Supplemental Online Content

Connors JM, Brooks MM, Sciurba FC, et al; ACTIV-4B Investigators. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4B randomized clinical trial. *JAMA*. doi:10.1001/jama.2021.17272

eTable 1. Baseline characteristics of randomized participants who initiated trial therapy stratified by assigned treatment

Characteristic	Aspirin 81 mg once daily (N=144)	Apixaban 2.5 mg twice daily (N=135)	Apixaban 5 mg twice daily (N=143)	Placebo (N=136)
Median age (IQR[a])—yr	54.0 (47.0, 58.5)	55.0 (46.0, 60.0)	53.0 (47.0, 58.0)	53.5 (45.0, 59.0)
Sex—no. (%)				
Female	89 (61.8)	76 (56.3)	92 (64.3)	85 (62.5)
Male	55 (38.2)	59 (43.7)	51 (35.7)	51 (37.5)
Race group—no.	131	131	131	132
American Indian or Alaska Native —no. (%)	0 (0.0)	0 (0.0)	2 (1.5)	1 (0.8)
Asian—no. (%)	3 (2.3)	1 (0.8)	1 (0.8)	2 (1.5)
Black or African American—no. (%)	18 (13.7)	18 (13.7)	15 (11.5)	14 (10.6)
Native Hawaiian or other Pacific Islander—no. (%)	0 (0.0)	2 (1.5)	2 (1.5)	0 (0.0)
White—no. (%)	106 (80.9)	103 (78.6)	109 (83.2)	110 (83.3)
Other—no. (%)	4 (3.1)	7 (5.3)	2 (1.5)	5 (3.8)
Hispanic ethnicity —no.	138	133	136	132
Yes —no. (%)	40 (29.0)	39 (29.3)	30 (22.1)	33 (25.0)
No —no. (%)	98 (71.0)	94 (70.7)	106 (77.9)	99 (75.0)
Median body mass index (IQR)—kg/m^2	29.4 (26.2, 34.2)	29.8 (25.7, 34.8)	30.1 (26.0, 35.4)	30.8 (26.3, 34.7)
Hypertension—no. (%)	47 (32.6)	52 (38.5)	50 (35.0)	44 (32.4)
Diabetes—no. (%)	23 (16.0)	31 (23.0)	27 (18.9)	18 (13.2)
History of smoking—no. (%)	35 (24.3)	22 (16.3)	31 (21.7)	27 (19.9)
Median Platelet count (IQR)—per mm^3	250.0 (197.0, 316.0)	254.0 (194.0, 299.0)	255.0 (211.0, 314.0)	239.0 (192.0, 320.0)
Median creatinine clearance (IQR)—mg/ml/1.73m^2	112.7 (89.9, 138.5)	111.9 (89.6, 144.8)	114.7 (92.9, 147.4)	114.5 (91.5, 141.5)
D-dimer—no. [b]	131	126	137	127
≤1 X upper limit of normal—no. (%)	87 (66.4)	85 (67.5)	89 (65.0)	85 (66.9)
>1 - ≤2 X upper limit of normal—no. (%)	33 (24.2)	26 (20.6)	30 (21.9)	29 (22.8)
>2 X upper limit of normal—no. (%)	11 (7.4)	15 (11.9)	18 (13.1)	13 (10.2)
Median hsCRP[c] (IQR)—mg/L	3.0 (1.0, 10.0)	4.0 (1.5, 13.0)	4.0 (1.5, 11.4)	4.0 (1.9, 10.0)

[a] IQR denotes interquartile range. [b] D-dimer assays varied from site to site. Upper limit of normal was captured for each site with individual participant results compared to local values to determine if within the normal range or elevated above the normal range. [c] hsCRP denotes high sensitivity C-reactive protein.

eTable 2. Suspected and adjudicated efficacy outcomes and hemorrhagic events within 45 days of randomization among all randomized trial participants stratified by assigned treatment

	Aspirin 81 mg once daily (N=164)	Apixaban 2.5 mg twice daily (N=165)	Apixaban 5 mg twice daily (N=164)	Placebo (N=164)
Suspected Outcomes				
Composite primary endpoint,[a] no. (%)	7 (4.3)	5 (3.0)	5 (3.1)	9 (5.5)
Risk difference (in percentage points) compared to placebo, RD[b] (95% CI)	-1.2 (-6.3, 3.8)	-2.5 (-7.4, 2.2)	-2.4 (-7.4, 2.2)	--
Components of primary endpoint, no. (%)				
Cardio-pulmonary hospitalizations	6 (3.7)	5 (3.0)	5 (3.1)	9 (5.5)
Deep vein thrombosis or pulmonary embolism	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.6)
Myocardial infarction, stroke or other arterial embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
Any acute medical event[c]	14 (8.5)	16 (9.7)	19 (11.6)	17 (10.4)
Risk difference (in percentage points) compared to placebo, RD (95% CI)	1.8 (-8.4, 4.7)	-0.7 (-7.4, 6.0)	1.2 (-5.7, 8.2)	--
Adjudicated Outcomes[d]				
Composite primary endpoint, no. (%)	6 (3.7)	5 (3.0)	5 (3.1)	8 (4.9)
Risk difference (in percentage points) compared to placebo, RD (95% CI)	-1.2 (-6.1, 3.5)	-1.9 (-6.6, 2.7)	-1.8 (-6.6, 2.7)	--
Components of primary endpoint, no. (%)				
Cardio-pulmonary hospitalizations	6 (3.7)	5 (3.0)	5 (3.1)	8 (4.9)
Deep vein thrombosis or pulmonary embolism	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
Myocardial infarction, stroke or other arterial embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
Suspected Hemorrhagic Events				
Any bleeding event,[e] no. (%)	7 (4.3)	11 (6.7)	14 (8.5)	3 (1.8)
Risk difference (in percentage points) compared to placebo, RD (95% CI)	2.4 (-1.6, 6.9)	4.8 (1.4, 9.9)	6.7 (1.9, 12.1)	--
Type of bleeding event, no. (%)				
Major bleeding	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clinically relevant non-major bleeding	4 (2.4)	6 (3.6)	4(2.4)	0 (0.0)
Minor bleeding	3 (1.8)	5 (3.0)	10 (6.1)	3 (1.8)
Adjudicated Hemorrhagic Events[f]				
Major bleeding, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clinically relevant non-major bleeding, no. (%)	0 (0.0)	3 (1.8)	3 (1.8)	0 (0.0)

[a] The primary endpoint is defined as the composite of all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary cause. [b] RD denotes risk difference. [C] Any acute medical event includes all emergency department visits, all acute outpatient clinic visits, and all hospitalizations, regardless of etiology during the 45-day follow-up period. [d] Medical records were collected for all suspected primary endpoint events reported by the medical monitor and these events were adjudicated by the Clinical Events Committee. [e] Suspected major and clinically relevant non-major bleeding events were reported by the trial medical monitor, and minor bleeding events were identified through follow-up with the research pharmacists. [f] All suspected major and clinically relevant non-major bleeding events were adjudicated by the Clinical Events Committee; minor bleeding events were not adjudicated.

