Endpoints / Event Definitions

5.1. Death

All deaths will be adjudicated and classified as cardiovascular, non- cardiovascular or undetermined. The intent of the death adjudication process is to capture all deaths with a potential cardiovascular cause (underlying, contributing and proximate) and to exclude those deaths where causality is clearly not cardiovascular and also unrelated to or precipitated by a cardiovascular event or underlying condition such as a terminal cancer patient admitted to a hospice unit, suicide, homicide, or sepsis.

Cardiovascular deaths are defined as all deaths excluding those for which the principal and underlying cause is solely non-cardiovascular. Any death for which a cardiovascular contributing cause is suspected will also be considered a cardiovascular death.

All deaths, both cardiovascular and non-cardiovascular, will be classified by primary causality. Cardiovascular cause of death includes myocardial infarction; sudden cardiac death; heart failure or cardiogenic shock; death due to other cardiovascular causes; complications of cardiac surgery; complications of non-surgical revascularization; hemorrhage (intracranial, or related to antithrombotic therapy) stroke; aortic aneurysm rupture; peripheral arterial disease and unexpected. Non-cardiovascular cause of death includes pulmonary, renal, gastrointestinal, infectious, hepatobiliary, pancreatic, malignancy (new or worsening of prior malignancy), accidental/trauma (where potential CV event, such as cardiac arrest, is not a plausible explanation e.g., suicide, homicide, non-cardiovascular system organ failure, non-cardiovascular surgery, and other not otherwise specified non-cardiovascular events.) Undetermined causes of death are instances in which no information is available to determine cause of death; these are classified as CV death.

In addition, cardiovascular contributions to non-cardiovascular death will be determined if a proximate or underlying cardiovascular condition is a contributing factor in a death also having non-CV causality. Cardiovascular contributing factors in non-cardiovascular deaths include, but are not limited to, underlying ischemia, myocardial infarction, hemodynamic instability related to cardiovascular causes, life-threatening brady or tachy arrhythmias, or heart failure. Stated differently, cardiovascular contribution should be denoted when the presence of underlying ischemic heart disease increased the risk of death for the patient with the non-cardiovascular acute condition such as pneumonia, renal failure or non-cardiovascular surgery.

For the primary CV mortality endpoint all deaths will be considered except those that are non- cardiovascular without a cardiovascular contributor as described above.

5.2. Myocardial Infarction

5.2.1. Overview

Two versions of MI will be adjudicated in ISCHEMIA: a primary definition and secondary

definition. Each definition includes a hierarchy of markers and threshold values as well as a set of rules for diagnosing MI when one or more key elements of the medical record are missing.

The Primary Definition is based upon the Universal Definition of MI, but relies upon site-reported MI decision limits for troponin (which may or may not be the same as the manufacturer 99%URL), and has selected unique marker criteria for MI after PCI or CABG (Type 4a, 5).

The Secondary Definition is also based upon the Universal Definition of Myocardial Infarction, but specifically uses the 99%URL from the assay manufacturer's package insert (which may or may not be the site's MI decision limit) and uses the same supporting criteria (eg. angiographic and ECG) as the UMI definition.

All MI events will be classified based on the Universal MI classification system as follows:

Type 1: Spontaneous MI
Type 2: Secondary MI
Type 3: Sudden Death MI
Type 4a: MI related to PCI
Type 4b: MI related to stent thrombosis
Type 4c: MI related to stent restenosis
Type 5: MI related to CABG
Silent MI

5.2.2. Spontaneous MI (Types 1, 2, 4b, 4c)

Diagnosis of spontaneous MI will be satisfied by a clinical setting consistent with acute myocardial ischemia and any one or more of the following criteria:

Marker elevation, as outlined below and at least 1 of the following:

- Symptoms of ischemia, usually lasting > 20 minutes in duration
- New ischemic ST and/or T wave and/or Q-wave ECG changes, or new LBBB, as described below
- Imaging evidence of new loss of viable myocardium in comparison to the baseline imaging test
- Angiographic evidence of intracoronary thrombus, stent thrombosis (4b) or high-grade in-stent restenosis (≥50%) (4c)

Marker data not available and at least 2 of the following:

- New ischemic ST and/or T wave and/or Q-wave ECG changes, or new LBBB, as described below
- Imaging evidence of new loss of viable myocardium in comparison to the baseline imaging test
- Angiographic evidence of intracoronary thrombus.

