Objectives
Upon completion of the STS Intermacs Database sessions, participants will be able to:

- Describe the Audit process
- Discuss the Quality Assurance Report and how to use it
- Explain the version upgrade
- Summarize how to capture and code chronic GI bleeding
- Identify different Intermacs patient profiles
- Summarize how to capture and code chronic driveline infections
- Identify temporary devices on the preimplant form
Adverse Event Definitions

Francis D. Pagani MD PhD
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Adverse Events

• AE reporting is a critical component of INTERMACS to accurately understand patient outcomes
• AE definitions are in need of updating as LVAD therapy evolves
  - e.g., totally implantable systems
• Goal to improve accuracy and ease of reporting and reduce data entry burden where possible
• Global harmonization of AE definitions
Adverse Events

• Recent national initiative to revise Adverse Event definitions in the MCS field
• Academic Research Consortium
• ARC – MCS Adverse Event Definitions
Academic Research Consortium (ARC)

The purpose of the ARC is to create a dynamic, transparent and collaborative forum for stakeholders to develop consensus definitions and standard nomenclature in pivotal clinical trials of medical devices and to disseminate such definitions and recommended processes into the public domain.

The ARC was founded in 2006 as an informal collaboration between clinical experts and 4 academic research organizations - the Harvard Clinical Research Institute (HCRI), Cardialysis, the Cardiovascular Research Foundation (CRF), and the Duke Clinical Research Institute (DCRI) - with advisory participation of the U.S. Food and Drug Administration (FDA) and other regulatory bodies across continents. Thought leaders from the medical industry are centrally involved as non-voting participants.
Adverse Events

• Refinement and clarification of current clinically relevant key AE definitions
• Use of information provided through other ARC initiatives to adopt and harmonize AE definitions where possible:
  - Neurologic ARC
  - Bleeding ARC
  - Valve ARC
• Provision of clear guidance for personnel recording the events
Adverse Events

• Development of an assignment of cause, based largely upon subjective criteria, whether the AE is:
  - device related
  - patient related
  - related to management practices.

• The goal of this assignment is to provide improved insight into possible contributing causes of AE’s in order to develop effective solutions whether they represent changes to best management practices, refinements to patient selection or education or improvements in device technology.
Standardized Bleeding Definitions for Cardiovascular Clinical Trials
A Consensus Report From the Bleeding Academic Research Consortium

Roxana Mehran, MD; Sunil V. Rao, MD; Deepak L. Bhatt, MD, MPH; C. Michael Gibson, MS, MD; Adriano Caixeta, MD, PhD; John Eikelboom, MD, MBBS; Sanjay Kaul, MD; Stephen D. Wiviott, MD; Venu Menon, MD; Eugenia Nikolsky, MD, PhD; Victor Serebruany, MD, PhD; Marco Valgimigli, MD, PhD; Pascal Vranckx, MD; David Taggart, MD, PhD; Joseph F. Sabik, MD; Donald E. Cutlip, MD; Mitchell W. Krucoff, MD; E. Magnus Ohman, MD; Philippe Gabriel Steg, MD; Harvey White, MB, ChB, DSc

Circulation. 2011;123:2736-2747
Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials

An Academic Research Consortium Initiative

Alexandra J. Lansky, MD, a,b,c Steven R. Messé, MD, d Adam M. Brickman, PhD, e Michael Dwyer, PhD, f H. Bart van der Worp, MD, PhD, g Ronald M. Lazar, PhD, e Cody G. Pietras, MS, a,b Kevin J. Abrams, MD, h Eugene McFadden, MD, i Nils H. Petersen, MD, j Jeffrey Browndyke, PhD, k Bernard Prendergast, MD, l Vivian G. Ng, MD, a,b Donald E. Cutlip, MD, m Samir Kapadia, MD, n Mitchell W. Krucoff, MD, o Axel Linke, MD, p Claudia Scala Moy, PhD, q Joachim Schofer, MD, r Gerrit-Anne van Es, PhD, s Renu Virmani, MD, t Jeffrey Popma, MD, u Michael K. Parides, PhD, u Susheel Kodali, MD, v Michel Bilello, MD, PhD, w Robert Zivadinov, MD, PhD, x Joseph Akar, MD, PhD, a Karen L. Furie, MD, MPH, x Daryl Gress, MD, y Szilard Voros, MD, z Jeffrey Moses, MD, y David Greer, MD, j John K. Forrest, MD, a David Holmes, MD, aa Arie P. Kappetein, MD, PhD, bb Michael Mack, MD, cc Andreas Baumbach, MD
INTERMACS Adverse Event Definitions: Adult and Pediatric patients

