PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	**Statin Therapy in Acute Influenza**
Principal Investigator	**Maureen Chase MD, MPH**

B1. PURPOSE OF PROTOCOL

Influenza is a large-scale public health issue for which considerable focus has been placed on vaccination programs and on the development of antiviral therapies. However, these strategies are confronted with the challenges of rapidly emerging influenza strains and increasing resistance to existing antiviral agents. In addition, these strategies do not address the contribution of the host inflammatory response in influenza pathogenicity as an overwhelming host cytokine response can lead to increased severity of the clinical illness, organ damage, and death.

The objective of this study is to determine the potential effect of statin therapy for the treatment of acute influenza infection. In addition, we will evaluate the mechanism by which statin therapy attenuates the host inflammatory response and the effect on clinical outcomes as follows:

Specific Aim #1: To determine if the administration of statin therapy to patients with acute influenza will attenuate the inflammatory cascade.

Specific Aim #2: To determine if the administration of statin drugs attenuates disease severity and improves time to clinical resolution of symptoms in patients with confirmed influenza.

Specific Aim #3: To determine the effect of influenza on host metabolic response to disease.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Influenza is associated with a high level of morbidity and mortality worldwide: The World Health Organization still estimates 3 to 5 million severe cases of influenza illness worldwide and attributes 250,000-500,000 deaths to seasonal influenza outbreaks each year.[1] While a reported 90% of influenza-associated deaths occur among adults aged ≥65 years, the morbidity associated with 2009 swine-origin influenza A (H1N1) resulted in a shift in the ages and baseline health of patients who became ill and died.[2-5] One epidemiologic study found that two-thirds of hospitalized patients and 40%of those who died had no pre-existing medical conditions.[6, 7] In addition, mortality rates in other major diseases also peak when influenza is circulating.[8, 9]

No universal influenza vaccine exists: The best means of controlling influenza outbreaks is the development of protective vaccines. Because it takes months to generate, produce and distribute a strain-specific vaccine, populations with no prior immunity may be left vulnerable in the event of pandemic-associated vaccine shortages.

Antivirals are currently the only primary defense: In the setting of inadequate vaccine supplies, the only line of treatment will be existing antiviral agents. There are challenges to using these agents including cost, utility late in disease, limited supplies and, perhaps most concerning with regard to using antivirals as a singular defense in influenza infection is emerging resistance.

The host inflammatory response is a key component of influenza pathogenicity: A severe inflammatory response elicited by the influenza virus is thought to contribute significantly to the infection-associated morbidity and mortality.[10-12] Kaiser and colleagues observed a positive

correlation between plasma IL-6 levels and influenza symptom scores and temperatures in 16 adult patients with influenza; there was no significant difference in viral replication or cytokine levels between patients treated with placebo and those treated with oseltamivir.[13] Paquette et al found that Il-6 levels were strongly associated with requirement for ICU level care and predicted fatal outcome in H1N1 infection.[14] These studies highlight the fact that anti-influenza strategies should target both viral proliferation and the cytokine host response.

For each of these reasons, it is essential to research alternative short-term adjunctive therapies in acute influenza treatment and pro-inflammatory mediators represent key therapeutic targets. The class of medications referred to as "statins" have pleiotropic anti-inflammatory and immunomodulatory effects including mitigation of the host pro-inflammatory cytokine response and protective effects on the vascular endothelium.

We hypothesize that the administration of a statin medication will attenuate the inflammatory response in patients with acute influenza, resulting in 1.) decreased levels of circulating cytokines (IL-6, VegF and TNF alpha) and 2.) a reduction in the severity of illness and time to clinical resolution of influenza symptoms. In order to test our hypotheses we will perform a prospective, randomized, double-blind study in which patients with acute influenza will be receive either statin therapy (atorvastatin 40mg) or placebo. We further hypothesize that influenza infection will cause a range of metabolic derangements in the host which will allow for elucidation of an influenza metabolomic profile and the potential identification of other anti-influenza therapeutic targets.