Autopsy evidence of a fresh myocardial infarction as stand-alone criterion

Spontaneous MI Marker Criteria
Troponin, including high-sensitivity troponin, is the preferred biomarker and takes precedence over CK-MB for both definitions.

Primary Definition: Preferentially uses a troponin threshold value reported as MI Decision Limit or the Upper Limit of Normal (ULN). Marker elevation is defined as troponin > ULN/MI decision limit. If troponin is not done or not available, then CK-MB > ULN will qualify. If both troponin and CK-MB are not done or not available, then CK >2 x ULN will qualify.

Secondary Definition: Preferentially uses a troponin threshold reported by the manufacturer, namely, the manufacturer 99th percentile. Marker elevation is defined as troponin > 99th percentile. If the troponin 99th percentile is not reported, then troponin > ULN will qualify. If troponin is not done or not available, then CK-MB > ULN will qualify. If both troponin and CK-MB are not done or not available, then CK > 2 x ULN will qualify.

Spontaneous MI ECG Criteria
ECG criterion is considered to be met if any of the following:

ST elevation: New ST elevation at the J-point in two contiguous leads with the cutpoints: ≥ 0.2 mV in men >age 40 and ≥ 0.25mV in men <40 years or ≥ 0.15 mV in women in leads V2–V3 and/or ≥ 0.1 mV in other leads, or new LBBB.

Any new Q-wave in leads V2–V3 ≥ 0.02 seconds or QS complex in leads V2 and V3 or Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4–V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4–V6; II, III, and aVF) or R-wave ≥ 0.04 seconds in V1–V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect.

ST depression and/or T-wave changes, new horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T-wave inversion ≥ 0.1 mV in two contiguous leads. The ST-T wave criteria only apply in the absence of findings that would preclude ECG analysis such as LBBB, LVH with repolarization abnormalities, pre-excitation and pacemakers.

5.2.3. Silent MI

This event includes evidence of new silent Q-wave MI detected during routine protocol or clinically obtained ECG follow-up. Silent MI events will be classified as a type 1 MI.

5.2.4 Sudden death MI (Type 3)

MI events in which a presentation consistent with infarction is present but the patient dies before the biomarkers are drawn or within the first few hours of the event before the biomarkers become positive. Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST-segment elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

5.2.5. PCI-Related MI (Type 4a)

Primary Definition
CK-MB is the preferred biomarker and takes precedence over troponin. For subjects with normal baseline biomarker level pre-PCI, peri-PCI MI requires a rise in CK-MB to >5-fold the ULN (or a rise in troponin to >35 times the MI Decision Limit/ULN, when CK-MB is unavailable) within 48 hours post-PCI. If pre-PCI cardiac markers (CKMB or cTn) are elevated, they must be stable or falling as indicated by two samples at least 6 h apart. The post-PCI CKMB level should reflect a rise of >20% over pre-PCI levels. In addition to biomarker criteria, peri-PCI MI requires at least one of the following:

- Post- procedure angiographic TIMI 0/1 flow in a major coronary artery or a side branch with reference vessel diameter ≥2.0 mm which had TIMI 2-3 flow at baseline, or TIMI 2 flow in a major coronary artery or a side branch with reference vessel diameter ≥3.0 mm which had TIMI 3 flow at baseline or Type C dissection (NHLBI classification) or greater in the target vessel.
- New ECG changes (ST segment elevation or depression >0.1mV in 2 contiguous leads), new pathologic Q-waves in ≥2 contiguous leads, or new persistent LBBB present on a post-PCI ECG obtained at least 30 minutes and up to 48 hours post procedure in the absence of any intervening coronary event between the time of the PCI procedure and the ECG showing changes.

