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CONSENSUS STATEMENT

Updated definitions of adverse events for trials and registries of mechanical circulatory support: A consensus statement of the mechanical circulatory support academic research consortium

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Over 25 years ago, it became clear that heart transplantation would become a treatment option for only a limited group of carefully selected patients with advanced heart failure (HF) because of limited donor heart organ availability and restrictive transplant eligibility criteria.[1] This reality energized research focused on clinical applications of implantable left ventricular assist devices (LVADs) for long-term mechanical circulatory support (MCS).[2,3] Applying LVAD therapy as a bridge to transplant not only reduced transplant waiting list mortality but also provided an opportunity to explore the feasibility of longer-term durable LVAD support for the ultimate application of LVAD support as permanent therapy.[3,4] Experiences from patients being supported for longer periods for bridge-to-transplant indication helped establish acceptable safety criteria of LVADs to support the feasibility for a clinical trial (i.e., Randomized Evaluation of Mechanical Assistances for Treatment of Congestive Heart Failure clinical trial), establishing an indication for permanent LVAD use

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(destination therapy) for those patients ineligible to receive a cardiac transplant.[3]

Historically, adverse event (AE) definitions for device clinical trials were agreed upon between the United States Food and Drug Administration (FDA) and device manufacturers. These trials were device-specific, with inconsistencies between criteria regarding patient selection, study endpoints, and most importantly, definitions of AEs, making reliable comparisons between individual trials and devices problematic. Initiatives to standardize AE definitions for clinical evaluation of outcomes in the field was initially fostered by registry development, with the MCS device database of the International Society for Heart and Lung Transplantation (ISHLT), first published in 2003, representing the earliest effort.[5,6] The experience with the ISHLT registry subsequently led clinicians to pursue the development of the National Heart, Lung, and Blood Institute supported Interagency Registry for Mechanically Assisted Circulatory Support (Intermacs) in 2005.[7–9] Intermacs, now maintained by The Society of Thoracic Surgeons, has become the cornerstone for MCS longitudinal study in the United States, providing the field with real-world evidence[10] and standardized AE definitions. This successful registry endeavor has led to similar MCS registry endeavors in Europe and Japan that have adopted similar Intermacs AE definitions, supporting the goal of global harmonization.[11,12]

Incremental improvements in survival on LVAD support have been demonstrated with nearly 50% of patients surviving to 5 years.[9] However, the persistent burden of key AEs associated with LVAD therapy seems to have resulted in a plateau of adoption of durable MCS therapy in the most recent era and a lack of equipoise for investigating the use of MCS in the less ill HF population.[13] The key AEs that dominate the LVAD profile include bleeding, infection, stroke and transient ischemic attack, device malfunction (particularly device thrombosis and electrical failures), and right HF and cardiac arrhythmias. These events are associated with reduced survival, frequent readmission rates, and higher costs of care.

Recently, AE reporting in device manufacturer-sponsored clinical trials has begun to deviate from the previously established Intermacs AE definitions.[14] This provides a strong incentive for a comprehensive update in AE definitions intended to adopt international standardization and harmonization. Without such a consensus on standardization of event definitions, interpretation of safety data and adjudication of outcome between clinical trials and in routine clinical care becomes difficult.

MCS academic research consortium composition and goals

The renewed interest in developing a consensus between clinicians, FDA, and device manufacturers for definitions of AEs stimulated the engagement with the Academic Research Consortium (ARC).[15] The ARC mission statement is focused on promoting informed and collaborative dialogue across stakeholders, supporting the development of consensus definitions and nomenclature for targeted areas of new medical device development, disseminating such definitions in the public domain.[15] Therefore, we convened the MCS-ARC to utilize the expertise of surgeons, HF cardiologists, infectious disease specialists, nurses, engineers, and other specialists representing relevant disciplines related to specific AEs, including infectious diseases, engineering, HF, and neurology. Comments were also solicited from FDA and device manufacturers. Although Intermacs collects data solely on durable MCS devices utilized for bridge-to-transplantation and destination therapy, the MCS-ARC was encouraged to also provide guidance on AE definitions for temporary percutaneous devices used primarily in the setting of acute cardiogenic shock and bridge to decision indications. The collaborative work of the group took place between November 2017 and December 2018 and included extensive discussions through conference calls, electronic communications, and 2 in-person meetings (November 20, 2017, in Washington, DC, and April 11, 2018, in Nice, France). These forums included the MSC-ARC study group members and invited international guest participants from FDA and device manufacturers.

This manuscript summarizes the recommendations of the MCS-ARC working group. The main goals of the MCS-ARC include (1) refinement and clarification of current clinically relevant key AE definitions adopted by Intermacs; (2) classification of AEs according to type, location, severity, and timing; (3) use of information provided through other ARC initiatives, including the Neurologic ARC,[16] the Bleeding ARC,[17] and the Valve ARC,[18] to adopt and harmonize AE definitions where possible; (4) provision of clear guidance for personnel recording the events; and (5) development of an assignment of cause based largely on subjective criteria including whether the AE is (1) device-related; (2) patient-related; or (3) related to management practices. The goal of this assignment is to provide improved insight into possible contributing causes of AEs to develop effective solutions whether they represent changes to best management practices, refinements to patient selection or education, or improvements in device technology. A future goal of the MCS-ARC group will be to also develop guidelines for MCS clinical trial end-points.

This report focuses on reporting the definitions of key AEs and the data required to reliably confirm their presence. The manuscript was intended as a guideline statement or a guidance document for AE interpretation and documentation within the field and should be viewed as a roadmap to facilitate the standardization of AE reporting in future MCS device clinical research and clinical care. As a living document, the plan is to review the definitions every 2 years and update definitions as necessary.

MCS-ARC adverse events

MCS-ARC bleeding adverse event

Bleeding is the most common AE after LVAD implantation and is a critical safety measure in all clinical trials utilizing

these devices.[19–22] Data from Intermacs suggest that the most frequent locations of the first bleeding episode after implantation is mediastinal (45%), thoracic pleural space (12%), lower gastrointestinal (GI) tract (10%), chest wall (8%), and upper GI tract (8%).[9,23] Early bleeding relates to either surgical procedural causes (surgical bleeding) and the need for early post-operative anti-coagulation or secondary to coagulation abnormalities that accompany liver and/or renal dysfunction seen with chronic HF. Following the peri-operative period, non-surgical bleeding has emerged as a major source of morbidity and mortality.[19–22] The mechanisms responsible for these events include the development of acquired von Willebrand disease, GI tract angiodysplasia formation, impaired platelet aggregation, and anti-coagulation therapy.[19–22]

The original Intermacs definition of a bleeding AE included a minimum transfusion requirement to meet the definition of bleeding during the immediate post-operative period. The initial criterion of requiring a minimal amount of blood transfusion to define bleeding was established over 20 years ago as it was recognized that patients with critically ill HF tended to have inherent coagulopathies that resulted in peri-operative bleeding, especially when a patient had undergone previous cardiac surgery before MCS device implantation. This definition has led to confusion as the primary focus appeared to be more on accounting for the number of units of blood transfused as opposed to identifying a specific bleeding event leading to the transfusion event. For this reason, the group felt it was important to adopt the bleeding definitions established in the consensus report from the bleeding ARC as the new definition for the MCS-ARC bleeding AE[17] (Table 1 and refer to Supplementary Material Figure S1 available online at www.jhltonline.org).

