Appendix XV: OUTCOME ADJUDICATION GUIDELINES
PLATELET-ORIENTED INHIBITION IN NEW TIA AND MINOR ISCHEMIC STROKE (POINT)

CLINICAL OUTCOME/FATAL SAE ADJUDICATION GUIDELINES

Version 4.0
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POINT Trial Adjudication Guidelines

I. Overview of Process if a Clinical Outcome/Fatal SAE Occurs

a. Site/Hub PI Responsibility

Serious Adverse Events (SAEs) and Clinical Outcomes (COs) may be discovered during the 7-day telephone follow-up, the 30-day telephone follow-up (no data collection), the 90-day follow-up appointment, or at any point during the study period. When a Fatal SAE or Clinical Outcome is discovered, the site PI is responsible for submitting it within 5 days of the discovery of the event using the online SAE/Clinical Outcome case report form (CRF) through the WebDCU™.

See Appendix 1 for Form 19: SAE/Clinical Outcome Reporting Form.

The Site Principal Investigator (PI) is responsible for the monitoring, follow-up and appropriate documentation of all SAEs/Clinical Outcomes until resolution or the end of study for the subject.

The Site PI will work with the appropriate Site Manager to prepare an Event Packet for SAEs/Clinical Outcomes, including copies of discharge summaries from both the index and outcome events, neurology, cardiology or other consultation notes, head imaging reports from both the index and outcome events, appropriate laboratory values, a narrative summary and other reports as appropriate (See Appendix 2 for Event Packet Checklist).

All unique identifiers must be removed from the documents in the Event Packet prior to submission.

b. NETT Clinical Coordinating Center (CCC) and POINT CRC Site Managers’ Responsibilities

Once a completed SAE/Clinical Outcome CRF has been submitted for an SAE/Clinical Outcome, the appropriate Site Manager for the NETT-CCC or the POINT CRC will receive an automatic email notification from WebDCU™. That Site Manager is then responsible for reviewing the information for completeness. If the information is deemed insufficient, the Site Manager will generate a query and an automatic email notification will be triggered to the site requesting additional information.
If the event is a Clinical Outcome or Fatal SAE, the Site Manager will then work with the Site/Hub PI to prepare an Event Packet using the Event Packet Checklist, as described above in section Ia, and upload it into the WebDCU™ system. When the information in the packet is deemed sufficient by the Site Manager, an automatic email notification will be triggered to the Clinician Event Monitor (CEM) at UCSF.

c. **Clinician Event Monitor Responsibility**

The CEM, who is blinded, will perform a Clinical Outcome Review (COR). The CEM will review the SAE/Clinical Outcome CRF and the Event Packet (if the event is a Fatal SAE or Clinical Outcome) independently. If clarifications or additional information are required, the CEM may contact the appropriate Site Manager, who will work with the Site/Hub PI to update the CRF and/or Event Packet. When all necessary information is available, the CEM will review, and, upon making a determination, access the POINT WebDCU™ Adjudication System and within the system indicate:

- That the Event Packet is complete (if the event is a Fatal SAE/Clinical Outcome)
- If the Event is serious
- If the Event is unexpected
- What is the relationship to study drug (not related, unlikely, possibly, probably or definitely)
- Type of Event (Neurological, Systemic, Cardiac or N/A (NOTE: An “N/A” Event will not be adjudicated; this designation is used for some types of non-fatal SAEs and TIAs))

See **Appendix 3** for the WebDCU CEM Screen.

The POINT WebDCU™ Adjudication System will create a new record in the database, record the event type of the Clinical Outcome/ Fatal SAE and assign reviewers to the packet based on the type of outcome. Events that require review and/or adjudication will be placed in the appropriate reviewer’s worklist.

See **Appendix 4** for the listing of POINT Adjudication Committee members.

