Appendix I: ORGANIZATIONAL CHARTS

The POINT study is a collaboration of established research networks connected through the leadership of the Principal Investigators. Day-to-day operational oversight is provided by an Operations Committee with assistance on clinical and implementation issues provided by an Advisory Committee. Each of the components and respective roles and responsibilities is detailed below. Figure 1 and Figure 2 provide high level illustrations of the organizational structure.

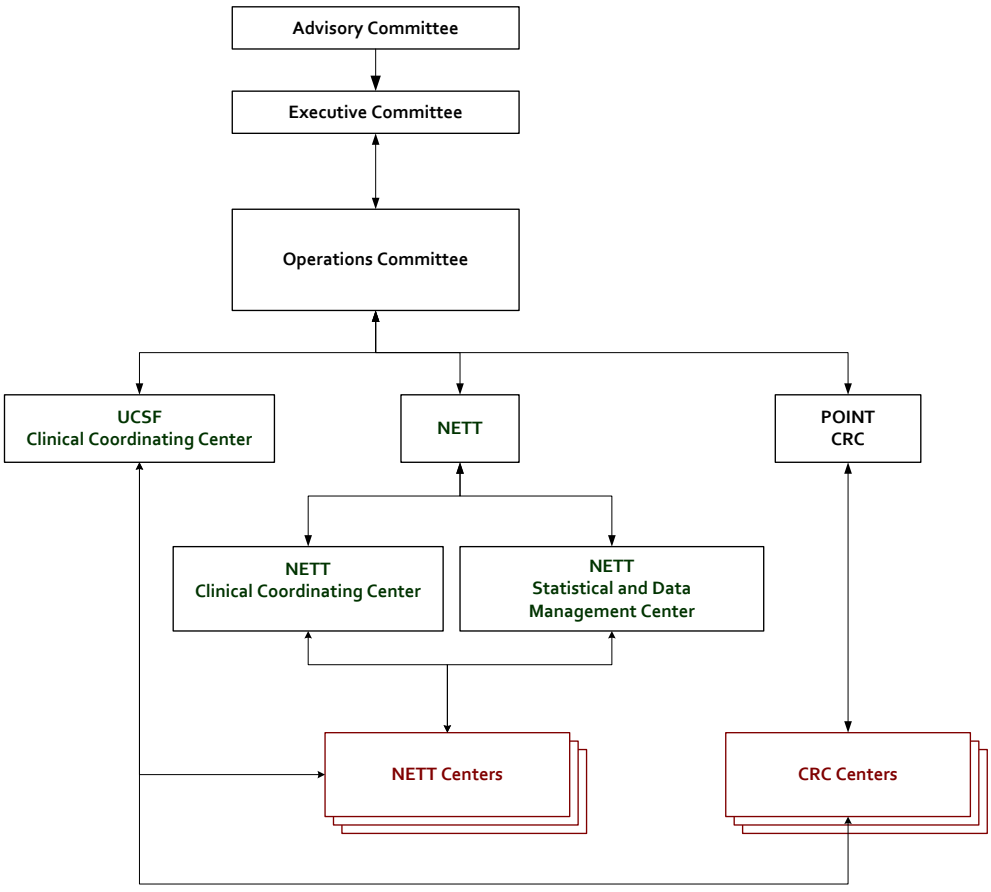

Figure 1. POINT Overall Organizational Structure

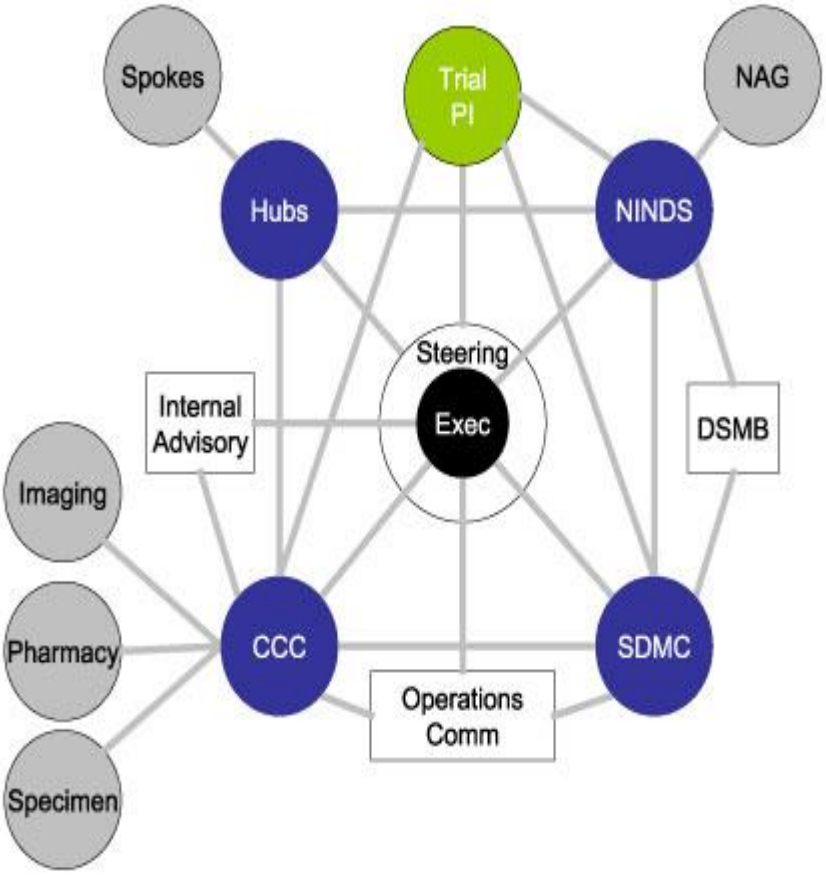

Figure 2. POINT Organizational Structure: NETT

Appendix II: OPERATIONS COMMITTEE

POINT OPERATIONS COMMITTEE

S. Claiborne Johnston, MD, PhD (Chair)
University of Texas, Austin
PI

J. Donald Easton, MD
University of California, San Francisco
Co-PI

Mary Farrant, MBA, BSN, RN
University of California, San Francisco
Operations Director

Catherine Dillon
NETT, MUSC
NETT SDMU Manager

Anthony Kim, MD, MAS
University of California, San Francisco
Institutional PI

Anne Lindblad, PhD
NINDS CRC
CRC Director

William Barsan, MD
NETT, University of Michigan
NETT PI

Yuko Palesch, PhD
NETT, MUSC
Blinded Statistician

Jordan Elm, PhD
NETT, MUSC
Unblinded Statistician

Robin Conwit, MD
NINDS
NETT Project Officer

Valerie Stevenson
NETT, University of Michigan
NETT Admin. Director

Michelle Weeks
NINDS CRC
CRC Operations Center Director

Appendix III: EXECUTIVE COMMITTEE

POINT EXECUTIVE COMMITTEE

S. Claiborne Johnston, MD, PhD (Chair)
University of Texas, Austin
PI

J. Donald Easton, MD
University of California, San Francisco
Co-PI

Mary Farrant, MBA, BSN, RN
University of California, San Francisco
Operations Director

Anne Lindblad, PhD
POINT CRC
CRC Director

William Barsan, MD
NETT, Univ of Michigan
NETT PI

Anthony Kim, MD, MAS
University of California, San Francisco
Institutional PI

Lewis Morgenstern, MD
NETT, University of Michigan
NETT Neuro Director

Robin Conwit, MD
NINDS
NETT Project Officer

Scott Janis, PhD (ex officio)
NINDS
NINDS Trials Officer

Jordan Elm
NETT, MUSC
Unblinded statistician

Yuko Palesch, PhD
NETT, MUSC
NETT SDMU Director

Appendix IV: ADVISORY COMMITTEE

POINT ADVISORY COMMITTEE

Philip Gorelick, MD, MPH
Rush Medical School, Chicago
Stroke Neurologist

Michael Hill, MD
University of Calgary
FASTER Co-PI

Irene Katzan, MD
Cleveland Clinic, Cleveland
Stroke Neurologist

Arthur Pancioli, MD
University of Cincinnati
Emergency Physician

Jeffrey Saver, MD
University of California, Los Angeles
Stroke Neurologist

Site PI
Highest NETT-CCC Enrolling Site

Site PI
Random NETT-CCC Enrolling Site

Site PI
Highest POINT CRC Enrolling Site

Site PI
Random POINT CRC Enrolling Site

Appendix V: ADJUDICATIONS COMMITTEE

POINT ADJUDICATIONS COMMITTEE

Neurology:

Darin B. Zahuranec, MD, MS
Assistant Professor,
Department of Neurology,
University of Michigan,
Ann Arbor, MI

Kevin A. Kerber, MD
Assistant Professor,
Department of Neurology,
University of Michigan,
Ann Arbor, MI

Matthew T. Lorincz, PhD
Assistant Professor,
Department of Neurology,
University of Michigan,
Ann Arbor, MI

Cardiology/Internal Medicine:

David Bach, MD
Professor, Internal Medicine,
University of Michigan
Ann Arbor, MI

Claire S. Duvernoy, MD
Associate Professor,
Department of Internal Medicine
Division of Cardiology,
University of Michigan
Ann Arbor, MI

Deborah A. Levine, MD, MPH
Assistant Professor of Medicine, tenure track,
Department of Internal Medicine,
Division of General Medicine, and
Department of Neurology,
University of Michigan Medical School,
Ann Arbor, MI

NOTE: THIS INFORMATION IS ALSO FOUND IN "CLINICAL OUTCOME ADJUDICATION GUIDELINES", APPENDIX # 15

Appendix VI: DATA AND SAFETY MONITORING BOARD (DSMB) MEMBERS

POINT Trial
Data and Safety Monitoring Board Meeting (DSMB)
2014 ROSTER

DSMB MEMBERS:
Chair: Dr. Gregory J. del Zoppo

Robert Côté, M.D.
Professor, Department of Neurology,
Neurosurgery, and Medicine
Division of Neurology
Montreal General Hospital
3755 chemin de la cote-Sainte-Catherine
Montréal, QC H3T 1E2
Phone: 514–934–8057
Fax: 514–934–8265
E-mail: robert.cote@mcgill.ca

Gregory J. del Zoppo, M.D.
Professor of Medicine (in Hematology)
Adjunct Professor of Neurology
University of Washington School of Medicine
Harborview Medical Center
325 Ninth Avenue
Campus Box 359756
Seattle, WA 98104

(For FedEx delivery):
Gregory J. delZoppo, M.D.
Medicine/Hematology
Harborview Medical Center
300 Ninth Avenue
R &T Room 503/521
Seattle, WA 98104
Phone: 206–897-5313
Fax: 206–343–5043
E-mail: grgdlzop@u.washington.edu
Assistant: Patti Allen
E-mail: pallen@u.washington.edu

Misha Eliasziw, Ph.D.
Associate Professor of Public Health and
Community MedicineTufts University School of
Medicine
136 Harrison Avenue
Boston, MA 02111
Phone: 617-636-0954
Fax: 617-636-4017
Email: misha.eliasziw@tufts.edu

Pierre Fayad, M.D., FAHA, FAAN
Reynolds Centennial Professor
Department of Neurological Sciences
University of Nebraska Medical Center (UNMC)
988435 Nebraska Medical Center
Omaha, NE 68198-8435
Phone: 402–559–4086
Fax: 402–559–9355
E-mail: pfayad@unmc.edu
Assistant: Tonya Moore-Paschall
E-mail: tonya.moorepaschall@unmc.edu

Ann M. Lowe, M.D.
Consultant
420 Cambridge Ave. Unit 3
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Phone: 650–323–6614
E-mail: amlowe@earthlink.net

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Professor of Medicine
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, NY 10467
Phone: 718-920-2248
E-mail: ilppina@aol.com
Assistant: Denise Balfour
E-mail: lbalfour@montefiore.org

Julie A. Swain, M.D.
Professor of Cardiovascular Surgery
Director, Center for Medical Devices, Mount Sinai
Icahn School of Medicine at Mount Sinai
910 W. Muirlands Dr.
LA Jolla, CA 92037
Phone: 858-652-0107
E-mail: Julie.Swain@mountsinai.org

Appendix VII: STUDY MILESTONES

A 7-year budget and recruitment plan have been created; key study milestones below.

