ADVANCED CARDIAC THERAPIES IMPROVING OUTCOMES NETWORK

Ventricular Assist Device Adverse Events

Definitions

action

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Introduction

Goal:
Harmonize AE definitions among the new pediatric ECMO-CENTRAL AE definitions, adult MCS AE definitions, and our current Intermacs/ACTION definitions, and/or adjust them for specific issues unique to children and congenital heart disease to optimize pediatric VAD patient management.

Process:
The AE definition changes were first drafted using the data from ACTION adjudication, learnings from our pediatric device trials and in person and virtual stakeholder meetings. Consensus was obtained by a broad stakeholder group that included representation from industry, regulatory bodies, clinical trial specialists, nursing and physicians (cardiothoracic surgery, cardiology, intensive care, neurology, hematology and infectious disease). There will be future revisions at set time points.

Adverse Event definition:
An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical/therapeutic product, irrespective of whether there is a causal relationship between the occurrence and the therapy.

Serious Adverse Event (SAE) definition:
An SAE is defined as any untoward medical occurrence that meets **any** of the following:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- requires medical or surgical intervention to prevent one of the above.

SAEs will be a subset of the below adverse events.

Further AE Categorization

Adverse Event Relatedness:

The AE definitions will be broadly categorized into 2 categories; Device/Procedure Related or Patient/Treatment AE. Any event can be categorized into either, but there will be an attempt to categorize some AEs as **always** device/procedure related. This will lead to a more efficient process when submitting AEs to regulatory bodies during future trials.

- Device/Procedure AEs (most probably related):
  The AE was a direct consequence of either the medical device or the procedure required to implant the device and would not have plausibly occurred in the absence of the device/procedure. An example would be device malfunction, even if it is deemed due to user error.
- Patient/Treatment AEs (most probably related):
  The AE was a direct consequence of the underlying clinical condition of the patient, including organ dysfunction and its consequences, and of the treatment being provided to the patient, including treatment provided to support a medical device.

Adverse Event Grade:

Each AE will have grades that will be used to determine seriousness. This will take the place of the minor and major classification. Not all grades will require additional data field collection. **An adverse event should be assigned the highest applicable grade during the duration of the event.** If an adverse event resolves and then another adverse event of the same type occurs, this should be considered an additional adverse event.

Grade 1 - **Mild** - Intervention not indicated.

Grade 2 - **Moderate** - Minimal or local or noninvasive intervention.

Grade 3 - **Severe** - Significant intervention for non-life threatening medical condition.

Grade 4 - **Life Threatening** - Significant and urgent intervention for life-threatening condition.

Grade 5 - **Fatal** - Death resulting from AE

Note: In the event of a patient death, the clinical team should assign the adverse event that was the most likely cause of death. This assignment may, at times, be ambiguous but the primary adverse event should be selected when that can be determined.

Adverse Event Resolution:

In most instances, an adverse event should be considered resolved when it has decreased in grade by one or more grades for at least 24 hours (or when the criteria for the grade are no longer met for 24 hours if there is no lower grade defined). Examples:

1. Grade 4 ischemic stroke treated with transcatheter thrombectomy is considered resolved on the day following the procedure (assuming that no further procedures are performed for the same stroke).
2. Grade 3 ischemic stroke treated with addition of new anti-epileptic therapy is considered resolved 24 hours after the medication has been started (and no other medications are being added for the same event), since no new medications are being introduced and the event would then downgrade to Grade 2 but will not be re-reported.
3. Grade 3 ischemic stroke treated with temporary inactivation of heart transplant listing will be considered resolved 24 hours after listing status is re-activated, although the clinical recovery is ongoing.
4. Grade 3 intra-pleural hemorrhage requiring blood transfusion and placement of pleural drain, should be considered resolved when transfusions are completed, and no new tubes are placed (even if there are tubes remaining in place).
5. Grade 2 pump thrombosis of paracorporeal device (treated with exchange of external component), will be considered resolved 24 hours after the procedure is performed.

Hematologic Events

1. Neurological Events

Timing: Identified anytime during VAD support, after leaving the OR/catheterization laboratory of the index procedure

Reporting: Each event will have an associated category, type, grade and severity

Categories of Neurological Events

Overt neurological event occurs when any of the following occurs:

- Neurological exam findings are discovered and are associated with abnormal neuroimaging or pathology.
- Neurological exam findings are present for >24 hours (documented in medical record by a neurologist) but neuroimaging and/or pathology is negative.
- Neurological exam findings are present for >24 hours (documented in medical record by a neurologist) but neuroimaging is unable to be obtained.

