12.0 Outcomes

12.1 Definitions

12.1.1 Neurologic Outcome Events

a. Ischemic stroke

An acute focal infarction of the brain or retina (and does not include anterior ischemic optic neuropathy (AION)).

Criteria:

(1) rapid onset of a new focal neurological deficit with clinical or imaging evidence of infarction and not attributable to a non-ischemic etiology (not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease); or,

(2) rapid worsening of an existing focal neurological deficit that is judged by the investigator to be attributable to new infarction.

Criteria for symptoms attributable to new infarction may include symptoms that persist and are judged by the investigator to be attributable to new infarction, imaging evidence of infarction, and/or no evidence of a non-ischemic etiology.

b. TIA

A neurological deficit of sudden onset, resolving completely, attributed to focal brain or retinal ischemia without evidence of associated acute focal infarction of the brain.

Criteria: rapid onset of a focal neurological deficit that is without evidence of acute focal infarction of the brain, and is not attributable to a non-ischemic etiology (brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease).

c. Symptomatic hemorrhagic transformation of an ischemic stroke

Any extravascular blood within an area of known acute/subacute ischemic infarction which is judged to be nontraumatic, and responsible for neurologic symptoms. To be considered symptomatic, the hemorrhagic transformation must be judged to be partially responsible for the subject’s clinical neurologic presentation (i.e., the area of Infarction is not adequate to explain the neurologic deficit, or a
secondary neurologic deterioration occurred corresponding to the timing of hemorrhagic transformation).

Criteria (must meet both of the following):

a. Imaging evidence (by CT or MR) of extravascular blood within the area of infarction.

b. Symptoms judged to be related to the hemorrhagic transformation. Scenarios which may be judged as symptomatic: (i) If blood is already present on imaging at presentation, symptoms are out of proportion to what would be expected for the size and location of the infarct at presentation; (ii) Clinical deterioration, defined by an increase of 4 points or more in the score on the NIHSS or leading to death, occurring after the initial ischemic event, and identified as the result of the hemorrhagic transformation; or (iii) Mass effect secondary to the hemorrhagic transformation causing symptoms.

d. Asymptomatic hemorrhagic transformation of an ischemic stroke

Any extravascular blood within an area of known acute/subacute ischemic infarct, judged to be nontraumatic, without any related neurologic symptoms.

Criteria (must meet both of the following)

a. Imaging evidence (by CT or MRI) of extravascular blood within the area of infarct.

b. No symptoms related to the hemorrhagic transformation, or clinical deterioration with less than a 4-point increase in score on the NIHSS judged to be related to the hemorrhagic transformation.

e. Symptomatic intracerebral hemorrhage

Any extravascular blood in the brain parenchyma, judged to be nontraumatic, and not in the area of an acute/subacute ischemic infarct, associated with and identified as the predominant cause of new neurologic symptoms (including headache) or death. In the case of a mixed intracranial hemorrhage (ICH, SAH, SDH and/or IVH), the event should be classified according to the primary site of hemorrhage by the judgment of the clinician.
For example, if a patient has a large ICH with a small amount of SAH, and the ICH is felt to be the primary site of bleeding, this should be classified as ICH.

Criteria: Evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery, or autopsy, which is not in the same territory of an underlying acute or subacute ischemic stroke, and is judged to be associated with any new neurologic symptoms (including headache) or leading to death.

f. Asymptomatic intracerebral hemorrhage

An acute extravasation of blood into the brain parenchyma, judged to be nontraumatic, and not in an area of an acute/subacute ischemic infarct, without associated neurologic symptoms or leading to death. In the case of a mixed intracranial hemorrhage (ICH, SAH, SDH and/or IVH), the event should be classified according to the primary site of hemorrhage by the judgment of the clinician.

For example, if a patient has a large ICH with a small amount of SAH, and the ICH is felt to be the primary site of bleeding, this should be classified as ICH.