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Richard C. Becker (Chair)
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ACTIVE-4B Investigators (city, state) enrolling at least one participant:
California (8 patients 2 centers) - Donald Schreiber, Palo Alto; Kabir Yadav, Torrance. **Colorado (3 patients, 1 center) -** Anthony Vecchiarelli, Colorado Springs. **Florida (254 patients, 15 centers) -** Godson Oguchi, Deland; Lisa Merck, Gainesville; Victoria Altagracia, Hialeah; Antonio Gonzalez, Immokalee; Dominick Angiolillo, Jacksonville; Fred Blind, Lakeland; John Cienki, Miami; Reinaldo Loy, Miami; Eddie Armas, Miami; Juvenal Martinez, Miami; Juan Ruiz Unger, Palmetto Bay; Vishal Gulati, Pensacola; Temple Robinson, Tallahassee; Claudia Kroker-Bode, Tallahassee; Jason Wilson, Tampa. **Illinois (76 patients, 4 centers) -** Janet Lin (*2 centers*), Chicago; David Beiser, Chicago; Jerry Krishnan, Chicago. **Kansas (1 patient, 1 center) -** Maggie Hagan, Wichita. **Massachusetts (32 patients, 1 center) -** Peter Hou, Boston. **Maryland (15 patients, 1 center) -** Jonathan Cohen, Gaithersburg. **Michigan (4 patients, 2 centers) -** Sascha Goonewardena, Plymouth; Jeffrey Fletcher, Wyoming. **North Carolina (11 patients, 2 centers) -** Rowena Dolor, Durham; Thomas Jarrett, High Point. **New Jersey (1 patient, 1 center) -** Vijay Patel, Matawan. **New Mexico (6 patients, 1 center) -** Ming-Li Wang, Albuquerque. **New York (10 patients, 1 center) –** Nicole Acquisto, Rochester. **Oklahoma (6 patients, 4 centers) -** Anderson Mehrle, Bartlesville; Khetpal Saangeeta, Durant; Nicholas Hanna, Tulsa; Hassan Abouhouli, Tulsa. **Pennsylvania (12 patients, 3 centers) -** Alexandra Weissman, Pittsburgh; Raman Purighalla, Pittsburgh; Nathan Bennett,

Pittsburgh. **Rhode Island (1 patient,1 center) -** Gregory Jay, Providence. **Texas (49 patients, 8 centers)** - David Barbham, Amarillo; TJ Milling, Austin; Dalla Abdelsayed, Highlands; David McPherson, Houston; Patricia Salvato, Houston; Chukwumeka Orgwu, Humble; Anuradha Mundluru, Mesquite; Patti Olusola, Tyler. **Utah (166 patents, 1 center) -** Sarah Majercik, Murray. **West Virginia (2 patients, 1 center) -** William Lewis, Harpers Ferry.

NIH/NHLBI
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CLINICAL ENDPOINTS COMMMITTEE (CEC) ADJUDICATION PROCEDURES

COVID-19 Outpatient Thrombosis Prevention Trial:

A multicenter adaptive randomized placebo-controlled platform trial evaluating the efficacy and safety of antithrombotic strategies in COVID-19 adults not requiring hospitalization at time of diagnosis

Center for Cardiovascular Disease Prevention
Brigham and Women's Hospital

Funding: National Heart Lung and Blood Institute, Bethesda, MD ACTIV-IV Consortium

Version 1.12

May 9, 2021

TABLE OF CONTENTS

1.0. SIGNATURE PAGE

REQUIRED SIGNATURES		
CEC Chair		
Brendan M. Everett, MD		05/09/2021
Print Name	Signature	Date
Trial Chair		
Paul M Ridker, MD		5.09.21
Print Name	Signature	Date

2.0. INTRODUCTION

The Clinical Event Committee (CEC) will be responsible for endpoint adjudication for the COVID-19 Outpatient Thrombosis Prevention Trial within ACTIV-4 (ACTIV 4b) in collaboration with SOCAR Research and the University of Pittsburgh. This Charter will set out the methodology and adjudication criteria to be used when adjudicating the study efficacy outcomes (primary and secondary) which have occurred up to 45 days after initiation of assigned treatment and the safety outcome major bleeds up to 75 days after initiation of study treatment.

3.0. MISSION OF THE CLINICAL ENDPOINT COMMITTEE

The CEC adjudication committee ("The Committee") is an independent clinical endpoint adjudication committee, convened to evaluate and adjudicate, in a blinded fashion, specified endpoints for the trial.

The primary endpoint of the ACTIV 4 Outpatient Thrombosis Prevention Trial is a composite endpoint of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization for cardiovascular/pulmonary events, and all-cause mortality for up to 45 days after initiation of assigned treatment.

The Committee will also adjudicate cases of major bleeding (safety outcome) up to 75 days after initiation of study treatment.

The following that will be adjudicated by the Clinical Endpoints Committee are:

- **Hospitalization or emergency department admission for cardiovascular or pulmonary events**
- **Pulmonary embolism**
- **Symptomatic deep venous thrombosis**
- **Arterial thromboembolism**
- **Myocardial infarction**
- **Stroke**
- **Major bleeding** (safety outcome)
- **Clinically relevant non-major bleeding** (safety outcome)
- **Disseminated intravascular coagulation** (safety outcome)
- **Death**

The Committee will fulfill its mission through remote adjudication, ad hoc meetings, teleconferences and mailings, in order to allow an ongoing and timely adjudication of events.