Notes:

1) In pediatrics, signs and symptoms may be non-localizing.
2) If there is discordance between the neuroimaging and exam findings, this will be regarded as a single event (e.g., if the patient has a left sided weakness but the imaging shows an infarct distribution that does not correlate).

Covert neurological event occurs when:

- Neurological exam findings are not present, but injury is detected by abnormal neuroimaging or pathology. This includes incidental findings on surveillance imaging.

Types of Neurological Events

- **Ischemic Stroke**
  - Ischemic stroke
  - Hemorrhagic conversion from an initial ischemic stroke
- **Intracerebral hemorrhage (blood in the brain or spinal cord)**
  - Intraventricular
  - Parenchymal
  - Spinal cord
- **Extra-axial Hemorrhage (blood around the brain or spinal cord)**
  - Epidural
  - Subdural
  - Subarachnoid
- **Undefined Type:** If there is an overt injury but no neuroimaging obtained or negative. Type unable to be defined (e.g., type of stroke can't be determined without imaging).
- **Hypoxic ischemic encephalopathy**: New encephalopathy attributed to hypoxia or cerebral hypoperfusion. Supporting findings include diffuse encephalopathy without

focal neurologic exam findings or pathology and/or neuroimaging in a non-vascular distribution.
- **Encephalopathy (other):** Non-focal neurological exam findings that may be associated with many patient-associated factors. Must have a neurology consultation and documentation in medical record (e.g., Fontan with Fontan Associated Liver Disease (FALD) that leads to encephalopathy post procedure).
- **Neuropathy**: Neuropathy due to a mechanical complication of a transcatheter placed VAD. This includes femoral, sciatic, or brachial injury.

Grade of Neurological Event

Grade 1: Not applicable

Grade 2: Neurological event requiring **no modification** in patient management (e.g., no antiepileptic started, no discontinuation or addition of an antithrombotic agent or no change in transplant listing status)

Grade 3: Neurological event resulting in 1 or more of **the following modifications** in patient management:
- New antiepileptic medication initiated
- Discontinuation of any antithrombotic therapy for > 24 hours or addition of a new antithrombotic agent
- Change in transplant listing status

Grade 4: Neurosurgical or interventional procedure performed

Grade 5: Death resulting directly or primarily from a neurological event

Severity of Stroke Sequelae

To assess stroke severity, the Pediatric Cerebral Performance Category (PCPC) scores will be used. The PCPC can be measured retrospectively from medical chart review from baseline (prior to event) and at a defined time (e.g., VAD explant). The delta from baseline score, prior to event, and at conclusion of VAD support will determine the severity of the sequelae (e.g., If the patient is a 2 prior to the stroke and a 4 at VAD explant the patient will be categorized as severe decline).

Neurological sequelae	**Delta in PCPC from prior to neurological event to discharge**
No change from baseline	No change in PCPC
Moderate decline	1-point increase in PCPC
Severe decline	2-point increase in PCPC
Fatal	PCPC 6 or brain death

The Pediatric Cerebral Performance Category Scale*

SCORE	CATEGORY	BRIEF DESCRIPTION
1	Normal	Age-appropriate level of functioning In preschool-aged children, appropriate development In school-aged children, attendance in regular
2	Mild Disability	Can interact at an age-appropriate level Minor neurologic disease that is controlled and does not interfere with daily functioning (eg, seizure disorder) In preschool aged children, possibly minor developmental delays, but with > 75% of all daily living developmental milestones above the 10th percentile In school-aged children, attendance in regular school but may be in a grade that is not appropriate for age
3	Moderate Disability	Below age-appropriate functioning Neurologic disease that is not controlled and severely limits activities In preschool-aged children, most daily living developmental milestones below the 10th percentile In school-aged children, can do ADLs but attend special classes because of cognitive difficulties or a learning deficit
4	Severe Disability	In preschool-aged children, ADL milestones below the 10th percentile and excessive dependence on others for ADLS In school-aged children, possibly severe impairment that prevents school attendance and dependence on others for ADLS In preschool-aged and school-aged children, possibly abnormal motor movements, including nonpurposeful, decorticate, or decerebrate responses to pain
5	Coma or vegetative state	Unawareness
6	Death	—

** Worst level of performance for any single criterion is used for categorizing. Deficits are scored only if they result from a neurologic disorder. Assessments are based on medical records or an interview with the caretaker.*

Adapted from Fiser DH. Assessing the outcome of pediatric intensive care. *J Pediatr* 121(1):68-74, 1992. doi:10.1016/s0022-3476(05)82544-2

ADLs = activities of daily living.