Table 1 MCS-ARC Bleeding Adverse Event

- **Type 1**: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional. This type is not relevant during a hospitalization.
- **Type 2**: Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for Type 3, 4, or 5 but does meet at least one of the following criteria:
  1. requiring non-surgical, medical intervention by a healthcare professional;
  2. leading to hospitalization or increased level of care; or
  3. prompting evaluation.
- **Type 3**
  1. **Type 3a**
     - Overt bleeding accompanied by hemoglobin drop of 3 to < 5 g/dl or (1.86–3.1 mmol/liter SI units) (provided hemoglobin drop is related to bleed)
     - Any transfusion with overt bleeding
  2 **Type 3b**
     - Overt bleeding plus hemoglobin drop 5 g/dl ((3.1 mmol/liter) or greater (provided hemoglobin drop is related to bleed)
     - Cardiac tamponade
     - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
     - Bleeding requiring intravenous vasoactive agents
- **Type 4:** VAD implantation-related bleeding (includes concomitant cardiac or non-cardiac surgical procedures)
  1. Reoperation after the closure of incision or incisions used to implant the VAD to control bleeding
  2. ≥ 50 kg: ≥ 4U PRBC within any 48 hours during the first 7 days post-implant.
  3. < 50 kg: ≥ 20 cm^3/kg PRBC within any 24 hours during the first 7 days post-implant.
  4. Chest tube output > 2 liters within 24 hours.
- **Type 5**: Fatal bleeding
  1. **Type 5a:** Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
  2. **Type 5b:** Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

The association of the bleeding event should be classified as follows:

- **Patient-related:** (e.g., coagulopathy unrelated to surgical technique such as non-adherence with anti-coagulation medication resulting in an inappropriately high level of anti-coagulation, hepatic failure)
- **Management-related: (**e.g., related to surgical technique; hypertension; bleeding in the setting of inappropriate levels of anti-coagulation) or to mismanagement of anti-coagulants.
- **Pump related: (**e.g., bleeding from the outflow graft, apical connector, or other internal components)

Abbreviations: MCS-ARC Mechanical Circulatory Support, Academic Research Consortium; PRBC, packed red blood cells; VAD, ventricular assist device.

Note: The forms recording the presence of bleeding will continue to record the key sources of bleeding as outlined in the Intermacs User Manual. These include mediastinal: chest wall; mediastinal: outflow-aorta anastomosis; mediastinal: outflow conduit; mediastinal: inflow conduit; mediastinal: cardiopulmonary bypass cannulation site; mediastinal: coagulopathy with no surgical site; mediastinal: other surgical sites; pump or implanted component pocket (battery or controller); mediastinal: unspecified; pleural space; intra-abdominal; retroperitoneal; pulmonary; genitourinary tract; GI: upper gastrointestinal (esophagus, stomach, duodenum, and small bowel); GI: lower gastrointestinal (colon, rectum, and anus); GI: unknown, but guaiac positive stools; ENT/dental; other.

MCS-ARC infection adverse event

Infection associated with the implantation of the MCS device or non-device–related infection is the second most common AE seen in LVAD recipients.[23–25] The broad definition adopted by the MCS-ARC group is essentially unchanged from the current Intermacs definition; however, a more granular approach was taken in recording the site and type of infection. In the original Intermacs definition, 4 broad categories were included: (1) localized non-device infection; (2) percutaneous site and/or pocket infection; (3) an infection involving any internal pump component and inflow or outflow tract, including the infection of blood-contacting surfaces of the LVAD; and (4) sepsis.

The MCS-ARC defines an infection AE as an infection accompanied by clinical evidence, including pain, fever, or radiologic findings consistent with infection accompanied by the need to treat with anti-microbial agents (therapeutic intent). Guidelines in the database procedure manual will indicate the importance of obtaining appropriate anti-microbial therapy guidance from specialists in infectious diseases. A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures or the absence of culture data. The general categories of infection for the MCS-ARC Infection AE can be found in Table 2[26] (Supplementary Material Figure S2 online).

Current Intermacs data forms provide fields for recording major potential locations for infection; however, we suggest that additional choices that account for newer implantable components, such as transcutaneous power elements, implantable controllers, and batteries, will need to be included. In addition, choices need to be provided to capture infections related to thoracotomy approaches for implantation of MCS devices and the separation of pulmonary infections into pneumonia and tracheobronchitis.

We recommend that although current data forms capture the initial organism type (bacterial, fungal, viral, or protozoal), there should be a mechanism to record the species of organism and if bacterial, whether it is gram-positive or -negative. Finally, although Intermacs records whether intravenous antibiotics are used, there is no information on the duration of use or type of antibiotic. Start and stop dates for the intravenous drug may be considered.

MCS-ARC neurologic dysfunction adverse event

Neurologic complications are among the most common AEs seen in patients with MCS and are strongly associated with disability, impaired quality of life, and mortality.[9,27,28] The MCS-ARC has adopted several new or revised definitions for neurologic events compared with previous iterations of Intermacs definitions. These changes align definitions and ascertainment methodology with other recent ARC statements addressing neurologic outcomes following cardiovascular procedures with several additions and adaptations that are required to best serve the unique patient population, disease state, devices, and procedures associated with MCS.[16,29]

Patients receiving MCS may experience central nervous system (CNS) injury, including ischemic infarction, hemorrhage, or hypoxic-ischemic injury. These CNS injuries may be associated with neurologic symptoms that are concordant with the anatomic location of injury (overt). Alternatively, CNS injury may be asymptomatic (covert) if it is noted on screening brain imaging or if the anatomic distribution of injury does not match the neurologic symptoms that led to an imaging study. It will be important to realize that if an imaging study reveals an area of brain injury and if on closer neurologic assessment, a symptom is discovered, then the event may be re-adjudicated as overt. In addition, patients may develop neurologic dysfunction without evidence of infarction on brain imaging (e.g., transient ischemic attack or encephalopathy and/or delirium).

Table 3 outlines the MCS-ARC neurologic dysfunction AE categories of neurologic dysfunction organized as overt (Type 1), covert (Type 2), or neurologic dysfunction without evidence of injury (Type 3). Importantly, although subdural hematoma is not classically considered a stroke, it is a common complication seen in patients receiving MCS, accounting for 13% to 22% of cases of intracranial hemorrhage.[28,30,31] Thus, the MCS-ARC neurologic dysfunction AE includes a description of overt symptomatic sub-dural hemorrhage (Type 1f), and sub-dural hemorrhage is included among the possible types of covert CNS hemorrhage (Type 2b) if no symptoms are noted.

