences; dialysis	Death
Definition: A disorder characterized by the breakdown of muscle tissue resulting in the release of muscle fiber contents into the bloodstream. **Navigational Note:** -					
Rotator cuff injury	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an injury of the rotator cuff. **Navigational Note:** -					
Scoliosis	<20 degrees; clinically undetectable	>20 - 45 degrees; visible by forward flexion; limiting instrumental ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by a malformed, lateral curvature of the spine. **Navigational Note:** -					
Soft tissue necrosis lower limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the lower extremity. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Soft tissue necrosis upper limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the upper extremity. **Navigational Note:** -					
Superficial soft tissue fibrosis	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by fibrotic degeneration of the superficial soft tissues. **Navigational Note:** -					
Trismus	Decreased ROM (range of motion) without impaired eating	Decreased ROM requiring small bites, soft foods or purees	Decreased ROM with inability to adequately aliment or hydrate orally	-	-
Definition: A disorder characterized by lack of ability to open the mouth fully due to a decrease in the range of motion of the muscles of mastication. **Navigational Note:** -					
Unequal limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 - 5 cm; shoe lift indicated; limiting instrumental ADL	Severe length discrepancy >5 cm; limiting self care ADL; operative intervention indicated	-	-
Definition: A disorder characterized by a discrepancy between the lengths of the lower or upper extremities. **Navigational Note:** -					
Musculoskeletal and connective tissue disorder - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Leukemia secondary to oncology chemotherapy	-	-	-	Present	Death
Definition: A disorder characterized by leukemia arising as a result of the mutagenic effect of chemotherapy agents. **Navigational Note:** -					
Myelodysplastic syndrome	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by insufficiently healthy hematapoietic cell production by the bone marrow. **Navigational Note:** -					
Skin papilloma	Asymptomatic; intervention not indicated	Intervention initiated	-	-	-
Definition: A disorder characterized by the presence of one or more warts. **Navigational Note:** -					
Treatment related secondary malignancy	-	-	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death
Definition: A disorder characterized by development of a malignancy most probably as a result of treatment for a previously existing malignancy. **Navigational Note:** -					
Tumor hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding in a tumor. **Navigational Note:** -					
Tumor pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort from a neoplasm that may be pressing on a nerve, blocking blood vessels, inflamed or fractured from metastasis. **Navigational Note:** -					
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

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Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the abducens nerve (sixth cranial nerve). **Navigational Note:** -					
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the accessory nerve (eleventh cranial nerve). **Navigational Note:** -					
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the acoustic nerve (eighth cranial nerve). **Navigational Note:** -					
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-
Definition: A disorder characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs. **Navigational Note:** -					
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
Definition: A disorder characterized by systematic and extensive loss of memory. **Navigational Note:** -					
Anosmia	Present	-	-	-	-
Definition: A disorder characterized by a change in the sense of smell. **Navigational Note:** Also consider Olfactory nerve disorder					
Aphonia	-	-	Voicelessness; unable to speak	-	-
Definition: A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic). **Navigational Note:** -					
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space. **Navigational Note:** -					

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Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-
Definition: A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities.					
Navigational Note: -					
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited movement in the arm or hand.					
Navigational Note: -					
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the brain and/or spinal cord.					
Navigational Note: -					
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by loss of cerebrospinal fluid into the surrounding tissues.					
Navigational Note: -					
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-
Definition: A disorder characterized by a conspicuous change in cognitive function.					
Navigational Note: -					
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in the ability to concentrate.					
Navigational Note: -					

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Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences; coma; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in ability to perceive and respond. **Navigational Note:** -					
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-
Definition: A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking. **Navigational Note:** -					
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-
Definition: A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech. **Navigational Note:** -					
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-
Definition: A disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation. **Navigational Note:** -					
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-
Definition: A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell. **Navigational Note:** -					
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-
Definition: A disorder characterized by impairment of verbal communication skills, often resulting from brain damage. **Navigational Note:** -					
Edema cerebral	-	-	New onset; worsening from baseline	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the brain. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a pathologic process involving the brain. **Navigational Note:** -					
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness. **Navigational Note:** Synonym: Restless legs					
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the facial muscles. **Navigational Note:** -					
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the facial nerve (seventh cranial nerve). **Navigational Note:** -					
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the glossopharyngeal nerve (ninth cranial nerve). **Navigational Note:** -					
Guillain-Barre syndrome	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated; intubation	Death
Definition: A disorder characterized by the body's immune system attacking the peripheral nervous system causing ascending paralysis. **Navigational Note:** -					
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.					
Navigational Note: -					
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-
Definition: A disorder characterized by characterized by excessive sleepiness during the daytime.					
Navigational Note: -					
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the hypoglossal nerve (twelfth cranial nerve).					
Navigational Note: -					
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the cranium.					
Navigational Note: -					
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.					
Navigational Note: Prior to using this term consider Nervous system disorder: TIA or Stroke					
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a decrease in consciousness characterized by mental and physical inertness.					
Navigational Note: -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum +/- mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum +/- moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death
Definition: A disorder characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation. **Navigational Note:** -					
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in memory function. **Navigational Note:** -					
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges. **Navigational Note:** -					
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by uncontrolled and purposeless movements. **Navigational Note:** -					
Muscle weakness left-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles on the left side of the body. **Navigational Note:** -					
Muscle weakness right-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles on the right side of the body. **Navigational Note:** -					