STUDY MILESTONES

Pre-enrollment Study Initiation	9 months
Recruitment and Follow-up	90 months
Completion of Follow-up	3 months
Data Analysis and Publication	6 months
Total Duration	**108 months**

Appendix VIII: PROTOCOL AMENDMENT FORM

POINT TRIAL PROTOCOL AMENDMENT FORM

Investigators are required to inform the Institutional Review Board (IRB), in writing, of protocol changes prior to their initiation. Minor changes in previously approved research are reviewed by the IRB Chair and may be granted expedited approval. Significant changes require full IRB review and voting at a convened meeting. **IRB approval is required prior to implementation of the change**.

Protocol Title:

CHR #:_____Principal Investigator:_____ Department:_____

Phone: (____)_____Fax: (____)_____E-mail:_____

Type of review requested: ☐ Expedited (Minor changes in previously approved research)

☐ Full Board (Significant protocol changes)

Changes must be highlighted in one copy.

1. **Amendment in study design or protocol:** ☐ Yes ☐ No (*If yes, summarize below)*

2. **Administrative amendment, grammatical corrections:** ☐ Yes ☐ No *(If yes, summarize below)*

3. **Consent form amendment:** ☐ Yes ☐ No
   (If yes, submit 2 copies. Changes must be highlighted in 1 copy.)

4. **Change in Investigator/Study Coordinator:** ☐ Yes ☐ No
   (If yes, complete information below)

   ☐ **Addition*** ☐ Investigator(s) - Name/title:
   ☐ Study Coordinator - Name/title:
   Provide copy of Investigator's CV. New investigator(s) must sign below.

   - Signature:_____ _____ _____

   ☐ **Deletion** ☐ Investigator(s) - Name/title:
   ☐ Study Coordinator - Name/title:
   Deleted investigator(s) must sign below

   - Signature:_____ _____ _____

***Investigators and study coordinators must be trained in the protection of human subjects.**

Signature of Principal Investigator:_____ Date:_____

Appendix IX: ANCILLARY STUDIES POLICY

POINT Trial
Ancillary Study Policy

Definitions

An **ancillary study** is a research activity undertaken to address a scientific question that requires access to data or records from the parent study and/or involves collection of additional data, specimens, or records from patients enrolled in the parent study. The **parent study** is the primary study funded through a grant mechanism or other form of support.

Policy Overview

The goal of the POINT Trial Ancillary Study Policy is to provide guidelines for proposing, reviewing and approving ancillary studies conducted within the POINT Trial framework.

Responsible Individuals

Members of the POINT Executive Committee

Procedures for Submitting a New POINT Trial Ancillary Study Proposal

1. All ancillary concepts must be reviewed and approved by the POINT Executive Committee before ancillary study initiation. The ancillary study investigator must complete a POINT Ancillary Study Protocol Summary form; see Appendix A. The form, along with the study protocol, must be submitted to the POINT Executive Committee for review.

2. The POINT Executive Committee reviews the application at its next scheduled meeting. The review is based on scientific merit and interest, consistency with POINT study objectives, non-duplication of or interference with ongoing activities, and burden level on POINT participants, staff or materials.

3. After review of submitted materials and comments, the Executive Committee will vote on the proposed study. The vote can take place at a face-to-face meeting or conference call with all members present; if this is not feasible, e-mail review and voting may be substituted.

   Criteria for Executive Committee approval of an ancillary study include:

   a) The proposed study addresses a question of importance.
   b) The proposed study should not compete with any previously approved ancillary study.
   c) Conduct of the study must not adversely affect the parent study.
   d) Funding for the study will be obtained by the PI and will be independent of the parent study funding.

e) Procedures for accessing necessary data and records from the parent study are explicit and acceptable.
f) The proposing PI has the appropriate expertise and facilities to conduct the study.
g) Plans for publication and authorship of study results are appropriate, including review and approval of manuscripts per the POINT publication policy.
h) Executive Committee members will be given adequate time to review the proposal before a vote is taken.

4. The ancillary study PI will be notified of the outcome of the Executive Committee vote.

5. A list of all proposed and approved ancillary studies will be maintained by the UCSF Clinical Coordinating Center (UCSF CCC).

6. After approval, if there are changes to the specific aims, substantial changes in the ancillary study design, or changes in the potential impact of the ancillary study on the main study, then the investigators must submit a revised protocol to the Executive Committee for review.

   The Executive Committee may, by majority vote, recommend termination of an ancillary study if it judges that a study has become too burdensome or its scientific value has diminished, or it has failed to make substantial progress toward the completion of its goals.

7. The appropriate Institutional Review Boards must eventually approve all ancillary studies before they are performed, but IRB approval is not required to submit a proposal.

8. Investigators applying for an ancillary study must be prepared to provide all additional funding needed for the study.

9. The Executive Committee will be concerned with both the obvious and hidden costs to POINT entailed by an ancillary study, including the costs to the POINT investigators for managing or overseeing POINT's role in the study, for obtaining appropriate IRB or other approvals, and coordinating additional data collection, data transfer, and archiving and distributing datasets (including, as necessary, preparing limited access data sets).

10. Proposers should allow at least **12 weeks** between submission of the ancillary study proposal to the Executive Committee and the funding application deadline.

11. Every six months, the primary investigator on each approved ancillary study will be asked to provide a one-page summary of the status of the study. The status of the studies will be reviewed and discussed every six months by the Executive Committee. If there is no progress on a plan for a year, or if serious conflicts with the specific aims or the daily conduct of the study arise, the POINT Executive Committee may vote to withdraw approval of the plan.

12. All manuscript proposals, publications, abstracts, and presentations derived from the ancillary study must be processed through the POINT approval process via the POINT Executive Committee prior to submission.

POINT Trial Ancillary Study APPENDIX A

POINT Ancillary Study Protocol Summary

Title of Study:	
Principal Investigator(s):	**Institution:**
Co-Investigator(s):	**Person providing statistical support:**
Proposed Performance Sites:	
All NETT Hubs ☐	**All NETT Hubs plus additional performance sites** ☐
Specific NETT Hubs ☐	**All Clinical Research Collaboration (CRC) sites** ☐
Please List:	**Specific CRC Sites** ☐
	Please List:
Will results of this study be submitted as part of a planning grant or grant application? Yes ☐ **No** ☐	
Will this trial require FDA approval? Yes ☐ **No** ☐	
Project Description	
Purpose of trial:	
Briefly describe the scientific rationale for the study:	
Briefly describe the investigator's qualifications:	
Number of subjects to be enrolled: _____	
Type of data and/or specimens requested:	
Study staff collecting data and/or specimens	
Study Coordinators ☐	**Data Coordinating Center staff** ☐
Site Investigators ☐	**Clinical Coordinating Center (CCC) staff** ☐

Other ☐ Please describe: **Clinical Research Collaboration (CRC)Staff ☐**
Potential impact (negative and/or positive) of ancillary study on parent study:
Study Abstract-(no more than 100 words):
Human Subject Considerations **Patient selection criteria:** 1. **List Inclusion Criteria** 2. **List Exclusion Criteria**
Describe method for identifying and recruiting subjects for the trial:
Describe the informed consent process:
Describe how the intervention will be administered, including dose and duration as applicable:
Explain method for obtaining and collecting regulatory documents and ensuring compliance:
Describe the interim monitoring plan, including the schedule of interim analyses and guidelines for stopping the study for reasons of efficacy, safety, futility, or poor study performance:
Describe ethical and consent considerations of the proposed protocol:
Describe plan for follow-up:
Data Collection, Analysis, Management and Quality Assurance **Define study outcomes:** **List study endpoints:**

Describe the method of data collection:
Where will study data be kept?
Person providing statistical support:
Describe the statistical and clinical basis for the sample size calculation:
Briefly describe the study design and indicate, in general terms, how the design will fulfill the intent of the study:
Financial Considerations **Funding source/sponsor(s):** Grant ☐ Corporate Sponsor ☐ In-kind/institutional ☐ **Name of sponsor:**
Resources required (check all that apply): Personnel ☐ Equipment ☐ **Please describe:**
Effort required at by study staff at each participating site (hours per month* number of staff):
Total estimated cost of project (direct + indirect): $
Do you or any member of the study group have a financial conflict of interest or hold a patent with the use of the intervention and/or investigational product employed with this protocol? Yes ☐ No ☐
I have read and agree to the POINT publications policy as outlined in the POINT Publications Policy. **Yes ☐ No ☐** **Date: /20** **Name:**_____

Appendix X: PUBLICATIONS POLICY

Platelet-Oriented Inhibition in TIA and minor Ischemic stroke (POINT) Trial

Publications Policy

Policy Overview

The goal of the POINT Trial Publications Policy is to provide guidelines for preparing, reviewing, submitting and maximizing productivity of high quality peer-reviewed publications.

Responsible Individuals

Members of the POINT Executive Committee.

Study-Specific Publication Procedure – POINT Executive Committee

The goal of this policy is to maximize the yield of high quality peer-reviewed publications. In addition to overseeing the performance of the trial, the Executive Committee is responsible for encouraging paper production, ensuring timely publication of data, maintaining a high standard for the quality of papers produced for POINT, and determining appropriate authorship. When the Committee is discussing manuscripts associated with ancillary studies, the PI of the ancillary study and his/her designee will also join the Executive Committee for that discussion.

Manuscript proposals will be submitted to the Executive Committee. These proposals will include the type (primary, secondary, tertiary and quaternary), list of authors and their qualifications for authorship, a statement that no others deserving authorship have been omitted, the scientific rationale for the paper, the data needed and a description of the proposed analyses and any deadlines for submission of abstracts or presentation dates if applicable.

Such proposals will be reviewed at the next Executive Committee meeting, no more than 1 month after submission. The Committee may suggest changes to the proposed analyses or to included authors, and may decline a proposal if it considers it scientifically unsound or if resources for the analyses are unavailable. As much as possible, the committee will work with the proposer to address any concerns. A proposer may request reconsideration if a proposal is initially declined; this request will be reviewed by the trial PI and co-PI who will have final authority.

All trial-related manuscripts will be reviewed prior to journal submission to ensure that statements made at the time of the paper proposal were carried forward in manuscript formation, and that the final

manuscript meets the highest standards regarding scientific rigor, thoroughness, clarity, and full disclosure of conflicts of interest.

Paper proposals will be divided into four distinct types based on their relation to the underlying study hypotheses. These designations are important to the Executive Committee since primary and secondary papers should be published early and authored by the POINT Trial PI and colleagues.

Proposal Types

- **Primary**: Primary papers are pre-specified as including the primary outcome data of the trial as described in the grant application.
- **Secondary**: Secondary papers are defined as containing the secondary, pre-specified data as described in the grant application.
- **Tertiary:** Tertiary papers are post-hoc analyses that relate to the central hypotheses being tested, but not pre-specified in the grant application.
- **Quaternary:** Quaternary papers utilize the dataset for data that do not relate to the hypotheses of the study.

The Trial PI and his or her designees have the first rights to publish collective study data per the Executive Committee approval. It is expected that within six months of analysis availability, the manuscript presenting the primary study results will be sent to the Executive Committee by the PI. The primary analysis of POINT will be submitted for publication within 3 months of study database lock.

POINT PIs and members of the NETT-CCC and SDMC are next in line for publication rights. Only the Trial PI and designees, POINT PIs, and members of the NETT CCC and SDMC have collective data rights until 2 years after the publication of the primary manuscript or 4 years after completion of the study, whichever comes first. Individual institutions shall retain ownership of all data that they generate. Institutions shall grant to the POINT PI and designees non-exclusive license to use data for educational and research purposes. Sites agree to delay any presentation or publication of their own site's data until the primary results of the trial have been published or 2 years after study completion, whichever comes first. The Executive Committee will retain oversight of the collective data and decision making authority with respect to the collective data for 2 years after publication of the primary study results or 4 years after study completion, whichever comes first.