**Note** – The CEM will review SAEs, verifying that the accompanying narrative is complete. If the CEM determines that the event is serious, unexpected and
study drug-related, then an automatic email notification is triggered to inform the participating sites so that staff there can comply with local reporting requirements for such events. The DSMB will also be notified through a monthly report of SAEs compiled by the unblinded study statistician. All fatal SAEs will be sent for adjudication. The proportion all Fatal SAEs is reported to the DSMB monthly.

d. **Adjudication Committee Responsibility**

Once the two adjudicators review the complete Event packet, they will adjudicate the outcome independently. If the adjudicators require further information, this will be communicated to the CEM by email, and he/she will go into WebDCU and create a Data Clarification Request (DCR). This request for additional documentation then goes to the site and the appropriate CRC or NETT Site Manager who will work with the Site/Hub PI to collect the additional documentation. A revised Event Packet will be uploaded to WebDCU™. When the site provides the additional information in WebDCU, it is posted with the updated Event Packet to the CEM as a “Responded CEM DCR.” The CEM decides if the information provided is adequate, and then either closes the DCR or writes back and asks for more information. Then the CEM, via the WebDCU, forwards it to the adjudicators for final action.

Once the information is deemed complete, the independent adjudications process will take place (see Section II), and the final adjudicated classification will be recorded in WebDCU™.

II. **Fatal SAE/Clinical Outcome Adjudications Process**

a. **Assignment to Independent Adjudicators**

The Clinician Event Monitor will identify all Clinical Outcomes/Fatal SAEs event as Neurologic, Cardiac or Systemic and the WebDCU™ Adjudication System will randomly assign the case to independent Adjudicators.

- The following will be assigned to neurologist Adjudicators: ischemic stroke, intracerebral hemorrhage (symptomatic or asymptomatic), and other intracranial hemorrhage (symptomatic or asymptomatic).
b. Independent Adjudication

The first two assigned Adjudicators will review the reported Fatal SAE/Clinical Outcome and the related Event Packet, and come to independent classifications of the Fatal SAE/Clinical Outcome. If clarifications or additional information are required, the Adjudicators may contact the CEM, who will obtain the additional information or clarification for the Adjudicators. The Adjudicators will enter the final classifications using the Adjudication System.

See Appendix 4 for the POINT Fatal SAE/Clinical Outcome Adjudication Screens for the adjudication system.

The logic in the Adjudication System will then compare the classifications entered by the Adjudicators.

c. Adjudicators agree on the event classification

If both Adjudicators agree on the event classification, the POINT WebDCU™ Adjudication System will close the record and remove it from both the Adjudicators’ worklists.

d. Adjudicators disagree with each other on the event classification

If the Adjudicators disagree with each other on the event classification, a third Adjudicator will be notified by an automatic e-mail that the Fatal SAE/Clinical Outcome requires his/her review. NOTE: although every Fatal SAE/Clinical Outcome is initially assigned to 3 reviewers, the third reviewer is only notified in the event the first two reviewers disagree on the classification of the Fatal SAE/Clinical Outcome.
The third Adjudicator, upon logging on to WebDCU™, will note that the main menu page displays an alert that the Fatal SAE/Clinical Outcome is pending review. (S)he will adjudicate the Fatal SAE/Clinical Outcome blinded to the classifications of the initial two reviewers, and enter her/his determination into the POINT WebDCU™ Adjudication System. If the third Adjudicator’s classification of the Fatal SAE/Clinical Outcome matches that of one of the two initial reviewers, this will be the final classification.

e. Third Adjudicator disagrees with both Adjudicators on the event classification

If the third Adjudicator disagrees with both of the original Adjudicators, then the POINT WebDCU™ Adjudication System will trigger an email to set up a conference call to review the discrepant classifications with the Adjudication Committee Chair. The Chair will adjudicate the Fatal SAE/Clinical Outcome and enter a final determination into the POINT WebDCU™ System. The Chair will attempt to gain consensus; however, the decision of the Chair will be the final classification.

f. Outcome Adjudication Screens

An Outcome Adjudication Screen will be completed by each Adjudicator for each Fatal SAE/Clinical Outcome adjudicated.

See Appendix 5 for the POINT WebDCU™ Adjudication System Workflow and Appendix 6 for the POINT WebDCU™ Adjudication System Schematic.

III. Clinical Outcomes Definitions

For complete definitions of Clinical Outcomes, please refer to CRF 19, SAE/Clinical Outcome Reporting Form:

https://webdcu.musc.edu/nett/CRFSchedule.asp

See Appendix 7 for definitions of cerebral infarction and TIA.

See Appendix 8 for definition of myocardial infarction.