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Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Myasthenia gravis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by weakness and rapid fatigue of any of the skeletal muscles. **Navigational Note:** -					
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by intense painful sensation along a nerve or group of nerves. **Navigational Note:** -					
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involuntary movements of the eyeballs. **Navigational Note:** -					
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the oculomotor nerve (third cranial nerve). **Navigational Note:** -					
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the olfactory nerve (first cranial nerve). **Navigational Note:** -					
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and/or warmth. **Navigational Note:** -					
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by damage or dysfunction of the peripheral motor nerves. **Navigational Note:** Also consider Nervous system disroders: Peripheral sensory neuropathy					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Peripheral sensory neuropathy	Asymptomatic	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by damage or dysfunction of the peripheral sensory nerves. **Navigational Note:** -					
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort related to a limb or an organ that is removed from or is not physically part of the body. **Navigational Note:** -					
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope. **Navigational Note:** -					
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination. **Navigational Note:** -					
Radiculitis	Mild symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root. **Navigational Note:** -					
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by paralysis of the recurrent laryngeal nerve. **Navigational Note:** -					
Reversible posterior leukoencephalopathy syndrome	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization	Life-threatening consequences	Death
Definition: A disorder characterized by headaches, mental status changes, visual disturbances, and/or seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition. Also known as posterior reversible encephalopathy syndrome (PRES). **Navigational Note:** -					

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Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Seizure	Brief partial seizure and no loss of consciousness	Brief generalized seizure	New onset seizures (partial or generalized); multiple seizures despite medical intervention	Life-threatening consequences; prolonged repetitive seizures	Death
Definition: A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin. **Navigational Note:** -					
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by characterized by excessive sleepiness and drowsiness. **Navigational Note:** -					
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening consequences; unable to move active or passive range of motion	Death
Definition: A disorder characterized by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances. **Navigational Note:** -					
Spinal cord compression	-	-	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by pressure on the spinal cord. **Navigational Note:** -					
Stroke	Incidental radiographic findings only	Mild to moderate neurologic deficit; limiting instrumental ADL	Severe neurologic deficit; limiting self care ADL; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage. **Navigational Note:** -					
Syncope	-	-	Fainting; orthostatic collapse	-	-
Definition: A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain. **Navigational Note:** -					
Tendon reflex decreased	Ankle reflex reduced	Ankle reflex absent; other reflexes reduced	Absence of all reflexes	-	-
Definition: A disorder characterized by less than normal deep tendon reflexes. **Navigational Note:** Also consider Nervous system disorders: Peripheral motor neuropathy or Peripheral sensory neuropathy					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-
Definition: A disorder characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit. **Navigational Note:** If >24 hours, Consider Nervous system disorders: Stroke					
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts. **Navigational Note:** -					
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the trigeminal nerve (fifth cranial nerve). **Navigational Note:** -					
Trochlear nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the trochlear nerve (fourth cranial nerve). **Navigational Note:** -					
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the vagus nerve (tenth cranial nerve). **Navigational Note:** -					
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve. **Navigational Note:** -					
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

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Pregnancy, puerperium and perinatal conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Fetal growth retardation	-	<10% percentile of weight for gestational age	<5% percentile of weight for gestational age	<1% percentile of weight for gestational age	-
Definition: A disorder characterized by inhibition of fetal growth resulting in the inability of the fetus to achieve its potential weight. **Navigational Note:** -					
Pregnancy loss	-	-	-	Fetal loss at any gestational age	-
Definition: Death in utero. **Navigational Note:** -					
Premature delivery	Delivery of a liveborn infant at >34 to 37 weeks gestation	Delivery of a liveborn infant at >28 to 34 weeks gestation	Delivery of a liveborn infant at 24 to 28 weeks gestation	Delivery of a liveborn infant at 24 weeks of gestation or less	-
Definition: A disorder characterized by delivery of a viable infant before the normal end of gestation. Typically, viability is achievable between the twentieth and thirty-seventh week of gestation. **Navigational Note:** -					
Pregnancy, puerperium and perinatal conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Psychiatric disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Agitation	Mild mood alteration	Moderate mood alteration	Severe agitation; hospitalization not indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by a state of restlessness associated with unpleasant feelings of irritability and tension. **Navigational Note:** -					
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by an inability to achieve orgasm. **Navigational Note:** -					
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus. **Navigational Note:** -					
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by a lack of clear and orderly thought and behavior. **Navigational Note:** -					
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by sexual dysfunction characterized by a delay in climax. **Navigational Note:** -					
Delirium	Mild acute confusional state	Moderate and acute confusional state; limiting instrumental ADL	Severe and acute confusional state; limiting self care ADL; urgent intervention indicated; new onset	Life-threatening consequences, threats of harm to self or others; urgent intervention indicated	Death
Definition: A disorder characterized by the acute and sudden development of confusion, illusions, movement changes, inattentiveness, agitation, and hallucinations. Usually, it is a reversible condition. **Navigational Note:** -					
Delusions	-	Moderate delusional symptoms	Severe delusional symptoms; hospitalization not indicated; new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by false personal beliefs held contrary to reality, despite contradictory evidence and common sense. **Navigational Note:** -					

Psychiatric disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by melancholic feelings of grief or unhappiness. **Navigational Note:** -					
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-
Definition: A disorder characterized by an exaggerated feeling of well-being which is disproportionate to events and stimuli. **Navigational Note:** -					
Hallucinations	Mild hallucinations (e.g., perceptual distortions)	Moderate hallucinations	Severe hallucinations; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by a false sensory perception in the absence of an external stimulus. **Navigational Note:** -					
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	-	-
Definition: A disorder characterized by difficulty in falling asleep and/or remaining asleep. **Navigational Note:** -					
Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self care ADL; inconsolable; medical or psychiatric intervention indicated	-	-
Definition: A disorder characterized by an abnormal responsiveness to stimuli or physiological arousal; may be in response to pain, fright, a drug, an emotional situation or a medical condition. **Navigational Note:** -					
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder characterized by a decrease in sexual desire. **Navigational Note:** -					
Libido increased	Present	-	-	-	-
Definition: A disorder characterized by an increase in sexual desire. **Navigational Note:** -					

