Anti-inflammatory therapy during percutaneous coronary intervention

Statistical Analysis Plan (SAP)

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This document provides the Statistical Analysis Plan for the Anti-inflammatory therapy during percutaneous coronary intervention study.

1 INTRODUCTION

This statistical analysis plan (SAP) incorporates all of the elements of study design, and analysis of primary and secondary endpoints for this randomized clinical trial (RCT). The SAP is a stand-alone section that describes the statistical design and analysis considerations.

2 STUDY OVERVIEW

2.0. Purpose of the study

We hypothesize that colchicine may effectively reduce inflammation and peri-procedural MI in patients not acutely loaded with high-dose statin prior to percutaneous coronary intervention (PCI). We further hypothesize that colchicine's effects would be additive in patients undergoing PCI on a background of acute high-dose statin pre-treatment. We aim to determine the effects of colchicine 1.2 mg administered 1 to 2 hours prior to coronary angiography, followed by a 0.6 mg dose 1 hour later, on post-procedural markers of inflammation and cardiac biomarkers and events.

2.1. Study Design

Prospective, randomized, double-blinded, placebo-controlled trial of patients undergoing coronary angiography in the Manhattan Veterans Affairs Hospital (primary site is Manhattan Veterans Affairs Hospital), Bellevue Hospital Center, and New York University (NYU) Langone Medical Center cardiac catheterization laboratories. Patients will be stratified into one of two groups:

1) Patients who received a load with high-dose statin therapy (an increase in the patient's maintenance regimen or started newly on a statin) 24 hours to 7 days prior to the procedure and continued on a daily regimen
2) Patients who did not receive a load with high-dose statin therapy 24 hours to 7 days prior to the procedure
   *The decision to load with high-dose statin therapy prior to PCI is made clinically by the treating physician.

Patients will then be randomized to one of two groups:

1) Colchicine 1.2mg 1 to 2 hours before coronary angiography, followed by colchicine 0.6mg 1 hour later
2) Placebo at the same time points above

2.2. Subject Population and Selection

2.2.1. Patient Population

Patients referred for coronary angiography at Manhattan Veterans Affairs Hospital (primary site is Manhattan Veterans Affairs Hospital), Bellevue Hospital Center, and NYU Langone Medical Center,

2.2.2. Gender of Subjects

Subjects will include both men and women. Every effort will be made to include equitable numbers of each gender.

2.2.3. Age of Subjects

Subjects more than 18 years of age will be eligible to participate in the study. The research in question applies to the entire adult population and therefore all adults may participate.

2.2.4. Racial and Ethnic Origin

Subjects of any racial or ethnic background may participate in the study. There will be no enrollment restrictions based on race or ethnic origin.

2.2.5. Inclusion Criteria

Patients must be more than 18 years of age and referred for coronary angiography with a possibility of PCI.

2.2.6. Exclusion Criteria

Patients will be excluded if they meet one of the following criteria: 1) Plan for diagnostic-only coronary angiography, 2) On colchicine chronically, 3) History of intolerance to colchicine, 4) Glomerular filtration rate <30mL/minute or on dialysis, 5) Active malignancy or infection, 6) History of myelodysplasia, 7) High-dose statin load <24 hours prior to procedure, 8) Use of oral steroids or non-steroidal anti-inflammatory agents other than aspirin within 72 hours or 3 times the agent's half-life (whichever is longer), 9) Use of strong CYP3A4/P-glycoprotein inhibitors (specifically ritonavir, ketoconazole, clarithromycin, cyclosporine, diltiazem and verapamil), 10) Unable to consent, 11) Participating in a competing study, 12) Pregnant women, or 13) any condition (e.g., psychiatric illness) or situation that, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's ability to adhere with study procedures.