Clinicians caring for patients with MCS are strongly encouraged to obtain neuroimaging if a neurologic event is suspected and the patient is stable enough to obtain the study. Magnetic resonance imaging will not be an option owing to the incompatibility with durable MCS devices; thus, head CT will be the preferred study. Fortunately, CT is equally sensitive to acute intracranial hemorrhage as magnetic resonance imaging, and this has the greatest potential impact on management. If the initial study is non-diagnostic and symptoms persist with continued suspicion for CNS injury, a repeat head CT 24–48 hours after the onset of symptoms will have a higher yield for evidence of ischemia. Clinicians caring for patients with MCS are strongly encouraged to obtain neurology consultation if CNS injury is suspected, so that a thorough neurologic assessment can be performed and documented and interventions initiated, if appropriate. If a stroke is suspected, a National Institutes of Health Stroke Scale and modified Rankin score should be performed to establish the severity of symptoms and disability.[32] Table 4 provides definitions for acute CNS injury severity, based on a National Institutes of Health Stroke Scale assessment[32] and recovery, based on a modified Rankin score[33] (Supplementary Material Figure S3 online).

Somewhat unique to the population of patients receiving MCS is that catastrophic HF may lead to CNS injury before the use of MCS. In addition, CNS injury may occur with the procedure to implant the MCS device, during ongoing use of MCS, or when the device is removed. Finally, given that anti-coagulation is required for MCS and acquired von Willebrand deficiency and thrombocytopenia are common,

Table 2 MCS-ARC Infection Adverse Event

1. **Percutaneous lead site infection**[s]
   - **Superficial percutaneous lead infection:** A positive culture from the skin surrounding the percutaneous lead when there is clinical evidence of infection such as pain, fever, drainage, erythema, or leukocytosis coupled with the need to treat with anti-microbial therapy. The percutaneous lead exit site may have drainage and/or the surrounding skin may have erythema. The epithelialization of the percutaneous lead exit site is preserved. The gram stain of the skin specimen at the driveline exit site will contain white blood cells (i.e., positive sign for inflammation).
   - **Deep percutaneous lead infection:** A positive culture from the driveline exit site deep to the epithelium, when there is clinical evidence of infection such as pain, fever, drainage, erythema, or leukocytosis coupled with the need to treat with anti-microbial therapy. The epithelialization of the percutaneous lead exit site is disrupted and no longer preserved or intact, or there is radiographic evidence of findings consistent with infection along the path of the percutaneous lead outside the mediastinum.
2. **Infection of external surfaces of an implantable component**[a]**:** A positive culture from the tissue surrounding the external housing of a pump or one of its components implanted within the body (including device components such as controllers, batteries, etc.), when there is clinical evidence of infection such as pain, fever, drainage, erythema, or leukocytosis coupled with the need to treat with anti-microbial therapy.
3. **Infection of blood-contacting surfaces of an implantable component (device endocarditis)**[a]**:** Infection of blood-contacting internal surfaces of the MCS device including inflow/outflow grafts: documented by positive blood cultures or radiographic or echocardiographic evidence of vegetation in blood flow path of the pump coupled with the need to treat with anti-microbial therapy.

Non—MCS-related infections.

1. **Infective Endocarditis: Non—MCS related**
   - Positive blood cultures and echocardiography findings for mass or vegetation only on native valves, ICD, or pacemaker leads.
2. **BSI**
   - Positive blood cultures with no other source identified
   - Bloodstream infection: non-VAD site or central venous catheter-related (definition from the Centers for Disease Control/National Healthcare Safety Network)[47]

   Should be coupled with the need to treat with anti-microbial therapy.
3. **Mediastinitis**[a]
   - Procedure-related mediastinitis
     - Deep sternal wound infection (isolated).
     - Deep sternal wound infection involving MCS device components (continuous with mediastinum or already situated in the mediastinum). Maybe contiguous with implanted components of the MCS device
   - **Non—MCS-related mediastinitis:**
     - Mediastinitis definitively owing to another cause (e.g., esophageal perforation during endoscopy, contiguous with empyema).
   - **Superficial mediastinal or thoracotomy wound infection**
     - Infection involving only skin, sub-cutaneous fat, and muscle of implant incision.

   Should be coupled with the need to treat with anti-microbial therapy.
4. **Sepsis**
   - **Life-threatening organ dysfunction caused by a dysregulated host response to infection with:**
     - Evidence of systemic involvement by infection, manifested by need to treat with anti-microbial therapy
     - Positive blood cutures and/or two of the following:
       - $PaO_2/FIO_2 < 400$ or respiratory rate ≥ 22/min or ventilated respiratory support
       - Hypotension with systolic BP < 100 mm Hg or MAP $\leq$ 65 mm Hg.
       - Platelet count < 150 or elevated prothrombin time or fibrinogen degradation products
       - Bilirubin (serum) > 50% above baseline
       - Altered mental status (Glasgow score < 15)
       - Creatinine (serum) > 50% above baseline
       - Need for intravenous vasoconstricting agents
       - For pediatric patients:
         - Hypotension defined as a decrease by 15 mm Hg systolic or mean BP, as compared with baseline
         - Platelet count < 150, or elevated PTT or FDP
         - Bilirubin increased by 50% from baseline
         - Creatinine increased by 50% from baseline
         - Altered mental status
5. **Localized non—MCS device infection**[a]
   - Infection localized to a site not involving the MCS device or components (e.g., pneumonia, urinary tract infection, cholecystitis, diverticulitis, dental abscess) coupled with the need to treat with anti-microbial therapy

The association of the infection event should be classified as:

- **Patient-related: (**e.g., non-adherence or poor management of driveline exit site or indwelling catheters, IV drug abuse, aspiration)
- **Management-related: (**e.g., improper tunneling, contamination of the intraoperative site, prolonged intubation)
- **Device-related: (**e.g., Device endocarditis diagnosed by radiological examination or detection of pannus within the conduits or device)

Abbreviations: BP, blood pressure; BSI, bloodstream infection; FDP, fibrinogen degradation product; FIO_2, fraction of inspired oxygen; ICD, implantable cardio-defibrillator; IV, intravenous; MAP, mean arterial pressure; MCS-ARC, Mechanical Circulatory Support, Academic Research Consortium; PaO_2, partial pressure of oxygen; PTT, partial thromboplastin time; VAD, ventricular assist device.

[a]A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures.