Finally, within 5 years of study completion, the public use data sets will be created by the SDMC and forwarded to the National Technical Information Service (NTIS) (website: www.ntis.gov), to whom requests for data can be addressed. All reasonable requests for data will be honored by the Executive Committee in accordance with the NIH policy on data sharing.

The POINT PI will be given 1 year from trial initiation to specify publications that he/she or his/her designee wishes to author using the collective data. After this time, ideas submitted to the Executive Committee will be evaluated on a first-come, first-served basis.

Group authorship is encouraged. This is especially true for primary publications. The appendix at the end of both group and named authored papers should contain the names of the POINT Trial PI, the POINT Executive Committee, the CRC Director, the NETT CCC, the NETT SDMC, NETT AND CRC investigators, and the NINDS Scientific Program Director. All publications from POINT will contain a list of PIs and

other independent trial PIs at the end of the publication. Additional investigators and coordinators should be listed as well, acknowledging whether they are arising from the NETT or the CRC.

Named authored papers should follow logical criteria for authorship. All investigators who make a creative, substantive contribution to the research should be listed as authors. This includes those who creatively participated in the study concept, design, funding, conduct and/or analysis, or who drafted the manuscript. Individuals whose involvement is limited to following the study protocol within the context of their job do not qualify for named authorship, but may be recognized in the acknowledgment section.

The first author for publications should be the individual who was most fully responsible for the concept, design, funding, conduct, analysis and drafting of the manuscript. The last author should be the senior member who contributed the most to the items listed above. The order of the remaining authors should follow from their relative contribution to the manuscript. The NINDS Scientific Program Director should be a co-author on the primary publication. All relevant individuals should receive a copy of the manuscript in a timely fashion and be offered the option to request that their name be listed, moved in order, or remove themselves from authorship. All grievances should be conveyed to the Executive Committee by the first author and Trial PI with a recommendation for resolution. The Executive Committee has the final word with respect to authorship decisions.

POINT PIs will be given seven days to review publications and offer any suggestions for change. If changes are suggested but not made by the Trial PI, the POINT PIs may elect to have their name removed from the publication, but they may not remove their data from the analysis.

Study-Independent Publication Procedures (POINT operations and methods papers)

Members of the NETT-CCC, SDMC, CRC and UCSF CCC, and PIs may wish to publish methods papers that describe their function, or papers that are otherwise wholly independent from the trials conducted. These paper proposals and final manuscripts will be submitted to the POINT Executive Committee.

Additional paper proposals and final manuscripts will be submitted to the NETT General Publications Committee if they are relevant to the operations or organization of the NETT. This committee does not have authority over individual study Publications Committees or policies. Papers published on such topics will not address topics in the study's specific aims, but will require an option for authorship and review by POINT PIs if POINT is referenced in the manuscript.

Individual POINT Site Investigator Publication Rights

A POINT Investigator who wishes to publish his or her own institution's data will be able to proceed with such publication, provided that publication is delayed for 1 year after the primary publication has been published or 2 years after the study has ended (database lock), whichever comes first.

Adherence to Policy

Participation in POINT requires adherence to the publication policy described in this document, even though PIs retain ownership of the data collected at their sites. Authors who publish articles that are not compliant with this policy must contact the journal and retract the publication.

POINT TRIAL PROPOSAL REVIEW PROCESS

1. Complete POINT Trial Manuscript Proposal Form (**Appendix A**)
2. Submit completed form via email to POINT Executive Committee for review.
3. Executive Committee reviews request and within 4 weeks approves, modifies or disapproves the request using the POINT Manuscript Proposal Review Form (**Appendix B**). More detailed information may be requested from the authors.
4. The final version of the completed abstract, poster, slides or manuscript must be sent to the POINT Executive Committee for review at least 6 weeks prior to the submission deadline or presentation date; for manuscripts, the submission cover letter must be included with the copy of manuscript.
5. The Executive Committee approves, approves with modification or disapproves the abstract, poster, slides or manuscript. (**Appendix C**)
6. If the manuscript is denied, feedback is given within 2 weeks of the denial, detailing the rationale for disapproval.
7. If changes are recommended, the revised version is submitted to the Executive Committee prior to submitting the manuscript or abstract for publication.
8. The Executive Committee is kept informed about acceptances, rejections or resubmissions of materials; if a manuscript is changed for resubmission, it should be submitted to Executive Committee for re-approval prior to being submitted for publication.
9. The Executive Committee reserves the right to make final determinations in conflicts or disputes about authorship ranking.

POINT Trial Publications Policy Appendix A

POINT Trial Publications Proposal Form

Please read the POINT Publications Policy before completing this form.

Date Submitted:

Is this the first review of this proposal by the POINT Executive Committee? Yes ☐ No ☐

1. **Proposal Type:**

   Primary ☐ Secondary ☐ Tertiary ☐ Quaternary ☐

2. **Title Information**

   Proposal Title:

3. **Lead Author Information**

   First Author's Name: **Institutional Affiliation:**

   Address: **Email Address:**

   Telephone: **Fax Number:**

4. **Co-author Information**

   Author's Name: **Institutional Affiliation:**

   Address: **Email Address:**

   Telephone: **Fax Number:**

5. **Have all authors reviewed and approved the manuscript/abstract? Yes ☐ No ☐**

6. **Rationale:**

7. **Data Needed:**

8. **Description of Proposed Analyses:**

9. **Deadlines for Submission of Abstract(s) or for Presentation:**

10. Journals Anticipated for Submission (list up to 3 in priority order):	
11. Will this manuscript be presented at an upcoming conference or meeting? Yes ☐ No ☐ **If yes, which one(s): Date(s):**	
12. Is this manuscript proposal based on an ancillary study? Yes ☐ No ☐	
I have read and agree to the POINT publications policy as outlined in the POINT Publications Policy.	
Name:_____	***Date:*** **/20**
Email the completed form and manuscript to POINT@ucsfmedctr.org	

POINT Trial Publications Policy Appendix B

POINT Trial Manuscript Proposal Review Form

Date of Review:

Reviewer:

Proposal Title:

Ratings:

	Excellent	Very Good	Good	Fair	Not Acceptable
Importance of Question					
Originality/Innovation					
Quality of Methods					
Overall Scientific Merit					
Relevance to POINT Key Scientific Questions					
Statistical Considerations					

Recommendation:

☐ Accept as is

☐ Accept pending revisions

☐ Reconsider after revisions

☐ Disapprove for reasons noted:

POINT Trial Publications Policy Appendix C

POINT Trial Manuscript Review Form

Date of Review:

Reviewer:

Proposal Title:

Ratings:

	Excellent	Very Good	Good	Fair	Not Acceptable
Importance of Question					
Originality/Innovation					
Quality of Methods					
Overall Scientific Merit					
Relevance to POINT Key Scientific Questions					
Statistical Considerations					

Recommendation:

☐ Accept as is

☐ Accept pending revisions

☐ Reconsider after revisions

☐ Disapprove for reasons noted:

Appendix XI: GCP TABLES

Table 1: Check List for Clinical Research Personnel	
Item	**Reference**
Investigators and nurses medical licensures updated annually and CVs and/or biosketches updated as needed.	ICH GCP 4.1.1 ICH GCP 8.2.10
Key personnel must be listed on each research trial.	IRB Requirement
Key personnel must be credentialed annually by IRB.	IRB Requirement
Key personnel involved in shipping specimens must be trained in Biomedical Safety every 2 years.	Site Requirement
Key personnel must complete safety training annually.	Site Requirement
Key personnel must undergo GCP training every 2 years.	Site Requirement

Table 2: Regulatory Documentation Requirements	
Item	**Reference**
Approved protocol – original copy and all revisions must be kept on file.	ICH GCP 8.2.2
Signed FDA 1572 for IND studies: original copy and revisions kept on file.	21 CFR 312.53(c)
Current subject enrollment log kept on file using the protocol schedule of events format for the study visits. For subject enrollment logs leaving site, identifiers must reflect only those listed in the subject's signed consent form.	ICH GCP 8.3.20 ICH GCP 8.3.21 ICH GCP 8.3.22
Research trials must be monitored. Documentation must be maintained that indicates: • Who is monitoring the trial. • How often the trial is monitored.	ICH GCP 8.3.10
Each research trial must have documentation and PI approval of research staff, staff title and delegation of responsibility. Documentation should include research staff signature and PI signature on the description of duties.	ICH GCP 4.1.5 ICH GCP 8.3.24
All versions of the Investigator Brochure of Drug and/or Device Manual for each research trial must be kept on file.	ICH GCP 7.1 ICH GCP 8.2.1 ICH GCP 8.3.1
For laboratory tests required during trial:	
Copies of the normal values must be kept on file.	ICH GCP 8.2.11
If not using local laboratory, a copy of the laboratory's certification and Laboratory Director's CV must be kept on file.	ICH GCP 8.2.12 ICH GCP 8.3.7
	ICH GCP 8.2.12 ICH GCP 8.3.7
Correspondence	
All IRB correspondence (e.g. emails, submissions) to and from the IRB must be kept on file.	ICH GCP 4.9.4

Table 2: Regulatory Documentation Requirements	
Item	**Reference**
All initial IRB approval letters for trial must be kept on file.	ICH GCP 8.2.7
All correspondence to/from the sponsor and/or FDA must be kept on file.	ICH GCP4.9.4
All renewal IRB approval letters for trial must be kept on file.	ICH GCP 8.2.7
All amendment IRB approval letters for trial must be kept on file.	ICH GCP 8.2.7
All adverse event IRB acknowledgment letters for trial must be kept on file.	ICH GCP 8.2.7
All violation/deviation (waiver) IRB acknowledgment letters for trial must be kept on file.	ICH GCP 8.2.7
All original copies of the IRB approved consent forms for trial must be kept on file.	ICH GCP 8.2.7 ICH GCP 8.3.3

Table 3: Record Keeping Regulations	
Item	**Reference**
Trial must have a separate binder or folder for regulatory documents.	ICH GCP 2.10 ICH GCP 4.9.4
Trial must have a separate binder or folder for IRB correspondence.	ICH GCP 2.10 ICH GCP 4.9.4
Trial must have a separate binder or folder for correspondence with sponsor for each research trial.	ICH GCP 2.10 ICH GCP 4.9.4
Trial must have a separate binder or folder for original informed consent.	ICH GCP 2.10 ICH GCP 4.9.4
Trial must have for a separate binder or folder for Confidentiality Agreements.	ICH GCP 2.10 ICH GCP 4.9.4
Trial must have for a separate binder or folder for research personnel as described Table 1.	ICH GCP 2.10 ICH GCP 4.9.4

Table 4: Delegation of Responsibilities				
	PI	**Co-PI**	**Coordinator**	**Comments**
Reporting changes in key personnel to IRB	X		X	
Reporting to key personnel the need for annual IRB research credentialing			X	
Ensuring key personnel maintain their IRB research credentialing throughout the life of			X	
Negotiating the budget/contract wording	X		X	
Preparing billing grid			X	With PI
IRB Activities:				
Preparing initial submission	X		X	
Preparing renewal submission	X		X	ICH GCP 4.1.5 ICH GCP 4.2.4
Submitting amendments	X		X	
Submitting progress reports	X		X	
Submitting SAE/AE reports	X		X	ICH GCP 4.10.2
Submitting protocol deviations, violations, waivers	X		X	

Table 5: Drug Dispensing	
Item	**Reference**
Dispensing log	21.CRF 312.2(a) ICH GCP 4.6.3
An individual responsible for shipping/receiving the agent	
Shipping receipts	ICH GCP 8.2.15

Appendix XII: SCHEDULE OF ACTIVITIES AND ASSESSMENTS

Contact Schedule and Measurements

Measurements	Screening	Baseline/ Randomization	Phone F/U Day 7 +/-2	Phone F/U Day 30[◊]	Phone or In-Person F/U Day 90 +/-14[†]	Event Visit***	End of Study
Screen Failure Log	x						
Eligibility Form		x					
Consent (including optional study)		x					
Randomization Form		x					
Enrollment/ Demographics		x					
ABCD[2] Score		x					
Modified Rankin Scale (mRS)					x	x	
NIH Stroke Scale		x			x	x	x
Medical History		x					
Prior Medications		x					
Index TIA/Minor Stroke Symptoms		x					
Vital Signs		x					
Blood Sample (optional)		x*[2]					
Head CT/MRI Scan		x*			x*	x*	
ECG		x*			x*	x*	
Carotid Imaging		x*[1]			x*[1]	x*	
Stroke-Free Questionnaire: QVSFS			x	(x)	x	x	
Morisky Questionnaire			x	(x)	x	x	
Concomitant Medications Form			x		x	x	
SAE/Clinical Outcome Reporting			x		x	x	
Study Drug Compliance				(x)			x
Final Diagnosis		x					
End of Study Form							x
Protocol Violation	x	x	x		x	x	x

*Part of standard evaluation; cost not covered by study.