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Psychiatric disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Mania	Mild manic symptoms (e.g., elevated mood, rapid thoughts, rapid speech, decreased need for sleep)	Moderate manic symptoms (e.g., relationship and work difficulties; poor hygiene)	Severe manic symptoms (e.g., hypomania; major sexual or financial indiscretions); hospitalization not indicated; new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by excitement of psychotic proportions manifested by mental and physical hyperactivity, disorganization of behavior and elevation of mood. **Navigational Note:** -					
Personality change	Mild personality change	Moderate personality change	Severe personality change; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	-
Definition: A disorder characterized by a conspicuous change in a person's behavior and thinking. **Navigational Note:** -					
Psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid, extreme disorganization); hospitalization not indicated; new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by personality change, impaired functioning, and loss of touch with reality. It may be a manifestation of schizophrenia, bipolar disorder or brain tumor. **Navigational Note:** -					
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an inability to rest, relax or be still. **Navigational Note:** -					
Suicidal ideation	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-
Definition: A disorder characterized by thoughts of taking one's own life. **Navigational Note:** -					
Suicide attempt	-	-	Suicide attempt or gesture without intent to die	Suicide attempt with intent to die which requires hospitalization	Death
Definition: A disorder characterized by self-inflicted harm in an attempt to end one's own life. **Navigational Note:** -					

Psychiatric disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Psychiatric disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; limiting self care ADL	Life-threatening consequences; hospitalization or urgent intervention indicated	Death
Definition: -					
Navigational Note: -					

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Renal and urinary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Acute kidney injury	-	-	Hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function (within 2 weeks) and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction). **Navigational Note:** Also consider Investigations: Creatinine increased					
Bladder perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the bladder wall. **Navigational Note:** -					
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characterized by a sudden and involuntary contraction of the bladder wall. **Navigational Note:** -					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Definition: A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure. **Navigational Note:** -					
Cystitis noninfective	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by inflammation of the bladder which is not caused by an infection of the urinary tract. **Navigational Note:** -					
Dysuria	Present	-	-	-	-
Definition: A disorder characterized by painful urination. **Navigational Note:** If associated with an infection, report the infection. For grades higher than Grade 1, consider Renal and urinary disorders: Bladder spasm or Cystitis noninfective; Infections and infestations: Urinary tract infection.					

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Renal and urinary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Glucosuria	Present	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate glucose in the urine.					
Navigational Note: -					
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate blood in the urine.					
Navigational Note: -					
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of free hemoglobin in the urine.					
Navigational Note: Report underlying AE if > Grade 1					
Nephrotic syndrome	-	-	Not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by symptoms that include severe edema, proteinuria, and hypoalbuminemia; it is indicative of renal dysfunction.					
Navigational Note: -					
Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	**Adult:** 2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs; **Pediatric:** Urine P/C {Protein/Creatinine} ratio 0.5 - 1.9	**Adult:** Urinary protein >=3.5 g/24 hrs; 4+ proteinuria; **Pediatric:** Urine P/C {Protein/Creatinine} ratio >1.9	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly albumin, but also globulin.					
Navigational Note: 24-hour urine collection takes precedence over dipstick					

Renal and urinary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Renal calculi	Asymptomatic or mild symptoms; occasional use of nonprescription analgesics indicated	Symptomatic; oral antiemetics indicated; around the clock nonprescription analgesics or any oral narcotic analgesics indicated	Hospitalization indicated; IV intervention (e.g., analgesics, antiemetics); elective invasive intervention indicated	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by the formation of crystals/kidney stones in the pelvis of the kidney. **Navigational Note:** -					
Renal colic	Mild pain not interfering with activity; nonprescription medication indicated	Moderate pain; limiting instrumental ADL; prescription medication indicated	Hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by paroxysmal and severe flank marked discomfort radiating to the inguinal area. Often, the cause is the passage of crystals/kidney stones. **Navigational Note:** -					
Renal hemorrhage	Mild symptoms; intervention not indicated	Analgesics and hematocrit monitoring indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the kidney. **Navigational Note:** -					
Urinary fistula	-	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between any part of the urinary system and another organ or anatomic site. **Navigational Note:** -					
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by urination at short intervals. **Navigational Note:** -					
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by inability to control the flow of urine from the bladder. **Navigational Note:** -					

