Colchicine For The Prevention Of Perioperative Atrial Fibrillation In Patients Undergoing Thoracic Surgery (COP-AF)

NCT03310125

ID: 2017-001-COPAF

Document Type: Statistical Analysis Plan

Document Date: 2023-06-15

Colchicine for the prevention of perioperative atrial fibrillation in patients undergoing major noncardiac thoracic surgery (COP-AF) trial

STATISTICAL ANALYSIS PLAN

Version 1.0, 2023-06-15

Lead SAP Author: Dr. David Conen

Principal Investigator: Dr. David Conen

Study Statistician: Zhuoru Li

Final Version 1.0
Created on 2023-06-15

Table of Contents

LIST OF ABBREVIATIONS 3
STUDY/TRIAL ACRONYMS 3
1. Introduction 4
2. Study Design 4
3. Study Objectives and Outcomes 4
3.1 Primary Objective and Outcomes 4
3.2 Secondary Objectives and Outcomes 5
3.3 Tertiary Objectives and Outcomes 5
3.4 Safety Outcomes 5
4. Populations to be Analyzed 6
5. Statistical Analysis 6
5.1 General Methods 6
5.1.2 Testing Strategy 6
5.1.3 Subgroup Analyses 7
6. Handling of Missing Data 7
7. Baseline and Calculated Visits 7
8. Efficacy Analyses 8
9. Safety Analysis 8
9.1 Serious Adverse Events 8
10. References 9
APPENDIX I: COP-AF EVENTS DEFINITIONS 10
APPROVAL 16

LIST OF ABBREVIATIONS

AF: Atrial fibrillation/atrial flutter
CABG: Coronary artery bypass graft
CI: Confidence interval
CT: Computed tomography
cTn: Cardiac troponin
EAC: Event Adjudication Committee
ECG: Electrocardiogram
eGFR: Estimated glomerular filtration rate
GCS: Glasgow Coma Scale
HR: Hazard ratio
LBBB: Left bundle branch block
MI: Myocardial infarction
MINS: Myocardial injury after noncardiac surgery
MRI: Magnetic resonance imaging
PCI: Percutaneous coronary intervention
qSOFA: quick Sequential Organ Failure Assessment
RCT: Randomized controlled trial
SAP: Statistical analysis plan
URL: Upper reference limit

STUDY/TRIAL ACRONYMS

COLCOT: Colchicine Cardiovascular Outcomes Trial
COP-AF: Colchicine for the Prevention of Perioperative Atrial Fibrillation
LoDoCo2: Low Dose Colchicine 2

1. Introduction

Atrial fibrillation (AF) and myocardial injury after noncardiac surgery (MINS) are among the most common cardiovascular complications occurring after noncardiac thoracic surgery. Both entities are associated with multiple postoperative complications, including adverse hemodynamic changes and an increased length of stay. Affected patients also face an increased risk of death and adverse cardiovascular events during both short- and long-term follow-up.

Higher levels of inflammatory biomarkers have been associated with a higher risk of both perioperative AF and MINS (1-5), but it is unclear whether anti-inflammatory treatment can decrease the incidence of these complications. Colchicine is an inexpensive drug with potent anti-inflammatory effects. Its efficacy as an anti-inflammatory agent has been demonstrated previously. Colchicine decreased the occurrence of perioperative AF after cardiac surgery (6, 7). More recently, the Low Dose Colchicine 2 (LoDoCo2) trial demonstrated a significant reduction in cardiovascular events. The Colchicine Cardiovascular Outcomes Trial (COLCOT) also found that colchicine significantly reduced the incidence of cardiovascular events.

The COP-AF trial was designed to evaluate whether low-dose colchicine prevents the occurrence of perioperative AF after major noncardiac thoracic surgery. After the publication of LoDoCo2 and COLCOT, MINS was added as a co-primary outcome to test the hypothesis that administration of colchicine reduces perioperative ischemic events, independent of the hypothesis related to perioperative AF.

This Statistical Analysis Plan (SAP) describes the statistical methods for the main COP-AF outcomes. This SAP will be finalized before any investigators are unblinded and without knowledge of any emerging results by trial treatment group. The final version of the SAP will be signed off before database freeze.