IV. Deaths
If a death occurs, it will be adjudicated according to the cause of death. For each SAE/Clinical Outcome (such as ischemic stroke, intracerebral hemorrhage or MI), there is a checkbox on the WebDCU™ CRF to indicate that the event was fatal. A death 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. **NOTE:** if a subject dies after (s)he has completed the End of Study visit, the death will not be considered a “study death” and there will be no further data collection or re-adjudication for POINT. 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 neurologic, cardiovascular or systemic hemorrhagic events will be adjudicated as “Other Serious Adverse Event” with fatality. For all deaths, whether the death was ischemic, hemorrhagic or nonvascular in etiology will be indicated.

**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.
APPENDIX 1. Form 19: SAE/Clinical Outcome Reporting Form

This CRF should only be completed if the subject experiences a Serious Adverse Event (SAE) or Clinical Outcome after the enrolling/index event. This form should be data entered and submitted within 5 days of discovery.

An Outcome Event Visit should be conducted if a subject experiences an ischemic stroke, TIA, or myocardial infarction. Outcome Event Visits can be done via telephone unless the subject experiences an ischemic stroke or TIA, in which case an in-person visit should be conducted.

Worsening of an enrolling stroke is an outcome event.

<table>
<thead>
<tr>
<th>POINT</th>
<th>Visit:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Form 19: SAE/Clinical Outcome Reporting Form (Version 8)  

1. Name of SAE/Clinical outcome: (100 character max)

2. Date of onset: ___ ___ - ___ ___ - ___ ___ (dd-mmm-yyyy)

3. Time of onset: (For clinical outcome events, this is the time the deficit was first recognized.) ___ : ___ (24 hour clock, hh:mm)

General Comments:

Name of person who collected these data (not for data entry):

[Data Coordinating Unit
Medical University of South Carolina]
## Form 19: SAE/Clinical Outcome Reporting Form (Version 8)