Renal and urinary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective invasive intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of urine within the bladder because of the inability to urinate. **Navigational Note:** -					
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but no hydronephrosis, sepsis, or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Altered organ function (e.g., hydronephrosis or renal dysfunction); invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of contents of the urinary tract. **Navigational Note:** -					
Urinary tract pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the urinary tract. **Navigational Note:** -					
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by a sudden compelling urge to urinate. **Navigational Note:** -					
Urine discoloration	Present	-	-	-	-
Definition: A disorder characterized by a change in the color of the urine. **Navigational Note:** -					
Renal and urinary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Amenorrhea	-	Present	-	-	-
Definition: A disorder characterized by the abnormal absence of menses for at least three consecutive menstrual cycles.					
Navigational Note: -					
Azoospermia	-	Absence of sperm in ejaculate	-	-	-
Definition: A disorder characterized by laboratory test results that indicate complete absence of spermatozoa in the semen.					
Navigational Note: -					
Breast atrophy	Minimal asymmetry; minimal atrophy	Moderate asymmetry; moderate atrophy	Asymmetry >1/3 of breast volume; severe atrophy	-	-
Definition: A disorder characterized by underdevelopment of the breast.					
Navigational Note: -					
Breast pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the breast region.					
Navigational Note: -					
Dysmenorrhea	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by abnormally painful abdominal cramps during menses.					
Navigational Note: -					
Dyspareunia	Mild discomfort or pain associated with vaginal penetration; discomfort relieved with use of vaginal lubricants or estrogen	Moderate discomfort or pain associated with vaginal penetration; discomfort or pain partially relieved with use of vaginal lubricants or estrogen	Severe discomfort or pain associated with vaginal penetration; discomfort or pain unrelieved by vaginal lubricants or estrogen	-	-
Definition: A disorder characterized by painful or difficult coitus.					
Navigational Note: -					
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde ejaculation	-	-	-
Definition: A disorder characterized by problems related to ejaculation. This category includes premature, delayed, retrograde and painful ejaculation.					
Navigational Note: -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Erectile dysfunction	Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)	Decrease in erectile function (frequency/rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump)	Decrease in erectile function (frequency/rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)	-	-
Definition: A disorder characterized by the persistent or recurrent inability to achieve or to maintain an erection during sexual activity. **Navigational Note:** -					
Fallopian tube obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents in the fallopian tube. **Navigational Note:** -					
Feminization acquired	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the development of secondary female sex characteristics in males due to extrinsic factors. **Navigational Note:** -					
Genital edema	Mild swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the genitals. **Navigational Note:** -					
Gynecomastia	Asymptomatic	Symptomatic (e.g., pain or psychosocial impact)	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by excessive development of the breasts in males. **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hematosalpinx	Minimal bleeding identified on imaging study or laparoscopy; intervention not indicated	Moderate bleeding; medical intervention indicated	Transfusion indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by the presence of blood in a fallopian tube. **Navigational Note:** -					
Irregular menstruation	Intermittent/irregular menses for no more than 3 consecutive menstrual cycles	Intermittent/irregular menses for more than 3 consecutive menstrual cycles	-	-	-
Definition: A disorder characterized by a change in cycle or duration of menses from baseline. **Navigational Note:** Also consider Reproductive system and breast disorders: Premature menopause, Amenorrhea.					
Lactation disorder	Mild changes in lactation, not significantly affecting production or expression of breast milk	Changes in lactation, significantly affecting breast production or expression of breast milk	-	-	-
Definition: A disorder characterized by disturbances of milk secretion. It is not necessarily related to pregnancy that is observed in females and can be observed in males. **Navigational Note:** -					
Menorrhagia	Mild; iron supplements indicated	Moderate symptoms; medical intervention indicated (e.g., hormones)	Severe; transfusion indicated; operative intervention indicated (e.g., hysterectomy)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormally heavy vaginal bleeding during menses. **Navigational Note:** -					
Nipple deformity	Asymptomatic; asymmetry with slight retraction and/or thickening of the nipple areolar complex	Symptomatic; asymmetry of nipple areolar complex with moderate retraction and/or thickening of the nipple areolar complex	-	-	-
Definition: A disorder characterized by a malformation of the nipple. **Navigational Note:** -					
Oligospermia	Sperm concentration > 0 to < 15 million/ml	-	-	-	-
Definition: A disorder characterized by a decrease in the number of spermatozoa in the semen. **Navigational Note:** -					
Ovarian hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the ovary. **Navigational Note:** -					

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Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ovarian rupture	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Transfusion; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by tearing or disruption of the ovarian tissue. **Navigational Note:** -					
Ovulation pain	-	Present	-	-	-
Definition: A disorder characterized by a sensation of marked discomfort in one side of the abdomen between menstrual cycles, around the time of the discharge of the ovum from the ovarian follicle. **Navigational Note:** -					
Pelvic floor muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic, not interfering with bladder, bowel, or vaginal function; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles of the pelvic floor. **Navigational Note:** -					
Pelvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the pelvis. **Navigational Note:** -					
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the penis. **Navigational Note:** -					
Perineal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the area between the genital organs and the anus. **Navigational Note:** -					
Premature menopause	-	Present	-	-	-
Definition: A disorder characterized by premature ovarian failure. Symptoms may include hot flashes, night sweats, mood swings, and a decrease in sex drive. Laboratory findings include elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH.) **Navigational Note:** -					
Prostatic hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the prostate gland. **Navigational Note:** -					

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Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Prostatic obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by compression of the urethra secondary to enlargement of the prostate gland. This results in voiding difficulties (straining to void, slow urine stream, and incomplete emptying of the bladder). **Navigational Note:** -					
Prostatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the prostate gland. **Navigational Note:** -					
Scrotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the scrotal area. **Navigational Note:** -					
Spermatic cord hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the spermatic cord. **Navigational Note:** -					
Spermatic cord obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents of the spermatic cord. **Navigational Note:** -					
Testicular disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but not interfering with sexual function; intervention not indicated; limiting instrumental ADL	Severe symptoms; interfering with sexual function; limiting self care ADL; intervention indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by abnormal function or appearance of the testis. **Navigational Note:** Also consider Reproductive system and breast disorders: Genital edema or other AE terms in the Renal and urinary disorders SOC or Reproductive system and breast disorders SOC.					
Testicular hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the testis. **Navigational Note:** -					