Table 3 MCS-ARC Neurologic Dysfunction Adverse Event

Type 1	Overt CNS injury: acutely symptomatic brain or spinal cord injury	
Type 1a	**Ischemic stroke**	Sudden onset of neurologic signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, that: 1) persist for ≥ 24 hours or until death, with pathology or neuroimaging evidence that demonstrates either: a) CNS infarction in the corresponding vascular territory (with or without hemorrhage); or b) absence of other apparent causes (including hemorrhage), even if no evidence of acute ischemia in the corresponding vascular territory is detected. or 2) Symptoms lasting < 24 hours with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory. Note: when CNS infarction location does not match the transient symptoms, the event would be classified as covert CNS infarction (Type 2a) and a TIA (Type 3a), but not an ischemic stroke. Signs and symptoms consistent with stroke typically include an acute onset of one of the following: focal weakness and/or numbness, impaired language production or comprehension, homonymous hemianopia or quadrantanopia, diplopia, altitudinal monocular blindness, hemispatial neglect, dysarthria, vertigo, or ataxia.For pediatric patients, generalized symptoms such as seizure, irritability, or altered wakefulness may be accepted as confirmation of acute stroke if imaging or pathology demonstrates previously undocumented CNS infarction.
Sub-type 1aH	**Ischemic stroke with hemorrhagic conversion**	Ischemic stroke includes hemorrhagic conversions. These should be sub-classified as Class A or B when an ischemic stroke is the primary mechanism and pathology, or neuroimaging confirms a hemorrhagic conversion. Class A **Petechial (non−space-occupying) hemorrhage:** Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect. Class B **Confluent (space-occupying) hemorrhage:** Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect.
Type 1b	**Symptomatic intracerebral hemorrhage**	Rapidly developing neurologic signs or symptoms (focal or global) caused by an intraparenchymal, intraventricular, spinal cord, or retinal collection of blood, not caused by trauma.
Type 1c	**Symptomatic sub-arachnoid hemorrhage**	Rapidly developing neurologic signs or symptoms (focal or global) and/or headache caused by bleeding into the sub-arachnoid space, not caused by trauma.
Type 1d	**Stroke, not otherwise specified**	An episode of acute focal neurologic signs or symptoms and/or headache presumed to be caused by CNS ischemia or CNS hemorrhage, persisting ≥ 24 hours or until death, but without sufficient evidence to be classified as one of the above (i.e., no neuroimaging performed).
Type 1e	**Symptomatic hypoxic-ischemic injury**	Non-focal (global) neurologic signs or symptoms due to diffuse brain, spinal cord, or retinal cell death (confirmed by pathology or neuroimaging) in a non-vascular distribution, attributable to hypotension and/or hypoxia.
Type 1f	**Symptomatic sub-dural hemorrhage**	An episode of acute focal neurologic signs or symptoms and/or headache accompanied by evidence of bleeding into the sub-dural space.
Type 2	**Covert CNS injury: Acutely asymptomatic brain or spinal cord injury detected by neuroimaging**	
Type 2a	**Covert CNS infarction**	Brain, spinal cord, or retinal cell death attributable to focal or multifocal ischemia on the basis of neuroimaging or pathologic evidence of CNS infarction, without a history of acute neurologic symptoms consistent with the lesion location.
Sub-type 2aH	**Covert CNS infarction with hemorrhagic conversion**	Covert CNS infarction includes hemorrhagic conversions. These should be sub-classified as Class A or B when CNS infarction is the primary mechanism and neuroimaging, or pathology confirms a hemorrhagic conversion. Class A **Petechial (non−space-occupying) hemorrhage** Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect Class B **Confluent (space-occupying) hemorrhage:** Confluent hemorrhage originating from within the infarcted area with space-occupying effect
Type 2b	**Covert CNS hemorrhage**	Neuroimaging or pathologic evidence of CNS hemorrhage within the brain parenchyma, sub-arachnoid space, sub-dural space, ventricular system, spinal cord or retina on neuroimaging that is not caused by trauma, without a history of acute neurologic symptoms consistent with the bleeding location.
Type 3	**Neurologic dysfunction (acutely symptomatic) without CNS injury**	
Type 3a	**TIA**	Transient focal neurologic signs or symptoms (lasting < 24 hours) presumed to be owing to the focal brain, spinal cord, or retinal ischemia, but without evidence of acute infarction by neuroimaging or pathology (or in the absence of imaging)
Type 3b	**Delirium without CNS injury**	Transient non-focal (global) neurologic signs or symptoms (variable duration) without evidence of cell death by neuroimaging or pathology

The association of the neurologic event should be classified as:

- **Patient-related:** (e.g., documentation of previous carotid or cerebrovascular disease, coagulopathy unrelated to surgical technique such as non-adherence with anti-coagulation medication resulting in an inappropriately high level of anti-coagulation, related to illicit drug use, non-adherence with other medications, trauma, associated with sepsis)
- **Management-related:** (e.g., over anti-coagulation or associated with the use of accessory assist device, hypotension or hypertension-related to surgical procedure)
- **Device-related:** (e.g. secondary to pump thrombosis or device malfunction)

Abbreviations: CNS, central nervous system; MCS-ARC, Mechanical Circulatory Support, Academic Research Consortium; TIA, transient ischemic attack.

Table 4 Classification of Acute Severity, Recovery and Long-Term Disability

Acute Severity	1. **Mild neurologic dysfunction:** NIHSS 0-5 2. **Moderate neurologic dysfunction:** NIHSS 6-14 3. **Severe neurologic dysfunction:** NIHSS ≥15 **NOTE:** Severity assessment should be performed at the time of diagnosis of any overt CNS injury (Types 1) to ensure accurate classification
Stroke Recovery	**Stroke with complete recovery**: A modified Rankin Score (MRS) at 30-90 days of 0 OR a return to the patient's pre-stroke baseline MRS, in the absence of any ongoing new symptoms due to the stroke.
Stroke Disability	• **Fatal Stroke**: Death resulting from a stroke where the cause of death is attributable to the stroke. • **Disabling stroke**: An MRS ≥2 at 30-90 days with an increase of at least 1 point compared to the pre-stroke baseline. • **Non-disabling stroke**: An MRS <2 at 30-90 days, or ≥2 without an increase of at least 1 compared to the pre-stroke baseline. **NOTE**: Disability assessment applies **only** to subjects with overt CNS injury (Type 1) and should be performed at 90± 14 days after the stroke event.

Abbreviations: CNS, central nervous system; MRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale
(For Pediatric Patients the pediatric NIH SS will be used.)

some CNS injury may be directly attributable to these coagulopathies. Thus, we are recommending that clinicians attempt to establish device- and/or procedure-relatedness, in addition to when and by what mechanism the CNS injury occurred, if possible.

Taken together, these revised neurology event definitions will lead to greater alignment with current concepts of stroke, existing ARC statements, and a greatly improved understanding of the frequency, spectrum, mechanisms, and sequelae of CNS injury in the MCS population.

MCS-ARC device malfunction adverse event

Device malfunction is, perhaps, one of the most critical events associated with durable MCS therapy.[9,34–36] Owing to the numerous components that comprise a durable MCS device and variation in design among different durable MCS devices, having a common definition that is expansive and can accurately capture and categorize different component failures is essential for clinicians and engineers to have the highest degree understanding of the safety and reliability of durable MCS systems. It is also essential that any definition of device malfunction captures sufficiently granular data to be meaningful to clinicians and engineers to determine the root cause of the malfunction and to develop corrective strategies to resolve the identified issues.

Historically, greater attention has been given to highlighting device malfunctions largely involving the pump, that is, pump thrombosis.[35,36] However, other components of the durable MCS device, that is, percutaneous driveline or controller, are critical for the proper function of the durable MCS device and can fail, resulting in harm to the patient or need for durable MCS device exchange.[34] It is essential that clinicians and health care providers capture all these events.

The new definition of device malfunction categorizes events into major and minor severity (Table 5) (Supplementary Material Figure S4 online). The criteria for defining a major event have been expanded to include several interventions or consequences to the patient not previously captured. Device thrombosis is a separate category of device malfunction denoted as major device malfunction-device thrombus and as previously captured in the older definition, it is categorized as suspected or confirmed. Criteria to define a suspected event have been broadened to include interventions or events not previously captured in the previous definition.

As with each of the AE definitions, clinicians will be asked whether the device malfunctions are patient-related, management-related, or device-related.

