**INTERMACS Adverse Event Definitions: Adult and Pediatric patients**

This document contains the following adverse event definitions:

* Hemolysis • Respiratory Failure
* Right Heart Failure • Venous Thromboembolism
* Device Malfunction • Wound Dehiscence
* Major Bleeding • Arterial Non-CNS Thromboembolism
* Major Infection • Other SAE
* Neurological Dysfunction • Hepatic Dysfunction
* Cardiac Arrhythmias • Hypertension
* Pericardial Fluid Collection *Adult definition*
* Myocardial Infarction *Pediatric definition*
* Psychiatric Episode • Renal Dysfunction

**Additional Notes:**

**Triggered Adverse Events:**

The adverse events, hypertension, hemolysis and right heart failure are not directly entered into the registry. Each of these events is a result of direct clinical measurements. The clinical information collected at the specific follow-up information is used to identify these adverse events. For example, blood pressure is collected at each follow-up visit. If the recorded mean blood pressure is above 110, then the event “hypertension” is internally identified. This strategy allows future adjustment of the “cut points” for an adverse event depending on the evolving clinical understanding of the event.

**Hemolysis:**

**Minor Hemolysis**: A plasma-free hemoglobin value greater than 20 mg/dl or a serum lactate dehydrogenase (LDH) level greater than two and one-half time (2.5x) the upper limits of the normal range at the implanting center occurring after the first 72 hours post-implant **in the absence** of clinical symptoms or findings of hemolysis or abnormal pump function.

**Major Hemolysis**: A plasma-free hemoglobin value greater than 20 mg/dl or a serum lactate dehydrogenase (LDH) level greater than two and one-half times (2.5x) the upper limits of the normal range at the implanting center occurring after the first 72 hours post-implant **and associated with** clinical symptoms or findings of hemolysis or abnormal pump function. Major Hemolysis requires the presence of one or more of the following conditions:

* Hemoglobinuria (“tea-colored urine”)
* Anemia (decrease in hematocrit or hemoglobin level that is out of proportion to levels explainable by chronic illness or usual post-VAD state)
* Hyperbilirubinemia (total bilirubin above 2 mg/dl, with predominately indirect component)
* Pump malfunction and/or abnormal pump parameters

**Right Heart Failure:**

Definition: Symptoms or findings of persistent right ventricular failure characterized by **both** of the following:

* Documentation of elevated central venous pressure (CVP) by:
  + Direct measurement (e.g., right heart catheterization) with evidence of a central venous pressure (CVP) or right atrial pressure (RAP) > 16 mmHg.

or

* + Findings of significantly dilated inferior vena cava with absence of inspiratory variation by echocardiography,

or

* + Clinical findings of elevated jugular venous distension at least half way up the neck in an upright patient.
* Manifestations of elevated central venous pressure characterized by:
  + Clinical findings of peripheral edema (>2+ either new or unresolved),

or

* + Presence of ascites or palpable hepatomegaly on physical examination (unmistakable abdominal contour) or by diagnostic imaging,

or

* + Laboratory evidence of worsening hepatic (total bilirubin > 2.0 mg/dl) or renal dysfunction (creatinine > 2.0 mg/dl).

**IF the patient meets the definition for right heart failure, the severity of the right heart failure will be graded according to the following scale below.**

**(NOTE: For right heart failure to meet severe or severe acute severity, direct measurement of central venous pressure or right atrial pressure must be one of the criteria)**

**Right Heart Failure Severity Grade**

**Mild Right Heart Failure**

**VAD Implant Admission**

**Patient meets both criteria for RHF plus:**

* Post-implant inotropes, inhaled nitric oxide or intravenous vasodilators not continued beyond post-op day 7 following VAD implant

**AND**

* No inotropes continued beyond post-op day 7 following VAD implant

**Surveillance periods (3 months, 6 months, 12 months and every 6 months thereafter) following VAD implant**

**Patient meets both criteria for RHF plus:**

* No readmissions for RHF since last surveillance period

**AND**

* No inotropes since last surveillance period.