### 4. Clinical outcomes / SAEs

<table>
<thead>
<tr>
<th>Event Listed</th>
<th>Clinical outcomes / SAEs (If applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ischemic stroke: An acute focal infarction of the brain or retina (and does not include anterior ischemic optic neuropathy [AION]). Criteria: (a) 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 infarction, trauma, tumor, seizure, severe metastatic disease, or degenerative neurological diseases); or (b) Rapid worsening of an existing focal neurological deficit that is judged by the investigator to be attributable to a new infarction. Criteria for symptoms attributable to new infarction may include symptoms that are not clearly attributable to a new infarction because they are judged by the investigator to be attributable to new infarction, imaging evidence of a new infarction, or evidence of a non-ischemic etiology.</td>
<td></td>
</tr>
<tr>
<td>2. 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.</td>
<td></td>
</tr>
<tr>
<td>3. Symptomatic hemorrhagic transformation of an ischemic stroke: Any extravasal blood within an area of known acute/subacute infarction which is judged to be nontraumatic, and responsible for neurologic symptoms. To be considered symptomatic, the hemorrhagic transformation must be judged to be nontraumatic, irreversible for the subject’s clinical improvement (i.e., the area of infarction is not worsening), or a secondary neurologic deterioration occurring corresponding to the timing of hemorrhagic transformation. Criteria (must meet both of the following):</td>
<td></td>
</tr>
<tr>
<td>a. Imaging evidence (CT or MRI) of extravasal blood within the area of infarction.</td>
<td></td>
</tr>
<tr>
<td>b. Symptoms judged to be related to the hemorrhagic transformation.</td>
<td></td>
</tr>
<tr>
<td>4. Asymptomatic hemorrhagic transformation of an ischemic stroke: Any extravasal blood within an area of known acute/subacute infarct, judged to be nontraumatic, without any related neurologic symptoms. Criteria (must meet both of the following):</td>
<td></td>
</tr>
<tr>
<td>a. Imaging evidence (CT or MRI) of extravasal blood within the area of infarct.</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>5. Symptomatic intracerebral hemorrhage: Any extravasal blood in the brain parenchyma, judged to be nontraumatic, and not in an 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 intracerebral 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.</td>
<td></td>
</tr>
<tr>
<td>6. 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 intracerebral 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.</td>
<td></td>
</tr>
<tr>
<td>7. Other symptomatic intracerebral hemorrhage: Any extravasal blood within the cranium judged to be nontraumatic, and the predominant cause of the clinical deterioration or death leading to death. Other Intracerebral Hemorrhage is defined as an acute extravasation of blood into the subarachnoid space, subdural space or intraventricular space with associated symptoms (including headache). In the case of a mixed intracerebral 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, subdural space, or intraventricular space demonstrated by head imaging, surgery, or autopsy.</td>
<td></td>
</tr>
<tr>
<td>8. Other asymptomatic intracerebral hemorrhage: An acute extravasation of blood into the subarachnoid space, subdural space or intraventricular space without associated symptoms, and judged to be nontraumatic. In the case of a mixed intracerebral 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, subdural space, or intraventricular space demonstrated by head imaging, surgery, or autopsy.</td>
<td></td>
</tr>
<tr>
<td>9. Myocardial infarction with coronary revascularization: Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia treated with coronary revascularization, such as angioplasty/stenting or coronary artery bypass graft (CABG), within 14 days. Criteria: The diagnosis of MI will be based on an algorithm developed from the Universal Definition of Myocardial Infarction (Circulation 2017 136:2643-2662) that takes into account 5 categories of clinical information from the acute event: rise and/or fall of cardiac biomarkers, ECG abnormalities, clinical imaging, evidence, and pathology.</td>
<td></td>
</tr>
<tr>
<td>10. 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 (Circulation 2017 136:2643-2662) that takes into account 5 categories of clinical information from the acute event: rise and/or fall of cardiac biomarkers, ECG abnormalities, clinical imaging, evidence, and pathology.</td>
<td></td>
</tr>
<tr>
<td>12. Major hemorrhage other than intracerebral hemorrhage (life-threatening or non-life-threatening): A hemorrhagic event, judged to be nontraumatic, that leads to severe symptoms or results in intracerebral bleeding causing less than or equal to 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 intracerebral hemorrhage. Life-threatening non-life-threatening hemorrhagic events will be defined as those that are fatal or require the use of invasive inotropic medication to maintain blood pressure, intensive treatment (including surgical, endoscopic or extravascular 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.</td>
<td></td>
</tr>
<tr>
<td>13. Minor hemorrhage other than intracerebral hemorrhage: An hemorrhagic event 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.</td>
<td></td>
</tr>
<tr>
<td>14. Other serious adverse event: Any adverse event, not belonging to the other outcome event categories, that is fatal or the threatening, is permanently or substantially disabling, requires or prolongs hospitalization, results in a congenital anomaly, or requires intervention to prevent permanent impairment or damage.</td>
<td></td>
</tr>
</tbody>
</table>
### Form 18: SAE/Clinical Outcome Reporting Form (Version 8)

<table>
<thead>
<tr>
<th>Code</th>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>If 'Symptomatic hemorrhagic transformation of an ischemic stroke' or 'Asymptomatic hemorrhagic transformation of an ischemic stroke', specify.</td>
<td>Of Index stroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Of Outcome stroke</td>
</tr>
<tr>
<td>16</td>
<td>If 'Other symptomatic intracranial hemorrhage' or 'Other asymptomatic intracranial hemorrhage', specify.</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subdural hemorrhage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intraventricular hemorrhage</td>
</tr>
<tr>
<td>17</td>
<td>If 'Myocardial infarction with coronary revascularization' or 'Coronary revascularization without myocardial infarction', specify.</td>
<td>Angioplasty/stent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coronary Artery Bypass Graft</td>
</tr>
<tr>
<td>18</td>
<td>If 'Major Hemorrhage other than Intracranial Hemorrhage', specify.</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Genitourinary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>19</td>
<td>If 'Other Major Hemorrhage other than Intracranial Hemorrhage', specify.</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Genitourinary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cutaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>20</td>
<td>If 'Minor hemorrhage other than intracranial hemorrhage', specify.</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Genitourinary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cutaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>21</td>
<td>If 'Other Minor hemorrhage other than intracranial hemorrhage', specify.</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Genitourinary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cutaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
</tr>
</tbody>
</table>

**DID the clinical outcome event meet the definition of serious?**

This should be skipped for non-clinical outcome events (when question 4 = 'Other serious adverse event')

- **No**
- **Yes**

**Serious is defined as 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.**

**Severity:**

Severity is used to describe the intensity (severity) of a specific event (as in mild myocardial infarction vs. severe myocardial infarction).