2.3. Methods and Procedures

Subjects who meet inclusion/exclusion criteria will be randomized in a double-blinded fashion to a pre-procedural loading dose of colchicine or placebo. Patients will undergo assessment of cardiac biomarkers at baseline, 6-8 hours post-PCI, and 22-24 hours post-PCI and clinical assessment at 30 days (maximum follow-up out to 5 years). Patients in the inflammatory marker substudy will undergo assessment of inflammatory biomarkers at baseline, 30 minutes to 1 hour post-PCI, 6-8 hours post-PCI, and 22-24 hours post-PCI.

3. RANDOMIZATION OF PARTICIPANTS

Recruitment will be conducted in accordance of the policies of the Manhattan VA Hospital, Bellevue Hospital, and NYU IRB and Federal guidelines. The attending interventional cardiology physician of all potential subjects will be contacted to determine if the subject is willing to be approached about the study. Informed consent will be sought and documented from all subjects at the earliest time possible, or at least 2 hours before coronary angiography. The rationale, procedures and potential risks of the procedures in the study will be explained to each participant by the Principal Investigator

or his appointed designee. Each subject will be told that participation in the studies described in this proposal is strictly voluntary, that refusal to participate will not alter the patient's relationship with their physician, that the studies constitute research and that the information obtained will not be specifically helpful to the individual patient's care. After the subject has read the consent form, comprehension of the key elements of the study procedures and risks will be tested with verbal questions of the consent form content. If the subject is willing to participate, the subject will sign the IRB-approved informed consent form.

A randomization code will be generated by an independent statistician using random block sizes and held by the research pharmacist. Study drug and a unique subject identifier linked to group assignment will be allocated by the research pharmacist. However, the research pharmacist will not release group assignment to the investigative team until after all subjects have completed the protocol and the database has been locked.

Patients will then be randomized to one of two groups:

1) Colchicine 1.2mg 1 to 2 hours before coronary angiography, followed by colchicine 0.6mg 1 hour later.
2) Placebo at the same time points above

4. DATA COLLECTION

4.1 Baseline Variables:

• Demographics, Height, Weight, Body mass index, Abdominal circumference (race-ethnicity self-reported, other variables measured)

• Medical history: Previous MI, previous PCI, previous coronary artery bypass surgery, hypertension, hypercholesterolemia, diabetes mellitus, peripheral vascular disease, previous stroke or transient ischemic attack, carotid artery disease (>50% stenosis), hepatitis C, and tobacco use (collected from medical records and confirmed by patient)

• Medications: statin (type and dose), aspirin, thienopyridine, cilostazol, dipyridamole, beta blocker, calcium channel blocker, nitrate, ranolazine, hydralazine, ACE inhibitor, angiotensin receptor blocker, statin, fibrate, niacin, ezetimibe, diuretic, aldosterone receptor blocker, digoxin, antiarrhythmic agent, unfractionated heparin, low molecular weight heparin within 12 hours of procedure, insulin, protease inhibitor (collected from medical records and confirmed by patient)

• Laboratory data: BUN, creatinine, glomerular filtration rate, glucose, white blood cell count, hemoglobin, total cholesterol, high density lipoprotein, low density lipoprotein, triglyceride, hemoglobin A1c, ejection fraction (normal, mild to moderately reduced, or severely reduced left ventricular systolic function) (collected from medical records)

4.2. Procedural data:

• Time of baseline blood draw and drug administration (recorded in real time)

• Indication for coronary angiography (determined by research team according to data provided in medical records)

- Time of procedural access and type of arterial access (femoral or radial) (collected from catheterization report)
- Type of contrast agent used (Hexabrix, Visipaque, Isovue) (collected from catheterization report)
- Number of native and graft vessels with greater than 70% stenosis (collected from catheterization report)
- Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score is a scoring system that provides information on atherosclerosis burden in patients undergoing revascularization (grouped as ≤17 (low), 17-32 (intermediate), or ≥33 (high) scores).