Criteria: Evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery, or autopsy, which is not in the same territory of an underlying acute or subacute ischemic stroke, and is not judged to be associated with any new neurologic symptoms or leading to death.

g. Other symptomatic intracranial hemorrhage

Any extravascular blood within the cranium judged to be nontraumatic, and the predominant cause of the clinical deterioration or that led to death. Other Intracranial Hemorrhage is defined as an acute extravasation of blood into the subarachnoid space, epidural space, subdural space or intraventricular space with associated symptoms (including headache). In the case of a mixed intracranial hemorrhage (ICH, SAH, SDH and/or IVH), the event should be classified according to the primary site of hemorrhage by the judgment of the clinician.

For example, if a patient has a large ICH with a small amount of SAH, and the ICH is felt to be the primary site of bleeding, this should be classified as ICH.
Criteria: evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy.

h. Other asymptomatic intracranial hemorrhage

An acute extravasation of blood into the subarachnoid space, epidural space, subdural space or intraventricular space without associated symptoms, and judged to be nontraumatic. In the case of a mixed intracranial hemorrhage (ICH, SAH, SDH and/or IVH), the event should be classified according to the primary site of hemorrhage by the judgment of the clinician.

For example, if a patient has a large ICH with a small amount of SAH, and the ICH is felt to be the primary site of bleeding, this should be classified as ICH.

Criteria: evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy.

12.1.2 Cardiac Outcome Events

a. Myocardial infarction with coronary revascularization

Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, treated with coronary revascularization within 14 days.

Criteria: The diagnosis of MI will be based on an algorithm developed from the Universal Definition of Myocardial Infarction (Circulation 2007 116:2634-2653) that takes into account 5 categories of clinical information from the acute event: rise and/or fall of cardiac biomarkers, ECG abnormalities, clinical setting, imaging evidence, and pathology.

i. Angioplasty/stent

ii. Coronary Artery Bypass Graft

b. Myocardial infarction without coronary revascularization

Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, not treated with coronary revascularization within 14 days.
Criteria: The diagnosis of MI will be based on an algorithm developed from the Universal Definition of Myocardial Infarction that takes into account 5 categories of clinical information from the acute event: rise and/or fall of cardiac biomarkers, ECG abnormalities, clinical setting, imaging evidence, and pathology.

c. Coronary revascularization without myocardial infarction

A procedure to improve coronary blood flow for documented coronary artery disease, but with no documentation of new post-randomization myocardial infarction.

Criteria: Documented coronary angioplasty, stenting, or bypass surgery for demonstrated or presumed coronary artery disease.

12.1.3 Systemic Outcome Events

Major hemorrhage other than intracranial hemorrhage (life-threatening or non-life-threatening)

A hemorrhagic event, judged to be nontraumatic, that results in intraocular bleeding causing loss of vision, the need for a transfusion of two or more units of red cells or the equivalent amount of whole blood, or the need for hospitalization or prolongation of existing hospitalization. This may include bleeding events related to surgical procedures but not those related to accidental trauma. Life-threatening hemorrhagic events will be defined as those that are fatal or require use of intravenous inotropic medication to maintain blood pressure, interventional treatment (including surgical, endoscopic or endovascular interventions), or transfusion of four or more units of red cells or the equivalent amount of whole blood. Non-life-threatening hemorrhagic events will be defined as those classified as major hemorrhagic events but not as life-threatening.

Minor hemorrhage other than intracranial hemorrhage

All hemorrhagic events leading to interruption or discontinuation of the study drug but not classifiable as major hemorrhagic events. This may include bleeding events related to surgical procedures but not those related to accidental trauma.

Other serious adverse event

Any adverse event, not belonging to the other outcome event categories,
that is fatal or life threatening, is permanently or substantially disabling, requires or prolongs hospitalization, results in a congenital anomaly, or requires intervention to prevent permanent impairment or damage.