MCS-ARC hemolysis adverse event

Hemolysis is now recognized as an important AE that is closely associated with device malfunction, specifically, pump thrombosis.[37–39] Although hemolysis may occur in patients supported with a durable MCS device from non−device-related causes, these events are unusual. A biomarker such as lactate dehydrogenase (LDH), which is a sensitive measure of the degree of hemolysis, has been demonstrated to be predictive of future pump thromboses, and elevated LDH levels significantly correlate with the presence of pump thrombus at the time of pump exchange.

It is important to understand that different durable MCS devices are associated with varying degrees of background hemolysis, such that biomarkers like LDH may be mildly elevated in patients supported with a durable MCS device in the presence of normal pump function and appropriate hemodynamic support. Previous data have supported an LDH rise to greater than 2.5 × the upper limits of normal as indicative of an abnormal degree of hemolysis and suggestive of pump thrombosis.[37,38] However, these data were largely based on the experience of 1 type of continuous flow-rotary pump. As the field moves forward and new technology is introduced into clinical practice, biomarker thresholds that define important levels of hemolysis for individual pumps may need to be modified. We also believe that a plasma-free hemoglobin > 20 mg/dl may be added as another indicator of hemolysis. An LDH rise may falsely

Table 5 MCS-ARC Device Malfunction Adverse Event

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 are further defined as major or minor:

Major Device Malfunction

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 categorized as major when one of the following conditions occurs:

1. Death.
2. Hospitalization, emergency room visit or prolongation of hospitalization, or escalation of the level of care in an ongoing hospitalization (i.e., transfer to the intensive care unit).
3. Life-threatening event (i.e., stroke or TIA, cardiac arrest, heart failure, syncope or near syncopal event, arrhythmia, etc.).
4. Results in significant disability or incapacity.
5. Requires an intervention to prevent impairment/injury including:
   a. Urgent transplantation listing (immediate urgent listing for the transplant).
   b. Pump replacement.
   c. Pump explant.
   d. Pump deactivation without explant or partial explant of components.
   e. Breach of integrity of percutaneous lead requiring repair.
   f. Operation to repair or replace any internal component of the circulatory support system.
   g Procedure to repair or stent an outflow graft.

Note**:** Replacement of external controller that is done in an inpatient setting for logistical reasons, in an otherwise stable patient, should be considered a minor device malfunction rather than major.

Minor Device Malfunction

Minor device malfunction includes inadequately functioning external components that require repair or replacement but do not result in 1a to g. Device malfunction does not apply to routine maintenance including replacement of external controller, pneumatic drive unit, electric power supplies, batteries, and interconnecting cables that are not related to a failed component.

Major Device Malfunction

Device thrombus: Intracorporeal device thrombus represents a special case of major device malfunction and can be categorized as a suspected device thrombus or confirmed device thrombus. Device thrombus will be classified as suspected (see definition below) on the basis of clinical, biochemical, or hemodynamic findings or confirmed (see definition below) on the basis of device inspection or incontrovertible radiologic studies or absence of appropriate Doppler flow signals that confirm thrombus within the device or its conduits that results in or could potentially induce circulatory failure.

1. **Suspected device thrombus** is a device-related malfunction in which clinical or MCSD parameters suggest thrombus on the blood-contacting components of the pump, cannula, or grafts. Suspected device thrombosis will be defined as signs and symptoms to include at least 1 of the 3 following criteria:
   - □ Presence of major hemolysis (including elevation of biochemical markers of hemolysis; i.e., lactate dehydrogenase or plasma-free hemoglobin, or clinical evidence of hemolysis; i.e., hemoglobinuria).
   - □ Presence of heart failure not explained by structural heart disease.
   - □ Abnormal pump parameters consistent with diminished pump output/pump efficiency/pump performance.

And;

Suspected device thrombus will be accompanied by 1 or more of the following events or interventions:

   i. Death
   ii. Stroke or TIA.
   iii. Arterial non-CNS thromboembolism.
   iv. De-novo need for inotrope therapy.
   v. Treatment with intravenous anti-coagulation (i.e., heparin), intravenous thrombolytics (i.e., tPA), or intravenous anti-platelet therapy (i.e., eptifibatide, tirofiban).
   vi. Pump replacement.
   vii. Pump explantation with or without exchange.
   viii. Pump deactivation without pump removal.
   ix. Operation to repair or replace any internal component of the circulatory support system.
   x. Urgent transplantation listing (immediate urgent listing for transplant).

2. **Confirmed device thrombus** is a major device-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 through 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.

   Para conduit device thrombus represents a special case of device malfunction whereby thrombus obstructs the outflow graft from the pump. This should be classified as major if the thrombus directly interferes with pump function by obstructing flow and if the pump is replaced because of the thrombus. The event should be classified as minor if there is visible thrombus with the preserved function of the pump but requires surgical intervention (difficult to define minor when it requires surgical intervention). In all instances, visual confirmation of the thrombus is sufficient for confirmation.

   If a suspected device thrombus event is ultimately confirmed through visual inspection following pump replacement, urgent transplantation or on autopsy following death, the event will be maybe reclassified to confirmed device thrombus.

The association of the device malfunction event should be classified as:

- **Patient-related**: (i.e., non-adherence with care of device or Instructions for Use, or its peripheral components, non-adherence with the anti-coagulation regimen**,** pro-coagulation abnormalities)
- **Management-related (**i.e., surgical protocol deviation, sub-optimal anti-coagulation)
- **Device-related:** (i.e., detected in a device at explant or on contrast studies or associated with hemolysis or other controller data consistent with device malfunction)

Abbreviations: MCS-ARC, Mechanical Circulatory Support, Academic Research Consortium; MCSD, mechanical circulatory support device; TIA, transient ischemic attack.

Table 6 MCS ARC Hemolysis Adverse Event

Minor Hemolysis

A plasma-free hemoglobin value greater than 20 mg/dl or a serum LDH level greater than two and one-half times (2.5 ×) 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 (see Major Hemolysis for a list of symptoms and findings) and thought not attributable to laboratory error.

Major Hemolysis

A plasma-free hemoglobin value greater than 20 mg/dl or a serum LDH level greater than two and one-half times (2.5 ×) 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 at least one 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 as per section on device malfunction

Note:

- Isolated LDH elevations should not be reported as hemolysis if attributable to laboratory error, hepatic or pulmonary dysfunction. If suspected, confirmatory testing of LDH, LDH isoenzymes and plasma-free hemoglobin within 24 hours should be obtained to rule out laboratory error.
- All causes of hemolysis should be reported regardless of whether they are thought attributable to the device or not.

The association of the hemolysis event should be classified as:

- **Patient related:** (i.e., hematologic abnormalities)
- **Management related:** (i.e., drug related, secondary pump or IABP related, pump malposition)

Device related: (i.e., related to pump thrombosis or device malfunction)

Abbreviations: IABP, intra-aortic balloon pump; LDH, lactate dehydrogenase; VAD, ventricular assist device.

indicate hemolysis if due to hepatic or pulmonary injury; therefore, the plasma-free hemoglobin level may substantiate hemolysis. In certain cases, however, the plasma-free hemoglobin elevation may also be inaccurate if the blood draw is traumatic and thus, should be repeated. Hemolysis as in the previous Intermacs definition has been categorized as minor and major in the MCS-ARC definition (Table 6 and Supplementary Material Figure S5 online).