- If PCI performed (collected from operator questionnaire administered in real time and catheterization report):
  - Segment treated (left main, left anterior descending, left circumflex, right coronary artery, saphenous vein graft, arterial graft) and single vessel or multivessel intervention
  - Single vessel or multivessel intervention
  - Percent diameter stenosis pre- and post-PCI on semi-quantitative coronary angiography
  - Type of lesion treated (de novo or restenotic, chronic total occlusion, bifurcation lesion, calcification, visible thrombus, lesion length ≥33 mm), lesion site (ostial, proximal, mid-vessel, distal), and number of lesions treated
  - Type of intervention with devices used (balloon only, balloon plus stent, cutting balloon, thrombectomy device, rotational atherectomy device, chronic total occlusion crossing device, filter basket, laser)
  - Time of first coronary balloon inflation
  - Number of pre-dilations or use of direct-stenting
  - Type of stent, number of stents, stent diameter and total stent length
  - Stent deployment pressure
  - Use of post-dilations and maximum pressure on post-dilation
  - Use of Intracoronary medications used (e.g. nitroglycerin, nitroprusside, glycoprotein IIb/IIIa inhibitors)
  - Pre- and post-TIMI flow grade
  - Procedural success (defined as residual stenosis <20% at the end of procedure)
- Time of end of procedure
- Complications
  - Abrupt vessel closure at any time during procedure (main vessel or side branch)
  - Perforation

- Distal embolization
- Plaque shift with side branch compromise (>70% residual stenosis in at conclusion of procedure)
- <TIMI 3 flow in any treated vessel at any time during procedure (also included in post-PCI TIMI flow)
- Uncovered dissection (grade 3 or higher in vessel >1.5 mm in diameter)
- Shock during procedure
- Acute pulmonary edema requiring intubation
- Dysrhythmia requiring defibrillation

All electronic data is de-identified and resides on password-protected computer. All hard copy of data are secured in a locked cabinet in a locked office.

5 KEY STUDY OUTCOMES

5.1 Primary outcomes:

The primary outcome of the overall trial will be peri-procedural myonecrosis using cardiac biomarkers (Troponin I) as defined by the 3rd Universal Definition [1] as follows (biomarkers are evaluated at 6 to 8 hours and 22 to 24 hours post-PCI):

- In subjects with normal baseline cardiac biomarkers, peak post-procedure cardiac biomarker above the 99th percentile upper reference limit
- In subjects with elevated baseline cardiac biomarkers and the biomarker levels are stable or falling, there should be a new cardiac biomarker elevation by ≥20% from the most recent pre-procedural level

The primary endpoint of the inflammatory marker substudy will be 1) change in soluble interleukin-6 level between baseline and 1 hour post-PCI

5.2 Secondary outcomes:

1) The secondary outcomes of the inflammatory marker substudy will be change in neutrophil surface L-selectin (CD62L) between baseline and peak level post-PCI.

Measurement of other relevant inflammatory markers (such as cell-associated beta-2 integrin CD11b, intercellular/vascular cell adhesion molecule-1, myeloperoxidase, NGAL, elastase, soluble L- and E-selectin, white blood cell count, and neutrophil count), as well as, neutrophil extracellular traps (NETs), neutrophil-derived microparticles, and extent of neutrophil-platelet aggregates at 1 hour post-procedure, 6 to 8 hours post-PCI and 22 to 24 hours post-PCI. A subset of patients will have neutrophil metabolism and mean number of neutrophils adherent to TNFα-stimulated endothelial cells assessed at baseline and 1 hour post-procedure.

2) In the overall trial:

a) Occurrence of major adverse cardiac events with composite of the earliest occurrence of death from any cause, non-fatal MI (defined by the 3rd universal definition of MI) [1],

or target vessel revascularization (bypass surgery or repeat PCI of the target vessel) assessed at 30 days, 6 months, and yearly for 5 years. Peri-PCI MI is a component of non-fatal MI and will be defined using the Universal Definition [1] (any elevation 5 times the 99th percentile upper limit of normal). No definition currently exists to define post-PCI myocardial necrosis or MI when biomarkers are elevated prior to procedure. In patients with elevated baseline levels of troponin or creatine kinase-MB, peri-procedural MI will be defined as a subsequent increase of more than 2-fold in troponin or creatine kinase-MB from baseline value.