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Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Testicular pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the testis. **Navigational Note:** -					
Uterine fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the uterus and another organ or anatomic site. **Navigational Note:** -					
Uterine hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the uterus. **Navigational Note:** -					
Uterine obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by blockage of the uterine outlet. **Navigational Note:** -					
Uterine pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the uterus. **Navigational Note:** -					
Vaginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-	-
Definition: A disorder characterized by vaginal secretions. Mucus produced by the cervical glands is discharged from the vagina naturally, especially during the childbearing years. **Navigational Note:** -					
Vaginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function or causing frequent discomfort	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-	-
Definition: A disorder characterized by an uncomfortable feeling of itching and burning in the vagina. **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Vaginal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the vagina and another organ or anatomic site. **Navigational Note:** -					
Vaginal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the vagina. **Navigational Note:** -					
Vaginal inflammation	Mild discomfort or pain, edema, or redness	Moderate discomfort or pain, edema, or redness; limiting instrumental ADL	Severe discomfort or pain, edema, or redness; limiting self care ADL; small areas of mucosal ulceration	Life-threatening consequences; widespread areas of mucosal ulceration; urgent intervention indicated	-
Definition: A disorder characterized by inflammation involving the vagina. Symptoms may include redness, edema, marked discomfort and an increase in vaginal discharge. **Navigational Note:** -					
Vaginal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by blockage of vaginal canal. **Navigational Note:** -					
Vaginal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the vagina. **Navigational Note:** -					
Vaginal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the vaginal wall. **Navigational Note:** -					
Vaginal stricture	Asymptomatic; mild vaginal shortening or narrowing	Vaginal narrowing and/or shortening not interfering with physical examination	Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination	-	Death
Definition: A disorder characterized by a narrowing of the vaginal canal. **Navigational Note:** -					

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Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Reproductive system and breast disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: -					
Navigational Note: -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Adult respiratory distress syndrome	-	-	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery. **Navigational Note:** -					
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an inflammation of the nasal mucous membranes caused by an IgE-mediated response to external allergens. The inflammation may also involve the mucous membranes of the sinuses, eyes, middle ear, and pharynx. Symptoms include sneezing, nasal congestion, rhinorrhea and itching. **Navigational Note:** -					
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by cessation of breathing. **Navigational Note:** -					
Aspiration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)	Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by inhalation of solids or liquids into the lungs. **Navigational Note:** -					
Atelectasis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., dyspnea, cough); medical intervention indicated (e.g., chest physiotherapy, suctioning); bronchoscopic suctioning	Supplemental oxygen indicated; hospitalization or elective operative intervention indicated (e.g., stent, laser)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by the collapse of part or the entire lung. **Navigational Note:** -					
Bronchial fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the bronchus and another organ or anatomic site. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Bronchial obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., mild wheezing); endoscopic evaluation indicated; radiographic evidence of atelectasis/lobar collapse; medical management indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by blockage of a bronchus passage, most often by bronchial secretions and exudates. **Navigational Note:** -					
Bronchial stricture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the bronchial tube. **Navigational Note:** -					
Bronchopleural fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Hospitalization; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between a bronchus and the pleural cavity. **Navigational Note:** -					
Bronchopulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; invasive intervention not indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the bronchial wall and/or lung parenchyma. **Navigational Note:** -					
Bronchospasm	Mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Limiting self care ADL; supplemental oxygen indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Chylothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., fat-restricted diet); thoracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by milky pleural effusion (abnormal collection of fluid) resulting from accumulation of lymph fluid in the pleural cavity. **Navigational Note:** -					
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound. **Navigational Note:** -					
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an uncomfortable sensation of difficulty breathing. **Navigational Note:** -					
Epistaxis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated (e.g., nasal packing, cauterization; topical vasoconstrictors)	Transfusion; invasive intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the nose. **Navigational Note:** -					
Hiccups	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; interfering with sleep; limiting self care ADL	-	-
Definition: A disorder characterized by repeated gulp sounds that result from an involuntary opening and closing of the glottis. This is attributed to a spasm of the diaphragm. **Navigational Note:** -					
Hoarseness	Mild or intermittent voice change; fully understandable; self-resolves	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated	Severe voice changes including predominantly whispered speech	-	-
Definition: A disorder characterized by harsh and raspy voice arising from or spreading to the larynx. **Navigational Note:** -					