4.0. MEMBERS OF THE CLINICAL ENDPOINT COMMITTEE

The CEC is an independent group consisting of physicians (MDs) who have expertise in the clinical adjudication of thrombotic and thromboembolic events, including venous thromboembolism, pulmonary embolus, coronary and cerebrovascular events, bleeding, and death. The following experts form the Clinical Endpoint Committee for ACTIV 4b:

Expert	Institution	City, Country	Subspecialty
Brendan Everett, MD (CEC Chair)	Brigham and Women's Hospital	Boston, USA	Cardiology
Sean Van Diepen, MD	University of Alberta Hospital	Alberta, Canada	Cardiology
Sheila Hegde, MD	Brigham and Women's Hospital	Boston, USA	Cardiology
Yuri Kim, MD	Brigham and Women's Hospital	Boston, USA	Cardiology
Natalia Rost, MD	Massachusetts General Hospital	Boston, USA	Neurology
Aneesh Singhal, MD	Massachusetts General Hospital	Boston, USA	Neurology
Gregoire Le Gal, MD, PhD	University of Ottawa	Ottawa, Canada	Hematology
Deborah Siegal, MD, MSc	University of Ottawa	Ottawa, Canada	Hematology
Jean-Philippe Galanaud, MD, PhD	Sunnybrook Health Sciences Centre	Toronto, Canada	Hematology

Appointments to the CEC will be made according to the required expertise and will accommodate the workflow of events collected in the trial and referred to the Committee for adjudication. Any such appointments would be made with the consent of the Chair of the CEC. CEC members will not participate directly in the recruitment of patients for the trial.

5.0. RESPONSIBILITIES LIST

Chairperson of the CEC:

The Chairperson of the CEC, a Cardiologist, is primarily responsible for overseeing the operations of the CEC in accordance with the CEC Charter. The Chairperson of the CEC will:

- Take part in adjudication process as an Adjudicator and receive relevant trainings
- Provide oversight to the CEC
- Finalize and approve the CEC charter
- Liaise with the NHLBI (the trial funder), the study chair and principal investigator, and the Data and Clinical Coordinating Centers of the trial.
- Provide the necessary training to CEC Members.
- Attend CEC Meetings
- Complete or delegate all administrative tasks related to the CECConsensus Meetings
- Ensure consistent adjudication throughout the program

- Communicate issues related to the adjudication of clinical events to the Data Coordinating Center and study chair and principal investigator.

CEC Adjudicator:

CEC Adjudicators are selected based on clinical expertise. They must be board-certified or board-eligible in the appropriate subspecialty (e.g. cardiovascular medicine, hematology/oncology, neurology) or licensed according to local legislation. An Adjudicator is free of conflict of interest. One of cardiologists will also be the CEC Chairperson.

The CEC Adjudicators are responsible to:

- Complete self-training on the clinical program protocols, CEC Charter and Electronic Adjudication System usage.
- Independently adjudicate clinical events according to the definitions in the CEC Charter and consistent with the clinical study protocols, and in a uniform, unbiased, and confidential manner.
- Communicate procedural concerns to the CEC Chairperson and CEC Coordinator.
- Provide queries for additional information to the Data Coordinating Center.

Data Coordinating Center:

- Develop the appropriate case report forms to ascertain and track reported potential events, collect supporting source documents for each event dossier, and review the event dossier for quality, accuracy and completeness of data and source documentation to allow for adjudication.
- Review and approve clinical event dossiers to be uploaded for the CEC adjudicators for adjudication.
- Process queries for additional information requests issued from the CEC

6.0. PROCEDURES OF THE CLINICAL ENDPOINT COMMITTEE

The CEC will consider for adjudication all cases of the following:

- **Hospitalization or Emergency Department Admission for Pulmonary or Cardiac Events**
- **Symptomatic deep venous thrombosis**
- **Pulmonary embolism**
- **Arterial thromboembolism**
- **Myocardial infarction**
- **Stroke**
- **Major bleeding** (safety outcome)
- **Clinically relevant non-major bleeding** (safety outcome)
- **Disseminated intravascular coagulation** (safety outcome)
- **Death**

A detailed definition for each of these clinical endpoints can be found in Section 6.0.

6.1. Identification and Reporting of Clinical Events to the CEC

Clinical events are identified for adjudication in three differentways:

1. Possible events are identified based on the patient-reported events collected bythe RCC Pharmacists during the weekly or ad-hoc calls with the patient

2. Possible events are identified by CEC adjudicators as they review case records sent for adjudication for other events. If CEC member identifies a possible as yet unreported event, the adjudication coordinating center will be informed.

3. Adverse events (AEs) will be reviewed by the Medical Monitor team at the Data Coordinating Center. If the Medical Monitor suspects that an adverse event report may actually represent a clinical endpoint that should be adjudicated by the CEC, the clinical episode will go through the endpoint adjudication process for independent review by the appropriate team of CEC adjudicators. All hospital admissions will be adjudicated by the CEC.

6.2. Assembly of Clinical Dossiers for CEC Review

Clinical records of possible endpoints will be collected and complied into a dossier by the Data Coordinating Center. Each event will be randomly assigned for remote review by 2 members of the CEC as noted in Section 6.3.

6.3. CEC Adjudication Process

Each complete clinical event dossier will be assigned to two CEC Adjudicators based on the event type. The cardiovascular events (hospitalization for cardiac or pulmonary reasons, arterial thromboembolism, myocardial infarction) will be assigned to 2 cardiologist CEC adjudicators who will independently, remotely review the complete clinical event dossier and render an adjudication decision in the electronic adjudication system. The strokes will be assigned to two neurologist CEC adjudicators who will independently review the complete clinical event dossier and render an adjudication decision in the electronic adjudication system. The bleeding and thrombosis events, including venous thrombosis, pulmonary embolism, and major bleeding, will be assigned to 2 adjudicators with expertise in bleeding and thrombosis (hematologists or cardiologists) who will render an adjudication decision in the electronic adjudication system. By default, deaths will be assigned and adjudicated by two cardiologist adjudicators. However, if a fatal event is considered to be associated with a venous thrombosis, pulmonary embolism, or major bleed, it may be assigned to two hematologist adjudicators, Fatal strokes may be assigned to two neurologist adjudicators.

If the adjudication result determined by each independent CEC adjudicator agrees, then the adjudication of that clinical event is considered to be complete and a final adjudication is rendered automatically. If the adjudication result determined by each independent CEC adjudicator disagrees or is discordant, then the CEC adjudicators will discuss the potential clinical event at a CEC meeting or teleconference. In most cases, adjudicators are able to reach consensus. If they are unable to arrive at consensus, a third CEC member will adjudicate the case and serve as the tiebreaker in the voting process. The case may also be reviewed by the CEC Chairperson, who will then render the final decision.