- Mild
- Moderate
- Severe
- Life threatening / Disabling
- Fatal

**General Comments:**

**Name of person who collected these data (not for data entry):**
Form 19: SAE/Clinical Outcome Reporting Form (Version 6)  

<table>
<thead>
<tr>
<th>Point</th>
<th>Visit:</th>
<th>Spoke Code</th>
<th>Subject ID</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcome:</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Resolved</td>
</tr>
<tr>
<td>○ Resolved w/ sequelae</td>
</tr>
<tr>
<td>○ Continuing (Follow up is required)</td>
</tr>
<tr>
<td>○ Continuing at end of study (No follow up is required)</td>
</tr>
<tr>
<td>○ Continuing at time of death</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date of resolution/death:</th>
</tr>
</thead>
<tbody>
<tr>
<td>__ __ - __ __ -  __ __ __ (dd-mm-yyyy)</td>
</tr>
</tbody>
</table>

What is the relationship of the SAE to the study drug?  
Q9 should only be answered if Q4 is ‘Other serious adverse event’.  

<table>
<thead>
<tr>
<th>Not related</th>
</tr>
</thead>
<tbody>
<tr>
<td>The temporal relationship between treatment exposure and the adverse event is unreasonable or incompatible and/or adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unlikely (must have 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Could readily have been produced by the subject’s clinical state, or environmental or other interventions.</td>
</tr>
<tr>
<td>• Does not follow known pattern of response to intervention.</td>
</tr>
<tr>
<td>• Does not reappear or worsen with reintroduction of intervention.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Possibly (must have 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Has a reasonable temporal relationship to intervention.</td>
</tr>
<tr>
<td>• Could not readily have been produced by the subject’s clinical state or environmental or other interventions.</td>
</tr>
<tr>
<td>• Follows a known pattern of response to intervention.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probably (must have 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Has a reasonable temporal relationship to intervention.</td>
</tr>
<tr>
<td>• Could not readily have been produced by the subject’s clinical state or have been due to environmental or other interventions.</td>
</tr>
<tr>
<td>• Follows a known pattern of response to intervention.</td>
</tr>
<tr>
<td>• Disappears or decreases with cessation of intervention.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definitely (must have all 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Has a reasonable temporal relationship to intervention.</td>
</tr>
<tr>
<td>• Could not readily have been produced by the subject’s clinical state or have been due to environmental or other interventions.</td>
</tr>
<tr>
<td>• Follows a known pattern of response to intervention.</td>
</tr>
<tr>
<td>• Disappears or decreases with cessation of intervention and recurs with re-exposure.</td>
</tr>
</tbody>
</table>

General Comments:

Name of person who collected these data (not for data entry):

Data Coordinating Unit  
Medical University of South Carolina
### Form 19: SAE/Clinical Outcome Reporting Form (Version 3)

<table>
<thead>
<tr>
<th>POINT</th>
<th>Visit:</th>
<th>Spoke Code</th>
<th>Subject ID</th>
</tr>
</thead>
</table>

#### 10. What actions were taken for this event? (Check all that apply):
- □ None
- □ Study drug reduced
- □ Study drug held
- □ Study drug discontinued
- □ Other medication change
- □ Procedure/Surgery
- □ Hospitalization/Prolonged hosp.
- □ Unknown

#### 11. Describe the event in detail:
Include a description of what happened and a summary of all relevant clinical information (medical status prior to the event, signs and/or symptoms, differential diagnosis for the event in question, clinical course, treatment outcome, etc).
DO NOT identify any study participant, physician, or institution by name.

#### 12. Relevant tests/laboratory data (both positive and negative), including dates:

#### 13. Last name of reviewing site investigator:

#### 14. Date of site investigator review: ___-___-___-___-___-___-___ (dd-mmm-yyyy)

---

Please note that Event Packets must be uploaded for all Clinical Outcome Events and SAEs. The Site/Mhub PI will work with the Site Manager to prepare Event Packets, including copies of discharge summaries, neurology, cardiology or other consultation notes, head imaging reports, appropriate laboratory values, and a narrative summary, with all unique identifiers removed.

The first page of all event packets should include the event packet checklist, indicating which procedures/tests/notes/etc. are contained in the event packet. In rare cases where no information was collected for the event packet, the event packet checklist must be uploaded indicating that no information is available and the reason why.