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

- $\geq 50$ kg: $\geq 4U$ packed red blood cells (PRBC) within any 24 hour period during first 7 days post implant.
- $< 50$ kg: $\geq 20$ 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).
Major Bleeding Adverse Event

• INTERMACS definition of a Bleeding Adverse Event is partly defined on need for transfusion

• Thus, a significant GI bleeding during the implant hospitalization that did not result in death, re-operation or need for transfusion would not necessarily meet the INTERMACS definition

• 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
<table>
<thead>
<tr>
<th>Type 5</th>
<th>Type 5A</th>
<th>Fatal bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious</td>
</tr>
<tr>
<td></td>
<td>Type 5B</td>
<td>Fatal bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation</td>
</tr>
</tbody>
</table>
Device Malfunction Adverse Event

• The new definition of Device Malfunction categorizes events into Major and Minor severity.

• 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 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 prior definition.
Any component of the MCS device ceases to operate to its designed specification or otherwise fails to perform as intended.

**Definition of Minor Device Malfunction**

Inadequately functioning external components which require repair or replacement but do not result in the situations 1-5 as in the definition of Major Device Malfunction.

**Major Device Malfunction**

Device malfunction resulting in:
1. Death
2. Hospitalization, emergency room visit or prolongation of hospitalization, or escalation of level of care in an ongoing hospitalization (e.g., transfer to the intensive care unit)
3. Life-threatening event (i.e., stroke, cardiac arrest, heart failure, syncope or near syncopal event, arrhythmia, etc.)
4. Significant disability or incapacity
5. Requires an intervention to prevent impairment/damage including:
   a. Urgent transplantation listing (immediate urgent listing for transplant)
   b. Pump replacement.
   c. Pump explant.
   d. Pump disconnection 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.

**Suspected Device Thrombosis**

Thrombus is confirmed by direct visualization of the blood contacting surfaces of any device component at the time of explant or exchange or by incontrovertible imaging evidence.

**Confirmed Device Thrombus**

If a Suspected Device Thrombus event is ultimately confirmed through visual inspection following pump replacement, urgent transplantation or upon autopsy following death, the event will be reassigned to Confirmed Device Thrombus.

**Suspicion of Pump Thrombus?**

- **YES**
  - Major Device Malfunction
- **NO**
  - Suspected Device thrombosis

**At least one of the following criteria**

- Presence of hemolysis (including elevation of biochemical markers of hemolysis, e.g., lactate dehydrogenase of plasma free hemoglobin, or clinical evidence of hemolysis, e.g., hemoglobinuria)
- Presence of heart failure not explained by structural heart disease
- Abnormal pump parameters

Accompanied with at least one of following events/interventions:

- Death
- Stroke
- Atrial non-CNS thromboembolism
- De-novo need for inotrope therapy
- Treatment with intravenous anticoagulation, intravenous thrombolytic/antiplatelet therapy
- Pump replacement
- Pump explantation
- Pump disconnection without pump removal
- Urgent transplantation listing (immediate urgent listing for transplant)
Right Heart Failure Adverse Event

• Right Heart Failure is currently recorded as a "Condition"
• If key variables are "checked" that define "Symptoms" and "Manifestations", the condition of RHF is present
• Does not require the center to report the presence or absence of RHF
• Difficult to include this AE definition in clinical trials and presented issues with the FDA
• The new definition will require reporting “RHF Adverse Event”
Presence ≥2 of the following clinical findings:
- Ascites
- Functionally limiting peripheral edema (> 2+)
- Elevated estimated jugular venous pressure at least half way up the neck in an upright patient.
- Elevated measured central venous pressure or right atrial pressure (≥ 16 mm Hg)
- OR at least one of the following manifestations:
  - Renal failure: serum creatinine > 2 X baseline values
  - Liver injury: elevation of at least 2X upper limit normal in AST/ALT or Total Bilirubin > 2.0
  - A reduction in pump flow of > 30% from previous baseline in absence of mechanical causes
  - SVO²: <50%
  - Cardiac index: <2.2 L/min/m²
  - Elevated lactate: >3.0 mm/L

