

Appendix 2. Tertiary outcomes definition

Acute respiratory distress syndrome: Defined based on degree of hypoxemia: mild ($200 \text{ mm Hg} < \text{PaO}_2/\text{FIO}_2 \leq 300 \text{ mm Hg}$), moderate ($100 \text{ mm Hg} < \text{PaO}_2/\text{FIO}_2 \leq 200 \text{ mm Hg}$), and severe ($\text{PaO}_2/\text{FIO}_2 \leq 100 \text{ mm Hg}$).

Congestive Heart failure (CHF): A documented history of CHF and medications for the treatment of CHF, such as diuretics (i.e., furosemide (Lasix™), +/- ACE inhibitors (i.e., ramipril (Altace™), etc.), or angiotensin 2 receptor blocker (i.e., losartan). Note that the use of these drugs does not necessarily mean that the patient has CHF.

ST elevation MI (STEMI): MI patient with chest discomfort or other ischaemic symptoms that develop ST elevation in two contiguous leads on ECG.

Non-ST elevation MI: MI patient with chest discomfort or other ischaemic symptoms without ST elevation in two contiguous leads on ECG.

Pneumonia (includes hospital-acquired pneumonia and Ventilator associated pneumonia): Definite infection (radiographic evidence of pulmonary abscess and positive needle aspirate OR histological proof on open lung biopsy or at post mortem), probable infection (positive culture of a pathogen known to cause pneumonia from a sputum or endotracheal aspirate specimen, from bronchial washings, bronchoalveolar lavage or bronchoscopy (regardless of quantitation)), possible infection (no microbial confirmation, with a clinical course compatible with hospital-acquired pneumonia and ventilator-associated pneumonia).

Bacteremia: The presence of viable bacteria in the circulating blood detected by hemoculture.

Surgical site infection: (i) Superficial: Within 30 days after surgery AND involves only skin and subcutaneous tissue of the incision AND patient has at least one of the following: a) purulent drainage from the superficial incision, b) organisms identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a microbiological method, c) superficial incision deliberately opened by a surgeon/physician and testing is not performed AND patient has at least one of the following: pain or tenderness, localized swelling, erythema, or heat, d) diagnosis of a superficial incisional surgical site infection. (ii) Deep: Within 30 or 90 days after surgery AND involves deep soft tissues of the incision, AND patient has at least one of the following a) purulent drainage from the deep incision, b) deep incision that spontaneously dehisces or is deliberately opened or aspirated by surgeon/physician and organism identified by microbiological method AND patient has at least one of the following: fever

(>38 °C), localized pain or tenderness, c) an abscess or other evidence of infection involving deep incision detected on gross anatomical or histopathologic exam.

Convulsion/seizure: A seizure is a brief episode that can range from uncontrolled jerking movements (convulsive seizure) to a subtle momentary loss of awareness (absence seizure). Seizures can occur in people who do not have epilepsy for reasons such as brain trauma, drug use, elevated body temperature (febrile seizure), or hypoglycemia.

Meningitis or Ventriculitis: At least one of the following criteria: 1) organism(s) identified from CSF by microbiological method, 2) patient has at least 2 of the following: fever (>38.0 °C) or headache, meningeal signs, cranial nerve signs, AND at least one of the following: a) increased white cells, elevated protein, and decreased glucose in CSF, b) organism(s) seen on Gram stain of CSF, c) organism(s) identified from blood by microbiological method, d) diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for organism.

Brain abscess: At least one of the following criteria: 1) organism(s) identified from brain tissue by microbiological testing method, 2) patient has an abscess or evidence of intracranial infection on gross anatomic or histopathologic exam, 3) patient has at least 2 of the following: headache, dizziness, fever (>38.0 °C), focal neurological signs, altered level of consciousness, or confusion, AND at least one of the following: a) organisms detected on microscopic examination of brain tissue, b) evidence suggestive of infection on imaging test (if equivocal supported by clinical correlation), c) diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for organism.

Sepsis: Life-threatening organ dysfunction caused by a dysregulated host response to infection.

Septic shock: A subclass of sepsis where circulatory and cellular/metabolic abnormalities are severe enough (persistent hypotension requiring vasopressors to maintain MAP \geq 65 mm Hg, and with a serum lactate level >2 mmol/L despite volume resuscitation) to substantially increase mortality.

Deep vein thrombosis (proximal DVT): Partially or completely incompressible venous segment of the proximal venous system, assessed at six sites (common femoral, proximal, middle, and distal superficial femoral, and popliteal veins and the venous trifurcation) by Doppler ultrasound. Wall thickening is not diagnostic of DVT.

Pulmonary embolism (PE): Definite (intraluminal filling defect on chest CT scan, a high-probability ventilation-perfusion scan, or autopsy finding), probable (high clinical suspicion and either no test results or nondiagnostic results on noninvasive testing), possible (clinical suspicion and nondiagnostic results on noninvasive testing).

Major bleeding: Defined as hemorrhage occurring at a critical site (i.e., intracranial, pericardial, or retroperitoneal), resulting in hypovolemic shock (i.e., ruptured abdominal aortic aneurysm, upper or lower GI bleed), resulting in the need for a major therapeutic intervention (i.e., surgery), requiring at least 2 units of RBC concentrates, or resulting in death.

Stroke: Poor blood flow to the brain resulting in cell death. There are two principle types of stroke: ischemic, due to lack of blood flow, and hemorrhagic, due to bleeding (or intracranial hemorrhage (ICH)).

Transfusion reactions: The most common complications of transfusions are febrile non-hemolytic reactions, and allergic reactions with urticaria. The most serious complications include an anaphylactic reaction, transfusion-associated cardiac overload (TACO), transfusion-related acute lung injury (TRALI), and acute hemolytic reaction due to ABO incompatibility. Transmission of infectious organisms (viral, bacterial, prion or parasitic) is also possible.

Febrile non-hemolytic reactions:

Fever (> 1 °C with respect to base temperature) with or without shivering at the end of the transfusion or shortly afterwards, that can be accompanied by tachycardia.

- No drop in blood pressure, no lumbar pain, no urticaria, no bronchospasm

Allergic reactions with urticaria:

Urticaria and pruritis at the end of the transfusion, rarely with cough or slight difficulty breathing.

- No drop in blood pressure, no chest tightness, no angioedema

Anaphylactic reaction:

Can happen soon after the start of transfusion. Urticaria, general malaise, chest tightness, edema of the face and glottis, difficulty breathing, drop in blood pressure, bronchospasm.

- Not necessarily with fever initially.

Transfusion-Associated Cardiac Overload (TACO):

Dyspnea during or after the transfusion with tachycardia, crackling sounds at base of lungs ± S3 galop. Sometimes with bronchospasm. Edema/overload on chest X-ray.

- No fever, no drop in pressure, no urticaria.

Transfusion-related acute lung injury (TRALI):

Dyspnea 2–6 h post-transfusion with progressive severe respiratory distress requiring O₂ and mechanical ventilation. Diffuse bilateral infiltrations on chest X-ray. Can present with fever and hypotension.

- No urticaria or angioedema. Difficult to distinguish from acute cardiogenic pulmonary edema.

Acute hemolytic reaction due to ABO incompatibility:

Typically 10–20 min after the start of transfusion. Sudden severe malaise with chest tightness, lumbar pain, fever, dyspnea, tachycardia and drop in pressure.

- No urticaria, no angioedema, no bronchospasm, no crackling in lungs on auscultation.

Transmission of infectious organisms (viral, bacterial, prion or parasitic) is also possible.

Note that expected events include transfusion reactions and therefore a transfusion reaction should not be reported as an SAE.