b) Peri-procedural MI will also be defined by the expert consensus document from the Society for Cardiovascular Angiography and Interventions on a new definition of clinically relevant MI after coronary revascularization as follows [2]:

- Subjects with normal baseline cardiac biomarkers
  - Peak post-procedure Troponin ≥70x upper limit of normal or CKMB ≥10x upper limit of normal
  - A lower threshold (Troponin ≥35x upper limit of normal, CKMB ≥5x) will be used in subjects with new pathologic Q-waves in ≥2 contiguous leads (or new persistent left bundle branch block)
- In subjects with elevated baseline cardiac biomarkers and stable or falling biomarker levels, there should be a new Troponin or CKMB elevation by an absolute increment of ≥70x (for Troponin) or ≥10x (for CKMB) upper limit of normal from the most recent pre-procedural level
- In subjects with elevated baseline cardiac biomarkers and the biomarker levels have not been shown to be stable or falling, there should be a further rise in Troponin or CKMB by an absolute increment ≥70x (for Troponin) or ≥10x (for CKMB) upper limit of normal plus new ST-segment change plus signs consistent with a clinically relevant MI (e.g. new onset or worsening heart failure or sustained hypotension)

c) The primary outcome of peri-procedural myonecrosis using CKMB as the biomarker

5.3. Sample Size

A) A total sample size of 400 subjects is needed to demonstrate a 40% reduction in proportion of subjects with peri-procedural myonecrosis (from 30% in the placebo group to 18% in the colchicine group) using a Chi squared test (80% power, 0.05 significance level). This trial is designed to study the effect of colchicine on all-comers to the cath lab. A greater effect is expected on both surrogate and clinical endpoints in the ACS compared with elective PCI population. Our sample size is based on the lowest relative risk reduction observed with anti-inflammatory therapy in elective PCI [3]. We approximate that 50% of the patients enrolled will either not have PCI performed after coronary angiography (majority) or will be excluded due to requirement of the use of any of the medications listed in the exclusion criteria prior to post-PCI blood collection (minority). We, therefore, estimate a total sample size of 800 be enrolled in this study to meet the 400 PCI sample size.

B) Sample size for the inflammatory marker substudy is calculated based on mean interleukin-6 level of 12pg/mL and standard deviation of 12pg/mL one hour after PCI in predominantly ACS patients reported by Aggarwal et al [4], and an estimated decrease in post-PCI interleukin-6 level by 40% if randomized to colchicine. A 40% decrease is a

conservative estimate relative to the 60% reduction of CRP noted in Nidorf's study examining the effect of colchicine in stable CAD patients on aspirin and high-dose statin therapy [5]. Furthermore, in Aggarwal's study, interleukin-6 levels increased by 58% from pre-procedural levels [4]. Based on the above assumptions, and a two-sided two sample t-test, the number of patients needed in each group to achieve 80% power at the 0.05 significance level is estimated to be 100. A minority of subjects (~16%) may experience no change in IL-6 after PCI [6]. To adjust for this possible floor effect, the sample size needed would also be 120 subjects in each group. If a 35% or 30% decrease in post-PCI IL-6 level is observed with colchicine, 129 or 175 subjects will be needed in each group, respectively (80% power, 0.05 significance).

If sample size for the inflammatory marker substudy was calculated with surface CD62L (the secondary endpoint) as endpoint, it would be based on the mean (± standard deviation) peak post-PCI surface expression of neutrophil CD62L of 9906 ± 6737 MFI (39% rise from pre-PCI) from our pilot AHA-funded project. Based on our volunteer data examining the effects of surface expression of CD62L after a 1.8 mg loading dose and earlier *in vitro* data, we would estimate a decrease in post-PCI CD62L level by ~25% with colchicine. Using a two-sided two sample t-test, the sample size using 80% power and 0.05 significance level would be ~120 subjects in each group. If a 23% or 20% decrease in post-PCI CD62L level is observed with colchicine, 138 or 182 subjects will be needed in each group, respectively (80% power, 0.05 significance).