2. Bleeding

Timing: Identified any time after the index procedure if it leads to a reoperation (grade 4). All other bleeding events are identified after 72 hours leaving the OR/Catheterization laboratory of the index procedure.

Reporting: Each event will have an associated location and grade

Location of Bleeding:

- Gastrointestinal
- Nasal/Oral Bleeding
- Pleural/Mediastinal
- Pericardial
- Pulmonary
- Genitourinary
- Cannula/driveline/percutaneous site bleeding
- Retroperitoneal
- Other

Grade of Bleeding

Grade 1: Not applicable

Grade 2: Bleeding that requires **any** of the following (after 72 hours):

- Local packing/dressing of any nature or duration
- Superficial cautery
- Use of local (topical) hemostatic agents

Grade 3: Bleeding that requires **any** of the following (after 72 hours):

- Blood (PRBC) transfusion, of any amount, as a result of the bleeding event. Does not include pre-existing anemia (per the treating provider)
- New percutaneous/surgical drain (e.g., chest or abdominal) placement
- Discontinuation of all anticoagulation for >24 hours, if it had already been started

Grade 4: Bleeding leading to an invasive procedure, **anytime** after leaving OR, to control bleeding (e.g., surgical exploration and/or transcatheter embolization)

Grade 5: Death resulting directly or primarily from bleeding

3. Hemolysis

Timing: Identified during VAD support

Reporting: Each event will have an associated grade

Laboratory criteria for hemolysis is met if **any** of the following is present, on 2 consecutive, separate lab draws:

- Plasma Free Hgb > 50 mg/dl with easy free flowing lab draw.
- LDH > 3x above upper limit of normal for implanting center, in the absence of an alternative explanation for the elevation (e.g., infection, hepatic or pulmonary dysfunction, red cell transfusion/transfusion reaction). Attribution of the reason for LDH elevation is a judgement by the treating provider.
- Moderate or greater hemolyzed cells on direct visualization of smear (unrelated to hemolyzed blood products administration).

Grade of Hemolysis

Grade 1: Not applicable

Grade 2: Isolated laboratory criteria without other clinical findings

Grade 3: Laboratory criteria met, and **any** of the following:

- Anemia requiring a transfusion of PRBC, with hemolysis being the main indication per a treating provider, of any amount
- Exchange of external paracorporeal pump or associated device components with hemolysis being the main indication per the treating provider

Grade 4: Laboratory criteria for hemolysis met, and **any** of the following:

- Surgical exchange of intracorporeal pump with hemolysis being the main indication per the treating provider
- Acute kidney injury attributed by hemolysis by the treating provider and requiring RRT

Grade 5: Death resulting directly or primarily from hemolysis

Device Related Events

1. Pump Thrombus (includes all device components)

Timing: Identified anytime during VAD support, after leaving the OR/catheterization laboratory, of the index procedure

Reporting: AE applies to pump thrombus that results in device component exchange. Each event will have an associated type, device component(s), and grade.

Type of Pump Thrombus

- Paracorporeal/transcatheter device and components: Pump thrombus AE criteria will be met if reason for exchange is secondary to thrombus/fibrin formation, documented in the medical record by the treating provider. Multiple device components can be exchanged during one procedure and count as one AE.

*Note: Paracorporeal device exchange will be categorized as pump thrombus if the pump is exchanged **due to thrombus/fibrin**, but the pump is functioning appropriately. If the device is not functioning appropriately, the exchange will qualify as a device malfunction AE.*

- Intracorporeal devices: Pump thrombus AE criteria will be met if reason for exchange is secondary to 2 or more of the following:
  - Unexpected device function or parameter changes outside of normal variability attributed to thrombus by the treating provider
  - Signs of inadequate cardiovascular support or an embolic event that is attributed to thrombus by the treating provider
  - Hemolysis that is attributed to thrombus in the device by the treating provider
  - Confirmed thrombus in an intracorporeal device, by direct visualization after explant and/or by non-invasive imaging

Note: Multiple AE definitions may be met (e.g., if there is hemolysis leading to concern for pump thrombosis and pump exchange, the AE criteria for hemolysis may be met as well).