Within operating room

Right Heart Failure

Outside operating room

Early Acute Right Heart failure

Temporary or durable RVAD implantation (including ECMO) concomitant with LVAD implantation

Early Post-Implant Right Heart Failure

≤ 30 days post-implant of LVAD

Temporary or durable RVAD implantation (including ECMO) ≤ 30 days following LVAD implantation

• Failure to wean from inotropic/vasopressor support or inhaled pulmonary vasodilators within 14 days after LVAD implantation
• OR initiation of inotropic/vasopressor support with 30 days post implant for ≥14 days

Death occurring in patients
• within 14 days of LVAD implantation,
• without RVAD but with inotropes/vasopressors,
• attributed to Right Heart Failure by the clinical team

Late Right Heart Failure

> 30 days post-implant of LVAD

Implantation of an RVAD (including ECMO) >30 days after an LVAD implantation

Hospitalization >30 days post-implant requiring intravenous diuretics and/or inotropic support for ≥ 72 hours
Summary

• International and collaborative effort to update AE definitions applicable to the MCS field

• Defined by domain experts in the field of cardiac surgery, cardiology, neurology, ID and engineering

• Where possible, the updated AE definitions have taken advantage of previously published definitions of AEs developed by the ARC
  - Bleeding
  - Neurological events

• Developing more global harmonization of AEs
Summary

• The MCS-ARC solicited input from North American as well other international experts through the partnership with the:
  - International Society for Heart and Lung Transplantation
  - The Society for Thoracic Surgeons
  - International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support Registry
  - Japanese Registry for Mechanically Assisted Circulatory Support
  - European Registry for Patients with Mechanical Circulatory Support

• Global harmonization of AE definitions is critical to the MCS field
Summary

• Where feasible, existing INTERMACS definitions served as a solid foundation for the new MCS-ARC definitions with the goal of not creating additional burden on data collection.

• There were, however, 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 congestive heart failure that are characterized by Intermacs Profile 4 or higher.
Questions?
Neurological Dysfunction

Ischemic Stroke

Type 1

Type 1a

Ischemic Stroke with Hemorrhagic conversion

Type 1aH

Ischemic Stroke

Type 1b

Symptomatic Subarachnoid Hemorrhage

Type 1c

Symptomatic Intracerebral Hemorrhage

Type 1d

Stroke, not otherwise specified

Type 1e

Symptomatic Hypoxic-ischemic injury

Type 1f

Symptomatic Subdural Hemorrhage

Covert CNS Infection: Acutely asymptomatic brain or spinal cord injury detected by neuroimaging

Covert CNS Infection with Hemorrhagic Conversion

Covert CNS Hemorrhage

Covert CNS Infarction

Covert CNS Infarction with Hemorrhagic Conversion

Covert CNS Hemorrhage

Neurologic Dysfunction (acutely symptomatic) without CNS Injury

Classified as Acute Severity, Recovery and long-term disability

Acute severity

- Mild neurologic dysfunction: NHSS 0-5
- Moderate neurologic dysfunction: NHSS 6-14
- Severe neurologic dysfunction: NHSS 215

NOTE: Severity assessment should be performed at the time of diagnosis of any overt CNS Injury (Types 1) to ensure accurate classification.

Stroke Recovery or Recovery

- Stroke with complete recovery: A modified Rankin Score (MRS) at 30-90 days of 0 or 1 in the absence of any ongoing new symptoms due to the stroke.
- Partial Stroke: Death resulting from a stroke where the cause of death is attributable to the stroke.
- Disabling stroke: An MRS of 2 or 3 at 30-90 days with an increase of at least 1 point compared to the pre-stroke baseline.
- Non-disabling stroke: An MRS of 0, 1, or 2 at 30-90 days with an increase of at least 1 point 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 days or 14 days after the stroke event.
Device malfunction does not apply to routine maintenance of peripheral components.