12.1.4 Deaths

If a death occurs, it will be adjudicated according to the cause of death. For each outcome (such as ischemic stroke, intracerebral hemorrhage, MI, etc.), there will be a checkbox to indicate that the event was fatal. Deaths related to an event may occur at the time of the event, or days or weeks later if in the best clinical judgment it is directly linked to the event. One way to help define what may be related to an outcome event is by asking the question, “would the death have occurred without the preceding outcome event?” For example, this may include hospital acquired infections or new congestive heart failure following MI. Deaths that are not related to any of the cerebrovascular, cardiovascular or systemic hemorrhagic events will be adjudicated as “Other Serious Adverse Event” with fatality. For all deaths, please indicate whether the death was ischemic, hemorrhagic or nonvascular in etiology.

a. Ischemic Vascular Death
   Death due to ischemic stroke, myocardial infarction, sudden cardiac death, arrhythmia, pulmonary embolism, bowel or limb infarction, or any death not readily attributable to a non-ischemic cause.

b. Hemorrhagic Vascular Death
   Death due to intracranial or systemic hemorrhage.

c. Nonvascular Death
   Any death felt not to be related either to an ischemic event or a hemorrhagic event. Examples: death related to neoplasm, infection, trauma, or toxin.

12.2 Procedures If Clinical Outcome Occurs

12.2.1 Event Visit

See Section 11.7.

12.2.2 Outcome Event Reporting

Outcomes will be detected by the participating centers during follow-up
evaluations or may be reported to the site coordinator or study investigator at another time during the subject’s enrollment. The participating centers will data enter and submit the SAE/Clinical Outcome CRF within 24 hours of first knowledge of the event, will compile an event packet, comprised of the hospital discharge summary and other relevant documents, and will send the packet to the appropriate coordinating center to be distributed for adjudication. Documents requiring translation will be checked for deletion of PHI by the country level manager, and a request for translation will be made to the CRC. The CRC will provide the translated documents back to the country level manager for upload.

12.3 Adjudication of Outcomes

12.3.1 Adjudications Committee Review

Since members of the Adjudications Committee have been appointed, in part, because of their clinical expertise, reported cardiac events will be reviewed independently by two cardiologists/internists. Similarly, reported ischemic and hemorrhagic strokes will be reviewed independently by two neurologists and classified by the TOAST criteria. All deaths and hemorrhages (other than intracerebral hemorrhages) will be reviewed independently by a cardiologist/internist and a neurologist and classified as hemorrhage, ischemic stroke, myocardial infarction, other vascular and non-vascular. See also Appendix XV.

12.3.2 Process

12.3.2.1 Both Adjudicators Agree

If both adjudicators agree with reported outcome or classification, the Adjudication System will close the record and remove it from the Adjudicator’s worklist, and the UCSF CCC will enter the final adjudicated classification in WebDCU™.

12.3.2.2 Both Adjudicators Disagree

If the Adjudicators disagree with each other on the event classification, a third Adjudicator will be assigned the Event Packet by the POINT Adjudication System, and will adjudicate the outcome event and complete the Adjudication CRF. If the third Adjudicator’s classification of the event matches that of one of the two initial reviewers, this will be the final classification of the event. The UCSF CCC will enter the final adjudicated classification in the WebDCU™.
12.3.2.3 Third Adjudicator disagrees with both of the two Adjudicators on the event classification

If the third Adjudicator disagrees with both of the original Adjudicators, then the POINT Adjudication System will trigger an email to set up a conference call to review the discrepant event classification with the Adjudication Committee Chair. The Chair will adjudicate the outcome event and complete the Adjudication CRF. The Chair will attempt to gain consensus; however, decision of the Chair will be the final classification of the event. The UCSF CCC will enter the final adjudicated classification in the WebDCU™.

If all three adjudicators disagree on the event classification, a conference will be held by the three adjudicators and the Adjudication Committee Chair to discuss the possible diagnoses. Based on this discussion, the chair will assign a final adjudication to the event. The UCSF CCC will enter the final adjudicated classification in WebDCU™.