** As needed (visit can occur more than once).

*** Event Visits for MI can be completed by telephone.

† Preferably as soon as possible after the completion of 90 days.

[1] Encouraged as part of best practices but not required for study entry or at 90 days. If performed, record results on CRF.

[2] Blood sample obtained with subject's consent for optional ancillary study

Ɵ No study data collected.

Note: Certain follow-up assessments, such as the mRS and QVSFS, by telemedicine are acceptable.

Note: The above table is found in the POINT protocol section 1.2

Appendix XIII: POINT TRIAL CRFs

Form 00: Eligibility Form

Form 10: Randomization Form

Form 01: Demographics

Form 02: $ABCD^2$ Score

Form 03: Modified Rankin Scale

Form 04: NIH Stroke Scale

Form 05: Medical History

Form 06: Prior Medications

Form 07: Index TIA/Stroke Symptoms

Form 08: Vital Signs

Form 09: Seven Day Follow Up

Form 11: CT / MRI Scan

Form 12: Electrocardiogram

Form 13: Carotid Imaging Results

Form 14: Questionnaire for Verifying Stroke Free Status (QVSFS)

Form 15: Morisky Questionnaire

Form 16: Study Drug Compliance

Form 17: End of Study

Form 18: Concomitant Medications

Form 19: SAE/Clinical Outcome Reporting Form

Form 20: Final Diagnosis

Form 21: Protocol Deviations/Violations

Form 22: Ancillary Biomarker

Appendix XIV: POINT DATA COMPLETION GUIDELINES

General CRF Completion Guidelines

For the most recent POINT CRF guidelines, please visit the POINT website Resources and Training section, https://www.nett.umich.edu/nett/point_resources_and_training.

General CRF Completion Guidelines

- Although it is not a requirement that you use paper worksheets for data collection, all data defined on the worksheets must be collected and entered into WebDCU™.
- If paper worksheets are used as source documents, they must be retained at the Clinical Site according to local and federal regulations.
- No data should be missing unless allowed by a skip pattern.
- If data for a numerical field is unknown or missing, please leave that field blank. Do not enter 0 (zero).
- Circles or radio buttons "O" indicate that you should choose only one answer.
- Boxes "□" indicate that you should 'check all that apply'.
- Use the following format for all date fields: DD-MMM-YYYY (e.g., 31-JAN-2010)
- Complete dates should be entered, whenever possible, for all date fields. If the complete date isn't known, partial dates are allowed for select data points.
- Use the following format for all time fields: hh:mm
  Please note: 24:00 is not an allowable response. 24 hour clock time goes from 00:00 to 23:59. Midnight should be entered as 00:00.

Time on Clock	24 Hour Clock Time
12:00 AM	00:00
01:00 AM	01:00
02:00 AM	02:00
03:00 AM	03:00
04:00 AM	04:00
05:00 AM	05:00
06:00 AM	06:00
07:00 AM	07:00
08:00 AM	08:00
09:00 AM	09:00

10:00 AM	10:00
11:00 AM	11:00
12:00 PM	12:00
01:00 PM	13:00
02:00 PM	14:00
03:00 PM	15:00
04:00 PM	16:00
05:00 PM	17:00
06:00 PM	18:00
07:00 PM	19:00
08:00 PM	20:00
09:00 PM	21:00
10:00 PM	22:00
11:00 PM	23:00

- Name of person who collected the CRF data must be entered on the bottom of the paper worksheet, when the paper worksheet is used as a source document. This field will not be data entered but is required for monitoring purposes.

- Data Entry Timelines:
  - Screen Failure Log - The Clinical Site staff should update the Screen Failure Log forms in WebDCU™ by the 10th of the following month, when a Screen Failure Log is required.
  - Baseline through End of Study CRFs - Within 5 days of collection.
  - *Please note that site payments are dependent upon the subject's data being entered and submitted.*

- Data Clarification Request (DCR) Timelines: All responses to DCRs must be submitted within 5 days of query generation with the exception of DCRs for SAEs/Clinical Outcomes which must be submitted within 24 hours of query generation.

Screen Failure Log

The Screen Failure Log is required for all NETT sites. Non-NETT sites should enter the Screen Failure Log if directed by the study team. The most current version of the Screen Failure Log is located in WebDCU™ under Project Documents. Paper versions of the Screen Failure Log will be reviewed during the monitoring visit, if applicable.

The Screen Failure Log is used to help identify the number of potential POINT subjects who are identified by phone or in person within a site's Emergency Department. Patients that are actively screened (in person or via telephone) for the POINT study by your study team but not randomized at your site should be included on the log.

Sites that are required to track screen failures should enter the data monthly into WebDCU™. Screen failures for the previous month must be reported by the 10th of the following month.

Any screen failures to report? Answer "No" or "Yes." If "No," no further information needs to be entered for that month. If "Yes," enter all screen failures as designated on the form.

Column F (Primary reason patient is not enrolled): Select the code that corresponds with the primary reason for non-enrollment.

Column G (Specify): If primary reason is 'consent declined for other reason' or 'other,' it must be specified in this column.

Screen Failure Code List:

1= TIA patient with ABCD2 score < 4.
2= Minor ischemic stroke patient with NIHSS > 3.
3= Inability to randomize within 12 hours of time last known free of new ischemic symptoms
4= Head CT or MRI does not rule out hemorrhage or other pathology, such as vascular malformation, tumor, or abscess, that could explain symptoms or contraindicate therapy
5= Age < 18 years
6= Inability to tolerate aspirin at a dose of 50-325 mg/day
7= Symptoms of TIA limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo
8= In the judgment of the treating physician, a candidate for thrombolysis, endarterectomy, or endovascular intervention.
9= Receipt of any intravenous or intra-arterial thrombolysis within 1 week prior to index event.
10= Gastrointestinal bleed or major surgery within 3 months prior to index event.
11= History of nontraumatic intracranial hemorrhage.
13= Clear indication for anticoagulation (e.g., warfarin, heparin) anticipated during the study period
14= Qualifying ischemic event induced by angiography or surgery.
15= Severe non-cardiovascular comorbidity with life expectancy < 3 months.
16= Contraindication to clopidogrel or aspirin.
17= Anticipated requirement for long-term (>7 day) non-study antiplatelet drugs or NSAIDs affecting platelet function.
18= Inability to swallow medications.
19= At risk for pregnancy: premenopausal or post-menopausal female within 12 months of last

menses without a negative pregnancy test or not committing to adequate birth control
20= Unavailability for follow-up.
21= Inability to provide informed consent.
22= Other neurological conditions that would complicate assessment of outcomes during follow-up.
23= Ongoing treatment in another study of an investigational therapy or treatment in such a study within the last 7 days
24= Consent declined due to confidentiality issues.
25= Consent declined due to protocol too restrictive.
26= Consent declined due to protocol too time intensive.
27= Consent declined due to travel requirements.
28= Consent declined due to family advised declining.
29= Consent declined for other reason.
30= Not willing or able to discontinue prohibited concomitant medications
96= Other

Column K: If the response to Column F (Primary reason patient not enrolled in POINT) is 24-29 on the Code List, this item asks if the patient was shown any portion of the Mytrus video during the consenting process.

Column L: If Column K is “Yes,” this item is where the Mytrus ID is entered.

POINT: Schedule of Activities and Assessments: CRF Schedule

	Visit:	Baseline/ Randomi-zation	Phone F/U Day 7 +/-2 days	Phone F/U Day 30Ɵ (No CRFs to complete)	90 Day FU: Phone or In-Person +/-14 days†	Outcome Event Visit*** (prior to 90 Day FU)	End of Study (-14 days to +60 days)
	Measurements:						
N/A	Screen Failure Log						
00	***Eligibility Form***	**X M**					
10	Randomization Form	**X M**					
01	Demographics	**X M**					
02	ABCD[2] Score	**X M**					
03	modified Rankin Scale (mRS)				**X M**	**X M**	
04	NIH Stroke Scale	**X M**			**X M**	**X M**	**X M**
05	Medical History	**X M**					
06	Prior Medications	**X M**					
07	Index TIA/Minor Stroke Sx	**X M**					
08	Vital Signs	**X M**					
11	Head CT/MRI Scan	**X* M R**			**O* M R**	**O* M R**	
12	ECG	**X* M R**			**O* M R**	**O* M R**	
13	Carotid Imaging Results	**O*[1] M R**			**O*[1] M R**	**O*[1] M R**	
14	Stroke-Free Questionnaire: QVSFS		**X M**	**O Ɵ**	**X M**	**X M**	
15	Morisky Questionnaire		**X M**	**O Ɵ**	**X M**	**X M**	
16	Study Drug Compliance			**O Ɵ**			**X M**
17	End of Study Form						**X M**
18	Concomitant Medications		**X M**		**X M**	**X M**	
19	SAE/Clinical Outcome	**O M R**	**O M R**		**O M R**	**O M R**	
20	Final Diagnosis	**X M**					
21	Protocol Violation	**X M**	**X M**		**X M**	**X M**	**X M**
22	Ancillary Biomarker	**O*[2] M**					

X=Required O=Optional R=Repeatable M=Monitor Verify Required

***Eligibility Form* must be data entered into WebDCU with all eligibility criteria met or randomization will be blocked.**

*****Part of standard evaluation; cost not covered by study.
****** As needed (visit can occur more than once).
******* Event Visits for MI can be completed by telephone.
† Preferably as soon as possible after the completion of 90 days.
[1] Encouraged as part of best practices; not required for study entry or at 90 days; if performed, record results on CRF.
[2] Blood sample obtained with subject's consent for optional ancillary biomarker study.
Ɵ No study data collected/no associated CRFs.

Form 00: Eligibility Form

This form is intended to document the subject's eligibility prior to randomization. This form must be data entered and submitted into WebDCU™ with all eligibility criteria met or randomization will be blocked.

To randomize a subject:

- Data enter this form. Then click save. Address any rule violations, then click submit.
- After selecting the "Subject CRF" tab from the main menu page data enter the Randomization Form (Form 10; see below). Then click save. Address any rule violations, then click submit.
- WebDCU™ will display the bottle number to be given to that subject.

Note: All eligibility criteria must be met or randomization will be blocked.

For Baseline labs collected on this form, the following labs must be recorded:

- Glucose
- White blood cell count
- Red blood cell count
- Hemoglobin
- Hematocrit
- Platelet count (must be ≥100 $x10^9$/l for randomization)

Eligibility criteria must be reviewed by a physician investigator before the form can be submitted. The reviewing physician investigator must be listed on the Physician Information form and the Delegation of Authority log.

NOTE: *In order to generate a randomization number, you must data enter and submit Form 10 after submitting Form 00.*

Form 10: Randomization Form

Before this form can be submitted and a randomization number assigned to the subject, the Eligibility Form (Form 00) must be data entered and submitted into WebDCU with all eligibility criteria met. See previous section, Form 00.

Select the appropriate responses for this form. Submit the form to obtain a randomization number. Randomization cannot be un-done. Once the randomization number is assigned, this subject is enrolled in the trial and must be followed until the 90 day visit or withdrawal of consent.
The time of randomization should be the time the Randomization Form is being submitted in local time, 24 hour format.

The randomization number corresponds to the study drug bottle number assigned to that subject. (The randomization/study bottle number is distinct from the subject ID number assigned to the patient at enrollment.)If you are unable to access the study database due to connectivity issues, please call the WebDCU™ Emergency Randomization Hotline at 1-866-450-2016. If you are

unable to call this number from your hospital, you can call the POINT Emergency Hotline at 1-866-947-6468 (1-866-94-POINT) to be routed to the WebDCU™ Emergency Randomization Hotline by pressing 2.