**Major Device Malfunction**

Definition of Major Device Malfunction

Device malfunction resulting in:
1. Death
2. Hospitalization, emergency room visit or prolongation of hospitalization, or escalation of level of care in an ongoing hospitalization (e.g., transfer to the intensive care unit)
3. Life-threatening event (i.e., stroke, cardiac arrest, heart failure, syncope or near syncopal event, arrhythmia, etc.)
4. Significant disability or incapacity
5. Requires an intervention to prevent impairment/damage including:
   a. Urgent transplantation listing (immediate urgent listing for 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

**Minor Device Malfunction**

Definition of Minor Device Malfunction

Inadequately functioning external components which require repair or replacement but do not result in the situations 1-5 as in the definition of Major Device Malfunction

**Suspected Device Thrombosis**

At least one of the following criteria:
- Presence of hemolysis (including elevation of biochemical markers of hemolysis; e.g., lactate dehydrogenase of plasma free hemoglobin, or clinical evidence of hemolysis; e.g., hemoglobinuria)
- Presence of heart failure not explained by structural heart disease
- Abnormal pump parameters

Accompanied with at least one of following events/interventions:
- Death
- Stroke
- Arterial non-CNS thromboembolism
- De-novo need for inotrope therapy
- Treatment with intravenous anti-coagulation, intravenous thrombolytics/antiplatelet therapy
- Pump replacement
- Pump explantation
- Pump deactivation without pump removal
- Urgent transplantation listing (immediate urgent listing for transplant)

**Confirmed Device Thrombus**

Thrombus is confirmed by direct visualization of the blood contacting surfaces of any device component at the time of explantation/exchange or by incontrovertible imaging evidence.

**If a Suspected Device Thrombus**: event is ultimately confirmed through visual inspection following pump replacement, urgent transplantation or upon autopsy following death, the event will be reclassified to Confirmed Device Thrombus.
Presence ≥2 of the following clinical findings:
- Ascites
- Functionally limiting peripheral edema (>2+)
- Elevated estimated jugular venous pressure at least half way up the neck in an upright patient.
- Elevated measured central venous pressure or right atrial pressure (≥ 16 mm Hg)
- OR at least one of the following manifestations:
  - Renal failure: serum creatinine > 2 X baseline values
  - Liver injury: elevation of at least 2X upper limit normal in AST/ALT or Total Bilirubin > 2.0
  - A reduction in pump flow of > 30% from previous baseline in absence of mechanical causes
  - Cardiac index: <2.2L/min/m²
  - Elevated lactate: >3.0 mm/L

Related to
- Examples
  - Patient: pre-implant right heart failure, volume overload secondary to non-compliance with medical management, severe aortic regurgitation, cardiorenal syndrome, arrhythmia induced pulmonary disease, elevated pulmonary vascular resistance
  - Management: Related to implant surgery, volume overload, inotropic agent withdrawal
  - Device: Associated with Pump malfunction, outflow graft compromise
Definition of Hemolysis

> 72 hours post-implant (at least one criterion):
  - Plasma-free hemoglobin > 20mg/dL
  - LDH > 2.5 times upper limit*

*Isolated LDH elevations should not be reported as hemolysis if attributable to laboratory error, hepatic or pulmonary dysfunction. If suspected, confirmatory testing of LDH and plasma-free Hemoglobin within 24 hours should be obtained to rule out laboratory error.

---

-related-boxes---

**Minor Hemolysis**

- No symptoms of hemolysis

**Major Hemolysis**

- Hemoglobinuria ("tea-colored urine")
- Anemia
- Hyperbilirubinemia (total bilirubin > 2 mg/dL, with predominantly indirect bilirubin)
- Pump malfunction / abnormal pump parameters