Minor hemolysis reflects the elevation of biomarkers without clinical signs or symptoms and normal durable MCS device function. Major hemolysis is associated with abnormal pump function or clinical symptoms or signs. In the previous version of Intermacs, hemolysis was captured as a triggered event, meaning that the event was automatically recorded if the LDH level alone was above the threshold for the definition, and no conscious effort had to be made by clinicians to record the event. If the value was not entered, then hemolysis as an event may have been missed, and if the value was a false-positive, then the event was recorded even if non-existent. We recommended that this event be tracked as a specific consciously recorded event as opposed to automatically. It is critical that centers interpret LDH values in the context of the assay's upper limits of normal.[37,38]

MCS-ARC right heart Failure adverse event

The incidence of right HF following LVAD implantation varies from 3% to 35% depending on patient selection and definition of right HF.[40–43] In the overwhelming instances, right HF is present at the time of LVAD implantation and function worsens in the immediate peri-operative period from changes in right ventricular function owing to intraoperative insults or changes in pulmonary vascular resistance or both.[40] In addition, LVAD unloading of the left ventricle unloads the septal wall and reduces the septal contribution to right ventricular function, causing further impairment of right ventricular function.[40–43] In a minority of cases, the worsening of right heart function can lead to severe right HF, requiring right ventricular assist device support (RVAD) or prolonged pharmacologic support with inotropes and/or pulmonary vasodilators.[40–43] Right HF following LVAD implantation that requires RVAD support significantly reduces overall survival, increases morbidity, and reduces the success of a bridge-to-transplant strategy. Overall survival for patients requiring continued RVAD support is approximately 50% at 1 year and is significantly less than that for patients requiring LVAD support alone.[9,40–43]

The occurrence of right HF evolved in Intermacs from a recorded event to a condition that was automatically entered on the basis of an algorithm of certain conditions or manifestations having been recorded. As a condition, the presence and severity of right HF were based on the presence of clinical (ascites, edema, and elevated central venous pressure or right atrial pressure) and echocardiographic imaging findings and interventions required (diuretic or inotropic agents) for the right heart. Although this strategy of defining the right HF as a condition informed the investigator of late manifestations, the working definition was cumbersome particularly for clinical trials attempting to identify a discrete event. Therefore, the MCS-ARC definition of right HF is now returning to an event-based entry process to identify the right HF as an event following LVAD implantation (Table 7 and Supplementary Material Figure S6 online).

Table 7 MCS-ARC Right Heart Failure Adverse Event

Right Heart Failure

Early Acute Right Heart Failure

- Need for implantation of a temporary or durable RVAD (including ECMO) concomitant with LVAD implantation (RVAD implanted before the patient leaving the operating room).

Early post-implant right heart failure

- Need for implantation of a temporary or durable RVAD (including ECMO) within 30 days following LVAD implantation for any duration of time; or,
- Failure to wean from inotropic or vasopressor support or inhaled nitric oxide within 14 days following LVAD implantation or having to initiate this support within 30 days of implant for a duration of at least 14 days.
  - The primary diagnosis of right heart failure is made by the presence of at least two of the following clinical findings:
    - Ascites
    - Functionally limiting peripheral edema (> 2+)
    - Elevated estimated jugular venous pressure at least halfway up the neck in an upright patient.
    - Elevated measured central venous pressure or right atrial pressure (≥16 mm Hg)
  - or is associated with at least one of the following manifestations:
    - Renal failure with serum creatinine > 2 × baseline values.
    - Liver injury with an elevation of at least 2 × upper limit normal in AST/ALT or total bilirubin > 2.0.
    - SVO_2 < 50%.
    - Cardiac index < 2.2 liter/min/m^2.
    - Reduction in pump flow of > 30% from the previous baseline in the absence of mechanical causes such as cardiac tamponade or tension pneumothorax.
    - Elevated lactate >3.0 mmol/liter.
- Death occurring in patients within 14 days of LVAD implant who have not received an RVAD but who remain on inotropes or vasopressors at the time of death and meet criteria for the diagnosis of Right Heart Failure on the basis of the above clinical findings (2 criteria) or manifestations (1 criterion) will be considered to have early post-implant right heart failure at the time of death. The contribution of early post-implant right heart failure to the death (primary or secondary) will be made by the clinical care team.
  - For pediatric patients, the diagnostic criteria above may be modified as follows:
    - Primary diagnosis of RHF based on at least 2 of the following clinical findings
    - Ascites
    - Significant peripheral edema (+2)
    - Elevated JVP (visible in an upright patient) or hepatomegaly (3+ cm below costal margin)
    - Elevated CVP or RA pressure:
      - For age 10—18 years: CVP > 14 mm Hg
      - For age 5—10 years: CVP >12 mm Hg
      - For age < 5 years: CVP > 10 mm Hg
    - Or at least one of the following manifestations:
      - Renal failure indicated by serum creatinine 1.5 × above baseline.
      - Liver injury with an elevation of AST, ALT or total bilirubin of 2 × upper normal.
      - Decrease in pump flow of 30% from a recent baseline in the absence of tamponade.
      - We need to decrease the pump rate by 20% or more from a recent baseline owing to the poor filling of LVAD in a pulsatile system.
      - Cardiac Index < 2.2 liter/min/m^2.

Late RHF

- Need for implantation of an RVAD (including ECMO) greater than 30 days after an LVAD implantation. This may occur within the index hospitalization for LVAD implant or during subsequent rehospitalization for any diagnosis which resulted in a need for temporary or permanent right-sided mechanical assist devices.
- Hospitalization that occurs greater than 30 days post-implant and which requires intravenous diuretics or inotropic support for at least 72 hours and is associated with:
  - The diagnosis of right heart failure is made by the presence of at least two of the following clinical findings:
    - Ascites
    - Functionally limiting peripheral edema (>2+).
    - Elevated estimated jugular venous pressure at least halfway up the neck in an upright patient.
    - Elevated measured central venous pressure (>16 mm Hg).
  - or which is associated with at least one of the following manifestations:
    - Renal failure with serum creatinine > 2 × baseline value
    - Liver injury with an elevation of at least 2 × upper limit normal in AST/ALT or total bilirubin > 2.0
    - A reduction in pump flow of > 30% from the previous baseline in the absence of tamponade
    - SVO2 < 50%
    - Cardiac index < 2.2 liter/min/m2
    - Elevated lactate >3.0 mmol/liter

(*continued on next page*)

- For pediatric patients, the criteria should be modified as follows.
  - Requirement for intravenous diuretics or inotropic support of at least 72 hours to treat right heart failure that was not present continuously since implantation (must have been without intravenous diuretics and inotropic support for at least 7 consecutive days at some time following implantation of LVAD)
    - Diagnosis of RHF must be based on at least 2 of the following clinical findings
      - Ascites
      - Significant peripheral edema (+2)
      - Elevated JVP (visible in the upright patient) or Hepatomegaly (3+ cm below costal margin)
      - Elevated CVP or RA pressure
        - For age 10−18 years: CVP > 14 mm Hg
        - For age 5−10 years: CVP >12 mm Hg
        - For age < 5 years: CVP > 10 mm Hg
    - Or at least one of the following manifestations
      - Renal failure indicated by serum creatinine 1.5 × above baseline.
      - Liver injury with elevation of AST, ALT or Total Bilirubin of 2 × upper normal.
      - Decrease in pump flow of 30% from a recent baseline in the absence of tamponade.
      - Need to decrease pump rate by 20% or more from a recent baseline because of poor filling of LVAD in a pulsatile system.
      - Cardiac index < 2.2 liter/min/m^2.