The CEC adjudicators may request additional information from the site in order to adjudicate the clinical event. The CEC Adjudicators' queries for additional information will be submitted in the endpoint adjudication system to the Data CoordinatingCenter for

resolution. If, after all reasonable measures to collect additional documentation regarding a clinical event fail, then the CEC Adjudicators will review and render an adjudication based on best-available data.

6.4. CEC Meetings

CEC Meetings will be held to address any cases requiring Committee review. The CEC will document the Committee decision by submitting an updated decision in the EAS.

6.5. Management of New Information Received after Adjudication

CEC Adjudicators will be provided with required clinical data prior to clinical event adjudication as feasible. However, additional source documents may be provided by the stie after an event has been adjudicated and is considered final. Any new information received after finalization of the adjudication for a specific event will be reviewed by the CEC Chair. The CEC Chair will be responsible for determining if the new information could materially impact the adjudication results. If the Chair believes the new clinical information could impact the adjudication results, the clinical event dossier with the new information will be submitted for re-adjudication. The new data that prompted the second event review will be identified on the case report form included with the clinical source material in the event dossier. The standard review process will be followed. The CEC adjudicators will update their adjudication form to reflect any changes to the initial adjudication.

6.6. Archiving of Adjudication Documentation and Outcome Results

CEC adjudication outcome results will be stored in the electronic adjudication system and may be extracted periodically for scheduled safety analyses and project status reports.

At study closeout, all files stored on the database will be transferred to the Trial sponsor

7.0. CLINICAL EVENT DEFINITIONS

7.1. Hospitalization or Emergency Department Admission for Pulmonary or Cardiac Events

The endpoint of hospitalization for pulmonary or cardiac cause will be defined as an event that meets ALL of the following criteria:

1. The patient is evaluated in the emergency department or admitted to the hospital has a primary cardiovascular or pulmonary diagnosis that does not already qualify for another adjudicated trial endpoint (symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, stroke, or death). Consistent with the trial protocol, an admission for hemorrhagic stroke will be considered an admission for a bleeding event, rather than an admission for cardiovascular cause.

AND

2. The patient’s length of stay in the emergency department, or the patient’s length of admission to the hospital, or combination of length of stay in the emergency room and

admission to the hospital, extends for at least 24 hours (or a change in calendar date if the time of the initial evaluation and the time of discharge are unavailable).

7.2. Symptomatic Deep Venous Thromboembolism

The diagnosis of definite symptomatic deep venous thromboembolism (DVT) requires symptoms of venous thromboembolism with at least one of the following:

- Abnormal compression ultrasound consistent with DVT or abnormal flow pattern or direct clot visualization in veins not amenable to compression.
- One or more new filling defects by venography, CT venography, or MR venography.
- Abnormal compression ultrasound where compression had been normal or, if known to be non-compressible, a substantial increase (≥4mm) in the diameter of a previously non-compressible venous segment.
- Point-of-care ultrasound (POCUS) performed by a provider and documenting DVT in a note.
- An extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of veins in the presence of a sudden cut-off on venography.
- Proximal DVT is defined as clot at or proximal to the trifurcation of the popliteal vein (in the lower extremity) OR clot at or proximal to the axillary vein segment (in the upper extremity).
- Distal DVT is defined as clot distal to the trifurcation of the popliteal vein (in the lower extremities) OR clot at or distal to the brachial vein segment (in the upper extremities).
- Non-limb venous thrombosis includes thrombosis of the cerebral, portal, mesenteric, hepatic, gonadal, splenic, renal, or retinal veins, or thrombosis of the superior or inferior vena cava.

The diagnosis of presumed deep venous thromboembolism requires the following:

- In the absence of objective testing, high pre-test probability according to investigator assessment
    - OR adjudicator's gestalt
    - OR Wells score
- AND a treatment plan for DVT was initiated (initiation of anticoagulation, or escalation of anticoagulation dose, frequency, or duration).

7.3. Pulmonary Embolism

The diagnosis of definite pulmonary embolism requires at least one of the following:

- New intraluminal filling defect at CT pulmonary angiography in a subsegmental or larger vessel.
- New intraluminal filling defect, or an extension of an existing defect, or a new sudden cut-off of vessels > 2.5 mm in diameter at pulmonary angiogram,
- Inconclusive CT pulmonary angiography, pulmonary angiography, or VQ scan evidence of a new or recurrent PE with demonstration of a new or recurrent DVT in the lower extremities by compression ultrasonography or venography. [2,3]
- New clot or intraluminal filling defect noted in the right heart ("clot in transit") or the

pulmonary vasculature at echocardiogram

- High probability (revised PIOPED criteria) on planar ventilation/perfusion (V/Q) scan OR positive PE on SPECT ventilation perfusion (V/Q) scan.
- Pulmonary embolism found at autopsy

The diagnosis of presumed pulmonary embolism requires at least one of the following: Clinical signs and symptoms of pulmonary embolism, including but not limited to: dyspnea, cough, hypoxemia, tachycardia, appropriate electrocardiographic changes, or evidence of right heart strain on echocardiogram; AND chest CT or pulmonary angiography are unable to be performed AND therapeutic dose anticoagulation or fibrinolytic therapy is prescribed by a physician

7.4. Arterial Thromboembolism

The diagnosis of arterial thromboembolism is defined as the following:

- A clinical history and presentation consistent with a sudden significant worsening of end organ or limb perfusion AND