NOTE: A type 4a MI will be diagnosed with a rise in CK-MB to >10-fold the ULN (or when CK-MB is unavailable, a rise in troponin to >70 times the MI Decision Limit/ULN) as a stand-alone criterion. If biomarkers are missing, a type 4a MI will be diagnosed if BOTH ECG criteria (new ST elevation or depression, Q-wave criteria, or new and persistent LBBB) AND angiographic criteria above are present. If pre-PCI cardiac markers are missing, they will be assumed to be normal in those without a preceding event.

Secondary Definition
Elevation of troponin values >5 X 99th percentile URL within 48 hours post-PCI in patients with normal baseline troponin values pre-PCI AND a rise of troponin values >20% if the baseline values are elevated pre-PCI and are stable or falling. If the troponin 99th percentile is not available, the MI Decision Limit / ULN may be used. If troponins are not available, CKMB elevation >5 X ULN will be used.

In addition to biomarker criteria, peri-PCI MI requires at least one of the following:

a. Symptoms suggestive of myocardial ischemia (≥20 min)
b. New ischemic ST changes or new pathological Q waves. (see "ECG Criteria" above) Note the UMI definition uses ≥0.05 mV of STD whereas the ISCHEMIA definition uses ≥ 0.1mV for PCI related ECG criteria
c. Angiographic evidence of a flow limiting complication, such as loss of patency of a side branch, persistent slow-flow or no re-flow, embolization, or Type C dissection (NHLBI classification) or greater in the target vessel.
d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

NOTE: A type 4a MI will be diagnosed with a rise in troponin to >70 times the 99th percentile URL (or, when troponin is unavailable, a rise in CK-MB to >10 times the ULN) as a stand-alone criterion. If biomarkers are missing, a type 4a MI will be diagnosed if BOTH ECG criteria (new ST elevation or depression, Q-wave criteria, or new and persistent LBBB) AND angiographic criteria above are present. If pre-PCI cardiac markers are missing, they will be assumed to be normal in those without a preceding event.

5.2.6. CABG-Related MI (Type 5)

Primary Definition
CK-MB is the preferred serum biomarker and takes precedence over cardiac troponin. For subjects with normal baseline biomarker level pre-CABG, peri-CABG MI requires a rise in CK-MB to >10-fold the ULN (or a rise in troponin to >70 times MI Decision Limit/ULN when CK-MB is unavailable) within 48 hrs post-CABG. In addition to biomarker criteria, peri-CABG MI requires at least one of the following:

a. A new substantial wall motion abnormality by cardiac imaging (CEC assessed), except new septal and apical abnormalities. The CEC will have latitude in determining whether a new wall motion abnormality is "substantial" in the context of the clinical event.
b. New pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB is present on post CABG ECG obtained day 3 post CABG, or hospital discharge, whichever comes earlier in the absence of any intervening coronary event between the time of the CABG procedure and the ECG showing changes.

NOTE: A type 5 MI will be diagnosed with a rise in CK-MB to >15-fold the ULN (or when CK-MB is unavailable a rise in troponin to >100 times the MI Decision Limit/ULN) as a stand-alone criterion. If biomarkers are missing, an MI will be diagnosed if the ECG criteria (New pathologic Q waves or new persistent LBBB) AND new substantial wall motion abnormality are BOTH present. If pre-CABG cardiac markers are missing, they will be assumed to be normal in those without a preceding event.

Secondary Definition
Elevation of troponin values >10 X 99th percentile URL within 48 hrs post-CABG in patients with normal baseline troponin values (≤ 99th percentile URL). If the troponin 99th percentile is not available, the ULN may be used. If troponins are not available, CKMB elevation >10 X ULN will be used. In addition to biomarker criteria, peri-CABG MI requires at least one of the following:

a. New pathologic Q waves or new LBBB
b. Angiographic evidence of new graft or new native coronary artery occlusion.
c. Imaging evidence of new loss of viable myocardium.

NOTE: A type 5 MI will be diagnosed with a rise in troponin to >100 times the 99th percentile URL (or when troponin is unavailable a rise in CK-MB to >15 times the ULN) as a stand-alone criterion. If biomarkers are missing, an MI will be diagnosed if the ECG criteria (New pathologic Q waves or new persistent LBBB) AND new substantial wall motion abnormality are BOTH present. If pre-CABG cardiac markers are missing, they will be assumed to be normal in those without a preceding event.