2. Study Design

COP-AF is an international randomized controlled trial (RCT) that will randomize 3,200 adults aged 55 years or older who are undergoing major noncardiac thoracic surgery. Patients are randomized to receive colchicine 0.5mg twice daily or matching placebo for 10 days. Patients, healthcare providers, data collectors, and outcome adjudicators are blind to colchicine or placebo treatment assignment. Outcome ascertainment occurs through direct patient follow-up and review of health records.

3. Study Objectives and Outcomes

3.1 Primary Objective and Outcomes

The *primary objective* of this trial is to determine whether the administration of colchicine compared with placebo independently reduces the occurrence of the co-primary outcomes within 14 days of randomization.

- The first co-primary outcome is time to clinically important perioperative AF (including atrial flutter) during 14 days after randomization.
- The second co-primary outcome is time to MINS, defined as an elevated troponin occurring between the initiation of surgery and the end of the 14-day follow-up, and that is considered to have resulted from myocardial ischemia.

3.2 Secondary Objectives and Outcomes

The *secondary trial objectives* are to determine whether the administration of colchicine compared with placebo reduces the following secondary outcomes within 14 days after randomization:

- First occurrence of the composite of all-cause mortality, nonfatal MINS, or nonfatal stroke;
- First occurrence of the composite of all-cause mortality, nonfatal MI, or nonfatal stroke;
- MINS not fulfilling the fourth universal definition of MI;
- MI;
- Time to chest tube removal; and
- Duration of stay in each of the following: intensive care unit, step-down, and in-hospital.

3.3 Tertiary Objectives and Outcomes

The *tertiary trial objectives* are to determine whether the administration of colchicine compared with placebo reduces the following outcomes within 14 days of randomization:

- All-cause mortality;
- Venous thromboembolism (i.e., deep vein thrombosis or pulmonary embolism);
- Acute heart failure;
- Number of days alive and at home; and
- Composite of life-threatening or major bleeding.

3.4 Safety Outcomes

The main *safety outcomes* of COP-AF during the 14-day period after randomization are:

- Composite of sepsis or infection; and
- Non-infectious diarrhea.

All COP-AF outcome definitions are provided in Appendix I.

4. Populations to be Analyzed

For outcome analyses, we will analyze patients in the treatment group to which they were allocated, according to the intention-to-treat principle. Any patients lost to follow-up will be censored on their last day of available contact during the study.

5. Statistical Analysis

5.1 General Methods

The day of randomization (Day 0) is the reference for all time-related analyses.

For both co-primary outcomes, we will plot the cumulative incidence curves between the two treatment groups and compare them using log-rank tests. We will use Cox proportional-hazards models with treatment group as the only covariate to obtain hazard ratios (HRs) and 95% confidence intervals (CIs). We will assess model assumptions including the proportionality of hazards assumption.

For all secondary, tertiary, or safety outcomes other than duration of stay and the number of days alive and at home, we will also calculate the HRs and 95% CIs based on Cox regression.

For continuous data that are positively skewed (e.g., for the duration of stay in the intensive care unit, step-down unit, and hospital), their medians will be compared between the two treatment groups using a non-parametric Wilcoxon test. The number of days alive and at home will be analyzed using quantile regression.

5.1.2 Testing Strategy

To address the possible multiplicity problem, we will use the 'fallback procedure' (9), and we will partition the total α of 0.05 among the two co-primary outcomes, with a significance level of 0.0324 for the first co-primary outcome and 0.0176 for the second co-primary outcome, before adjustment for potential overlap. By this partition, we will provide a power of 80% for the second co-primary outcome of MINS, and power of 83% for the first co-primary outcome AF. According to the 'fallback procedure', if the first co-primary outcome is found to be significant at the 0.0324 α level, then this α is "unused", and is passed to the second co-primary outcome. Therefore, if the first co-primary outcome is found to be significant, the second co-primary outcome will be evaluated at the α=0.05 level. If the first co-primary outcome is found to be non-significant, we are still able to test the second co-primary, but at the overlap-accounted-for α level. We will evaluate the actual amount of overlap between the two co-primary outcomes at the end of the trial, and we will adjust the α of the second co-primary outcome accordingly.

We will follow the intention-to-treat principle for all analyses. If patients decline to complete their follow-up, die before the end of their follow-up, or are lost to follow-up, they will be censored at the time they leave the trial.

5.1.3 Subgroup Analyses

Cox proportional-hazards models individually assessing each co-primary outcome provide the basis for evaluating subgroup effects. We will consider the possibility that a subgroup effect is present if the interaction term of treatment and subgroup is statistically significant at a p-value less than $\alpha=0.05$. We will also consider other credibility criteria to judge the credibility of a subgroup effect (10).