C) Other secondary endpoints: Sample size for neutrophil-endothelial cell adhesion assay is based on *in vitro* data by our group that demonstrated reductions in neutrophil-endothelial adhesiveness with addition of colchicine (108 ± 11 to 31 ± 5 adherent neutrophils/200x field) [7]. Based on a conservative estimate of 20% reduction and a two-sided two sample t-test, the sample size to achieve 95% power (0.05 significance) is ~10 subjects in each group.

Sample size for neutrophil-platelet aggregates is based on data by our group from the peri-procedural glycemic control trial (mean leukocyte platelet aggregation 10.57 ± 4.10%) [8]. Based on a ~30% reduction and a two-sided two sample t-test, the sample size to achieve 95% power (0.05 significance) is ~45 subjects in each group. Since these subjects must meet dual anti-platelet therapy criteria and the probability of one subject satisfying these criteria in the colchicine group is 0.5, increasing the sample size by 10% (100 subjects) will make the probability of achieving at least 45 subjects in each group (placebo/colchicine) ~68%. Increasing the sample size to 107 subjects will make the probability of achieving at least 45 subjects in each group (placebo/colchicine) ~90%. Subjects in the inflammatory marker substudy that meet dual anti-platelet therapy criteria will undergo neutrophil-platelet aggregate evaluation.

6. DATA ANALYSIS AND DATA MONITORING

Categorical variables will be presented as proportions, normally distributed continuous variables as mean ± standard deviation, and skewed continuous variables as median [interquartile range] (distributions assessed for normality using histogram, quantile-quantile plot and Shapiro-Wilk test). Categorical endpoints will be compared between placebo and colchicine groups using tests of proportions (exact and asymptotic), and continuous endpoints will be compared between placebo and colchicine groups using t-

test. Non-parametric alternatives (e.g. Wilcoxon test) and mathematical transformations (e.g. Box-Cox) will be considered as needed for skewed distributions. Statistical significance will be tested using a 2-sided alpha level of 0.05 with appropriate multiple testing correction (Bonferroni or Benjamini-Hochberg) when needed.

To not incur excess bias by deviating from classification according to assigned treatment, an intention-to-treat approach will be utilized as a primary analytic approach. A secondary analysis will be performed utilizing a non-intention-to-treat approach, where subjects are classified according to the treatment actually received and subjects who do not receive treatment are excluded. We believe crossover and pre-procedure withdrawal will be relatively low. Adopting both approaches, however, will allow for assessment of the robustness of findings.

Pre-specified subgroup analyses will be performed in subjects presenting with versus without ACS and with versus without in-lab complications, as defined below.

In-lab complications: 1) Vessel closure any time during procedure (main vessel or side branch); 2) Perforation; 3) Distal embolization; 4) Plaque shift with side branch compromise (>70% residual stenosis in side branch at conclusion of procedure); 5) <TIMI 3 flow in any treated vessel at any time during procedure (also included in post-PCI TIMI flow); 6) Uncovered dissection (grade 3 or higher in vessel >1.5 mm in diameter); 7) Shock during procedure; 8) Acute pulmonary edema requiring intubation; or 9) Dysrhythmia requiring defibrillation

A) To delineate changes in neutrophil activation during acute vascular injury using a PCI model, markers of neutrophil activity will be assessed by comparison of post- versus pre-PCI samples in the placebo group using paired t-test or paired sample Wilcoxon signed rank test. In addition, to account for all 4 time points (1 pre- and 3 post-PCI), a significant change in markers over time will be determined in the placebo group by estimating speed of change using slope in a linear mixed effects regression model at a 0.05 level of significance cut-off. Markers will then be categorized descriptively as increasing versus not increasing post- compared to pre-PCI.