For more information regarding the Event Packet please refer to the POINT MoP.

**General Comments:**

**Name of person who collected these data (not for data entry):**
# APPENDIX 2. Outcome Event Packet Checklist

## POINT Clinical Outcome-Specific Checklist for Preparing Event Packets

Please use this form as a face page, and order the Event Packet documents in the order in which they appear below.

NOTE: All protected health information (PHI) must be removed from documents. (Event Packets must be de-identified.)

<table>
<thead>
<tr>
<th>Category:</th>
<th>Checklist Item</th>
<th>Submitted</th>
<th>Not Done</th>
<th>Done but Unavailable*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic Packet for ALL Events:</td>
<td>Clinical Outcome Reporting Form (CRF 19)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>Discharge Summary (Index Event)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>Discharge Summary (Outcome Event)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>All Head Imaging Reports (Index Event)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>All Head Imaging Reports (Outcome Event)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>Consult Notes (neurology, cardiology, etc.)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Depending on event category, include the following documents in the packet:

- **All Deaths**
  - Autopsy Report: ☐ ☐ ☐
  - Includes Fatal SAEs
    - Death Certificate: ☐ ☐ ☐
    - Emergency Team/Ambulance Report: ☐ ☐ ☐
    - Nursing Home Report: ☐ ☐ ☐

- **Ischemic Stroke**
  - Carotid Imaging Report: ☐ ☐ ☐
  - With or Without Hemorrhagic Transformation
    - Operative Report: ☐ ☐ ☐

- **TIA***
  - Carotid Imaging Report: ☐ ☐ ☐

- **Intracranial Hemorrhage (Symptomatic ICH, Asymptomatic ICH, Other)**
  - Operative Report: ☐ ☐ ☐

- **Cardiac Outcomes (MI with or without Coronary Revasc)**
  - All Cardiac Enzyme Reports: ☐ ☐ ☐
    - ECG Report(s): ☐ ☐ ☐

- **Hemorrhage Other than Intracranial (Major & Minor)**
  - Number of Transfusions: ☐ ☐ ☐
  - Operative Report: ☐ ☐ ☐

**Comments:**

---

*Not adjudicatable.*

---

*If unavailable, explain.*
## APPENDIX 3. WebDCU™ Adjudication Screens

### Clinician Event Coordinator/Monitor Screen

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td></td>
<td>What actions were taken for this event? (Check all that apply)</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>Describe the event in detail</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>Relevant tests/laboratory data (both positive and negative), including dates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Include a description of what happened and a summary of all relevant clinical information (medical status prior to the event, signs and symptoms, differential diagnosis for the event in question, clinical course, treatment, outcome, etc.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DO NOT identify any study participant, physician, or institution by name.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Testing</td>
</tr>
</tbody>
</table>

Please note that Event Packets must be uploaded for all Clinical Outcomes Events and SAEs. The SiteHub PI will work with the Site Manager to prepare Event Packets, including copies of discharge summaries, radiology, cardiology or other consultation notes, head imaging reports, appropriate laboratory values, and a narrative summary, with all unique identifiers removed.

The first page of all event packets should include the event packet checklist, indicating which procedures/tests/photos/etc. are contained in the event packet. In rare cases where no information was collected for the event packet, the event packet checklist must be uploaded indicating that no information is available and the reason why.

For more information regarding the Event Packet please refer to the POINT MOP:

- [Event Packet Checklist.pdf](#)

---

### Clinical Outcome/SAE Review - NEW UPDATE

<table>
<thead>
<tr>
<th>Review Case</th>
<th>Reviewer</th>
<th>Date/Time</th>
<th>Record Version</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Comments</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEC Review</td>
<td>Aaron PERLMUTTER</td>
<td></td>
<td>Event packet complete:</td>
<td>No</td>
<td>Yes</td>
<td>Serious:</td>
<td>No</td>
<td>Unexpected:</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## POINT Site Manager Screen

### 10. What actions were taken for this event? (Check all that apply)
- [ ] Study drug discontinued
- [ ] Other medication change
- [ ] Procedure/Surgery
- [ ] Hospitalization/Prolonged hosp.
- [ ] Unknown

### 11. Describe the event in detail
Include a description of what happened and a summary of all relevant clinical information (medical status prior to the event, signs and/or symptoms, differential diagnosis for the event in question, clinical course, treatment outcome, etc). DO NOT identify any study participant, physician, or institution by name.