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Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypoxia	-	Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a decrease in the level of oxygen in the body. **Navigational Note:** -					
Laryngeal edema	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., dexamethasone, epinephrine, antihistamines)	Stridor; respiratory distress; hospitalization indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the larynx. **Navigational Note:** -					
Laryngeal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the larynx and another organ or anatomic site. **Navigational Note:** -					
Laryngeal hemorrhage	Mild cough or trace hemoptysis; laryngoscopic findings	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by bleeding from the larynx. **Navigational Note:** -					
Laryngeal inflammation	Mild sore throat; raspy voice	Moderate sore throat; analgesics indicated	Severe throat pain; endoscopic intervention indicated	-	-
Definition: A disorder characterized by an inflammation involving the larynx. **Navigational Note:** -					
Laryngeal mucositis	Endoscopic findings only; mild discomfort with normal intake	Moderate pain, analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by ulceration or inflammation involving the mucous membrane of the larynx. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Laryngeal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the laryngeal airway. **Navigational Note:** -					
Laryngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the laryngeal airway. **Navigational Note:** -					
Laryngopharyngeal dysesthesia	Mild symptoms; no anxiety; intervention not indicated	Moderate symptoms; mild anxiety, but no dyspnea; short duration of observation and/or anxiolytic indicated; limiting instrumental ADL	Severe symptoms; dyspnea and swallowing difficulty; limiting self care ADL	Life-threatening consequences	Death
Definition: A disorder characterized by an uncomfortable persistent sensation in the area of the laryngopharynx. **Navigational Note:** -					
Laryngospasm	-	Transient episode; intervention not indicated	Recurrent episodes; noninvasive intervention indicated (e.g., breathing technique, pressure point massage)	Persistent or severe episodes associated with syncope; urgent intervention indicated (e.g., fiberoptic laryngoscopy, intubation, botox injection)	Death
Definition: A disorder characterized by paroxysmal spasmodic muscular contraction of the vocal cords. **Navigational Note:** -					
Mediastinal hemorrhage	Mild symptoms; intervention not indicated; radiologic evidence only	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the mediastinum. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-
Definition: A disorder characterized by obstruction of the nasal passage due to mucosal edema. **Navigational Note:** -					
Oropharyngeal pain	Mild pain	Moderate pain; altered oral intake; non-narcotics initiated; topical analgesics initiated	Severe pain; severely altered eating/swallowing; narcotics initiated; requires parenteral nutrition	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the oropharynx. **Navigational Note:** -					
Pharyngeal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the pharynx and another organ or anatomic site. **Navigational Note:** -					
Pharyngeal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pharynx. **Navigational Note:** -					
Pharyngeal mucositis	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain, analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation involving the mucous membrane of the pharynx. **Navigational Note:** -					
Pharyngeal necrosis	-	-	Inability to aliment adequately by GI tract; invasive intervention indicated; tube feeding or TPN indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the pharynx. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pharyngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the pharyngeal airway. **Navigational Note:** -					
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the pharyngolaryngeal region. **Navigational Note:** -					
Pleural effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., diuretics or therapeutic thoracentesis)	Symptomatic with respiratory distress and hypoxia; operative intervention including chest tube or pleurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort. **Navigational Note:** -					
Pleural hemorrhage	Asymptomatic; mild hemorrhage confirmed by thoracentesis	Symptomatic or associated with pneumothorax; chest tube drainage indicated	>1000 ml of blood evacuated; persistent bleeding (150-200 ml/hr for 2 - 4 hr); persistent transfusion indicated; elective operative intervention indicated; hospitalization	Life-threatening consequences; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pleural cavity. **Navigational Note:** -					
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the pleura. **Navigational Note:** -					
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma. **Navigational Note:** -					