Remember, the POINT Emergency Hotline is to be used for emergency situations only.

Form 01: Demographics

This form is intended to capture basic demographic information. In addition to this information, the time the informed consent form was signed should also be recorded on this form.

It is important that all demographic information be verified by self-report by the subject, medical records, or a reliable individual accompanying the subject.

Ethnicity is a self-reported or self-identified data field that is required by the NIH. This field should be marked "Unknown" unless the subject/family members/medical records can provide the information.

Form 02: ABCD^2 Score

This form should be completed for subjects who do not have ongoing symptoms at the time of randomization or evidence of acute infarct on baseline imaging.

This form documents the ABCD^2 score at **baseline**. The assessor collecting these data must be a study team member on the Delegation of Authority log who has completed the ABCD^2 certification. For ABCD^2 certification, or to review the training information, please visit https://www.nett.umich.edu/nett/point_resources_and_training .

For the POINT trial, the ABCD^2 score is defined as:

- **A**ge ≥ 60 =1
- **B**lood Pressure (systolic ≥ 140 or diastolic ≥ 90 on **initial evaluation)** =1
- **C**linical (focal weakness=2; speech impairment w/o weakness=1)
- **D**uration (≥60min=2; 10-59min=1; <10 min=0)
- **D**iabetes (clinically diagnosed by a physician=1)

For eligibility purposes, the total score must be **≥4** for the subject to be enrolled in POINT.

Form 03: Modified Rankin Scale

The Modified Rankin Scale (mRS) should reflect the subject's current status. The mRS is a functional disability scale heavily weighted toward neurological disability. It is widely used and has strong face validity worldwide. The scale is best scored by medical personnel in person. However, a structured interview has been shown to have good reproducibility by telephone.

Unlike ABCD^2, there is no mRS score cut-off for eligibility purpose in the POINT study.

For mRS certification, or to review the training information, please visit: https://www.nett.umich.edu/nett/point_resources_and_training.

The assessor must be a study team member who has completed the mRS certification, and one who is listed on the Delegation of Authority log.

Form 04: NIH Stroke Scale

The NIHSS is a well-validated clinical tool to score the stroke neurological examination. The scale is scored from a minimum of 0, indicating no measurable neurological deficit, to a maximum score of 42. In practice, a score of <5 is a mild stroke, 6-15 is a moderate to severe stroke, and >15 is a severe stroke. The scale can be administered in about 10 minutes. All health care personnel (in any role) can be certified in the use of the scale. Regardless of who administered the scale, the resulting NIHSS must be assessed in person by a clinical investigator at the site who has a current NIHSS certification and is included on the Delegation of Authority log. Certification is available through the American Stroke Association. For more information regarding certification, please visit: https://www.nett.umich.edu/nett/point_resources_and_training

At the baseline visit, this form should be completed for subjects who have ongoing symptoms at the time of randomization or evidence of acute infarct on baseline imaging. At Outcome Event visits, this form should be completed for subjects who experienced a **stroke or TIA**, as an outcome event. At the 90 Day visit, complete this form for all subjects.

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, and orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation. For coma, score 3.

0 = Alert; keenly responsive.
1 = Not alert, but aroused by minor stimulation to obey, answer, or respond.
2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped).
3 = Responds only with reflex motor or autonomic effects, or totally unresponsive, flaccid, and are flexic.

1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not

secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues. For coma, score 2.

0 = Answers both questions correctly.
1 = Answers one question correctly.
2 = Answers neither question correctly.

1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored. For coma, score 2.

0 = Performs both tasks correctly
1 = Performs one task correctly
2 = Performs neither task correctly

2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of partial gaze palsy. For coma, score as examined.

0 = Normal
1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis is not present.
2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1 and the results are used to answer question 11. Score as examined.

0 = No visual loss
1 = Partial hemianopia
2 = Complete hemianopia
3 = Bilateral hemianopia (blind including cortical blindness)

NOTE*: **In the case of a patient with blindness that precedes the onset of a minor ischemic stroke that causes the patient to be considered for POINT, it is necessary to add 3 points for blindness. As a result of the total score (NIHSS > 3), the patient would not be eligible for POINT.***

4. Facial Palsy: Ask, or use pantomime to encourage, the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or noncomprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscure the face, these should be removed to the extent possible.

0 = Normal symmetrical movements
1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling)
2 = Partial paralysis (total or near-total paralysis of lower face)
3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)

5 & 6. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. In the case of amputation or joint fusion at the shoulder or hip, the examiner should check the appropriate box on the CRF and enter an explanation. For coma, score 4.

0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds.
1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.
2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 degrees
3 = No effort against gravity, limb falls.
4 = No movement
Amputation, joint fusion – provide an explanation in the box below if selected.

5a. Left Arm
5b. Right Arm

0 = No drift, leg holds 30 degrees position for full 5 seconds.
1 = Drift, leg falls by the end of the 5 second period but does not hit bed.
2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity.
3 = No effort against gravity, leg falls to bed immediately.
4 = No movement
Amputation, joint fusion – provide an explanation in the box below if selected.

6a. Left Leg
6b. Right Leg

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, insure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. In the case of amputation or joint fusion, the examiner should check the appropriate box on the CRF and enter an explanation. In case of blindness, test by touching nose from extended arm position. For coma, score 0.

0 = Absent
1 = Present in one limb
2 = Present in two limbs

8. Sensory: Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to check accurately for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in coma (item 1a=3) are automatically given a 2 on this item. For coma, score 2.

0 = Normal; no sensory loss.
1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware he/she is being touched.
2 = Severe or total sensory loss; patient is not aware of being touched in the face, arm, and leg.

9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences (see the end of this section for the attachments). Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will automatically score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one step commands. For coma, score 3.

0 = No aphasia, normal
1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card from patient's response.
2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.
3 = Mute, global aphasia; no usable speech or auditory comprehension.

10. Dysarthria: If patient is thought to be normal an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. If the patient is intubated or has other physical barrier to producing speech, the examiner should check the appropriate box on the CRF and enter an explanation. Do not tell the patient why he/she is being tested. For coma, score 2.

0 = Normal

1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty.
2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.
Intubated or other physical barrier – check the box and enter an explanation

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable. For coma, score 2.

0 = No abnormality.
1 = Visual, tactile, auditory, spatial, or personal inattention, or extinction to bilateral simultaneous stimulation in one of the sensory modalities.
2 = Profound hemi-inattention or extinction to more than one modality. Does not recognize own hand or orients to only one side of space.

For NIHSS certification, or to review the training information, please visit: https://www.nett.umich.edu/nett/point_resources_and_training.

The assessor must be a study team member who has completed the NIHSS certification, whose certification is current and who is listed on the Delegation of Authority log.

Form 05: Medical History

This form is intended to document both the data obtained from the patient, his/her family and the medical record while screening the patient, and pre-existing conditions that are discovered after randomization into the trial.

For pre-existing conditions discovered after a patient is randomized and after the Medical History CRF has been submitted, the Study Coordinator, or data entry staff, should edit the CRF accordingly **AND** enter a notation in the General Comments section at the bottom of the CRF. The General Comments notation should indicate the date the information became available and a brief description of the circumstances (e.g., dd-mmm-yyyy – Pre-existing condition X revealed by patient when admitted for Y on dd-mmm-yyyy at Hospital Z.)

Form 06: Prior Medications

Indicate whether the subject has taken any medications listed on the form within one month prior to randomization. Include any medications received while in the ED prior to randomization.

Lists of prohibited and discouraged medications (specific to the participating country) can be found in the NETT Toolbox https://weblogin.umich.edu/ (Login ID and Password required for access).

Form 07: Index TIA/Stroke Symptoms

Page 1 of the Index TIA/Stoke Symptoms form is intended to capture the subject's time and date of ED/clinic arrival, time and date the loading dose was given, and to collect information about the symptoms associated with the index event at the time when symptoms were most severe.

Note: the loading dose should be administered within the first two hours after randomization and witnessed by a member of the study team. It is important that the loading dose time is recorded after all 8 tablets have been swallowed by the subject. The subject should also receive an initial aspirin dose (50–325 mg).
Page 2 of the form is intended to capture the symptoms which were present at the time of randomization. Select "no" for subjects who did not have symptoms ongoing at the time of randomization. If no is selected, complete question 24, then the form is complete. This question should be consistent with the question on the Eligibility Form that asks if the subject's neurologic symptoms associated with the index event completed resolved at the time of randomization.

The information collected should be based upon the judgment of the evaluating physician

Form 08: Vital Signs

The first measurements taken in the ED/clinic for systolic/diastolic blood pressure should be recorded on this form.

The vital signs CRF has instructions that say "enter the first measurements taken in the ED/clinic." If the first professional measurements of blood pressure after presentation with symptoms were taken at an outside hospital, these measurements should be entered on the Vital Signs CRF.

Form 11: CT/MRI Scan

This form should be completed at Baseline and all Event visits for all CT and MRI images obtained. A separate form should be completed for each imaging type. Please record the date as dd-mmm-yyyy; time should be recorded as hh:mm. For the baseline CT/MRI, there should be a scan date/ time that is prior to the randomization date/ time as the CT/MRI is required to rule out hemorrhage or other pathology.

Form 12: Electrocardiogram (ECG)

The ECG and the presence or absence of atrial fibrillation/atrial flutter must be reviewed by an Investigator (PI, Co-PI or Sub-I) listed on the Delegation of Authority log at Baseline and Event visits if applicable. Please record the date as dd-mmm-yyyy; time should be recorded as hh:mm.

Form 13: Carotid Imaging Results, if needed

This form should be completed whenever carotid imaging is done as part of clinical care. A separate form should be completed for each of the following imaging types:

- Ultrasound
- CTA
- MRA
- Catheter Angiogram
- Other

NOTE: Please specify if "Other" is marked on the form.

Form 14: Questionnaire for Verifying Stroke Free Status (QVSFS)

This form should be completed at the Day 7, Day 90, and Event visits. The interviewer should verify whether it is the subject and/or relative, caregiver, or friend providing the information for the survey. This instrument is validated as a questionnaire, and, as such, the responses may not be entered as the result of a medical record review.

The interviewer (listed on the Delegation of Authority log) should only capture the appropriate answers relevant to events that occurred after the index event and since last contact. The index event for which the subject was enrolled in the study should be excluded.

Form 15: Morisky Questionnaire

This form documents the subject's adherence to both the prescribed study drug and aspirin regimen. The form should be completed at Day 7, Day 90, and any Event visits.

The Morisky scale is a commonly used, validated adherence screening tool. It is important that the interviewer allows the subject to provide a "negative response" (no) or "positive response" (yes) by asking the questions indicated on this form. The interviewer (listed on the Delegation of Authority log) should not provide examples for the questions. Instead, if a subject is asking for clarification, the interviewer should repeat the question on the existing form.

If the subject was instructed to discontinue study medications by his/her physician, check no for 'data collected' in the header of the form.

If the subject stopped both study drug and aspirin, mark data collected=no for the form. But, if the subject continued to take aspirin, leave Q1-Q4 about study drug blank (there is only one warning to dismiss for these) and then answer Q5-8.

Form 16: Study Drug Compliance

This form is intended to document the subject's compliance at the end of the subject's involvement in the POINT Trial. In order to accurately complete this form, the subject should bring the bottle to the last visit, and the study drug bottle should be emptied. The remaining pills will be counted twice for accuracy. Pill count should be the standard for monitoring medication adherence for the

trial. The number of pills remaining in the bottle will be recorded. If the pill bottle is not returned, and/or the visit is conducted by phone, the subject's self-reporting of the number of study drug pills remaining at the end of study is allowable. Include a General Comment if the study drug bottle was not returned and the reason.

In addition, it is important that the last day the study drug was taken is confirmed with the subject. After confirmation, the date should be recorded on the form as dd-mmm-yyyy. Those taking more than 80% of the tablets based on the last day the study drug was taken, will be considered adherent as assessed by pill count.