Univariate and multivariate predictors of markers that demonstrate a significant increase post- compared with pre-PCI (as defined above) will be determined using baseline demographic, clinical, and procedural covariates of interest. Major covariates of interest may include age, sex, race, abdominal circumference, diabetes mellitus, chronic kidney disease, MI within 7 days of PCI, ejection fraction $\leq$40%, pre-procedural TIMI 0 or 1 flow, multivessel CAD, visible thrombus or ulcerated lesions, SYNTAX score $\geq$23, and presence of one of the in lab complications as defined above. Based on our biomedical knowledge and experience in variable selection and statistical modeling, we will balance model richness against a danger to overfit. First, a screening procedure based on the correlation between the outcome and each variable will be used to choose the variables in the multivariate model, and then a stepwise variable selection method including both forward and backward methods will be employed to search for an optimal model gauged by the Akaike information criterion. We will also conduct the principal component analysis for parsimonious modeling, which uses the correlation matrix to identify a small number of components capturing most of the variability and include them in the multivariate logistic regression model.

To determine changes in subsequent cellular interactions, neutrophil adhesion to endothelial cells and neutrophil-platelet aggregates will be assessed post- compared with pre-PCI samples in the placebo group using paired t-test or paired sample Wilcoxon signed rank test.

Finally, a mediation analysis will be performed in a logistic regression model to test the hypothesis that an increase in markers of neutrophil activation is associated with peri-procedural myonecrosis, and that this association is mediated by neutrophil-endothelials cell and neutrophil-platelet adhesion.

Similar analyses will be performed in the evaluation of the change in NETs and neutrophil-derived microparticles post- versus pre-PCI. A mediation analysis will be performed in a logistic regression model to test the hypothesis that an increase in these neutrophil extracellular fragments is associated with peri-procedural myonecrosis, and that this association is mediated by tissue factor pathway inhibitor/thrombin generation.

B) To determine the effect of colchicine on changes in markers of neutrophil activation and subsequent cellular interactions during acute vascular injury, pre- to post-PCI changes will be examined between the placebo and colchicine groups using two-sample t test or Wilcoxon rank sum test. To further study the time-varying pattern of treatment effect, with the observations at pre-PCI and multiple post-PCI time points, a repeated measurements or longitudinal data analysis modeling will be used by incorporating both individual-specific terms and the treatment by time interaction. The Analysis of Variance Analysis will be conducted using the Generalized Estimating Equations or Quasi-Likelihood approach. Alternatively, proportion of subjects with significantly increased markers of neutrophil activity post- compared to pre-PCI (defined above using estimated slope of change) will be compared between the placebo and colchicine groups using tests of proportions. Finally, an interaction with pre-procedural use of colchicine versus placebo will also be evaluated to determine whether or not colchicine modulates the mediation analyses described above.

C) To explore the association between markers of neutrophil activation and outcomes after acute vascular injury, the association between tertiles of markers of neutrophil activity at baseline and dichotomous outcome of peri-procedural myonecrosis will be assessed using logistic regression modeling and presented as odds ratio and 95% confidence interval. Similar analyses will be performed to evaluate the association between tertiles of markers of neutrophil activity at baseline and dichotomous outcome of peri-procedural MI, as well as long-term composite of all-cause mortality, non-fatal MI, and target vessel revascularization.

However, the capacity for neutrophil activity to increase in the setting of acute vascular injury may be more pertinent than baseline activity. Therefore, using the estimated speed of change in neutrophil activity over time from pre- to post-PCI, markers of neutrophil activity will be categorized as increasing or non-increasing (no change or decreasing) based on analysis of slope and a 0.05 level of significance cut-off. The association between increasing versus non-increasing markers of neutrophil activity and peri-procedural myonecrosis will be evaluated using logistic regression modeling (increasing marker as main predictor, peri-procedural myonecrosis as dichotomous outcome). Similar analyses will be performed to evaluate the association between increasing versus non-

increasing markers of neutrophil activity and peri-procedural MI, and long-term composite of all-cause mortality, non-fatal MI, and target vessel revascularization.