EITHER

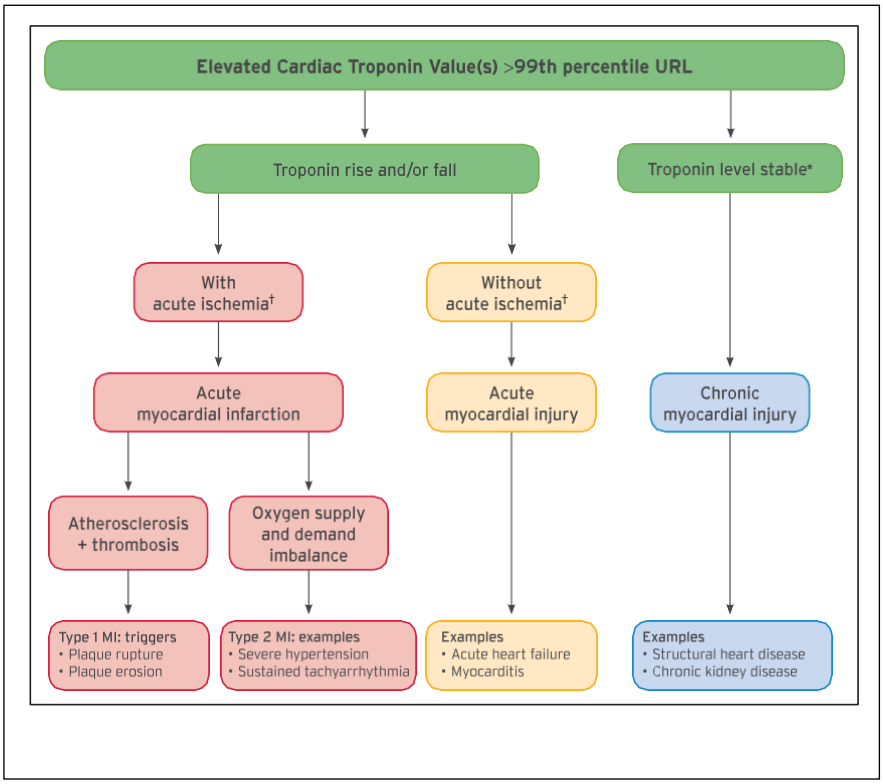
- Confirmation of arterial obstruction by imaging, hemodynamics, intraoperative findings, or pathological evaluation

OR

- Requirement for thrombolysis, thrombectomy, or urgent bypass.

Note that arterial thromboembolism includes both acute *in situ* thrombotic events and acute embolic events. Note that while ischemic stroke and myocardial infarction can be arterial thromboembolic events, those events will be adjudicated according to the separate standardized criteria included below.

7.5. Myocardial Infarction



COVID-19 patients are well known to have elevations in cardiac troponin concentrations, and these elevations often do not represent arterial thrombosis and downstream myocardial ischemia. Therefore, the CEC will make an effort to distinguish true myocardial infarction from coronary artery obstruction, typically from atherothrombosis (usually considered a "type 1 myocardial infarction") from myocardial infarction due to demand ischemia (usually defined as a "type 2 myocardial infarction") and myocardial injury (an elevation in cardiac troponin typically without symptoms of chest pain or signs of arterial thrombosis). These definitions will be consistent with the 4th Universal Definition of Myocardial Infarction and will take into considerations suggestions made about classification of certain conditions as type 1 as compared to type 2 myocardial infarction.[1, 4] Regional coronary venous thrombosis with associated regional myocardial infarction has been reported in COVID. If this mechanism is documented, these will be considered and type 1 MI. The trial and CEC are focused on ascertaining and adjudicating cases of acute myocardial injury and acute myocardial infarction, and classifying those cases as described below. COVID also causes microvascular thrombi which are associated with patchy myocardial necrosis. These will be grouped with myocardial injury.

2. UNIVERSAL DEFINITIONS OF MYOCARDIAL INJURY AND MYOCARDIAL INFARCTION: SUMMARY

Universal definitions of myocardial injury and myocardial infarction

Criteria for myocardial injury

The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least 1 value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

Criteria for acute myocardial infarction (types 1, 2 and 3 MI)

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and at least 1 of the following:

- Symptoms of myocardial ischemia;
- New ischemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs).

Postmortem demonstration of acute atherothrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute atherothrombosis meets criteria for *type 2 MI*. Cardiac death in patients with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes before cTn values become available or abnormal meets criteria for *type 3 MI*.

Criteria for coronary procedure–related myocardial infarction (types 4 and 5 MI)

Percutaneous coronary intervention (PCI)–related MI is termed *type 4a MI*.

Coronary artery bypass grafting (CABG)–related MI is termed *type 5 MI*.

Coronary procedure–related MI ≤48 hours after the index procedure is arbitrarily defined by an elevation of cTn values >5 times for *type 4a MI* and >10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated preprocedural cTn values, in whom the preprocedural cTn level are stable (≤20% variation) or falling, must meet the criteria for a >5 or >10 fold increase and manifest a change from the baseline value of >20%. In addition with at least 1 of the following:

- New ischemic ECG changes (this criterion is related to *type 4a MI* only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischemic etiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

Isolated development of new pathological Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn values are elevated and rising but less than the prespecified thresholds for PCI and CABG.

Other types of 4 MI include *type 4b MI* stent thrombosis and *type 4c MI* restenosis that both meet *type 1 MI* criteria.

Postmortem demonstration of a procedure-related thrombus meets the *type 4a MI* criteria or *type 4b MI* criteria if associated with a stent.

Criteria for prior or silent/unrecognized myocardial infarction

Any 1 of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of nonischemic causes.
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischemic etiology.
- Patho-anatomical findings of a prior MI.

CABG indicates coronary artery bypass grafting; cTn, cardiac troponin; ECG, electrocardiogram; MI, myocardial infarction; PCI, percutaneous coronary intervention; URL, upper reference limit.

Figure 2. Table from the 4th Universal Definition of Myocardial Infarction summarizing the different definitions of myocardial injury and infarction.[1]

Myocardial Injury: The increasing sensitivity of cardiac troponin (cTn) assays means that ongoing myocardial injury is frequently detected. Myocardial injury is a prerequisite for myocardial infarction (MI), but as noted below, criteria in addition to myocardial injury are necessary to make the diagnosis of MI. Adjudicators must distinguish between acute myocardial injury that is not secondary to ischemia but may be due to other conditions (Table 2).

Criteria for Myocardial Injury: Detection of an elevated cTn value above the 99th percentile upper reference limit (URL) is defined as myocardial injury. The injury is considered acute if there is a rise and/or fall of cTn values.[1]

Criteria for Procedure Related Myocardial Injury: Cardiac procedural myocardial injury is arbitrary defined by increased in cTn values (>99th percentile URL) in patients with normal baseline values (<99th percentile URL) or a rise of cTn values >20% of the baseline value when it is the above the 99th percentile URL but is stable or falling.