Pill counts will not be done for aspirin. Compliance with aspirin regimen will only be captured via the Morisky Questionnaire.

Form 17: End of Study

This form should be completed once a subject has completed the study. The site PI, listed on the Delegation of Authority log, must review and affirm (by providing a signature and date the forms were reviewed) the accuracy of the information reflected in **ALL** of the case report forms for the study subject.

If the subject cannot be reached to schedule or complete the 90 day follow-up visit, contact should be attempted up to 150 days from the date of subject randomization. Only after 150 days should the subject be coded as lost to follow up. If a subject decides to prematurely discontinue the study drug but agrees to be followed off the study drug, that subject has not withdrawn consent and therefore the subject has not prematurely terminated the study. The early study drug discontinuation is captured on Form 16: Study Drug Compliance.

Form 18: Concomitant Medications

This form is intended to document whether or not a subject has taken the following medications after the randomization period:

NSAIDS
- Anticoagulants (both oral and parenteral)
- Thienopyridines
- Thrombolytics
- Other antiplatelets
- Proton Pump Inhibitors
- Other prohibited medications
- Other discouraged medications
- Statins

This information should be captured at day 7, day 90, and all Event visits as well as the 30-day phone call even though there is no data collected for this call. Please refer to the current version of the prohibited and discouraged medication list when completing this form.

Lists of prohibited and discouraged medications can be found in the NETT Toolbox https://weblogin.umich.edu/ (Login ID and Password required for access.

Form 19: SAE/Clinical Outcome Reporting Form, if needed

This form should only be completed if the subject experiences a Serious Adverse Event (SAE) or Clinical Outcome. **This form should be data entered and submitted within five days of discovery.**

An Outcome Event Visit should be conducted only if a subject experiences an **ischemic stroke, TIA, or myocardial infarction**, and Form 19 should be completed under the Outcome Event Visit. Outcome Event Visits can be done by telephone unless the subject experiences an ischemic stroke or TIA, in which case an in-person visit should be conducted. If an in-person visit is not possible a video telemedicine visit may be conducted. **For all 'other serious adverse events', Form 19 can be entered under the last visit that was conducted.** It will be known that the 'other SAE' did not actually occur at the previous visit because of the date/time of onset questions on the form.

The following events (after randomization) are tracked for SAE/Clinical Outcome Reporting:

- Ischemic Stroke
- TIA
- Symptomatic hemorrhagic transformation of an ischemic stroke
- Asymptomatic hemorrhagic transformation of an ischemic stroke
- Symptomatic Intracerebral Hemorrhage
- Asymptomatic Intracerebral Hemorrhage
- Other Symptomatic Intracranial Hemorrhage
- Other Asymptomatic Intracranial Hemorrhage
- Myocardial Infarction with Coronary Revascularization
- Myocardial Infarction without Coronary Revascularization
- Coronary Revascularization without Myocardial Infarction
- Major Hemorrhage other than Intracranial Hemorrhage (life threatening/non-life-threatening)
- Minor Hemorrhage other than intracranial Hemorrhage
- Other Serious Adverse Event

This form is used for documenting all SAEs/Clinical Outcomes. This form should only be completed when a SAE/Clinical Outcome has occurred**.** All SAEs/Clinical Outcomes will be documented on the SAE/Clinical Outcome CRF from randomization through end of study.

In the event of a SAE/Clinical Outcome, this CRF must be data entered AND submitted in WebDCU™ within five days of first knowledge of the event**.** The PI at each Clinical Site is responsible for reviewing all SAEs/Clinical Outcomes, ensuring the submission of SAE/Clinical Outcome data into the study database within the required timelines, and for submitting follow up data in a timely manner.

If a SAE/Clinical Outcome changes in severity or frequency, it is considered a separate SAE/Clinical Outcome and must be reported on a *new* SAE/Clinical Outcome CRF. In this case, the outcome date of the first SAE/Clinical Outcome and the onset date of the new SAE/Clinical Outcome will both be the date upon which the severity or frequency changed.

Regarding hemorrhagic transformation of an ischemic stroke, several scenarios could occur after randomization:

1. If a subject enters into the study with a minor ischemic stroke, and is later discovered to have hemorrhagic transformation, a SAE/Clinical Outcome CRF will be filled out indicating symptomatic or asymptomatic hemorrhagic transformation of an ischemic stroke as the event. In addition, question 15 of this CRF, the "of index stroke" category should be answered.

2. If a subject has an ischemic stroke after randomization, and presents with hemorrhagic transformation on their initial imaging study, a SAE/Clinical Outcome CRF should be filled out, indicating symptomatic or asymptomatic hemorrhagic transformation of ischemic stroke as the event. In addition, question 15 of this CRF, the "of outcome stroke" category should be answered.
3. If a subject has an ischemic stroke after randomization, and does not have any hemorrhagic transformation on the initial imaging study, a SAE/Clinical Outcome CRF should be filled out, indicating ischemic stroke as the event. If the subject is later discovered to have hemorrhagic transformation of the stroke, the SAE/Clinical Outcome CRF that was initially entered for the ischemic stroke should be modified to reflect symptomatic or asymptomatic hemorrhagic transformation of ischemic stroke as the event. In addition, question 15 of this CRF, the "of outcome stroke" category should be answered.

If a SAE/Clinical Outcome fully resolves and then recurs at a later date, the second occurrence is considered a new SAE/Clinical Outcome and a new SAE/Clinical Outcome CRF must be completed. Resolution is the normalization or return to baseline (of laboratory values, clinical signs or symptoms).

Name of SAE/Clinical Outcome — Please note that when reporting a SAE/Clinical Outcome, you should report the diagnosis and not each individual symptom. For example, it would be incorrect to report serious pneumonia as 4 separate events (fever, cough, chest pain, crackles). Serious pneumonia should be reported as one SAE with the SAE/Clinical Outcome name (question 1) being 'pneumonia'.

Death, surgery, intubation, etc. are not adverse events. They are *outcomes* of adverse events. When a subject dies, has surgery, is intubated, etc., please enter the reason for the death, surgery, intubation, etc. in the response to Q1.

SAEs/Clinical Outcomes — The SAE/Clinical Outcome in Q1 will correlate to one of the formal definitions. Mark the appropriate circle.

Severity — Severity is often used to describe the intensity (severity) of a specific event (as in mild, moderate, severe myocardial infarction). However, the event itself may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Adverse events will be documented using the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE) (**see MoP**). The CTCAE provides a grading (severity) scale for each AE term and AEs are listed alphabetically within categories based on anatomy or pathophysiology.

The CTCAE (v 4.0) displays Grades 1-5 with unique clinical descriptions of severity for each AE based on this general guidance:

Grade 1: Mild AE
Grade 2: Moderate AE
Grade 3: Severe AE
Grade 4: Life-Threatening or Disabling AE
Grade 5: Death related to AE

Serious — The seriousness of a Clinical Outcome is based on subject/event outcome or action (i.e., usually associated with events that pose a threat to a subject's life or functioning).
Serious Adverse Events are:

- Fatal
- Life-Threatening
- Result in hospitalization (or prolonged hospitalization)
- Result in disability/congenital anomaly or
- Require intervention to prevent permanent impairment or damage

Outcome — Any SAE that is not resolved must be followed until resolution or end of study, whichever comes first. Once a subject reaches end of study, 'Continuing (Follow up is required)' should no longer be selected as the outcome.

Relationship to study drug (for non-clinical outcomes only)–- This question should be skipped if the event was a clinical outcome. However, this is a required item for reporting SAEs.

One of the most important components of SAE reporting is determining the cause of the SAE. It is imperative that the investigator assess SAE causality in terms of overall study participation and make an independent determination as to whether the SAE was thought to be related to any study-related activity (i.e., study intervention, test article administration, study-related tests or procedures).

For each Serious Adverse Event, the relationship to the study treatment must be recorded as one of the choices on the following scale:

Not Related

The temporal relationship between treatment exposure and the serious adverse event is unreasonable or incompatible and/or adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)

Unlikely (must have 2)

May have reasonable or only tenuous temporal relationship to intervention.

1. Could readily have been produced by the subject's clinical state, or environmental or other interventions.
2. Does not follow known pattern of response to intervention.

Possibly (must have 2)

1. Has a reasonable temporal relationship to intervention.
2. Could not readily have been produced by the subject's clinical state or environmental or other interventions.
3. Follows a known pattern of response to intervention.

Probably (must have all 3)

1. Has a reasonable temporal relationship to intervention.
2. Could not **readily** have been produced by the subject's clinical state or have been due to environmental or other interventions.
3. Follows a known pattern of response to intervention.

Definitely (must have all 3)

1. Has a reasonable temporal relationship to intervention.
2. Could not **possibly** have been produced by the subject's clinical state or have been due to environmental or other interventions.
3. Follows a known pattern of response to intervention.

Modified for POINT [in which dose reductions and re-introduction of intervention do not occur] from: Adverse Events Reporting Requirements SOP. NIH-NIAID.
http://www.niaid.nih.gov/researchfunding/tool/documents/clinmonitorreport.ppt

SAE and Clinical Outcome Narratives —These sections are used to provide additional relevant details about SAEs/Clinical Outcomes. This section should be as complete as possible, but only include information pertinent to the SAE/Clinical outcome. All narratives must be in English. The Site Manager will utilize an outcome specific checklist to ensure that the event packet is sufficient for the medical monitor's review. These narratives should not include any patient identifying information.

To assist in the review of all SAEs/Clinical Outcomes, certain information is required for each SAE/Clinical Outcome entered.

Describe the event in detail. DO NOT identify any study participant, physician, or institution by name.

The following are specific items to include in the SAE and Clinical Outcome narrative:

1. Provide age, race, gender, most pertinent history, and time and date of enrollment.
2. Indicate whether subject previously experienced a TIA or minor stroke.
3. Include dates and times for the event and relevant procedures/clinical assessments.
4. Include a description of what happened and a summary of all relevant clinical information (medical status prior to the event, signs and or symptoms.
5. Provide differential diagnosis for the event in question.
6. Provide complete clinical course information (relevant test/laboratory data: both positive

and negative results with corresponding dates.
7. Include all treatment outcomes.
8. Provide the discharge summary at length (if applicable).

Please note that Event Packets must be uploaded for all Clinical Outcomes Events and SAEs. The Site/Hub 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 participant 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. All documents should include an English translation if not originally in English. Both the original and the English translation should be included. For more information regarding the Event Packet please refer to the following table, or to the POINT MoP.

Event Packet Checklist and Cover Page

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).

Category:	Checklist Item	Submitted	Not Done	Done but Unavailable*
Basic Packet for ALL Events:	Clinical Outcome Reporting Form (CRF 19)	☐	☐	☐
	Discharge Summary (Index Event)	☐	☐	☐
	Discharge Summary (Outcome Event)	☐	☐	☐
	All Head Imaging Reports (Index Event)	☐	☐	☐
	All Head Imaging Reports (Outcome Event)	☐	☐	☐
	Consult Notes (neurology, cardiology, etc.)	☐	☐	☐
Depending on event category, also 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	☐	☐	☐
*Not adjudicated				
Intracranial Hemorrhage	Operative Report	☐	☐	☐
(Symptomatic ICH, Asymptomatic ICH, Other Symp ICranialHem & Other Asymp ICranial Hem)				
Cardiac Outcomes	All Cardiac Enzyme Reports	☐	☐	☐
(MI with or without	ECG Report(s)	☐	☐	☐

Coronary Revascularization)				
Hemorrhage Other than	Number of Transfusions	☐	☐	☐
Intracranial (Major & Minor)	Operative Report	☐	☐	☐
			*If unavailable, explain	
***Comments:**				

The basic packet for all events will include the following:

- Event Packet Checklist/Face Page
- Discharge Summary (Index Event)
- Discharge Summary (Outcome Event)
- All Head Imaging Reports (Index Event)
- All Head Imaging Reports (Outcome Event)
- Consultation notes (neurology, cardiology, and other relevant source)

While the event packet items are not limited to the above list, each Clinical Outcome/SAE should be treated as a unique case requiring the submission of all supporting documentation (e.g., all subject deaths will require a death certificate and autopsy report). Depending on the event category, additional documents must be included in the packet. Please be sure that all unique identifiers are removed prior to uploading these documents.