**Moderate Right Heart Failure**

**VAD Implant Admission**

**Patient meets both criteria for RHF plus:**

* Post-implant inotropes, inhaled nitric oxide or intravenous vasodilators continued beyond post-op day 7 and up to post-op day 14 following VAD implant

**Surveillance periods (3 months, 6 months, 12 months and every 6 months thereafter) following VAD implant**

**Patient meets both criteria for RHF plus:**

* Limited to **one (1)** readmission for intravenous diuretics/vasodilators to treat RHF since last surveillance period

**AND**

* No inotropes since last surveillance period

**Severe Right Heart Failure**

**VAD Implant Admission**

**Patient meets both criteria for RHF plus**:

* Central venous pressure or right atrial pressure greater than 16mm Hg

**AND**

* Prolonged post-implant inotropes, inhaled nitric oxide or intravenous vasodilators continued beyond post-op day 14 following VAD implant

**Surveillance periods (3 months, 6 months, 12 months and every 6 months thereafter) following VAD implant**

**Patient meets both criteria for RHF plus:**

* Need for inotropes at any time since last surveillance period

**OR**

* Two (2) or more readmissions for intravenous diuretics/vasodilators to treat RHF since last surveillance period

**OR**

* Requiring RVAD support at any time after hospital discharge

**OR**

* Death at any time following discharge from the VAD implant hospitalization with RHF as the primary cause.

**Severe-Acute Right Heart Failure**

**VAD Implant Admission**

**Patient meets both criteria for Right Heart Failure plus:**

* Central venous pressure or right atrial pressure greater than 16 mmHg

**AND**

* Need for right ventricular assist device at any time following VAD implant

**OR**

* Death during the VAD implants hospitalization with RHF as the primary cause.

**Device Malfunction:**

A **Device Malfunction** occurs when any component of the MCSD system ceases to operate to its designed performance specifications or otherwise fails to perform as intended. Performance specifications include all claims made in the Instructions for Use.

Device malfunctions can be further defined as **major** or **minor**:

1. **Major device malfunction,** otherwise known as failure, occurs when of one or more of the components of the MCSD system either directly causes or could potentially induce a state of inadequate circulatory support (low cardiac output state) or death. A failure that was iatrogenic or recipient-induced will be classified as an Iatrogenic/Recipient-Induced Failure. A device malfunction or failure is considered major when one of the following conditions occurs:
   1. Suspected or confirmed pump thrombus (see below)
   2. Urgent transplantation (immediate 1A listing for transplant)
   3. Pump replacement
   4. Pump explant
   5. Breach of integrity of drive line that required repair
   6. Death
2. **Minor device malfunction** includes inadequately functioning external components which require repair or replacement but do not result in 1a-f. Device malfunction does not apply to “routine” maintenance which includes repair/replacement of: external controller, pneumatic drive unit, electric power supplies, batteries and interconnecting cables.

**Pump Thrombus** represents a special case of major device malfunction and can be delineated as **suspected pump thrombus** or **confirmed pump thrombus**. Pump thrombus will be classified as “SUSPECTED” (see definition below) based upon clinical, biochemical, or hemodynamic findings or “CONFIRMED” (see definition below) based upon device inspection or incontrovertible radiologic studies or absence of appropriate Doppler flow signals that confirms thrombus within the device or its conduits that results in or could potentially induce circulatory failure.

1. **Suspected pump thrombus** is a pump-related malfunction in which clinical or MCSD parameters suggest thrombus on the blood contacting components of the pump, cannulae, or grafts. Signs and symptoms should include at least 2 of the 3 following criteria:
   1. **Presence of hemolysis**
   2. **Presence of heart failure not explained by structural heart disease**
   3. **Abnormal pump parameters**

Suspected pump thrombus should be accompanied by 1 or more of the following events or interventions:

1. treatment with intravenous anticoagulation (e.g., heparin), intravenous thrombolytics (e.g., tPA), or intravenous antiplatelet therapy (e.g., eptifibatide, tirofiban)
2. pump replacement
3. pump explantation
4. urgent transplantation (UNOS status 1A)
5. stroke
6. arterial non-CNS thromboembolism
7. death
8. **Confirmed pump thrombus** is a major pump-related malfunction in which thrombus is confirmed within the blood contacting surfaces of device inflow cannula or outflow conduit or grafts. This can be reported via direct visual inspection or by incontrovertible contrast radiographic evidence or by the absence of an appropriate Doppler flow signal that results in or could potentially induce circulatory failure or result in thromboembolism.