For the two co-primary outcomes, we have identified the following subgroups:

1. Age <65 years versus ≥65 years;
2. Non-thoracoscopic (open) versus thoracoscopic (minimally invasive) surgery; and
3. Preoperative calculated creatinine clearance (using Cockcroft-Gault Formula) <45, 45-<60, and ≥60 mL/min.

We expect that colchicine has a stronger effect in older patients, in those undergoing non-thoracoscopic surgery, and in those with lower renal function.

6. Handling of Missing Data

All efforts will be made to collect complete data for all patients in this study. Patients will be followed to the study end and will complete all required data collection, regardless of their compliance with study visits.

In general, missing values within follow up will be treated as 'missing'. No attempt will be made to impute missing post-randomization values and only observed values will be used for analysis.

When an event date is not known, the site investigator will be asked to provide a best estimate as to when the event occurred. Even though the exact date of an event is unknown, the investigator often does know some information that would indicate the approximate date. If no information is known, then the date in the middle of the plausible time period should be given, based on the last contact with the patient before the event and the date of contact when information about the event was known.

7. Baseline and Calculated Visits

The randomization visit (Day 0) is the reference for all time-related analyses.

For the purposes of the main analyses (i.e., the focus of this SAP), the primary follow-up period is 14 days after randomization.

Follow-up time will be defined as the date of last contact for an individual, or the date of death if available.

8. Efficacy Analyses

The primary analyses will be based on the intention to treat principle (i.e. participants will be analyzed in the treatment group to which they were randomized) and will include all unrefuted events.

The plausibility of the proportional hazards assumption will be assessed by visually examining the plots of the log of the negative log of Kaplan-Meier estimates of the survival function versus the time for the two treatment arms, for evidence of non-parallelism.

From the Cox regression models, we will report hazard ratios and 95% confidence intervals. Statistical significance will be claimed as described in section 5.1. No adjustment for multiple comparisons is needed, as alpha is divided between two co-primary endpoints using a fallback procedure.

The secondary and tertiary outcomes that have a specific event date will be analyzed using the same method as the primary outcomes. These outcomes include all-cause mortality, nonfatal MINS, nonfatal stroke, MINS that do not fulfill the fourth universal definition of MI, MI, time to chest tube removal. Additionally, other outcomes like venous thromboembolism, acute heart failure, and a composite of life-threatening or major bleeding will also be analyzed. The same approach used for the primary outcomes will be applied to these outcomes, but without the fallback procedure and with a significance level of 0.05.

Continuous and ordinal data will be analyzed as described in section 5.1. For each effect size estimate for these outcomes, we will calculate corresponding 95% CI and associated p values, and we will infer statistical significance if the computed 2-sided p-value is less than α=0.05.

9. Safety Analysis

9.1 Serious Adverse Events

Serious Adverse Events (SAEs) will be tabulated by MedDRA System Organ Class and by randomized treatment group, with frequencies and percentages.

Effect of the related study intervention on SAEs will be assessed by comparing total number of participants with reported outcomes at the end of the study in the colchicine and placebo group, using a chi-square test. We will evaluate the consistency of effect, the number of events, and strength of association to inform potential effects of colchicine on SAEs. Given the vast literature on the safety of colchicine we do not except to find any new SAEs potentially associated with colchicine treatment.