Investigator Review –- Each SAE/Clinical Outcome must be reviewed by a Site Investigator prior to data submission.

Form 20: Final Diagnosis

This form is intended to capture the final diagnosis of the index event based on symptoms, signs, and imaging data. The form should be completed for all subjects. The data should be submitted within 12 days (+/- 2) of randomization but should be updated, as needed, if the final diagnosis for the subject changes prior to the End of Study Visit. The reviewing investigator should be the Principal Investigator at the site.

Form 21: Protocol Violations

Protocol deviations include both purposeful and accidental variances in the procedures outlined for a study in its approved protocol or by State or Federal regulations.

This form should be updated, as needed, to capture certain protocol violations that occur from enrollment through the subject's End of Study Visit. Many deviation/violations can be derived more consistently from CRF data already existing in the study database, as opposed to the self-report data captured on Form 21. Therefore, Form 21 should only be used to document specific protocol deviations.

Examples of deviation/violations that **should not** be documented on the form because they can be better derived from already existing data:

- Concomitant medications (There is a separate CRF to document prohibited/discouraged medications.)
- Visit is performed outside of the window (This can be derived from visit date.)
- Subject was non-compliant with the study medication (This is captured on Form16: Study Drug Compliance.)
- Inclusion Exclusion Violation (This should be captured on Form 00 Eligibility Form instead.)
- Subject receives a different bottle from the one assigned to which he/she was randomized (This is captured in the Randomization table in the database.)

Examples deviation/violations that **should** be documented on the form include:

- Overdoses of study medication
- Errors in loading dose

NOTE: Your local Institutional Review Board should be notified of such occurrences. In addition, please upload documentation of IRB acknowledgement of the violation(s) to "IRB Study Modification Notification" in WebDCU.

Form 22: Ancillary Biomarker
This form is intended to capture information about those subjects who have consented to participate in the Optional Ancillary Biomarker Study, and whether those consenting to the biomarker study also consent to permit their blood sample for future research. The data should be submitted within 12 days (+/- 2) of Ancillary Biomarker Study consent.

Refer to the POINT Ancillary Biomarker Study Blood Specimen Procedure Manual for instructions on specimen collection and preparation, storage, packaging, and shipping.

**********Forms and Visit Checklist **********

<u>Baseline Visit</u>
Please submit the following forms for this visit within 5 days of collection (unless otherwise indicated):

- Eligibility (Form 00)
- Consent
- Randomization (Form 10)
- Demographics (Form 01)
- ABCD2 Score (Form 02)
- NIHSS (Form 04)
- Medical History (Form 05)
- Prior Medications (Form 06)
- Index TIA/Minor Stroke Symptoms (Form 07)
- Vital Signs (Form 08)
- Head CT/MRI Scan (Form 11)
- ECG (Form 12)
- Carotid Artery Imaging (Form 13), if needed
- SAE/Clinical Outcome Reporting Form (Form 19), if needed

- *Final Diagnosis (Form 20)
- **Protocol Deviations/Violations (Form 21)
- Ancillary Biomarker (Form 22), if site is participating

**Please complete Form 20 within 12 days of randomization. It can be updated, as needed, if the final diagnosis changes prior to the end of study visit.*
***Form 21 should be updated as needed*

7 Day Follow Up (+/- 2 days)

Please submit the following forms for this visit within 5 days of collection:

- Stroke-Free Questionnaire: QVSFS (Form 14)
- Morisky Questionnaire (Form 15)
- Concomitant Medications (Form 18)
- SAE/Clinical Outcome Reporting Form (Form 19), if needed

30 Day Follow Up Phone Call (+/- 2 days)

The Site Coordinator will contact subjects by telephone at 30 days to uncover any issues or concerns that might impact study drug compliance and/or retention in the study. While no study data will be collected for the 30-day phone contact, if subject contact suggests that a possible stroke, TIA or myocardial infarction may have occurred, an Outcome Event Visit will be scheduled.

90 Day Visit (+/- 14 days)

Please submit the following forms for this visit within 5 days of collection:

- mRS (Form 03)
- NIHSS (Form 04)
- Head CT/MRI Scan (Form 11), if needed
- ECG (Form 12), if needed
- Carotid imaging (Form 13), if needed
- Stroke-Free Questionnaire-QVSFS (Form 14)
- Morisky Questionnaire (Form 15)
- Concomitant Medication (Form 18)
- SAE/Clinical Outcome Reporting Form (Form 19), if needed

Event Visit, if needed

Please submit the following forms for this visit within 5 days of collection:

- mRS (Form 03)
- NIHSS (Form 04)
- Head CT/MRI Scan (Form 11), if needed
- ECG (Form 12), if needed
- Carotid Imaging (Form 13), if needed
- Stroke-Free Questionnaire-QVSFS (Form 14)
- Morisky Questionnaire (Form 15)
- Concomitant Medications (Form 18)
- SAE/Clinical Outcome Reporting Form (Form 19) , if needed

End of Study Visit

Please submit the following forms for this visit within 5 days of collection:

- End of Study (Form 17)
- Study Drug Compliance (Form 16)
- Update Final Diagnosis Form (Form 20), if needed

NOTE: *This visit may occur prior to the subject reaching the 90 day visit due to withdrawal of consent or death.*

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

Contents

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).

- The following will be assigned to cardiologist/internist Adjudicators: myocardial infarction (with or without coronary revascularization) and coronary revascularization without myocardial infarction.
- The following will be assigned to one neurologist, one cardiologist/internist Adjudicator, and a second neurologist or cardiologist/internists, all assigned randomly: major hemorrhage other than intracranial hemorrhage and other Serious Adverse Events resulting in death, i.e., fatal SAEs.

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

POINT	Visit:	__ __ __ __ Spoke Code	__ __ __ __ Subject ID		

Form 19: SAE/Clinical Outcome Reporting Form (Version 8) Page 1 of 5

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.

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):

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Medical University of South Carolina

POINT	Visit:	——— Spoke Code	——— Subject ID		

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

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4	Clinical outcomes / SAEs If the event listed in Question 1 matches any of these clinical outcomes/ SAEs, mark the appropriate circle.	○ **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 a 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 or no evidence of a non-ischemic etiology. ○ **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). ○ **Symptomatic hemorrhagic transformation of an ischemic stroke:** Any extravascular 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 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. ○ **Asymptomatic hemorrhagic transformation of an ischemic stroke:** Any extravascular 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): 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. ○ **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 [Intracerebral Hemorrhage (ICH), Subarachnoid Hemorrhage (SAH, Subdural Hemorrhage (SDH), and/or Intraventricular Hemorrhage (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. ○ **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. ○ **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. ○ **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. ○ **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 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. ○ **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 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. ○ **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. ○ **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.

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POINT	Visit:	____ Spoke Code	____ Subject ID		

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

15	If 'Symptomatic hemorrhagic transformation of an ischemic stroke' or 'Asymptomatic hemorrhagic transformation of an ischemic stroke', specify:	○ Of Index stroke ○ Of Outcome stroke
16	If 'Other symptomatic intracranial hemorrhage' or 'Other asymptomatic intracranial hemorrhage', specify:	○ Subarachnoid hemorrhage ○ Subdural hemorrhage ○ Intraventricular hemorrhage
17	If 'Myocardial infarction with coronary revascularization' or 'Coronary revascularization without myocardial infarction', specify:	○ Angioplasty/stent ○ Coronary Artery Bypass Graft
18	If 'Major Hemorrhage other than Intracranial Hemorrhage', specify:	○ Gastrointestinal ○ Genitourinary ○ Other
19	If 'Other Major Hemorrhage other than Intracranial Hemorrhage', specify:	
20	If 'Minor hemorrhage other than intracranial hemorrhage', specify:	○ Gastrointestinal ○ Genitourinary ○ Oral ○ Cutaneous ○ Other
21	If 'Other Minor hemorrhage other than intracranial hemorrhage', specify:	
5	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") 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.	○ No ○ Yes
6	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):		

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POINT	Visit:	___ ___ ___ ___ Spoke Code	___ ___ ___ ___ Subject ID		

Form 19: SAE/Clinical Outcome Reporting Form (Version 8) Page 4 of 5

7	Outcome:	○ Resolved ○ Resolved w/ sequellae ○ Continuing (Follow up is required) ○ Continuing at end of study (No follow up is required) ○ Continuing at time of death
8	Date of resolution/death:	___ ___ - ___ ___ ___ - ___ ___ ___ ___ (dd-mmm-yyyy)
9	What is the relationship of the SAE to the study drug? Q9 should only be answered if Q4 is '**Other serious adverse event'.**	○ Not related 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) ○ Unlikely (must have 2) • Could readily have been produced by the subject's clinical state, or environmental or other interventions. • Does not follow known pattern of response to intervention. • Does not reappear or worsen with reintroduction of intervention. ○ Possibly (must have 2) • Has a reasonable temporal relationship to intervention. • Could not readily have been produced by the subject's clinical state or environmental or other interventions. • Follows a known pattern of response to intervention. ○ Probably (must have 3) • Has a reasonable temporal relationship to intervention. • Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions. • Follows a known pattern of response to intervention. • Disappears or decreases with cessation of intervention. ○ Definitely (must have all 4) • Has a reasonable temporal relationship to intervention. • Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions. • Follows a known pattern of response to intervention. • Disappears or decreases with cessation of intervention and recurs with re-exposure.
General Comments:		
Name of person who collected these data (not for data entry):		

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POINT	Visit:	___ ___ ___ ___ Spoke Code	___ ___ ___ ___ Subject ID		

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

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/Hub 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):

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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.)				
Category:	**Checklist Item**	**Submitted**	**Not Done**	**Done but Unavailable***
Basic Packet for ALL Events:	Clinical Outcome Reporting Form (CRF 19)	☐	☐	☐
	Discharge Summary (Index Event)	☐	☐	☐
	Discharge Summary (Outcome Event)	☐	☐	☐
	All Head Imaging Reports (Index Event)	☐	☐	☐
	All Head Imaging Reports (Outcome Event)	☐	☐	☐
	Consult Notes (neurology, cardiology, etc.)	☐	☐	☐
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	☐	☐	☐
*Not adjudicatable				
Intracranial Hemorrhage	Operative Report	☐	☐	☐
(Symptomatic ICH,				
Asymptomatic ICH, Other				
Symp ICranialHem & Other				
Asymp ICranial Hem)				
Cardiac Outcomes	All Cardiac Enzyme Reports	☐	☐	☐
(MI with or without	ECG Report(s)	☐	☐	☐
Coronary Revasc)				
Hemorrhage Other than	Number of Transfusions	☐	☐	☐
Intracranial (Major & Minor)	Operative Report	☐	☐	☐
			*If unavailable, explain	
Comments:				

APPENDIX 3. WebDCU™ Adjudication Screens

Clinician Event Coordinator/Monitor Screen

10	What actions were taken for this event? (Check all that apply)	☐ 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.	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-MMM-YYYY)*
Please note that Event Packets must be uploaded for all Clinical Outcomes Events and SAEs. The Site/Hub 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. Event Packet Checklist.pdf		
22	Event Packet File	F1159.PDF
a	General Comments	test

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

Clinical Outcome/SAE Review - NEW UPDATE										
Review Step	Reviewer	Date	Record Version	Q1	Q2	Q3	Q4	Q5	Comments	Action
PM Completeness Review	Aaron PERLMUTTER	6/10/2011 9:29:48 AM	137	Report type = *New Event Report*	Requires review by CEC = *Yes*					
CEC Review	Aaron PERLMUTTER			Event packet complete : ○ No ○ Yes	Serious : ○ No ○ Yes	Unexpected : ○ No ○ Yes	Relationship to study drug : ○ Not related ○ Unlikely ○ Possibly ○ Probably ○ Definitely	Type : ○ Neurological ○ Systemic ○ Cardiac ○ N/A	*limit to 1000 char.*	Save Cancel