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Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pneumothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated	Sclerosis and/or operative intervention indicated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormal presence of air in the pleural cavity resulting in the collapse of the lung. **Navigational Note:** -					
Postnasal drip	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by excessive mucous secretion in the back of the nasal cavity or throat, causing sore throat and/or coughing. **Navigational Note:** -					
Productive cough	Occasional/minimal production of sputum with cough	Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL	-	-
Definition: A disorder characterized by expectorated secretions upon coughing. **Navigational Note:** -					
Pulmonary edema	Radiologic findings only; minimal dyspnea on exertion	Moderate dyspnea on exertion; medical intervention indicated; limiting instrumental ADL	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death
Definition: A disorder characterized by accumulation of fluid in the lung tissues that causes a disturbance of the gas exchange that may lead to respiratory failure. **Navigational Note:** -					
Pulmonary fibrosis	Radiologic pulmonary fibrosis <25% of lung volume associated with hypoxia	Evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25 - 50% associated with hypoxia	Severe hypoxia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50 - 75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing	Death
Definition: A disorder characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnea, respiratory failure or right heart failure. **Navigational Note:** -					
Pulmonary fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the lung and another organ or anatomic site. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pulmonary hypertension	Minimal dyspnea; findings on physical exam or other evaluation	Moderate dyspnea, cough; requiring evaluation by cardiac catheterization and medical intervention	Severe symptoms, associated with hypoxia, right heart failure; oxygen indicated	Life-threatening airway consequences; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by an increase in pressure within the pulmonary circulation due to lung or heart disorder. **Navigational Note:** -					
Respiratory failure	-	-	-	Life-threatening consequences; urgent intervention, intubation, or ventilatory support indicated	Death
Definition: A disorder characterized by impaired gas exchange by the respiratory system resulting in hypoxia and a decrease in oxygenation of the tissues that may be associated with an increase in arterial levels of carbon dioxide. **Navigational Note:** -					
Retinoic acid syndrome	Fluid retention; <3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Moderate signs or symptoms; steroids indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; ventilatory support indicated	Death
Definition: A disorder characterized by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trans retinoic acid. **Navigational Note:** -					
Rhinorrhea	Present	-	-	-	-
Definition: A disorder characterized by excessive mucous secretions draining from the nose. **Navigational Note:** -					
Sinus disorder	Asymptomatic mucosal crusting; blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow; limiting instrumental ADL	Stenosis with significant nasal obstruction; limiting self care ADL	Necrosis of soft tissue or bone; urgent operative intervention indicated	Death
Definition: A disorder characterized by involvement of the paranasal sinuses. **Navigational Note:** -					
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the face, between the eyes, or upper teeth originating from the sinuses. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Sleep apnea	Snoring and nocturnal sleep arousal without apneic periods	Moderate apnea and oxygen desaturation; excessive daytime sleepiness; medical evaluation indicated; limiting instrumental ADL	Oxygen desaturation; associated with pulmonary hypertension; medical intervention indicated; limiting self care ADL	Cardiovascular or neuropsychiatric symptoms; urgent operative intervention indicated	Death
Definition: A disorder characterized by cessation of breathing for short periods during sleep. **Navigational Note:** -					
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the involuntary expulsion of air from the nose. **Navigational Note:** -					
Sore throat	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL; limiting ability to swallow	-	-
Definition: A disorder characterized by marked discomfort in the throat. **Navigational Note:** -					
Stridor	-	-	Respiratory distress limiting self care ADL; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a high pitched breathing sound due to laryngeal or upper airway obstruction. **Navigational Note:** -					
Tracheal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the trachea and another organ or anatomic site. **Navigational Note:** -					
Tracheal mucositis	Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammation or ulceration involving the mucous membrane of the trachea. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Tracheal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Stridor or respiratory distress limiting self care ADL; invasive intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the trachea. **Navigational Note:** -					
Voice alteration	Mild or intermittent change from normal voice	Moderate or persistent change from normal voice; still understandable	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology	-	-
Definition: A disorder characterized by a change in the sound and/or speed of the voice. **Navigational Note:** -					
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe respiratory symptoms limiting self care ADL; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the respiratory airways. **Navigational Note:** -					
Respiratory, thoracic and mediastinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Alopecia	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	Hair loss of >=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by a decrease in density of hair compared to normal for a given individual at a given age and body location. **Navigational Note:** -					
Body odor	Mild odor; physician intervention not indicated; self care interventions	Pronounced odor; psychosocial impact; patient seeks medical intervention	-	-	-
Definition: A disorder characterized by an abnormal body smell resulting from the growth of bacteria on the body. **Navigational Note:** -					
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10 - 30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid. **Navigational Note:** If infectious, consider Infections and infestations: Rash pustular or other site-specific infections and infestations term.					
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	-
Definition: A disorder characterized by flaky and dull skin; the pores are generally fine, the texture is a papery thin texture. **Navigational Note:** -					
Eczema	Asymptomatic or mild symptoms; additional medical intervention over baseline not indicated	Moderate; topical or oral intervention indicated; additional medical intervention over baseline indicated	Severe or medically significant but not immediately life-threatening; IV intervention indicated	-	-
Definition: A disorder characterized by skin which becomes itchy, red, inflamed, crusty, thick, scaly, and/or forms blisters. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Erythema multiforme	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10 - 30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by target lesions (a pink-red ring around a pale center). **Navigational Note:** -					
Erythroderma	-	Erythema covering >90% BSA without associated symptoms; limiting instrumental ADL	Erythema covering >90% BSA with associated symptoms (e.g., pruritus or tenderness); limiting self care ADL	Erythema covering >90% BSA with associated fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves > 90% of the body surface area. **Navigational Note:** -					
Fat atrophy	Covering <10% BSA and asymptomatic	Covering 10 - 30% BSA and associated with erythema or tenderness; limiting instrumental ADL	Covering >30% BSA; associated with erythema or tenderness; limiting self-care ADL	-	-
Definition: A disorder characterized by shrinking of adipose tissue. **Navigational Note:** -					
Hair color changes	Present	-	-	-	-
Definition: A disorder characterized by change in hair color or loss of normal pigmentation. **Navigational Note:** -					
Hair texture abnormal	Present	-	-	-	-
Definition: A disorder characterized by a change in the way the hair feels. **Navigational Note:** -					
Hirsutism	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by the presence of excess hair growth in women in anatomic sites where growth is considered to be a secondary male characteristic and under androgen control (beard, moustache, chest, abdomen). **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hyperhidrosis	Limited to one site (palms, soles, or axillae); self care interventions	Involving >1 site; patient seeks medical intervention; associated with psychosocial impact	Associated with electrolyte/hemodynamic imbalance	-	-
Definition: A disorder characterized by excessive sweating. **Navigational Note:** Synonym: Night sweats, diaphoresis					
Hyperkeratosis	Present	-	Limiting self-care ADLs	-	-
Definition: A disorder characterized by a thickening of the outer layer of the skin. **Navigational Note:** -					
Hypertrichosis	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal	Increase in length, thickness or density of hair at least on the usual exposed areas of the body (face (not limited to beard/moustache area) plus/minus arms) that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race. **Navigational Note:** -					
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death
Definition: A disorder characterized by reduced sweating. **Navigational Note:** -					
Lipohypertrophy	Asymptomatic and covering <10% BSA	Covering 10 - 30% BSA and associated tenderness; limiting instrumental ADL	Covering >30% BSA and associated tenderness and narcotics or NSAIDs indicated; lipohypertrophy; limiting self care ADL	-	-
Definition: A disorder characterized by hypertrophy of the subcutaneous adipose tissue at the site of multiple subcutaneous injections of insulin. **Navigational Note:** -					
Nail changes	Present	-	-	-	-
Definition: A disorder characterized by a change in the nails. **Navigational Note:** -					

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Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Nail discoloration	Asymptomatic; clinical or diagnostic observations only	-	-	-	-
Definition: A disorder characterized by a change in the color of the nail plate.					
Navigational Note: -					
Nail loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by loss of all or a portion of the nail.					
Navigational Note: -					
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by vertical or horizontal ridges on the nails.					
Navigational Note: -					
Pain of skin	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the skin.					
Navigational Note: -					
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self care ADL	-	-
Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet. Also known as Hand-Foot Syndrome.					
Navigational Note: -					
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity of the skin to light.					
Navigational Note: -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Widespread and constant; limiting self care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	-	-
Definition: A disorder characterized by an intense itching sensation. **Navigational Note:** -					
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow color. **Navigational Note:** -					
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back. **Navigational Note:** -					
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritis. **Navigational Note:** -					