If a Suspected Pump Thrombus event is ultimately confirmed through visual inspection following pump replacement, urgent transplantation or upon autopsy following death, the event will be adjudicated by the CEC for reclassification to Confirmed Pump Thrombus.

**Major Bleeding:**

An episode of SUSPECTED INTERNAL OR EXTERNAL BLEEDING that results in one or more of the following:

a. Death,

b. Re-operation,

c. Hospitalization,

d. Transfusion of red blood cells as follows:

If transfusion is selected, then apply the following rules:

During first 7 days post implant

**•** ≥ 50 kg: ≥ 4U packed red blood cells (PRBC) within any 24 hour period during first 7 days post implant.

• < 50 kg: ≥ 20 cc/kg packed red blood cells (PRBC) within any 24 hour period during first 7 days post implant.

After 7 days post implant

**•** A transfusion of packed red blood cells (PRBC) after 7 days following implant with the investigator recording the number of units given. (record number of units given per 24 hour period).

Note: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

**Major Infection:**

A clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

**Localized Non-Device Infection**

Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

**Percutaneous Site and/or Pocket Infection**

A positive culture from the skin and/or tissue surrounding the drive line or from the tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis.

**Internal Pump Component, Inflow or Outflow Tract Infection**

Infection of blood-contacting surfaces of the LVAD documented by positive site culture. (There should be a separate data field for paracorporeal pump that describes infection at the percutaneous cannula site, e.g. Thoratec PVAD).

**Sepsis**

Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

**Neurological Dysfunction:**

Any new, temporary or permanent, focal or global neurologic dysfunction ascertained by a standard neurological history and examination administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note; or an abnormality identified by surveillance neuroimaging. The examining physician will classify the event as a cerebrovascular event as defined below or as a non-vascular acute neurologic event.  A neurologic event may be recognized by a clinically evident sign or symptom, or by clinically-silent electrographic seizure activity, or as a clinically silent lesion detected by surveillance neuroimaging. Each neurologic event should be classified by the clinical provider following complete neurologic assessment as one of the following event types:

* 1. Transient ischemic attack, defined as an acute transient neurologic deficit conforming anatomically to arterial distribution cerebral ischemia, which resolves in < 24 hours and is associated with no infarction on brain imaging (head CT performed >24 hours after symptom onset; or MRI\*).
  2. Ischemic stroke, defined as a new acute neurologic deficit (or acute encephalopathy or seizures in children <6 months\*\*) of any duration associated with acute infarction on imaging corresponding anatomically to the clinical deficit. Ischemic stroke should be sub classified as due to arterial-distribution ischemia or due to venous thrombosis.
  3. Acute symptomatic intracranial hemorrhage, defined as new acute neurologic deficit (or acute encephalopathy or seizures in children < 6 months\*\*) attributable to Intracranial hemorrhage (ICH). ICH subtype should be specified as one or a combination of the following types: subarachnoid, intraventricular, parenchymal, subdural.
  4. Clinically covert ischemic stroke or ICH: infarction or ICH seen by surveillance imaging, without clinical findings of stroke or ICH at the time of event recognition.
  5. Hypoxic-Ischemic Encephalopathy: Acute new encephalopathy\*\*\* due to hypoxic-ischemic injury (HIE), manifest as clinically- evident signs or symptoms, or subclinical electrographic seizures found by complete neurological diagnostic evaluation to be attributable to acute global or focal hypoxic or ischemic brain injury not meeting one of ischemic stroke or ICH events as defined above.
  6. Acute new encephalopathy\*\*\*  due to other causes, manifest as clinically-evident signs or symptoms or subclinical electrographic seizures found by complete neurological diagnostic evaluation to be attributable causes other than stroke, ICH or HIE, as defined above. This category of "other" acute encephalopathy includes neurologic signs or symptoms or subclinical seizures found to be attributable to other conditions such as meningitis, toxic-metabolic or drug-related processes.