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-MMM-YYYY)*
	Please note that Event Packets must be uploaded for all Clinical Outcomes Events and SAEs. The Site/Hub 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. Event Packet Checklist.pdf	
22	Event Packet File	F1159.PDF
a	General Comments	test

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

Clinical Outcome/SAE Review - NEW UPDATE

Review Step	Reviewer	Date	Record Version	Q1	Q2	Q3	Q4	Q5	Comments	Action
PM Completeness Review	Aaron PERLMUTTER			Report type : ○ New Event Report ○ Follow-up Report ○ Data Correction	Requires review by CEC : ○ No ○ Yes				*limit to 1000 char.*	Save Cancel

Adjudicator Form

Clinical Outcome/SAE Review - NEW UPDATE

Review Step	Reviewer	Date	Record Version	Q1	Q2	Q3	Q4	Q5	Comments	Action
Adjudicator 2 Review	Matthew LORINCZ	3/29/2011 7:12:22 AM	98	Adjudicated outcome : Ischemic stroke	If Q6 (Severity) is fatal, what type of death? : ○ Ischemic Vascular Death ○ Hemorrhagic Vascular Death ○ Nonvascular Death ◉ Not Fatal				*limit to 1000 char.*	Save Cancel

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

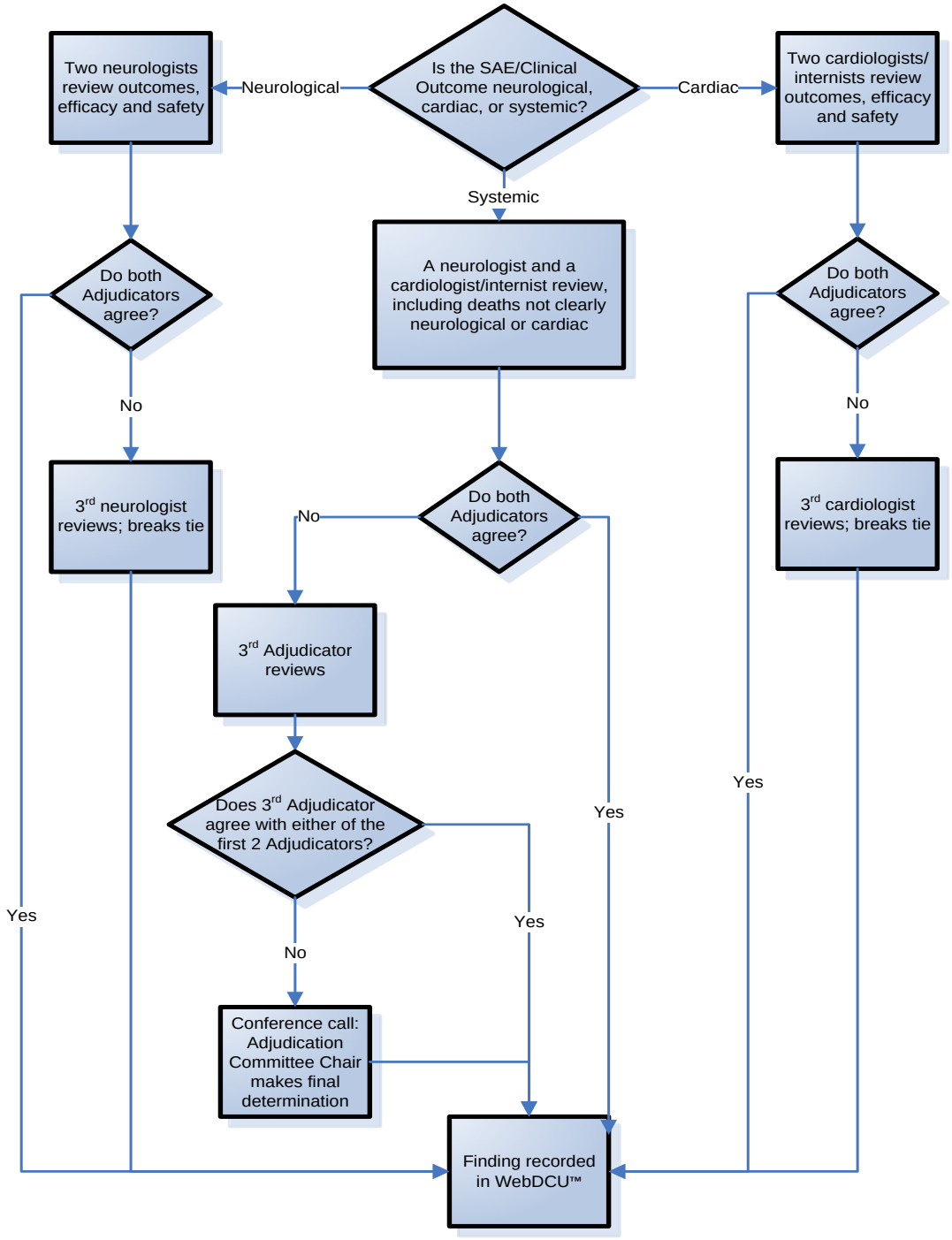
Cardiology/Internal Medicine:

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

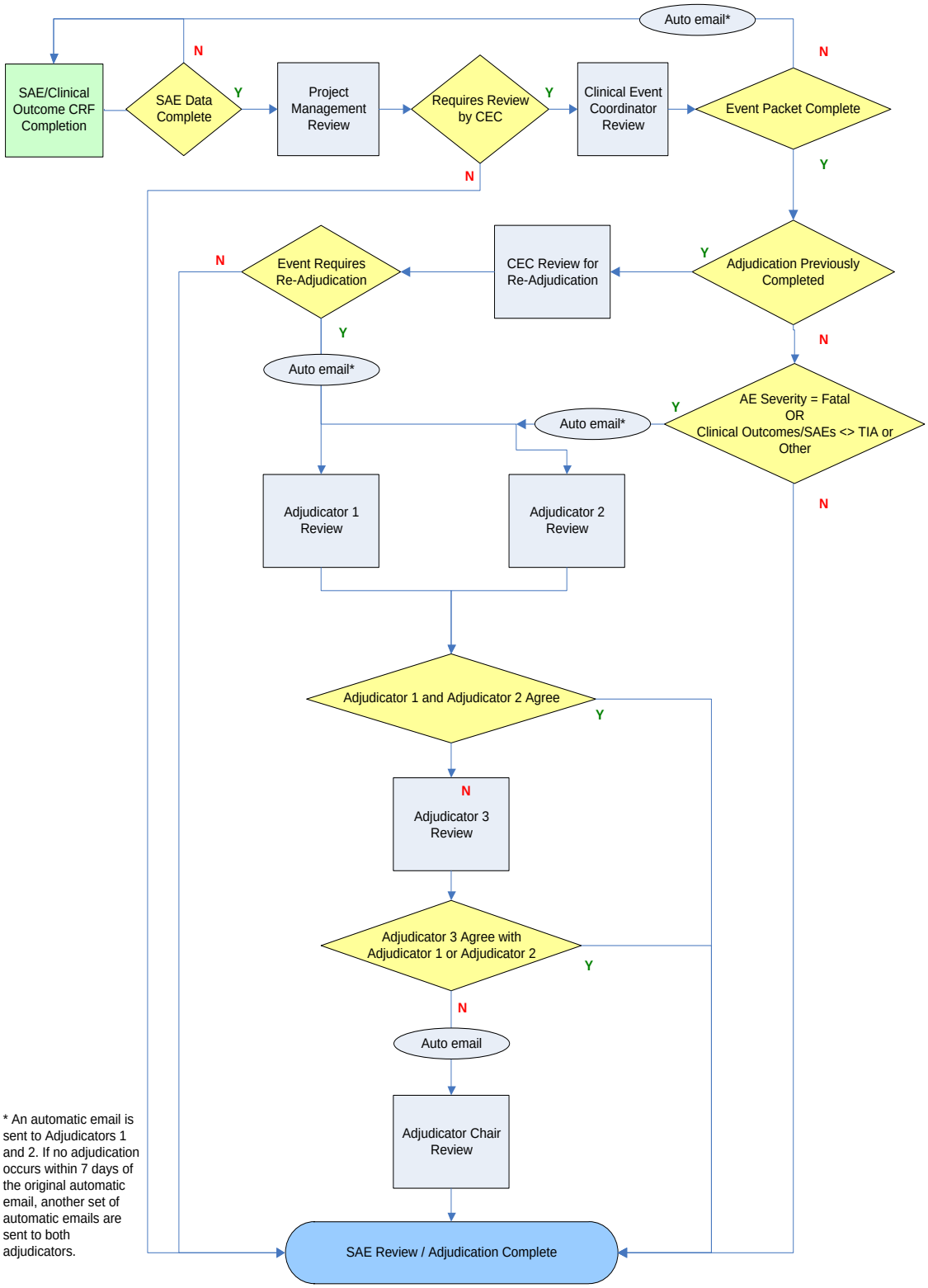
Claire S. Duvernoy, M.D.
Associate Professor,
Department of Internal Medicine
Division of Cardiology
University of Michigan

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



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; TIAs 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 × 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 × 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.

Appendix XVI: PROHIBITED MEDICATIONS

See current versions for the U.S. and international sites in the NETT POINT Toolbox.

NSAIDS Generic Name	**NSAIDS Brand Name**
Aspirin	Anacin, Ascriptin, Bayer, Bufferin, Ecotrin, Excedrin
Choline and magnesium salicylates	CMT,Tricosal, Trilisate
Choline salicylate	Arthropan
Celecoxib	Celebrex
Diclofenac potassium	Cataflam
Diclofenac sodium	Voltaren, Voltaren XR
Diclofenac sodium with misoprostol	Arthrotec
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen calcium	Nalfon
Flurbiprofen	Ansaid
Ibuprofen	Advil, Motrin, Motrin IB, Nuprin
Indomethacin	Indocin, Indocin SR
Ketoprofen	Actron,Orudis, Orudis KT, Oruvail
Magnesium salicylate	Arthritab, Bayer Select, Doan's Pills, Magan, Mobidin, Mobogesic
Meclofenamate sodium	Meclomen
Mefenamic acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Naprelan
Naproxen sodium	Aleve, Anaprox
Oxaprozin	Daypro
Piroxicam	Feldene

Rofecoxib	Vioxx
Salsalate	Amigesic, Anaflex 750, Disalcid, Marthritic, Mono-Gesic, Salflex, Salsitab
Sulindac	Clinoril
Tolmetin sodium	Tolectin
Valdecoxib	Bextra

Anticoagulants Generic Name	**Anticoagulants Brand Name**
Dalteparin	Fragmin
Danaparoid	Orgaran
Enoxaparin	Lovenox
Heparin	Hep-Lock, Hep Pak CVC, Heparin Lock Flush
Tinzaparn	Innohep
Warfarin	Coumadin

Thienopyridines Generic Name	**Thienopyridines Brand Name**
Clopidogrel	Plavix
Ticlopidine	Ticlid

Thrombolytics Generic Name	**Thrombolytics Brand Name**
Urokinase	Abbokinase
Activase	Alteplase
Kinlytic	Urokinase
Retavase	Reteplase
Retevase Half-Kit	Reteplase
TNKase	tenecteplase

Proton Pump Inhibitors Generic Name	Proton Pump Inhibitors Brand Name
omeprazole	Prilosec, Zegarid
lansoprazole	Prevacid, Prevacid 24HR
rabeprazole	AcipHex
pantoprazole	Protonix
esomeprazole	Nexium
cimetidine	Tagamet, Tagamet HB
dexlansoprazole	Kapidex

Miscellaneous Generic Name	Miscellaneous Brand Name
ketocanazole	Nizoral (anti-fungal)
voriconazole	VFEND (anti-fungal)
fluconazole	Diflucan (anti-fungal)
felbamate	Felbatol (antiepileptic)
etravirine	Intelence (antiretroviral)
fluvoxamine	Luvox (antidepressant)
fluoxetine	Fluctin, Fontex, Prozac, Serafem, Seromex, Seronil, Symbyax (antidepressant)
olanzapine	Symbyax (antidepressant)
dipyridamole	Persantine (antithrombotic)