Logistic regression models will be built hierarchically to include main covariates. As above, age, sex, race, abdominal circumference, diabetes mellitus, chronic kidney disease, MI within 7 days of PCI, ejection fraction $\leq$40%, pre-procedural TIMI 0 or 1 flow, multivessel CAD, visible thrombus or ulcerated lesions, SYNTAX score $\geq$23, and presence of one of the in lab complications as defined above. Based on our biomedical knowledge and experience in variable selection and statistical modeling we will balance model richness against a danger to overfit as described above.

Finally, to explore the effects of colchicine on peri-procedural myonecrosis in a PCI model, the rate of peri-procedural myonecrosis and peri-procedural MI in subjects randomized to the placebo vs colchicine groups will be assessed using the tests of proportions. This association will also be assessed using logistic regression modeling and will include the main covariates described above.

D) The low-dose colchicine regimen in the current proposal has been studied and demonstrates an excellent side effect profile. A Data Safety Monitoring Committee (DSMC) will be formed to review ongoing safety data. This committee will be a group consisting of three physicians and, when needed, one biostatistician. The DSMC meetings will include an initial open meeting for discussion with the Principal Investigator and the presentation of reports by the study coordinator followed by a closed meeting of voting DSMC members. The DSMC will review blinded safety data three times a year (or more often as necessary) to ensure the safe and proper treatment of subjects. The committee will also review recruitment data, study subject withdrawals, data on drug tolerability, and protocol violation data to determine whether any substantial deviations from the initial study plan might alter the original risk benefits analysis. If the frequency and/or severity of adverse events are thought to be study related, or if other logistical issues related to study drug tolerability, are thought to compromise the integrity of the study protocol, the DSMC can make recommendations for protocol modification or early termination of the study. After each meeting, the committee will prepare a brief report to be submitted to the Principal Investigator that will recommend: 1) study continuation without modification, 2) study continuation with modification, or 3) study discontinuation. A recommendation of study modification or study discontinuation will lead to an immediate cessation of study enrollment, but in the event of a recommendation of study modification, study enrollment may be allowed to resume once the human subjects safety issues and/or other logistical issues have been adequately addressed to the satisfaction of the DSMC and IRB. In the event of identification of any relevant safety findings that may change the original risk benefit analysis for the human subjects in the study, these findings will be forwarded to the IRB committee and will be incorporated into a revised protocol and consent form. All current participants and future participants will be required to sign the revised consent form. The Principal Investigator will be responsible for reporting of adverse events to the DSMC and IRB according to standard definitions.

Missing Data

Missing Outcomes. The impact of missing data on the results of the primary analysis will be investigated by inferring a relationship between the covariates and the 0-1 indicator that defines whether or not the outcome of a subject is observed. This analysis will help to elucidate characteristics likely to cause outcomes to be missing and test whether the covariate-response relationship obtained from the subjects with non-missing outcomes represents the larger population.
Missing Covariates. The relationship between the 0-1 indicators that defines whether or not the covariate is observed and variables will be examined using logistic regression techniques. Should a substantial proportion of cases (> 10%) be missing for a critical independent variable and evidence found of nonrandomness, missing data will be incorporated using multiple imputation methods and Inverse Probability Weighting.

7. DATA STORAGE AND CONFIDENTIALITY

All patient data will be kept strictly confidential, except when published for purposes of reporting data. In that case, the patients are never identified. As noted previously, all electronic data will be de-identified and resides password-protected computers. All hard copy of data will be secured in a locked cabinet in a locked office on Manhattan VA Hospital property. All biological specimens will be encoded with no identifying information and stored at NYU School of Medicine Research Building that can only be traced back to the individual by the research team. There is a minimal risk of loss of confidentiality though every precaution will be taken to avoid this. The statistician will have access to only the de-identified data for analysis.

8. REFERENCES

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