10. References

1. Ackland GL, Abbott TEF, Cain D, Edwards MR, Sultan P, Karmali SN, et al. Preoperative systemic inflammation and perioperative myocardial injury: prospective observational multicentre cohort study of patients undergoing non-cardiac surgery. Br J Anaesth. 2019;122(2):180-7.
2. Larmann J, Handke J, Scholz AS, Dehne S, Arens C, Gillmann HJ, et al. Preoperative neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are associated with major adverse cardiovascular and cerebrovascular events in coronary heart disease patients undergoing non-cardiac surgery. BMC Cardiovasc Disord. 2020;20(1):230.
3. Sanders RD, Craigova L, Schessler B, Casey C, White M, Parker M, et al. Postoperative troponin increases after noncardiac surgery are associated with raised neurofilament light: a prospective observational cohort study. Br J Anaesth. 2021;126(4):791-8.
4. Martins OM, Fonseca VF, Borges I, Martins V, Portal VL, Pellanda LC**.** C-Reactive protein predicts acute myocardial infarction during high-risk noncardiac and vascular surgery. Clinics (Sao Paulo). 2011;66(5):773-6.
5. Crispi V, Isaac E, Abah U, Shackcloth M, Lopez E, Eadington T, et al. Surgical factors associated with new-onset postoperative atrial fibrillation after lung resection: the EPAFT multicentre study. Postgrad Med J. 2020.
6. Imazio M, Brucato A, Ferrazzi P, Rovere ME, Gandino A, Cemin R, et al. Colchicine reduces postoperative atrial fibrillation: results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) atrial fibrillation substudy. Circulation. 2011;124(21):2290-5.
7. Imazio M, Trinchero R, Brucato A, Rovere ME, Gandino A, Cemin R, et al. COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS): a multicentre, randomized, double-blind, placebo-controlled trial. Eur Heart J. 2010;31(22):2749-54.
9. Wiens BL, Dmitrienko A**.** The fallback procedure for evaluating a single family of hypotheses. J Biopharm Stat. 2005;15(6):929-42.
10. Sun X, Briel M, Walter SD, Guyatt GH**.** Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010;340:c117.

APPENDIX I: COP-AF EVENTS DEFINITIONS

Atrial fibrillation/atrial flutter (AF):

AF is defined as the replacement of the consistent P waves on 12-lead ECG, rhythm strip or documented telemetry tracing, by rapid oscillation or fibrillatory/flutter waves.

Clinically important perioperative atrial fibrillation/atrial flutter (AF):

Clinically important perioperative AF is defined as AF developing after randomization until the end of follow-up 14 days after randomization, that is documented on an ECG, rhythm strip or telemetry tracing, and that results in angina, heart failure, symptomatic hypotension, or that requires treatment with a rate controlling drug, antiarrhythmic drug or electrical cardioversion.

Sub-classification of death:

Vascular death is defined as any death with a vascular cause and includes those deaths following a myocardial infarction (MI), cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause. Non-vascular death is defined as any death due to a clearly documented non-vascular cause (e.g. trauma, infection, malignancy).

Myocardial Injury after Noncardiac Surgery (MINS)

MINS is defined as any MI (as defined below) and any elevated troponin (higher than the local lab threshold) judged to be due to myocardial ischemia (i.e., without evidence of a non-ischemic etiology [e.g., chronic elevation, pulmonary embolism, sepsis, cardioversion]) that occurred within the first 14 days after the initiation of surgery. The only exceptions to the definition of an elevated troponin will be to use a higher threshold for troponin T (TnT) of ≥30 ng/L, and for high-sensitivity troponin T (hsTnT) of 20 to <65 ng/L with an absolute change of at least 5 ng/L or an hsTnT level ≥65 ng/L.

Myocardial Injury after Noncardiac Surgery (MINS) not fulfilling the Fourth Universal Definition of Myocardial Infarction:

Using the MINS definition above, MINS not fulfilling the fourth Universal Definition of MI includes all MINS events that do not fulfil the definition of MI below (i.e., MINS without ischemic signs or symptoms, ischemic changes on the ECG and evidence of new loss of viable myocardium or new regional wall motion abnormality on non-invasive tests).

Myocardial infarction (Fourth Universal Definition of MI)

The diagnosis of MI requires any one of the following criteria:

1. Detection of a rise or fall of a cardiac troponin value (cTn) with at least one value above the 99th percentile of the upper reference limit (URL) with at least one of the following:

a. Ischemic signs or symptoms (i.e. chest, arm, neck, or jaw discomfort, shortness of breath, pulmonary edema).

b. Development of pathologic Q waves present in any two contiguous leads that are >30 milliseconds.

c. New, or presumed new, ECG changes indicative of ischemia (i.e. ST elevation [≥2mm in leads V1, V2, or V3 and ≥1mm in the other leads], ST segment depression [≥1mm], or symmetric inversion of T waves ≥1mm in at least two contiguous leads, or development of new LBBB.

d. Imaging evidence of new loss of viable myocardium or new or presumed new, cardiac regional wall motion abnormality in a pattern consistent with an ischemic etiology.

e. Identification of a coronary thrombus by angiography or autopsy (Post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial hemorrhage).