The association of the RHF event should be classified as:
Patient-related: (e.g., pre-implant right heart failure, volume overload secondary to non-adherence with medical management, severe aortic regurgitation, cardiorenal syndrome, arrhythmia induced, pulmonary disease, elevated pulmonary vascular resistance).
Management-related: (e.g., related to implant surgery, volume overload, inotropic agent withdrawal).
Device-related: (e.g., associated with Pump malfunction, outflow graft compromise).

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; JVP, Jugular venous presure; LVAD, left ventricular assist device; RA, right atrium; RHF, right heart failure; RVAD, right ventricular assist device; SVO_2, mixed venous oxygen saturation.

The symptomatic, hemodynamic, and echocardiographic criteria to qualify for right HF will be retained from the original definition, however, a conscious decision to enter this event with its date of diagnosis will be required and it will no longer occur automatically. The new definition also provides some guidance through the recording of the associations with the right HF event to allow clinicians to identify pre-implant right HF leading to a planned vs unplanned RVAD implant.

Other adverse events

The original Intermacs definition of renal dysfunction was defined as either acute or chronic renal dysfunction, but the severity of renal dysfunction was not collected. The definition of renal dysfunction has been upgraded to include the severity of the renal compromise. In this newly proposed MCS-ARC renal dysfunction AE definition, the severity of renal dysfunction is sub-divided into 3 stages (Table 8). Unlike other AEs addressed in this consensus statement, we recommend that several other AEs that are tracked by Intermacs should continue to be included with little or no change in the substance of their definitions or data needing to be collected (Table 9 additional AEs). These include cardiac arrhythmia; respiratory failure; venous thromboembolism; wound dehiscence; arterial non-CNS thromboembolism, hypertension, and hepatic dysfunction. The definition of an occurrence of a psychiatric episode will follow the traditional diagnostic and statistical manual of mental disorders classifications.

The association of some of these AEs as being patient-related, management-related, or device-related in their origins will now be identified and collected. We recommend elimination of the need to track the Intermacs AEs for myocardial infarction, other AEs, and pericardial fluid collection. The event of cardiac tamponade will be captured under the MSC-ARC bleeding AE.

Short-term or temporary MCS devices

In recent years, there has been an increase of interest in the use of temporary MCS devices for specific sub-groups of patients.[44–47] Some cohorts that might benefit from temporary MCS devices are patients with myocardial infarction resulting in cardiogenic shock, patients with acute or acute-on-chronic left ventricular failure with cardiogenic shock with specific etiologies of HF, and patients with right HF (e.g., post-LVAD implantation or heart transplantation).[44–47] The MCS-ARC recognizes the importance and increasing usage of these devices and has, therefore, reformulated some of the AE definitions for these devices, including hemolysis and device malfunction. All other AE definitions for durable MCS devices noted above will apply for short-term or temporary MCS devices. Furthermore, because many devices are inserted percutaneously, definitions of the vascular access site AEs were adapted from the valve ARC.[18]

As of the date of publication, the short-term device definitions proposed in this consensus are specifically applicable to the following technologies: Impella (CP, 5.0, LD, RP) (Abiomed, Danvers, MA), Centrimag (Levitronix, Waltham, MA), and TandemHeart (LivaNova, London,

Table 8 MSC-ARC Renal Dysfunction Adverse Event

Acute Renal Dysfunction

- Stage 1
  - Increase in serum creatinine to 150% to 199% (1.5−1.99 × increase compared with baseline) or increase of > 0.3 mg/dl (> 26.4 mmol/liter) or
  - Urine output < 0.5 ml/kg/h for > 6 but < 12 hours.
- **Stage 2**
  - Increase in serum creatinine to 200% to 299% (2.0 × −2.99 × increase compared with baseline) or
  - Urine output < 0.5 ml/kg/h for > 12 but < 24 hours.
- **Stage 3**
  - Increase in serum creatinine to >300% (>3 × increase compared with baseline) or
  - Serum creatinine of > 4.0 mg/dl (>354 mmol/liter) with an acute increase of at least 0.5 mg/dl (44 mmol/liter) or
  - Urine output <0.3 ml/kg/h for >24 hours or
  - Anuria for >12 hours or
  - Need for renal replacement therapy (includes dialysis or ultrafiltration) regardless of above criteria.

Chronic Renal Dysfunction

An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for renal replacement therapy, either of which is sustained for at least 90 days.

The association of the renal dysfunction event should be classified as follows:

- **Patient-related: (**e.g., non-adherence to medical therapy resulting in renal dysfunction).
- **Management-related: (**e.g., overprescribing of diuretic therapy or administration of renal toxic drugs or contrast agents that result in renal dysfunction).
- **Device-related: (**e.g., device failure resulting in renal dysfunction).

Abbreviations: CNS, central nervous system; DSM, diagnostic and statistical manual of mental disorders; MCS-ARC, mechanical circulatory support, academic research consortium; VAD, ventricular assist device.

United Kingdom), but not for the intra-aortic balloon pump and extracorporeal membrane oxygenation (Table 10).

Discussion

This report summarizes an international and collaborative effort to update AE definitions that apply to the field of MCS. The updated AEs have been defined by domain experts in the field of cardiac surgery, cardiology, neurology, infectious diseases, and engineering. Where possible, the updated AE definitions have taken advantage of previously published definitions of AEs developed by the ARC for cardiac surgery, specifically those developed for the AEs for bleeding and neurologic events, for developing more global harmonization of AEs within the cardiovascular field, in general. The MCS-ARC solicited input from North American and international experts through the partnership with the STS and ISHLT Mechanically Assisted Circulatory Support Registry, the Japanese Registry for Mechanically Assisted Circulatory Support, and European Registry for Patients with MCS. Global harmonization of AE definitions is critical to the MCS field as more clinical trials evaluating safety with new devices are contemplated in centers around the World. In addition, AE definitions were modified for Pedimacs applications, where appropriate.

Where feasible, existing Intermacs definitions served as a solid foundation for the new MCS-ARC definitions, with the goal of not creating an additional burden on data collection. However, there were cases where more granularity was requested by domain experts, especially as the field considers clinical trials with MCS devices that are targeted to a population of patients with ambulatory HF that are characterized by Intermacs Profile 4–7.