Device Component (s)

- Pump
- Tubing
- Connectors
- Inflow Cannula
- Outflow cannula

Grade of Pump Thrombosis

Grade 1: Not applicable

Grade 2: Pump thrombus **without** clinical findings of embolization but that prompts treating team to replace an external device component

Grade 3: Pump thrombus **with** clinical findings of embolization (i.e., stroke AE) that prompts treating team to replace an external device component

Grade 4: Pump thrombus **with or without** clinical findings of embolization (i.e., stroke AE), leading to surgical or transcatheter replacement of an internal device component (e.g., paracorporeal cannula replacement or intracorporeal pump)

Grade 5: Death resulting directly or primarily from pump thrombosis or attempted treatment of pump thrombus

2. Device Malfunction (includes all device components)

Timing: Device is not functioning at the manufacturer's specifications. Identified anytime during or after the OR/catheterization laboratory of the index procedure. If the device is not yet implanted it will be a manufacturer complaint*, not an AE.

Reporting: Each event will have an associated location, type and grade

Report all device malfunction AEs even if it is secondary to user error or human factors (e.g., non-FDA approved accessories, leading to overheating or damage). This does not include routine device maintenance.

Location of Device Malfunction

- Pump
- Oxygenator
- Power (IKUS, C2 Driver, Mobile Driver)
- Accessories (Flow Probe, Batteries, Monitor)
- Tubing/Connectors
- Other

Type of Device Malfunction

- Mechanical failure- A mechanical fault in any component (e.g., controller overheating)
- Structural failure- A structural component loses integrity (e.g., membrane or cannula rupture)
- Device or component dysfunction- Device not working as it is expected (e.g., battery not charging)
- None- Device functioning properly but exchanged due to concern

Grade of Device Malfunction

Grade 1: Not applicable

Grade 2: Device must **be functioning properly** and have one of the following:

- Non-routine device alert/alarm requiring reset of device or change of power source or service. Device function fully preserved (e.g., defective battery or external power source alarm that requires change of external power component, S4 alarm)
- Non-routine replacement or repair of an **external** paracorporeal pump or device components. Device functioning properly (e.g., sound from pump, abnormal membrane appearance, cannula issue other than thrombus)

Grade 3: Device **not working properly** **without** clinical symptoms of congestion or low cardiac output. Treatment required includes either of the following:

- Non-routine replacement or repair of an **external** paracorporeal/percutaneous device component. This includes changing the external pump components or tubing if not functioning properly (e.g., abnormal membrane, cannula or tubing crack or tear)
- Non-routine replacement or repair of an intracorporeal device's **external** component if not functioning properly (e.g., driveline repair or controller failure)

Grade 4: Device **not working properly** and either of the following are required:

- Patient **with** clinical symptoms and requires the initiation of vasoactive infusions, deemed to be due to device malfunction by treating team. Additional treatment required includes **one** of the following:
  - Non-routine replacement or repair of an **external** paracorporeal/transcatheter device component (e.g., membrane rupture, cannula or tubing crack or tear)
  - Non-routine replacement or repair of an **external** intracorporeal device component (e.g., driveline repair or controller failure)
- Patient may be **with or without** clinical symptoms and requires surgical replacement of an internal device component (e.g., intracorporeal device or cannula issue involving internal component)

Grade 5: Death resulting directly or primarily from device malfunction

Note: A paracorporeal pump or device component replacement for a problem with the pump or a device component, not related to thrombus, will be classified as a device malfunction (e.g., valve or membrane issue). If the exchange is due to pump thrombus, but the device works properly, it will be meet the pump thrombus AE.