5.2.7. Complicated MI and Large MI

Complicated MI: Prognostically important MIs may also be identified as those with complications such as hemodynamic instability, cardiogenic shock, drop in EF >10% from baseline, electrical instability with life-threatening VT or VF, or heart failure complicating MI. Complicated myocardial infarctions may typically require ICU care, invasive support (eg. intubation, IABP, PA catheters) and intravenous medications (eg. inotropes or antiarrhythmics.) CEC adjudicators will identify complicated MIs based upon the information available to them in the eCRF and source documents.

- Hemodynamic instability: requiring fluids, inotropic or vasopressor support to maintain end-organ perfusion. May progress to shock if also accompanied by end-organ underperfusion.
- Shock: Compromise of end-organ perfusion due to hemodynamic instability and sustained hypotension. Often manifested by hypotension, increased creatinine, shock liver, and decreased mentation.

- Life-threatening VT or VF: Requiring antiarrhythmics or defibrillation to return sinus rhythm. Transient runs of VT (eg. during reperfusion) are not associated with hemodynamic instability are not usually considered life-threatening.
- Decreased EF ≥ 10%: EF assessment during the event which indicates a drop from prior assessments (eg. EF 30% from previous EF 55%)
- HF in the setting of an MI is defined on the basis of the physician's decision to treat HF with an intravenous (IV) diuretic, IV inotropic agent or IV vasodilator and at least 1 of the following:
  - Presence of pulmonary edema or pulmonary vascular congestion on chest radiograph believed to be of cardiac cause.
  - Rales greater than 1/3 up the lung fields believed to be due to HF.
  - Pulmonary Capillary Wedge Pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) greater than 18 mmHg.
  - Dyspnea, with documented paO2 less than 80 mmHg on room air or O2 saturation less than 90% on room air, without significant lung disease

Large MI: The size of MI will be assessed by examining peak levels of cardiac biomarkers as a continuous function.

5.3. Hospitalization for Unstable Angina

Prolonged ischemic symptoms at rest (usually ≥10 minutes in duration), or accelerating pattern of chest pain that occurs with a lower activity threshold (CCS class III or IV) considered to be myocardial ischemia upon final diagnosis resulting in an unscheduled visit to a healthcare facility resulting in an overnight stay generally within 24 hours of the most recent symptoms, cardiac biomarkers not meeting MI criteria, and at least one of the following:

(1) New or worsening ST or T wave changes on resting ECG* (core laboratory assessed)
(2) Angiographic evidence of a ruptured/ulcerated plaque, or thrombus in an epicardial coronary artery believed to be responsible for the ischemic symptoms/signs (core laboratory assessed).

*ECG Criteria:
ST segment shifts and T-wave changes: New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads; and/or T inversion ≥0.1 mV in two contiguous leads, or new ST segment elevation ≥0.1mV in 2 contiguous leads. The ST-T wave criteria only apply in the absence of findings that would preclude ECG analysis such as LBBB, LVH with repolarization abnormalities, pre-excitation and pacemakers.

5.4. Resuscitated Cardiac Arrest

Resuscitated cardiac arrest is defined as successful resuscitation for documented cardiac arrest out-of-hospital (or ER) in a patient subsequently admitted to hospital, and then discharged. A patient who is successfully resuscitated but dies before hospital discharge of complications related to the

cardiac arrest (e.g., anoxic encephalopathy, septic shock), will be classified as a coronary heart disease death. An uncomplicated procedure-related cardiac arrest with prompt resuscitation and without adverse sequelae will not be counted as an event. Events that meet the MI criteria will be categorized as MI.

5.5. Hospitalization for Heart Failure

While patients may have multiple simultaneous disease processes, for the end point event of heart failure requiring hospitalization, the diagnosis of congestive heart failure would need to be the primary process. Heart failure (HF) requiring hospitalization is defined as an event that meets the following criteria:

a. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that result in at least a 24 hour stay (or a date change if the time of admission/discharge is not available).