Table 2. Causes of non-ischemic myocardial injury[1, 5]

Heart failure
Myocarditis
Cardiomyopathy
Takotsubo syndrome
Coronary revascularization procedure
Cardiac procedure other than revascularization
Catheter ablation
Defibrillator shocks
Cardiac contusion
Sepsis, infectious disease
Chronic kidney disease
Stroke, subarachnoid hemorrhage
Pulmonary embolism, pulmonary hypertension
Infiltrative disease, e.g., amyloidosis, sarcoidosis
Chemotherapeutic agents
Critically ill patients
Strenuous exercise
Other

Myocardial Infarction Type 1:

Detection of rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia
- New ischemic ECG changes indicative of new ischemia (new ST-T changes or new LBBB)*
- Development of pathological Q waves in the ECG**
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy†
- *ECG manifestation of acute myocardial ischemia (in the absence of LVH and LBBB):
    - ST Elevation: New ST elevation at the J-point in two contiguous leads with the cut-point: ≥ 1 mm in all leads other than leads V2-V3, where the following cut-points apply: ≥2mm in men ≥40 years; ≥2.5 mm in men <40 years; or ≥ 1.5 mm in women regardless of age.
    - ST-depression and T-wave changes: New horizontal or down-sloping ST depression ≥ 0.5 mm in 2 contiguous leads and/or T inversion ≥ 1 mm in two contiguous leads with prominent R waves or R/S ratio >1.
- **Pathological Q waves:
    - Any Q-wave in leads V2-V3 >0.02 seconds or QS complex in leads V2-V3
    - Q-wave ≥ 0.03 seconds and ≥1 mm deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any 2 leads of a contiguous lead grouping (I, aVL;V1-V6; II, III, aVF; V7-V9).
    - R-wave ≥ 0.04s in V1–V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect
- †Postmortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial hemorrhage meets the type 1 MI criteria regardless of cTn values.
- Consideration will be given to recent proposals to modify myocardial infarction type 1 to

include coronary obstruction by spontaneous coronary artery dissection, coronary embolism, or coronary vasospasm or microvascular dysfunction.[4]

Myocardial Infarction Type 2: Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL, and evidence of imbalance between myocardial oxygen supply and demand unrelated to coronary atherothrombosis, requiring at least 1 of the following:

- Symptoms of acute myocardial ischemia
- New ischemic ECG changes
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with ischemic etiology

Myocardial Infarction Type 3: Patients who suffer cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

Myocardial infarction Type 4a and 4b (myocardial infarction associated with percutaneous coronary intervention): Criteria for percutaneous coronary intervention (PCI)-related MI ≤48 hours after the index procedure are as follows: Coronary intervention-related MI is arbitrarily defined by an elevation of cTn values >5 times the 99the percentile URL in patients with normal baseline values. In patients with elevated preprocedural cTn in whom the cTn levels are stable (≤20% variation) or falling, the post procedure cTn must rise by >20%. However, the absolute procedural value must still be at least 5 times the 99th percentile URL. In addition, 1 of the following elements is required:

- New ischemic ECG changes
- Development of new pathological Q waves; note that the development of new pathological Q waves meets the criteria for procedure-related MI if the cTn values are elevated and rising but <5 times the 99th percentile URL.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or side branch occlusion/thrombus, disruption of collateral flow, or distal embolization.
- Type 4a MI is an MI associated with PCI
- Type 4b MI is an MI associated with stent/scaffold thrombosis

Myocardial Infarction Type 4c: A type 4c MI is an MI associated with restenosis associated with prior PCI. Possible Type 4c MI is evaluated using the same criteria as Type 1 MI.

Myocardial Infarction Type 5: Criteria of coronary artery bypass grafting (CABG)- related MI ≤ 48 hours after the index procedure. CABG-related MI is arbitrarily defined as elevation of cTn values >10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated preprocedural cTn in whom cTn are stale (≤20% variation) or falling, the post procedure cTn must rise by >20%. However, the absolute postprocedural values must still be >10 times the 99th percentile URL. In addition, 1 of the following elements is required:

- Development of new pathological Q waves; note that the development of new pathological Q waves meets the criteria for procedure-related MI if the cTn values are elevated and rising but <10 times the 99th percentile URL.
- Angiographically documented new graft occlusion or new native coronary artery occlusion;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology

Special or unusual circumstances: Further guidance on distinguishing myocardial injury from myocardial infarction in the context of non-cardiac surgery, heart failure, myocarditis, Takotsubo syndrome, kidney disease, and in critically ill patients, and myocardial infarction nonobstructive coronary arteries is included in the 4th Universal Definition of MI.[1]

7.6. Stroke

The definition of stroke used here is drawn from the definitions proposed by Hicks et al. and Sacco et al.[6, 7] Stroke is defined as the acute onset of focal neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Note that while all strokes will be adjudicated, only ischemic stroke is part of the primary efficacy endpoint. Hemorrhagic stroke is considered a major bleed (see section 6.7).

A stroke is the acute onset of a new persistent neurological deficit attributed to an obstruction in cerebral blood flow with no apparent nonvascular cause (e.g. tumor, trauma, infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. To the extent possible, all strokes will be classified as ischemic, hemorrhagic or unknown. While all types of strokes will be adjudicated by the CEC, only ischemic strokes will be included in the primary endpoint.

For the diagnosis of stroke, the following criteria should be fulfilled:

1. Rapid onset of a focal neurological deficit not related to any other known non-cerebrovascular process with at least one of the following:

- Change in level of consciousness
- Hemiplegia
- Hemiparesis
- Numbness or sensory loss affecting one side of the body
- Dysphasia/aphasia
- Hemianopia
- Other new neurological sign/symptom(s) consistent with stroke
- If the timing of onset is uncertain, a diagnosis of stroke may be made provided that there are no plausible non-stroke causes for the clinical presentation.

AND

2. Duration of a focal/global neurological deficit that is:

- EITHER ≥ 24 hours,

- OR < 24 hours if:
    - Resolution of symptoms is due to least one of the following interventions:
        1. Pharmacologic: intravenous or intraarterial thrombolysis
        2. Non-pharmacologic: (i.e. neuro-interventional procedure such as intracranial angioplasty)
- OR available MRI clearly documents a new hemorrhage or infarct
- OR available head CT clearly documents a new hemorrhage or infarct or excludes a mimic of stroke
- OR the neurological deficit results in death.

Ideally, at least one of should be present to confirm the diagnosis of stroke:

- Confirmation by neurology or neurosurgery specialist
- Brain imaging procedure (at least one of the following): CT scan, MRI scan, or cerebral vessel angiography
- Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

If the acute focal signs represent a worsening of a previous deficit, these signs must persist for more than 24 hours and be accompanied by an appropriate new MRI or CT scan finding.

Strokes are sub-classified as follows:

Ischemic (non-hemorrhagic): An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke, but would also be listed as a major bleeding safety event.

Hemorrhagic: An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. Hemorrhage in the brain is documented by neuroimaging or autopsy or lumbar puncture. Note that subdural hematomas are intracranial hemorrhagic events and not strokes.