Infection Events

1. Device-Specific Infections

Timing: Identified during VAD support any time after leaving the OR/catheterization laboratory, of the index procedure

Reporting: Each event will have an associated type of infection and grade

Type of Infection

- Superficial driveline/cannula or peripheral cannulation site infection:
  Blood culture must be negative and at least **one** of the following criteria must be present:
  - Purulence from driveline/cannula/percutaneous site with or without positive culture
  - Pain, erythema or induration at driveline/cannula/percutaneous site

- Deep percutaneous driveline/cannula or peripheral cannulation site infection:
  Must meet the above criteria *(Superficial driveline/cannula or peripheral cannulation site infection)* and at least **two** of the following criteria:
  - Fluid collection at driveline/cannula/percutaneous site with or without positive culture
  - Imaging study consistent with deep infection (e.g., fluid collection or findings consistent with infection along the path of the lead)
  - Signs or symptoms such as fever, leukocytosis, tachycardia or systemic inflammatory response

- Device-specific bloodstream infection:
  Positive blood culture associated with signs and symptoms of systemic inflammatory response and one of the following:
  - Deep percutaneous driveline/cannula or peripheral cannulation site infection.
  - Positive blood culture from the device circuit
  - Persistently positive blood culture with the same organism >72 hours apart
  - Radiographic or echocardiographic evidence of vegetation or thrombus of the intravascular aspect of the device component

- Sternal Wound Infection with Extension into Mediastinum:
  An infection that involves the external components of the pump (e.g., cannulas for paracorporeal devices or external housing for intracorporeal devices). Must have all of the following:
  - Positive culture from the tissue or fluid collection surrounding the external surface of the pump or cannula
  - Signs and symptoms of infection such as fever, leukocytosis, tachycardia or other signs of systemic inflammatory response

Grade of Infection

Grade 1: Superficial infections that require only an increase in the frequency of dressing changes, use of an antimicrobial dressing or addition of topical antimicrobials

Grade 2: Superficial infections, **with no** systemic findings (e.g., fever, leukocytosis, tachycardia or other signs of systemic inflammatory response) and treatment with enteral antimicrobials for > 72 hours

Grade 3: Either of the following:

- Superficial infections, **with** systemic findings (e.g., fever, leukocytosis, tachycardia or other signs of systemic inflammatory response) and treatment with IV/IM antimicrobials for > 72 hours
- Superficial infections, **with or without** systemic findings (e.g., fever, leukocytosis, tachycardia or other signs of systemic inflammatory response) requiring one of the following
    - External device component exchange for infection
    - Driveline/cannula site incision/drainage
    - Long-term therapy (>4weeks) with IV or oral antimicrobials

Grade 4: Deep device infection resulting in at least one of the following:

- Internal device component exchange
- Surgical/invasive procedure performed for presumed deep device infection (e.g., sternum opened for wash out, chest tube to drain purulence)
- Persistent, 3 or more positive cultures with the same organism over 7 days, necessitating long term (> 4 weeks) of IV antimicrobials

Grade 5: Death resulting directly or primarily from device-specific infection

2. Non-Device Related Infections

Timing: Identified any time after leaving the OR/catheterization laboratory, of the index procedure

Reporting: Each event will have an associated type of infection and grade

Type of Non-Device Related Infections:

- Viral upper/lower respiratory infection
- Viral gastroenteritis
- Sternal wound infection without extension into mediastinum; involves the superficial mediastinal or thoracotomy wound involving the skin, subcutaneous fat and muscle at surgical site
- Pneumonia (characteristic radiographic abnormalities and clinical findings)
- UTI (clinical suspicion and positive culture)
- Central line infection
- Other

Grade of Non-device Related Infections

Grade 1: Infections that require observation only. This also includes short term (rule-out) use, < 72 hours, of antimicrobial agents.

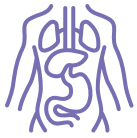
Grade 2: Infections treated with primarily **enteral** antimicrobial therapies for >72 hours and/or admission to the hospital for observation

Grade 3: Infections requiring **IV/IM** antimicrobial therapies for >72 hours and/or fluid bolus resuscitation <40mL/kg in 24 hours

Grade 4: Infection requiring **IV/IM** antimicrobials and resulting in at least one of the following:

- Fluid bolus resuscitation with >/= 40 ml/kg in 24 hours
- Initiation of vasoactive infusions for sepsis to prevent or support end-organ dysfunction per treating team
- Surgical or invasive treatment

Grade 5: Death resulting directly or primarily from non-device related infection



End-Organ Failure Events

1. Right Heart Dysfunction *(only in biventricular circulation)*

Timing:
- Identified any time after the index operation, if RVAD or ECMO is needed
- If only medical management required, criteria can be met any time after 10 days of leaving the OR/catheterization laboratory of the index procedure