\*\*\* Acute encephalopathy is a sign or symptom of some underlying cerebral disorder, and is manifest as depressed consciousness with or without any associated new global or multifocal neurologic deficits in cranial nerve, motor, sensory, reflexes and cerebellar function.

**Cardiac Arrhythmias:**

Any documented arrhythmia that results in clinical compromise (e.g., abnormal VAD function [e.g., diminished VAD flow or suction events], oliguria, pre-syncope or syncope, angina, dyspnea), or requires hospitalization or treatment (drug therapy, defibrillation, cardioversion, ICD therapy (e.g., shock or anti-tachycardia pacing) or arrhythmia ablation procedure). Cardiac arrhythmias are classified as 1 of 2 types:

* 1. Sustained ventricular arrhythmia resulting in clinical compromise, or requiring hospitalization or drug treatment, defibrillation, cardioversion, ICD therapy, or arrhythmia ablation procedure.
  2. Sustained supraventricular arrhythmia resulting in clinical compromise, or requiring hospitalization or drug treatment, cardioversion, ICD therapy, or arrhythmia ablation procedure.

**Pericardial Fluid Collection:**

Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac/VAD output) and those without signs of tamponade.

**Myocardial Infarction:**

Two categories of myocardial infarction will be identified:

**Peri-Operative Myocardial Infarction**

The clinical suspicion of myocardial infarction together with CK-MB or Troponin > 10 times the local hospital upper limits of normal, found within 7 days following VAD implant together with ECG findings consistent with acute myocardial infarction. (This definition uses the higher suggested limit for serum markers due to apical coring at the time of VAD placement, and does not use wall motion changes because the apical sewing ring inherently creates new wall motion abnormalities.)

**Non-Perioperative Myocardial Infarction**

The presence at > 7 days post-implant of two of the following three criteria:

a) Chest pain which is characteristic of myocardial ischemia,

b) ECG with a pattern or changes consistent with a myocardial infarction, and

c) Troponin or CK (measured by standard clinical pathology/laboratory medicine methods) greater than the normal range for the local hospital with positive MB fraction (≥ 3% total CK). This should be accompanied by a new regional LV or RV wall motion abnormality on a myocardial imaging study.

**Psychiatric Episode:**

Disturbance in thinking, emotion or behavior that causes substantial impairment in functioning or marked subjective distress and requires intervention. Intervention is the addition of new psychiatric medication, hospitalization, or referral to a mental health professional for treatment. Suicide is included in this definition.

**Respiratory Failure:**

Impairment of respiratory function requiring reintubation, tracheostomy or the inability to discontinue ventilatory support within six days (144 hours) post-VAD implant. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.

**Venous Thromboembolism:**

Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

**Wound Dehiscence**

Disruption of the apposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.

**Arterial Non-CNS Thromboembolism:**

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

1) standard clinical and laboratory testing

2) operative findings

3) autopsy findings

This definition excludes neurological events.

**Other SAE:**

An event that causes clinically relevant changes in the patient’s health (e.g. cancer).

**Hepatic Dysfunction:**

An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/**AST and** alanine aminotranferease/**ALT**) to a level greater than three times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death).

**Hypertension:**

New onset blood pressure elevation greater than or equal to 140 mm Hg systolic or 90 mm Hg diastolic (pulsatile pump) or 110 mm Hg mean pressure (rotary pump).

**PediMACS**: **Hypertension is defined as systolic, diastolic, or mean blood pressure greater than the 95th percentile for age which requires the addition of a new IV or oral therapy for management. The event shall be considered resolved upon the discontinuation of the treatment.**

**Renal Dysfunction:**

Two categories of renal dysfunction will be identified:

**Acute Renal Dysfunction**

Abnormal kidney function requiring dialysis (including hemofiltration) in patients who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 3 times baseline or greater than 5 mg/dL **(in children,** creatinine greater than 3 times upper limit of normal for age) sustained for over 48 hours.

**Chronic Renal Dysfunction**

An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for hemodialysis sustained for at least 90 days.