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Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the skin covering the top and the back of the head. **Navigational Note:** -					
Skin atrophy	Covering <10% BSA; associated with telangiectasias or changes in skin color	Covering 10 - 30% BSA; associated with striae or adnexal structure loss	Covering >30% BSA; associated with ulceration	-	-
Definition: A disorder characterized by the degeneration and thinning of the epidermis and dermis. **Navigational Note:** -					
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by darkening of the skin due to excessive melanin deposition. **Navigational Note:** -					
Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by loss of skin pigment (e.g., vitiligo). **Navigational Note:** -					
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by an area of hardness in the skin. **Navigational Note:** -					
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the skin. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes. **Navigational Note:** -					
Subcutaneous emphysema	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by air in the subcutaneous tissue. **Navigational Note:** -					
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >=10% BSA; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by local dilatation of small vessels resulting in red discoloration of the skin or mucous membranes. **Navigational Note:** -					
Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death
Definition: A disorder characterized by greater than 30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes. **Navigational Note:** -					
Urticaria	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	-	-
Definition: A disorder characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Skin and subcutaneous tissue disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: -					
Navigational Note: -					

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Social circumstances					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Social circumstances - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: -					
Navigational Note: -					

Surgical and medical procedures					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Surgical and medical procedures - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: -					
Navigational Note: -					

Vascular disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Arterial thromboembolism	-	-	Urgent intervention indicated	Life-threatening consequences; hemodynamic or neurologic instability; organ damage; loss of extremity(ies)	Death
Definition: A disorder characterized by occlusion of an arterial vessel by a blood clot that develops in an artery. **Navigational Note:** Consider Nervous system disorders: TIA or Stroke for CNS-related events or Cardiac disorders: Myocardial infarction					
Capillary leak syndrome	Asymptomatic	Symptomatic; medical intervention indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of intravascular fluids into the extravascular space. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. It can lead to generalized edema and multiple organ failure. **Navigational Note:** -					
Flushing	Asymptomatic; clinical or diagnostic observations only	Moderate symptoms; limiting instrumental ADL	Symptomatic, associated with hypotension and/or tachycardia; limiting self care ADL	-	-
Definition: A disorder characterized by episodic reddening of the skin, especially face, neck, or chest. **Navigational Note:** -					
Hematoma	Mild symptoms; intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the wall of a blood vessel. **Navigational Note:** -					
Hot flashes	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an uncomfortable and temporary sensation of intense body warmth, flushing, sometimes accompanied by sweating upon cooling. **Navigational Note:** -					

Vascular disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypertension	**Adult:** Systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg; **Pediatric:** Systolic/diastolic BP >90th percentile but< 95th percentile; **Adolescent:** BP ≥120/80 even if < 95th percentile	**Adult:** Systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg; monotherapy indicated initiated; **Pediatric and adolescent:** Recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated; systolic and /or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile; **Adolescent:** Systolic between 130-139 or diastolic between 80-89 even if < 95th percentile	**Adult:** Systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated; **Pediatric and adolescent:** Systolic and/or diastolic > 5 mmHg above the 99th percentile	**Adult and Pediatric:** Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death
Definition: A disorder characterized by a pathological increase in blood pressure. **Navigational Note:** -					
Hypotension	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated; hospitalization indicated	Life-threatening consequences and urgent intervention indicated	Death
Definition: A disorder characterized by a blood pressure that is below the normal expected for an individual in a given environment. **Navigational Note:** -					
Lymph leakage	-	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the loss of lymph fluid into the surrounding tissue or body cavity. **Navigational Note:** -					

Vascular disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Lymphedema	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by excessive fluid collection in tissues that causes swelling. **Navigational Note:** -					
Lymphocele	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by a cystic lesion containing lymph. **Navigational Note:** -					
Peripheral ischemia	-	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characterized by impaired circulation to an extremity. **Navigational Note:** -					
Phlebitis	-	Present	-	-	-
Definition: A disorder characterized by inflammation of the wall of a vein. **Navigational Note:** -					
Superficial thrombophlebitis	-	Present	-	-	-
Definition: A disorder characterized by a blood clot and inflammation involving a superficial vein of the extremities. **Navigational Note:** -					
Superior vena cava syndrome	Asymptomatic; incidental finding of SVC thrombosis	Symptomatic; medical intervention indicated (e.g., anticoagulation, radiation or chemotherapy)	Severe symptoms; multi-modality intervention indicated (e.g., anticoagulation, chemotherapy, radiation, stenting)	Life-threatening consequences; urgent multi-modality intervention indicated (e.g., lysis, thrombectomy, surgery)	Death
Definition: A disorder characterized by obstruction of the blood flow in the superior vena cava. Signs and symptoms include swelling and cyanosis of the face, neck, and upper arms, cough, orthopnea and headache. **Navigational Note:** -					

Vascular disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Thromboembolic event	Medical intervention not indicated (e.g., superficial thrombosis)	Medical intervention indicated	Urgent medical intervention indicated (e.g., pulmonary embolism or intracardiac thrombus)	Life-threatening consequences with hemodynamic or neurologic instability	Death
Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream. **Navigational Note:** Consider Nervous system disorders: TIA or Stroke for CNS-related events. Use Vascular disorders: Arterial thromboembolism for arterial thrombi.					
Vasculitis	Asymptomatic, intervention not indicated	Moderate symptoms, medical intervention indicated	Severe symptoms, medical intervention indicated (e.g., steroids)	Life-threatening consequences; evidence of peripheral or visceral ischemia; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the wall of a vessel. **Navigational Note:** -					
Vascular disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					