Reporting: Each event will have an associated grade

One finding from both the hemodynamics and imaging categories, must be met, **>10 days** after the index operation, in the presence of a properly functioning LVAD:

- Hemodynamics:
  - Right sided or systemic venous filling pressure elevated above 14 mmHg >24 hours
  - Clinical evidence of high CVP (e.g., effusions, ascites, hepatomegaly) in the setting of inadequate delivery of preload to the LVAD (calculated CO that is <50% expected, not responsive to pump parameter changes)
- Imaging:
  - Moderate/Severe TR
  - Moderate/severely reduced RV systolic function, documented in medical record

OR

One of the following must be met, **any time** after the index operation, in the presence of properly functioning LVAD:
- Transition to ECMO (for right sided failure)
- Implantation of an RVAD

Grade of Right Heart Failure

Grade 1: Not applicable

Grade 2: Not applicable

Grade 3: Use of vasoactive infusions and/or one or more of the following per treating provider **>10 days post procedure**:
- New invasive management of effusions/ascites
- Inability to remove surgical drains due to the need to treat right heart failure manifestations

Grade 4: Use of ECMO for right heart failure or implantation of RVAD as separate procedure anytime

Grade 5: Death resulting directly or primarily from right heart failure

2. Renal Dysfunction

Timing: Identified any time after the index procedure

Reporting: Each event will have an associated grade

To define renal dysfunction, one of the following laboratory values, on 2 consecutive, separate lab draws will be assessed:

- Creatinine
- GFR calculated by either Cystatin C or modified Schwartz or CKiD

Grade of Renal Dysfunction (Acute)

Grade 1: Not applicable

Grade 2: Peak Cr to 2–3x baseline* or an eGFR of 35-60 mL/min per 1.73 m^2 on 2 consecutive lab draws

Grade 3: Peak Cr to >/= 3x baseline* or eGFR < 35mL/min per 1.73 m^2 on 2 consecutive lab draws

Grade 4: New requirement for renal replacement therapy following VAD index operation

Grade 5: Death resulting directly or primarily from acute kidney disease

**Baseline = last lab draw, before the index operation*

3. Hepatic Dysfunction

Timing: Identified any time after leaving the OR/catheterization laboratory, of the index procedure

Reporting: Each event will have an associated grade

Presence of at least **TWO** of the following laboratory abnormalities on 2 sequential lab draws:

- Total Bilirubin >3x the upper limit of normal at the implanting center **or,** if elevated prior to implant, 3x baseline*
- Coagulopathy – INR >3 and not attributable to antithrombotic therapy, dilution or Vitamin K deficiency
- AST and/or ALT >3x the upper limit of normal at the implanting center (not attributable to hemolysis, myositis, rhabdomyolysis) **or,** if elevated prior to implant, 3x baseline*
- Hepatic encephalopathy, diagnosed by neurologist

*Baseline = last lab draw, before the index operation

Grade of Hepatic Dysfunction

Grade 1: Not applicable

Grade 2: Laboratory criteria (as stated above)

Grade 3: Laboratory findings (as stated above) and/or:

- Hepatic encephalopathy
- Liver associated coagulopathy (as stated above) requiring administration of cryoprecipitate, FFP, and/or other clotting factor preparations

Grade 4: Hepatic encephalopathy requiring mechanical ventilation, deemed to be liver related by treating team, and/or need for hepatic replacement therapy (MARS)

Grade 5: Death resulting directly or primarily from hepatic failure

4. Respiratory Dysfunction

Timing:

- Addition of ECMO, oxygenator, and/or tracheostomy placement **anytime during VAD support**
- New escalation in PPV (non-invasive or invasive) respiratory support, **unrelated to diagnostic or therapeutic procedure, > 10 days post-implant**

Respiratory dysfunction related to infectious etiologies should be coded under Non-Device Related Infections AE

Reporting: Each event will have an associated grade

Grade of Respiratory Dysfunction

Grade 1: Not applicable

Grade 2: Respiratory dysfunction, >10 days after index procedure, requiring **new** requirement of non-invasive PPV (CPAP or BiPap). Does not include pre-VAD prescribed PPV or night PPV.