- [ ] Testing

### 12. Relevant tests/laboratory data (both positive and negative), including dates
- [ ] Test

### 13. Last name of reviewing site investigator
- Cronin

### 14. Date of site investigator review
- 24-APR-2011 (DD-MM-YYYY)

---

Please note that Event Packets must be uploaded for all Clinical Outcomes Events and SAEs. The SiteHub PI will work with the Site Manager to prepare Event Packets, including copies of discharge summaries, neurology, cardiology or other consultation notes, head imaging reports, appropriate laboratory values, and a narrative summary, with all unique identifiers removed.

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For more information regarding the Event Packet please refer to the POINT MoP.

### Event Packet Checklist.pdf

---

**Last updated by Cassidy CONNER on 20-MAY-2011 08:39**

### Clinical Outcome/SAE Review - NEW UPDATE

<table>
<thead>
<tr>
<th>Review Step</th>
<th>Reviewer</th>
<th>Date</th>
<th>Record Version</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM Completeness</td>
<td>PERLMUTTER</td>
<td></td>
<td></td>
<td>Report type:</td>
<td>Event Report</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Review</td>
<td></td>
<td></td>
<td></td>
<td>Follow-up Report</td>
<td>Correct</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**limit to 1000 chr.**

---

### Adjudicator Form

**Adjudicated outcome:**
- Ischemic strokes

---

**limit to 1000 chr.**
APPENDIX 4. POINT Adjudications Committee

Neurology:

Eric Adelman, M.D. (Committee Chair)
Assistant Professor
Department of Neurology
University of Michigan

Kevin A. Kerber, M.D.
Assistant Professor
Department of Neurology
University of Michigan

Matthew T. Lorincz, M.D., Ph.D.
Assistant Professor
Department of Neurology
University of Michigan

Cardiology/Internal Medicine:

David Bach, M.D.
Professor, Internal Medicine
University of Michigan

Claire S. Duvernoy, M.D.
Associate Professor,
Department of Internal Medicine
Division of Cardiology
University of Michigan

Deborah A. Levine, M.D., M.P.H.
Assistant Professor of Medicine
Department of Internal Medicine
Division of General Medicine, and
Department of Neurology
University of Michigan Medical School
APPENDIX 5. Adjudication System Workflow

Two neurologists review outcomes, efficacy and safety

Is the SAE/Clinical Outcome neurological, cardiac, or systemic?

Neurological

Cardiac

Systemic

A neurologist and a cardiologist/internist review, including deaths not clearly neurological or cardiac

Two cardiologists/internists review outcomes, efficacy and safety

Do both Adjudicators agree?

No

3rd neurologist reviews; breaks tie

3rd Adjudicator reviews

Does 3rd Adjudicator agree with either of the first 2 Adjudicators?

No

Conference call: Adjudication Committee Chair makes final determination

Finding recorded in WebDCU™

Yes

Yes

Yes

Yes

No

No

No

Yes
APPENDIX 6. Adjudication System Schematic

* An automatic email is sent to Adjudicators 1 and 2. If no adjudication occurs within 7 days of the original automatic email, another set of automatic emails are sent to both adjudicators.
APPENDIX 7. Definition of Cerebral Infarction and TIA

POINT will use the tissue-based definition of stroke and TIA. TIA is a transient episode of neurological dysfunction caused by focal brain ischemia, without acute infarction. An ischemic stroke is a cerebral infarction, demonstrated by imaging or clinical features. Some infarcts cannot be visualized, even with state-of-the-art imaging techniques. Therefore, in some situations, the diagnosis of an ischemic stroke will be rendered on the basis of clinical features despite the lack of imaging confirmation; for example, prolonged deficits lasting several days and a clinical syndrome consistent with an infarct. In other situations, the imaging study is performed too soon to identify tissue injury; for example, a patient may present with a clinical syndrome typical of a stroke and have a CT scan performed, especially within the first few hours, that does not reveal acute ischemic abnormalities. If the symptoms persist, the patient is left with permanent neurological disability, and no follow-up imaging studies are performed, a diagnosis of ischemic stroke can be inferred.