AND

b. Clinical symptoms of heart failure, including at least one of the following: New or worsening

- Dyspnea
- Orthopnea
- Paroxysmal nocturnal dyspnea
- increasing fatigue/worsening exercise tolerance

AND

c. Physical signs of heart failure, including at least two of the following:

1. Edema (> 2+ lower extremity)
2. Pulmonary rales (pulmonary edema not occurring as the consequence of an arrhythmia in the absence of worsening heart failure. If pulmonary edema complicates acute MI event should be coded as MI)
3. Jugular venous distension
4. Tachypnea (respiratory rate > 20 breaths/minute)
5. Rapid weight gain
6. S3 gallop
7. Increasing abdominal distension or ascites
8. Hepatojugular reflux
9. Radiological evidence of worsening heart failure
10. A right heart catheterization within 24 hours of admission showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mm Hg and/or a cardiac output < 2.2 L/min/m2

NOTE: Biomarker results (e.g., brain natriuretic peptide (BNP)> 500 or Pro-NT BNP > 2500) consistent with congestive heart failure will be supportive of this diagnosis, but the elevation in BNP cannot be due to other conditions such as cor pulmonale, pulmonary embolus, primary pulmonary hypertension, or congenital heart disease. Increasing levels of

BNP, although not exceeding the ULN, may also be supportive of the diagnosis of congestive heart failure in selected cases (e.g. morbid obesity).

AND

d. Need for additional/increased therapy

Initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure and including at least one of the following:

1. Initiation of or a significant augmentation in oral therapy for the treatment of congestive heart failure
2. Initiation of intravenous diuretic, inotrope, or vasodilator therapy
3. Uptitration of intravenous therapy, if already on therapy
4. Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure.

AND

e. No other non-cardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms are identified.

5.6. Stroke

Stroke is defined as the rapid onset of a new neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (eg. trauma, tumor, or infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke.

Classification:

a. Transient Ischemic Attack

A Transient Ischemic Attack is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an ischemia of central nervous system tissue which resolves within 24 hrs and without neuroimaging evidence of acute infarction.

b. Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.

Signs/ symptoms $\geq$ 24 hrs regardless of neuroimaging findings:

Ischemic stroke can be defined clinically- by persistence of signs and symptoms $\geq$ 24 hrs, usually supported by evidence of infarction on

neuroimaging (CT or MRI) although very early neuroimaging (usually with CT) may not demonstrate the infarction.

Signs/ symptoms < 24 hrs with neuroimaging evidence of infarction:
Ischemic stroke can be defined by neuroimaging- where neuroimaging (usually MRI diffusion weighted or flair images) confirms the presence of acute infarction even if signs/ symptoms resolve within 24 hrs.

Patients admitted for an acute stroke treated with thrombolysis or interventions that have no residual neurologic symptoms after treatment will be classified as an ischemic stroke.

c. Ischemic Stroke with Symptomatic Hemorrhagic Conversion
Hemorrhagic conversion may be a consequence of ischemic stroke and may be symptomatic, resulting in neurologic deterioration, or asymptomatic. Symptomatic Hemorrhagic Conversion is defined neuroimaging evidence of hemorrhage within the area of infarction associated with clinical deterioration (eg. increase in NIHSS of ≥ 4 points) or death, symptoms to hemorrhage related mass effect, or symptoms out of proportion to what would be expected from the ischemic stroke or cerebral edema alone. When an Ischemic Stroke with Symptomatic Hemorrhagic Conversion is identified, the date and time of stroke onset will refer to the first onset of the Ischemic Stroke and will not be counted as two events.

d. Hemorrhagic Stroke
Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a non-traumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

e. Undetermined- or Uncertain type- of Stroke
Undetermined stroke is defined as a stroke with insufficient information to allow categorization as Ischemic Stroke or Hemorrhagic Stroke. If possible, speculate on the stroke subtype and note in Comments. This is not to signify an indeterminate event where there is insufficient evidence to suspect a stroke had occurred.