Undetermined: An acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.

7.7. Major Bleeding

Major bleeding is defined as acute clinically overt bleeding associated with one or more of the following (as per International Society for Thrombosis and Haemostasis (ISTH) guidelines):[8, 9]

- Decrease in hemoglobin of 2 g/dL or more;
- Transfusion of 2 units or more of packed red blood cells;
- Bleeding that occurs in at least one of the following critical sites:
    - Intracranial
    - Intraspinal
    - Intraocular (within the corpus of the eye. A conjunctival bleed is not an intraocular bleed)

    - Pericardial
    - Intraarticular
    - Retroperitoneal
    - Intramuscular with compartment syndrome
- Bleeding that leads to death (primary cause of death or contributes directly to death)

7.8. Clinically Relevant Non-Major Bleeding

Clinically relevant non-major bleeding is defined in consistent with ISTH guidelines.[8] The definition is:

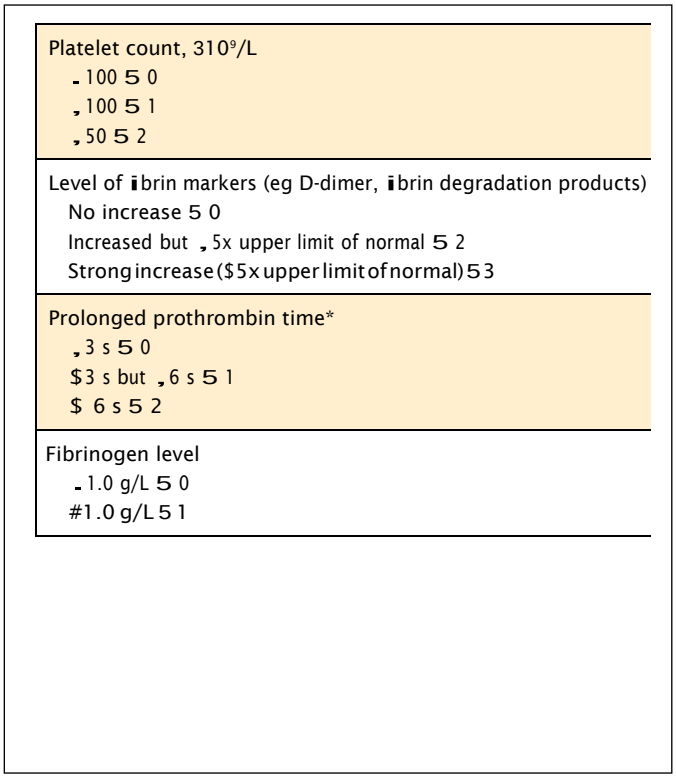
Any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for ISTH major bleeding but does meet at least one of the following criteria:

- Requiring medical intervention by a healthcare professional
- Leading to a hospitalization or increased level of care
- Prompting an unscheduled clinical evaluation, including in-person or remote (video or telephone) evaluations

7.10. Disseminated Intravascular Coagulation (DIC)

DIC is secondary to an underlying condition, such as severe infection, malignancy, trauma, or obstetrical complications, vascular malformations, immunologic reactions, post cardiac resuscitation, or other conditions. The clinical diagnosis of DIC uses a scoring system originally defined by the ISTH and first published by Taylor and colleagues,[10] and updated by Levi and Scully in 2018 (Figure 3).[11] The clinical use ofthis score was validated by Bakhtiari and colleagues in critically ill patients.[12]

The diagnosis of DIC is a clinical diagnosis, so the adjudicators will use a combination of the score outlined here and their clinical experience to determine whether cases referred to Committee are consistent with DIC.



7.11. Definitions of Cardiovascular, Non-cardiovascular, and Undetermined Causes of Death

Definitions of Cardiovascular, Non-Cardiovascular, and Undetermined Cases of Death
are drawn from Hicks et al.[6] Death is classified into one of three categories: cardiovascular, non- cardiovascular, and undetermined cause of death. The intent is to identify one of these categories as the underlying cause of death.

Cardiovascular death can be due to acute myocardial infarction (MI), sudden cardiac death, heart failure, stroke, pulmonary embolism, a cardiovascular procedure, cardiovascular hemorrhage, or other cardiovascular cause.

Cardiovascular death due to acute MI: Death by any cardiovascular mechanism (arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, PAD) within 30 days after an acute MI, related to the immediate consequences of the MI, such as progressive heart failure or recalcitrant arrhythmia. While there may be assessable (attributable) mechanisms of cardiovascular death during this time period, for simplicity, if the cardiovascular death occurs within 30 days of an acute MI, it will be considered a death due to MI.
Note: Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat an MI (PCI or CABG), or to treat a complication resulting from MI, should also be considered death due to acute MI. Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to an MI that occurs as a direct consequence of a cardiovascular investigation/ procedure/operation should be considered as a death due to a cardiovascular procedure.

Cardiovascular death due to sudden cardiac death: Death that occurs unexpectedly and not within 30 days of an acute MI. Sudden cardiac death includes the following scenarios:

- Death witnessed and occurring without new or worsening symptoms
- Death witnessed within 60 min of the onset of new or worsening cardiac symptoms unless the symptoms suggest acute MI
- Death witnessed and attributed to an identified arrhythmia (e.g., captured on an

electrocardiographic recording, witnessed on a monitor, or unwitnessed but

found on ICD review)
- Death after unsuccessful resuscitation from cardiac arrest (e.g., ICD unresponsive sudden cardiac death, pulseless electrical activity arrest)
- Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology
- Unwitnessed death in a subject seen alive and clinically stable ≤24 h before being found dead without any evidence supporting a specific non- cardiovascular cause of death (information about the patient's clinical status preceding death should be provided if available)

Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is seen alive ≤24 h before being found dead, sudden cardiac death should be recorded. For patients who were not observed alive within 24 h of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed but who had not been seen by family members for >24 h).

Cardiovascular death due to heart failure (HF): Death associated with clinically worsening symptoms and/or signs of HF, regardless of HF etiology. Note: Deaths due to HF can have various etiologies, including single or recurrent MIs, ischemic or nonischemic cardiomyopathy, hypertension, or valvular disease.

Death due to stroke: Death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Note: acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

Cardiovascular death due to cardiovascular procedure: Death caused by the immediate complication(s) of a cardiovascular procedure.