For the purposes of defining the index ischemic events for trial entry, we will use the diagnosis given to each subject at the time of randomization based on all of the information available at that time. For example, a subject whose symptoms have completely resolved by the time of randomization who has not had any imaging studies suggestive of infarction will be considered a TIA patient. In contrast, a subject whose symptoms have resolved, but who has an MRI demonstrating acute infarction prior to randomization will be considered a stroke. Any subject who has continuing symptoms at the time of randomization will be considered a stroke patient.

In considering the diagnoses of TIA and minor stroke in secondary analyses for safety, POINT will use further information gathered after the initial entry diagnosis to adjudicate whether the subjects had a TIA or stroke. In the case of subjects who were initially diagnosed with TIA because symptoms had resolved by the time of randomization, but who had an MRI scan performed after randomization demonstrating acute infarction, they will be adjudicated as stroke for the purposes of this secondary analysis. (Possibility #1: Any patient initially diagnosed with stroke who does not have further brain imaging with evidence of infarction, but who does have complete resolution of symptoms within 24 hours will be considered TIA).

For the purpose of adjudicating outcome events the tissue-based definition of TIA will be used. If a subject has rapid resolution of symptoms, and no brain imaging suggesting tissue infarction, they will be considered to have had a TIA; TIA will not be adjudicated in POINT. Any brain imaging evidence of infarction or clinical evidence (such as ongoing symptoms) will qualify the event as having been stroke.
APPENDIX 8. Definition of Myocardial Infarction

Definition of myocardial infarction

Criteria for acute myocardial infarction

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
  - Symptoms of ischaemia;
  - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)];
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary 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.
- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.
- Pathological findings of an acute myocardial infarction.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a healed or healing myocardial infarction.
APPENDIX 9. WebDCU Instructions

Clinical Event Coordinator/Monitor Review
(For Clinical Event Coordinators/Monitors Only)

From the main menu page, under ‘Medical Safety’ click on ‘SAE Review’. The submitted Clinical Events/SAEs for all subjects will be posted on the List Record Table in the middle of the screen.

To view records that require review, select the ‘Pending CEC Review’ system query from the ‘Page Actions’ drop down box. This query includes records that have never been CEC reviewed as well as those that require re-review due to data changes.

Click on ▶ adjacent to the record requiring review and review the record.

Click on [Add New CEC review] at the bottom of the page. Enter the required information and click [Save Record]. As appropriate, an automatic email notification will be sent to the Adjudicators indicating that CEC review is complete and adjudication is required.

To view the audit trail which shows all revisions/updates to the CRF, click on [View Audit Trail] at the top of the screen (see Audit Trail).

Adjudication Review (for Adjudicators Only)

From the main menu page under ‘AE Alerts,’ click on ‘Pending Adjudicator Review.’ This link will bring you to the List Records: SAE Adjudication Table, which will be limited to those events pending adjudicator review that have been assigned to you.

Click on ▶ adjacent to the record requiring adjudication and review the record.

After you have reviewed the record including all of the files in the event packet, click on [Add New Adjudicated Outcome]. Enter the required information and click [Save Record].

NOTE: If you do not have enough information for adjudication, you may request additional information by contacting the Clinical Event Coordinator (CEC), who will work with the Site Manager and the site to provide the information being requested, whether it is in the form itself or the event packet. This event will be removed from your list of events requiring adjudication while the form/event
packet is being updated but will return to your list once the additional information is added and reviewed by the Site Manager/CEC.

There may be cases where you are asked to submit an adjudication for an event you have already reviewed and adjudicated. You will be able to see your previous adjudication review, and in order to know the changes that have been made to the SAE/ Clinical Outcome Reporting Form since your last review, click on [View Audit Trail] at the top of the screen (see Audit Trail).

The flow of the adjudication process is as follows:

- If the first two adjudicators assigned to an event agree, no further action is required.
- If there are discrepancies between the first and second adjudicators, a third adjudicator is asked to adjudicate.
- If the third adjudicator agrees with either of the first two adjudicators, no further action is required.
- If all three adjudicators disagree, the Adjudicator Chair reviews the event and attempts to gain consensus among the other adjudicators, though ultimately it is his/her adjudication that is assigned to the event.