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<table>
<thead>
<tr>
<th>Related to</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Hematologic abnormalities</td>
</tr>
<tr>
<td>Management</td>
<td>Drug related, secondary pump / IABP related, pump malposition</td>
</tr>
<tr>
<td>Device</td>
<td>Related to pump thrombosis / device malfunction</td>
</tr>
<tr>
<td>Type</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Type 1</td>
<td>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.</td>
</tr>
<tr>
<td>Type 2</td>
<td>Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging a condition alone) that does not fit the criteria for Type 3, 4, or 5 but does meet at least one of the following criteria:</td>
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<tr>
<td></td>
<td>- Requiring nonsurgical, medical intervention by a healthcare professional</td>
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<td></td>
<td>- Leading to hospitalization or increased level of care</td>
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<td></td>
<td>- Prompting evaluation.</td>
</tr>
<tr>
<td>Type 3</td>
<td>One or more of the following criteria with bleeding as cause:</td>
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<tr>
<td></td>
<td>- A drop of 3 to &lt; 5 g/dL (1.86 to 3.3 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>- Any transfusion with overt bleeding</td>
</tr>
<tr>
<td>Type 3A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>One or more of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>- Hemoglobin drop 5 g/dL (1.86 mmol/L) or greater (prolonged hemoglobin drop is related to bleed)</td>
</tr>
<tr>
<td></td>
<td>- Cardiac tamponade</td>
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<tr>
<td></td>
<td>- Bleeding requiring surgical intervention for control (excluding dental/anasal/skin/hemorrhoid)</td>
</tr>
<tr>
<td></td>
<td>- Bleeding requiring intravenous vasodilatory agents.</td>
</tr>
<tr>
<td>Type 3B</td>
<td></td>
</tr>
<tr>
<td>Type 4</td>
<td>LVAD-implantation-related bleeding (includes concomitant cardiac or non-cardiac surgical procedures):</td>
</tr>
<tr>
<td></td>
<td>- Reoperation after closure of sternotomy for the purpose of controlling bleeding</td>
</tr>
<tr>
<td></td>
<td>- ≥ 50 kg: ≥ 4U packed red blood cells within any 48-hour period during first 7 days post implant.</td>
</tr>
<tr>
<td></td>
<td>- &lt; 50 kg: ≥ 20 cc/kg packed red blood cells within any 24-hour period during first 7 days post</td>
</tr>
<tr>
<td></td>
<td>- Chest tube output &gt; 2L within a 24-h period.</td>
</tr>
<tr>
<td>Type 5</td>
<td>Fatal bleeding:</td>
</tr>
<tr>
<td></td>
<td>- Probable fatal bleeding: no autopsy or imaging confirmation but clinically suspicious</td>
</tr>
<tr>
<td></td>
<td>- Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Related to</th>
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</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Coagulopathy unrelated to surgical technique, noncompliance with anticoagulation medication resulting in inappropriate levels of anticoagulation.</td>
</tr>
<tr>
<td>Management</td>
<td>Surgical technique related, hypertension, bleeding in the setting of inappropriate levels of anticoagulation.</td>
</tr>
<tr>
<td>Device</td>
<td>Bleeding from the outflow graft, apical connector or other internal components.</td>
</tr>
</tbody>
</table>
Clinical evidence of infection (pain, fever, erythema, drainage, leukocytosis or radiological findings consistent with infection) coupled with the need to treat with antimicrobial therapy.

### MCS specific infections

#### Percutaneous Site Infections
- **Superficial Driveline Infection**
  - A positive culture from the skin surrounding the drive line **AND**
  - The driveline exit site may have drainage and/or the surrounding skin may have erythema.
  - The epithelialization of the driveline 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 Driveline Infection**
  - A positive culture from the driveline exit site deep to the epithelium

#### Infection of implantable components
- **External Surface**
  - A positive culture from the tissue surrounding the external housing of a pump or one of its components (controllers, batteries, etc.) implanted within the body

- **Blood contacting surfaces**
  - Infection of blood-contacting internal surfaces of the VAD including inflow/outflow grafts: documented by positive blood cultures or radiographic or echocardiographic evidence of vegetation in blood flow path of the pump.

### non-MCS infections

#### Infective Endocarditis
- Positive blood cultures and positive echocardiography for mass or vegetation on native valves or implantable cardio defibrillator (ICD) pacemaker leads

#### Bloodstream Infection
- Positive blood culture with no other source identified
- Non-VAD or CVC related (definitions CDC/NHSN2)

#### Mediastinitis
- Deep sternal wound infection (isolated).
- Deep sternal wound infection involving MCS device components (continuous with mediastinum or already situated in the mediastinum). May be contiguous with implanted components of the MCS device

#### Superficial Mediastinal/Thoracotomy Wound Infection
- Mediastinitis definitively due to another cause (e.g., esophageal perforation during endoscopy, contiguous with empyema).
- Infection involving only skin, subcutaneous fat and muscle of implant incision.

#### Other infections
- Other infections: i.e.: pneumonia, urinary tract infections

### 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 antimicrobial therapy PLUS:
  - Positive blood cultures **AND/OR ≥ 2 of the following criteria:**
    - PaO2/FIO2<400 or respiratory rate ≥12/22/min or ventilated respiratory support
    - Hypotension with systolic BP < 100 mmHg or MAP ≤65 mmHg.
    - 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

### Related to
- **Examples**
  - **Patient**
    - non-compliance or poor management of driveline exit site, indwelling catheters, IV drug abuse, aspiration
  - **Management**
    - Improper tunneling, contamination of intraoperative site, prolonged intubation
  - **Device**
    - Associated with pump malfunction, outflow graft compromise