Cardiovascular death due to cardiovascular hemorrhage: Death related to hemorrhage such as a non-stroke intracranial hemorrhage (e.g., subdural hematoma) nonprocedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

Cardiovascular death due to other cardiovascular causes: Cardiovascular death not included in the above categories with specific, known cause (e.g., PE, PAD).

Definition of Non-cardiovascular Death: When death is due to a non-cardiovascular cause, a cardiovascular cause of death is excluded.

- Pulmonary (excludes malignancy)
- Renal
- Gastrointestinal (disease of the esophagus, stomach, or intestines (excludes malignancy)
- Hepatobiliary (disease of the liver, gall bladder, or biliary ducts (excludes malignancy)
- Pancreatic (disease of the pancreas (excludes malignancy)
- Infection (including sepsis)

- Inflammatory/immune (death attributable to an inflammatory or immune-mediated disease or process, including systemic inflammatory response syndrome (SIRS), immunological, and autoimmune disease and disorders. Includes anaphylaxis from environmental allergies)

- Hemorrhage (bleeding that is not considered cardiovascular hemorrhage or stroke
- Non-CV procedure or surgery (death caused by the immediate complications of a non-cardiovascular procedure or surgery)
- Trauma (death attributable to trauma. Includes homicide)
- Suicide
- Nonprescription drug reaction or overdose
- Prescription drug reaction or overdose (includes anaphylaxis)
- Neurological (excludes malignancy, as well as death from ischemic stroke, hemorrhagic stroke, or undetermined cause of stroke, or cardiovascular hemorrhage of central nervous system)
- Malignancy (leukemia, lymphoma, or other malignancy)
- Other (death attributable to a cause other than those listed in thisclassification; specify organ system)

Undetermined cause of death: Causality may be difficult to determine if information available from the time of death is minimal or nonexistent.

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National Institutes of Health
National Heart, Lung, and
Blood Institute

Bethesda, Maryland 20892

DATE: June 18, 2021

TO: Jean Connors, M.D.
Paul Ridker, M.D.
Stephen Wisniewski, Ph.D.
(*to provide to site IRBs*)

APP

FROM: Amy P. Patterson, M.D., Deputy Director for Clinical Research and Strategic Initiatives, National Heart, Lung, and Blood Institute (NHLBI), and Co-chair, Executive Committee, Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies (CONNECTS)

SUBJ: Report of the June 16, 2021 meeting of the NHLBI-CONNECTS DSMB Antithrombosis Section and Final NHLBI Determinations for:

A multicenter adaptive randomized placebo-controlled platform trial evaluating the efficacy and safety of antithrombotic strategies in COVID-19 adults not requiring hospitalization at time of diagnosis.

Short Title: ACTIV-4B (COVID-19 Outpatient Thrombosis Prevention Trial)

The purpose of this memorandum is to inform Study Investigators of an NHLBI determination made based on the review of data from ACTIV 4B, informed by the NHLBI-CONNECTS DSMB Antithrombosis Section deliberations, and in consultation with the Chairs of the CONNECTS Steering and Executive Committees and with the concurrence of the DSMB Chair.

We request that you provide this information to your Institutional Review Board(s).

Study Description

ACTIV-4B is a trial to compare the effects of treatment in COVID-19 patients not requiring hospitalization at time of diagnosis (WHO COVID-19 ordinal score 1-3) with (i) prophylactic dose anticoagulation; with (ii) therapeutic dose anticoagulation; with (iii) antiplatelet therapy; and with (iv) placebo relative to each other on the primary composite endpoint of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, need for hospitalization

for cardiovascular/pulmonary events, and all-cause mortality for up to 45 days among the study population of non-hospitalized COVID-19 patients aged > 40 years. Key secondary endpoints are individual outcomes of the composite primary endpoint, the time-to-event for the composite primary endpoint, and a clinical rank-based score. Primary safety endpoint is major bleeding (as defined by the International Society of Thrombosis and Haemostasis) at end of randomized therapy (45 days) and after an additional 30 days of safety follow up (day 75).

DSMB Description and Charge

This DSMB was appointed by NHLBI and tasked with independent monitoring of data and overseeing participant safety for NHLBI-supported COVID-19 antithrombosis clinical trials. The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the ACTIV-4 outpatient trial. This independent Board includes senior experts in ethics, biostatistics, clinical trials, and coagulopathy for COVID-19 related thrombo-embolic disease.

The CONNECTS ACTIV-4 DSMB met on June 16, 2021. This was a regularly scheduled meeting to assess trial recruitment and retention, as well as safety data. In addition, the investigators requested to present information on the primary endpoint event rate after completion of 322 participants.

DSMB Recommendations

Because of the unexpectedly low event rate, the DSMB recommends that the study not continue in its current configuration enrollment should cease, and participants should be told to stop taking study prescribed medication with appropriate follow-up by their primary health care provider. Importantly, the DSMB notes that the risk of thrombotic events and benefit from antithrombotic therapy in other types of SARS-CoV-2 infected outpatient populations (e.g., populations who are at higher risk and/or are earlier in the course of the disease) has yet to be determined. In addition, the impact of the emergence of new SARS-CoV-2 variants and mutations on the risk of such events and any potential benefit from anti-thrombotics also remain to be determined.

The DSMB noted the importance of and requested clarity regarding the plans for study termination including: how participants will be notified and specifically what they will be told, efforts to detect signs or symptoms of thrombosis prior to discontinuing study medication, and a concrete plan for establishing for a smooth transition to continued clinical monitoring by participants' health care provider.

Determination

The determination of NHLBI outlined below is based on review of data from ACTIV 4B; informed by the DSMB deliberations; and made in consultation with the Chairs of the CONNECTS Steering and Executive Committees and with the concurrence of the DSMB Chair. NHLBI underscores that the conclusions of the study are applicable to the specific outpatient population studied and that the potential utility of antithrombotic interventions in other SARS-CoV-2 infected outpatient populations, as described above, is yet to be determined.

Enrollment and study prescribed treatment of patients in ACTIV4B should not continue as currently configured because the primary event rate in this particular outpatient population is too low to justify continuing the study. Subjects who are currently enrolled should continue to be followed according to

protocol, decisions about their care should be made according to the judgment of the primary care physician, and concrete plans developed for ensuring a smooth transition to continued clinical monitoring by participants' health care provider.

CC: Dr. Richard Becker
Dr. Robert Harrington
Dr. Clyde Yancy
Dr. Gary Gibbons
Dr. Keith Hoots
Dr. David Goff
Dr. Gail Weinmann
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