Grade 3: PPV via endotracheal intubation or pre-existing tracheostomy >10 days after index procedure for >24 hours

Grade 4: Use of ECMO for oxygenation or addition of oxygenator to VAD circuit, and/or insertion of durable tracheostomy **any time** after index procedure

Grade 5: Death resulting directly or primarily from respiratory causes

5. Vasoplegia

Timing: Low SVR state within 72 hours of leaving the OR/catheterization laboratory of the index procedure

Reporting: Each event will have an associated grade

One additional finding, must be met, **within 72 hours** after the index operation, in the presence of a properly functioning VAD:

- Severe hypotension for age, with an elevated or normal device flow (CI > 2.4 L/min/m^2) directly measured or calculated by device and without alternate cause (e.g.,, bleeding, sepsis, right heart failure, anaphylaxis, anatomic issues).
- End-organ hypoperfusion and new kidney and liver dysfunction (as defined by the AE definitions grade 3 and higher)

Grade of Vasoplegia

Grade 1: Not Applicable

Grade 2: Not applicable

Grade 3: Use of 3 or more vasoconstrictors (in the presence of hypotension and a normal or elevated CI) attributed to vasoplegia by the treating provider

Grade 4: Use of 3 or more vasoconstrictors (in the presence of hypotension and a normal or elevated CI) attributed to vasoplegia by the treating provider and any **one** of the following:

- ECMO initiation
- Distal extremity necrosis requiring surgical treatment

Grade 5: Death related directly or primarily to vasoplegia and the direct circulatory consequences

Gastrointestinal Events

1. Feeding Intolerance

Timing: Feeding intolerance occurs if the patient is not taking adequate (per defined individual patient goal), daily caloric demands enterally >10 days from the initial device implantation

Reporting: Each event will have an associated grade

If feeding intolerance occurs in association with a prior GI anatomic abnormality, that explains the feeding intolerance, this should not be recorded as an AE. Feeding intolerance secondary to another AE such as chylous effusion, NEC or GI bleeding, does not meet criteria.

Grade of Feeding Intolerance

Grade 1: Not applicable

Grade 2: Caloric goal is met with combination of enteral intake and TPN/IL

Grade 3: TPN/IL dependence without enteral intake

Grade 4: Any **one** of the following:
- TPN/IL dependence with evidence of TPN cholestasis defined as elevated conjugated bilirubin > 2x upper limit of normal
- The patient is not meeting caloric needs by any route

Grade 5: Not applicable for this definition

2. Chylothorax

Timing: Identified any time after leaving the OR/catheterization laboratory of the index procedure

Reporting: Each event will have an associated grade

Chylothorax is defined as an effusion (pleural or peritoneal) which has **any** of the following properties:

- Triglyceride level > 110mg/mL
- Serum triglyceride concentration < pleural triglyceride concentration
- Lymphocyte % count >80% of all cells in the pleural fluid

Grade of Chylothorax

Grade 1: Not applicable

Grade 2: Patient made NPO for > 72 hours specifically for chylothorax management

Grade 3: Patient NPO and/or intravenous or subcutaneous medication (e.g., Octreotide) and/or new chest tube placed to treat chylothorax

Grade 4: Surgical intervention performed to treat chylothorax

Grade 5: Death resulting directly or primarily from chylothora

3. Necrotizing Enterocolitis (NEC)

Timing: Identified any time after leaving the OR/catheterization laboratory of the index procedure

Reporting: Each event will have an associated grade

Necrotizing enterocolitis is diagnosed by Modified Bell Criteria if **both** of the following criteria are met:

- Intestinal dilation, pneumatosis intestinalis, pneumoperitoneum or portal gas on abdominal imaging
- **AND TWO** or more of the following:
  - Temperature instability
  - Apnea/Bradycardia
  - Grossly bloody stool
  - Thrombocytopenia or DIC deemed by the treating team to be abdominal in origin
  - Abdominal distension with or without tenderness

Grade of NEC

Grade 1: Not applicable

Grade 2: Not applicable

Grade 3: NEC requiring medical management only (e.g., antibiotics for >72 hours, and/or NPO status for >72 hours for presumed NEC)

Grade 4: NEC requiring surgical treatment

Grade 5: Death resulting directly or primarily from NEC or complications of NEC

***Note:** NEC is considered an Infection, therefore, you **DO NOT** need to enter a separate non-device related infection AE for a patient with confirmed NEC.*