2. Cardiac death, with symptoms suggestive of myocardial ischemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cTn were obtained, or before cTn values would be increased.
3. Percutaneous coronary intervention (PCI) related MI is defined by elevation of a cTn value (>5 x 99th percentile URL) in patients with a normal baseline cTn value (≤99th percentile URL) or a rise of a cTn measurement >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
4. Stent thrombosis or restenosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cTn values with at least one of value above the 99th percentile URL (as defined under 1).
5. Coronary artery bypass grafting (CABG) related MI is defined by elevation of cTn values (>10 x 99th percentile URL) in patients with a normal baseline cTn value (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
6. Isolated development of new pathological Q waves with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.

Myocardial infarction <u>after MINS</u>:

MI after MINS requires the following criteria:

1. Detection of a rise or fall of a cardiac biomarker with at least one value above the 99th percentile of the upper reference limit (URL) and 20% higher than the last troponin measurement related to the preceding event together with evidence of myocardial ischemia with at least one of the following:

    a. Ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema);

    b. Development of pathologic Q waves present in any two contiguous leads that are >30 milliseconds;

    c. New or presumed new ECG changes indicative of ischemia (i.e., ST segment elevation [>2 mm in leads V1, V2, or V3 OR >1 mm in the other leads], ST segment depression [>1mm], or symmetric inversion of T waves >1 mm) in at least two contiguous leads;

    d. New LBBB;

    e. New cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging; or

    f. Identification of intracoronary thrombus on angiography or autopsy.

Stroke:

Stroke is defined as the rapid onset of a new persistent neurologic deficit attributed to focal ischemia of the brain, retina or spinal cord and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection). Signs or symptoms must last at least 24 hours, unless supported by clear evidence of infarction on neurologic imaging (magnetic resonance imaging [MRI] or computerized tomography (CT)). 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. Stroke will be sub-classified into hemorrhagic and non-hemorrhagic stroke, or uncertain (used when no imaging is available to exclude hemorrhage). Non-hemorrhagic stroke will sub-classified into ischemic, ischemic with secondary transformation, or stroke of uncertain classification. Hemorrhagic stroke will be sub-classified into primary intracerebral hemorrhage and primary subarachnoid hemorrhage.

1. Ischemic stroke: focal brain infarction caused by an arterial (or rarely venous) obstruction (see above, this excludes flow related infarcts distal to stenosis) and as documented by CT scan /MRI that is consistent with infarction.

2. Secondary hemorrhagic transformation of ischemic stroke: hemorrhagic transformation of ischemic stroke may be symptomatic or asymptomatic.

a. Symptomatic transformation of ischemic stroke is defined as a hematoma occupying 30% or more of the infarcted tissue associated with a significant neurologic deterioration (i.e., a decrease of at least 4 points in the NIHSS) compared to immediately before the worsening and an absence of an alternative explanation for deterioration.

b. Asymptomatic transformation of ischemic stroke is defined as a hemorrhagic transformation not meeting the criteria for symptomatic transformation.

3. Undetermined stroke: definite stroke that does not meet the criteria for ischemic or hemorrhagic stroke because CT scan or MRI are not done and there are no autopsy data. Rarely it cannot be determined with confidence whether the stroke was ischemic vs. hemorrhagic, even after review of CT/MRI images (e.g. primary intracerebral hemorrhage vs. severe hemorrhagic transformation); these stroke events will be classified as undetermined.

4. Hemorrhagic stroke: hemorrhagic stroke requires neuroimaging or autopsy confirmation and includes two subcategories: primary intracerebral hemorrhage (intraparenchymal or intraventricular) and primary subarachnoid hemorrhage. Intracranial bleeding caused by head trauma, bleeding associated with tumors, hemorrhagic transformation of ischemic stroke and subdural/epidural hematomas are not considered as hemorrhagic strokes (but these will be counted separately as major hemorrhages). Microbleeds are not considered intracranial hemorrhage.

    a. Primary intracerebral hemorrhage: These are symptomatic hemorrhagic strokes with CT/MRI or autopsy evidence of bleeding into the substance of the brain or ventricular spaces. Large or superficial intracerebral hemorrhages often are associated with minor amounts of subarachnoid hemorrhage, but these should be classified as intracerebral hemorrhages. Does not include secondary hemorrhage into cerebral infarct (i.e. hemorrhagic transformation which is defined separately), or intracerebral bleeding (i.e. contusions) due to trauma, or microbleeds detected by MRI.

    b. Primary subarachnoid hemorrhage: Typical clinical syndrome of sudden onset headache, with or without focal signs (subarachnoid hemorrhage may not have focal deficits), and CT or cerebrospinal fluid evidence of bleeding primarily into the subarachnoid space. Subarachnoid bleeding due to ruptured intracranial aneurysms and vascular malformation are counted as hemorrhagic strokes, but traumatic subarachnoid hemorrhage is not.