Importantly, the MCS-ARC group agreed that for each major AE, there should be a determination regarding the associations that contributed to the event. This would be expressed as either patient-related, management-related, or device-related. The group believed that this additional insight to the probable contributory factors to the AE would provide critical information regarding patients' non-adherence or failure to follow the manual of operations for the device as a potential cause for an event, such as device malfunction. It will also help to guide the interpretation of the factors that are related to thrombosis when protocols for anti-coagulation cannot be followed. It is also possible that a significant AE burden exists pre-operatively in some patients with an MCS device and that these events are transmitted to the post-operative period and recorded in databases as new early events after the MCS device is implanted. The designation of AEs being patient-related may clarify these situations. For example, this association will aid in identifying those patients who present to surgery with significant pre-existing right HF and thus, can be identified as having patient-related factors as a cause for right HF after surgery. This helps to clarify the difference between a planned and unplanned RVAD at the time of surgery. Similarly, other examples exist in cases where pre-operative renal, hepatic, neurologic, and pulmonary complications are present pre-operatively.

Table 9 Other Adverse Events

MCS-ARC 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:

The association of the cardiac arrythmia event should be classified as:

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.
   - **Patient-related:** (e.g., recurrence of pre-operative arrhythmia non-adherence with medications).
   - **Management-related**: (e.g., related to uncorrected electrolyte imbalance, Swan Ganz malposition, secondary to cardiac tamponade).
   - **Device-related**: (e.g., Pump malfunction, malposition of pump, or inflow cannula).

MCS-ARC Respiratory Failure

Impairment of respiratory function requiring reintubation, tracheostomy, or the inability to discontinue ventilatory support within 6 days (144 hours) post-VAD implant. This excludes intubation for reoperation or temporary intubation for diagnostic or therapeutic procedures.

The association of the respiratory failure event should be classified as follows:

- **Patient-related: (**e.g., non-adherence to medical therapy resulting in respiratory failure).
- **Management-related: (**e.g., inadequate diuretic therapy resulting in respiratory dysfunction).
- **Device-related: (**e.g., device failure resulting in respiratory dysfunction).

MCS-ARC Venous Thromboembolism

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

MCS-ARC Wound Dehiscence

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

MCS-ARC Arterial non-CNS Thromboembolism

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by 1 or more of the following: This definition excludes neurologic events.

1) standard clinical and laboratory testing
2) operative findings
3) autopsy findings

MCS-ARC Hepatic Dysfunction

An increase in any two of the following hepatic laboratory values (total bilirubin, AST, and ALT) to a level greater than 3 times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death).

MCS-ARC Hypertension: Adult

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).

Pediatric:

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 on the discontinuation of the treatment.

MCS-ARC 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.

The psychiatric event should be classified according to the DSM 5 classification:

- Axis I: Clinical disorders, including anxiety disorders, mood disorders, schizophrenia and other psychotic disorders.
- Axis II: Personality disorders and mental retardation.
- Axis III: General medical conditions.
- Axis IV: Psychosocial and environmental problems.

Abbreviations: CNS, central nervous system; DSM, diagnostic and statistical manual of mental disorders; MCS-ARC, Mechanical Circulatory Support, Academic Research Consortium; VAD, ventricular assist device.

The success of the utilization of the new MCS-ARC definitions for Intermacs will depend not only on global acceptance by clinicians, device manufacturers, and the regulatory agencies but also on the development of a clear and detailed user guide. This guide will need to provide guidance to the coordinators and clinicians who make decisions about each AE and whether the clinical presentation meets the definitions. Although, in many cases, these definitions seem complex, in reality, filling out Intermacs fields will be far simpler utilizing drop-down boxes for choices. In many cases, the exact forms for data collection may require only modest modifications, with

Table 10 Short-Term or Temporary Mechanical Circulatory Support (MCS) Device-Specific Adverse Events

Hemolysis

Minor Hemolysis: a plasma-free Hgb value >20 but < 40 mg/dl or a serum lactate dehydrogenase (LDH) level greater than 2.5 × 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: Two plasma-free Hgb values > 40 mg/dl with the 2 readings taken within a single 48-hour period. If plasma-free Hgb not available, hemolysis will be defined by the combination of clinical signs (see below) and laboratory testing including increased LDH, increased bilirubin and decreased hemoglobin (all 3 required). It requires the presence of one or more of the following conditions:

- Hemoglobinuria
- Anemia
- Hyperbilirubinemia
- Pump malfunction and/or abnormal pump parameters

Vascular Access Site Adverse Events

These Adverse events (AEs) related only to devices inserted through the percutaneous route.

Proposed Definitions:

Minor Complications: Any of the events below that required a diagnostic investigation to be confirmed and were treated without the need for surgical intervention.

1. Pseudo-aneurysm
2. Arteriovenous fistula
3. Vessel thrombosis/Distal embolization
4. Vessel dissection, perforation or rupture
5. Vessel stenosis
6. Cannulation site bleeding
7. Limb ischemia
8. Vascular access site infection

Major Complications: Any of the events below that required a diagnostic investigation to be confirmed and required surgical or endovascular intervention.

1. Pseudo-aneurysm
2. Arteriovenous fistula
3. Vessel thrombosis/Distal embolization
4. Vessel dissection, perforation or rupture
5. Vessel stenosis
6. Cannulation site bleeding (would have to fulfill durable device bleeding definition)
7. Limb ischemia
8. Vascular access site infection

Device Malfunction

Device Failure: Unexpected and sudden stop of the functioning of the pump that cannot be corrected by restarting the pump following recommended instructions. It can be caused by the failure of any of the components of the system and impacts negatively on the treatment of the patient. Includes device malfunction due to device thrombus.

Device Malfunction: Unexpected change in device performance that is contradictory to the labeling and/or negatively impacts the treatment of the patient, when the device is used in adherence to the instructions for use (IFU). A stoppage that can be corrected by restarting the pump would fall under this category. Includes device malfunction due to device thrombus.

The association of the Short-Term or Temporary MCS-Specific Adverse Event should be classified as follows:

- **Patient-related: (**e.g., non-adherence to medical therapy)
- **Management-related: (**e.g., improper anti-coagulation management resulting in thrombosis or stroke)
- **Device-related: (**e.g., device failure)

more detailed instructions on how to determine the presence of an AE.

This is an effort to once again harmonize and refine definitions of AEs. Furthermore, the MCS-ARC has tried to improve the granularity of some AEs either by changing definitions or by adding a possible attribution. MCS will continue to evolve in the future, and indeed the MCS-ARC intends to promote this and improve intertrial comparability between devices because of harmonized end-points.

A major addition to these definitions included recognition of the need to track events in patients receiving temporary MCS as none existed to date except for the Impella percutaneous pump managed by the Abiomed. Percutaneous complications were included utilizing the valvular ARC definitions as well as definitions from the Abiomed registry.

To date, considerable experience has been obtained in the field of MCS. Major safety issues remain with MCS devices and the overall AE burden for patients receiving durable and temporary MCS devices remains high. Currently, bleeding, stroke, device infection, device malfunction, and right HF remain the major obstacles to broader

adoption of this therapy, both for existing indications and for newer indications for patients with less-advanced stages of HF. We believe that the new MCS-ARC definitions presented here, largely focusing on the 5 major AEs associated with MCS therapy, provide an updated platform in which to assess MCS device therapy. Limitations in previous definitions were recognized and evaluated by experts in the field with modifications made to nearly all definitions. We believe that the adoption of new MCS-ARC definitions for AEs will contribute to improved patient outcomes and MCS device development.

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Supplementary materials

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