Inadequate Support

1. Inadequate Hemodynamics After VAD

Timing: Identified any time after 10 days of the index operation, or if inadequate hemodynamics resulted in death before 10 days

Reporting: Each event will have an associated etiology, and grade

After implantation of any combination of VAD (LVAD, RVAD, BIVAD, TAH or SVAD), evidence of inadequate hemodynamics or systemic perfusion and/or ongoing congestion, in the presence of a properly functioning device, persisting either beyond 10 days from the initial device implantation or resulting in death before 10 days (deemed by the treating provider to be due to inadequate VAD support), recognized by **one** of the following:

- Ongoing treatment with any vasoactive infusion (excluding any other explanation for the vasoactive medication), including milrinone, and new onset or lack of improvement in pre-existing end-organ dysfunction by 10 days post op. For this definition, end-organ dysfunction is defined by AE definitions grade 3 and higher. At least **two** of the following end-organ AEs must be met:
  - Respiratory
  - Hepatic
  - Renal
  - Feeding intolerance

  Note: Complete corresponding end-organ failure AE

Grade of Inadequate Hemodynamics following VAD Implant

Grade 1: Not applicable

Grade 2: Not applicable

Grade 3: Criteria for inadequate hemodynamic support following VAD are met but end-organ dysfunction consists solely of abnormal laboratory values (no invasive therapy required) and patient is stabilized with use of vasoactive medications

Grade 4: Criteria for inadequate hemodynamic support following VAD are met and at least one of the following new end-organ replacement therapies is required or existing end-organ therapy is ongoing after 10 days:

- Renal replacement therapy
- Hepatic replacement therapy
- Mechanical ventilation
- Full TPN dependence

Grade 5: Death resulting directly or primarily from inadequate hemodynamics following VAD support

2. Fontan Venous Failure After SVAD

Timing:

- Transition to ECMO or addition of Fontan Venous (right sided) VAD anytime during VAD support
- >10 days after leaving the OR/catheterization laboratory of the index procedure worsening clinical evidence of high venous pressures (e.g., effusions, ascites, lymphatic dysfunction) in the setting of inadequate delivery of preload to the SVAD (CO <50% than expected and unresponsive to parameter changes)

Reporting: Each event will have an associated grade

Grade of Fontan Venous Failure

Grade 1: Not applicable

Grade 2: After 10 days from index operation, still with high output effusions but < 25 mL/kg/day for > 3 consecutive days from all drains combined

Grade 3: After 10 days from index operation, still with high output effusions > 25 mL/kg/day for >3 consecutive days from all drains combined

Grade 4: Use of ECMO or implantation of Fontan venous VAD as separate procedure from index VAD implantation

Grade 5: Death resulting directly or primarily from Fontan venous failure

Other Events

1. Arrhythmia

Timing: Identified any time after leaving the OR/catheterization laboratory of the index procedure

Reporting: Each event will have an associated type and grade

Any arrhythmia that results in clinical compromise and requires any treatment, other than oral therapy or temporary pacing, should be collected

Grade of Cardiac Arrhythmia

Grade 1: Not applicable

Grade 2: Not applicable

Grade 3: Arrhythmia requiring new IV medical treatment

Grade 4: Arrhythmia requiring cardioversion, defibrillation, ICD therapy, permanent pacemaker or ablation

Grade 5: Death resulting directly or primarily from arrhythmia

2. Vascular Injury

Timing: Identified any time after leaving the OR/catheterization laboratory of the index procedure

Reporting: Each event will have an associated type and grade

This AE pertains only to devices inserted through the percutaneous route. Do not use this AE definition to describe vascular injuries unrelated to cannulation.

Type of Vascular Injury

- Cardiac or caval Perforation
- Pneumothorax from penetrating injury
- Pseudo-aneurysm
- Arteriovenous fistula
- Vessel Thrombosis
- Vessel Dissection
- Vessel Stenosis
- Cannulation site bleeding
- Limb hypoperfusion/ischemia

Grade of Vascular Access Site Injury

Grade 1: Not applicable

Grade 2: Not applicable

Grade 3: Vascular access injury that does not require surgical or interventional procedure.

Grade 4: Vascular access injury requiring **one** of the following:

- Surgical or interventional procedure
- Results in loss of limb /digit

Grade 5: Death resulting directly or primarily from Vascular Site Injury