Acute heart failure:

Acute heart failure is defined as a clinical sign (i.e., at least one of the following: elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) and at least one of the following:

1. Radiographic findings (i.e., at least one of the following: vascular redistribution, interstitial pulmonary edema, frank alveolar pulmonary edema, or multiple and diffuse bilateral B lines on ultrasonography);
2. Elevated levels of natriuretic peptides; or
3. Heart failure treatment implemented with diuretics with documented clinical improvement.

Pulmonary embolism:

The diagnosis of pulmonary embolism requires any one of the following:

1. A high probability ventilation/perfusion lung scan;
2. An intraluminal filling defect of segmental or larger artery on a helical CT scan;
3. An intraluminal filling defect on pulmonary angiography; or
4. A positive diagnostic test for deep vein thrombosis and one of the following:
    a. Non-diagnostic (i.e. indeterminate or intermediate probability) ventilation/perfusion lung scan; or
    b. Non-diagnostic (i.e. subsegmental defect or technically inadequate study) helical CT scan.

Deep venous thrombosis of leg or arm:

The diagnosis of deep venous thrombosis requires any one of the following:

1. A persistent intraluminal filling defect on contrast venography;
2. Noncompressibility of one or more venous segments on B mode compression ultrasonography; or
3. A clearly defined intraluminal filling defect on contrast enhanced computed tomography.

Life-threatening bleeding:

Life-threatening bleeding is bleeding that is fatal, or leads to: significant hypotension that requires inotrope therapy/vasopressor therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.

Major bleeding:

Major bleeding is defined as bleeding that is not specified under “life-threatening bleeding” above, and

1. Results in a postoperative hemoglobin of ≤70g/L and the patient receiving a transfusion of ≥2 units of red blood cells;

2. Results in a hemoglobin drop of ≥50 g/L and the patient receiving a transfusion of ≥2 units of red blood cells;
3. Results in the patient receiving a transfusion of ≥4 units of red blood cells within a 24-hour period;
4. Leads to one of the following interventions: embolization, superficial vascular repair, nasal packing; **OR**
5. Is retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging).

Sepsis/infection:

Infection is defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms.

The Third International Consensus Definitions Task Force defines sepsis as a "life-threatening organ dysfunction due to a dysregulated host response to infection." Based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) criteria, sepsis will require a quick Sequential Organ Failure Assessment (qSOFA) Score ≥2 points due to infection. The qSOFA includes the following items and scoring system:

1. Glasgow Coma Scale (GCS) score of 13 or less (1 point);
2. Systolic blood pressure of 100 mm Hg or less (1 point); and
3. Respiratory rate of 22 breaths/min or more (1 point).

Noninfectious diarrhea:

Noninfectious diarrhea is defined as a new onset of >3 loose bowel movements per day. The diarrhea should not be caused by an infectious organism.

APPROVAL

Version #	1.0
Version Date (yyyy/mm/dd)	2023-06-15

By signing the below, I designate my approval of the above-named version of the COP-AF Statistical Analysis Plan on behalf of all named authors.

Name	Dr. David Conen
Role	Lead SAP Author & Principal Investigator
Signature	DocuSigned by: David Conen Signer Name: David Conen Signing Reason: I approve this document Signing Time: 2023-06-15 | 7:56:35 PM EDT B5A1DA3F25254A62B89235AD34C2ED9A
Date (yyyy/mm/dd)	2023-06-15 | 7:56:40 PM EDT

By signing the below, I designate my approval of the above-named version of the COP-AF Statistical Analysis Plan on behalf of PHRI Statistics.

Name	Zhuoru Li
Role	Study Statistician
Signature	DocuSigned by: Zhuoru Li Signer Name: Zhuoru Li Signing Reason: I approve this document Signing Time: 2023-06-15 | 7:58:42 PM EDT F1DE69EFAA9B414998CCC1D86B9C7C50
Date (yyyy/mm/dd)	2023-06-15 | 7:58:50 PM EDT