Statins are inexpensive and widely available; if effective, statins may have a profound effect on the morbidity, mortality and economic burden associated with influenza worldwide. Thus, our investigation could lead to a practice-changing therapeutic intervention that complements the current strategies of prevention (vaccination) and direct antiviral therapy.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study Design: Prospective, double-blind, randomized clinical trial.
Our primary hypothesis is that statin therapy will attenuate the inflammatory response in patients with influenza and lead to improved clinical outcomes.

Randomization: We will create a master randomization list of 174 randomized assignments, with 87 for the treatment group, and 87 for the control group. The master list will be maintained in the pharmacy area and the pharmacy staff will assign treatment allocation to ensure both study subject and investigational staff remains blinded.

Sources of Materials
Following written, informed consent trained research assistants will review and extract pertinent data and information from the patient's medical record including but not limited to patient demographics (including race), co-morbidities, initial and worst vital signs and laboratory tests (basic chemistry, complete blood counts, liver function tests and creatinine kinase). We will draw a small amount of blood (approximately 30mL) to assess baseline inflammatory biomarkers, CoQ10 levels and for metabolomic profiling.

Patients who are enrolled in the trial and remain in the hospital will have data collected at the following time points 0, 12, 36, 48 and daily until hospital discharge. Safety lab testing (ALT, AST, CPK) will be performed at 24hrs and 72hrs. Any patient who is discharged from the hospital prior to the 72hr point will have a follow-up appointment at the GCRC for safety labs and follow-up measurements. Patients who are discharged without in-patient hospitalization will have all baseline measurements performed at enrollment and will be required to attend the 72-hour GCRC follow-up appointment for blood sample collection for inflammatory biomarker profiling and safety monitoring.
If a subject has nasopharyngeal samples obtained as part of their routine medical care, we will obtain discarded samples from the laboratory and freeze them. These samples will subsequently be used to evaluate the virus type and correlate with other disease parameters.

Screening Protocol:

- Prior to presenting the written informed consent form for the main study to the subject or LAR, subjects will be verbally asked to undergo a bedside Rapid Antigen Test for influenza confirmation (Influenza A and B). Alternatively, another methodology for testing influenza, performed in a clinical lab setting for respiratory secretions may be used in place of the RAT test performed at bedside and interpreted by study staff.A urine or serum pregnancy test (females of childbearing potential only) will be performed if one is not already done as part of standard of care.
- A negative pregnancy test result should be confirmed prior to the first dose.

Treatment Protocol:

- Patients will be administered study medication (either atrovastatin 40 mg or placebo) orally once daily for 5 days or or for a maximum of 7 days for those remain hospitalized:
  - -Patients seen in the ED will receive a 5 day supply of the study medication.
  - - Patients who are hospitalized will receive a minimum of 5 day supply (7 days maximum for those who remain hospitalized after 5 days)
- We will ask patients to provide an email address and telephone number for follow-up.
- For patients who are in hospital study staff will go over the online diary at the bedside each day of the interventional period.

- For patients who are not admitted to the hospital or discharged before Day10, they will receive email or telephone reminders daily up to Day 10 to complete the diary online. If internet access is not available, study stuff will fill out the diary with patients over the phone.
- A 14-day telephone follow up interview will be conducted and patients will be asked about relapse, recurrence of symptoms or re-hospitalization.
- Female patients of child bearing potential and males capable of fathering children will be asked to provide a method of contraception and advised to continue for 2 weeks after finishing the study drug.

Laboratory Analysis:

- Blood draws will occur at enrollment and every 24 hours for admitted patients (up to 7 days) and at 72 ±12 hours for discharged patients (at GCRC). For patients who remain in the hospital with ongoing influenza-related symptoms after day 7, blood draws will occur every other day while hospitalized to hospital day 14 maximum.

Specific Aim 1: To determine if the acute administration of statin drugs to patients with confirmed influenza will attenuate the inflammatory cascade.

- The **primary endpoint** for this study is change in inflammatory biomarker IL-6 from the time of enrollment to 72 hours.
- Secondary endpoints will include change on additional markers of inflammation including VegF and TNFa.

Specific Aim 2: To determine if the administration of statin drugs attenuates disease severity and improves time to clinical resolution of symptoms in patients with confirmed influenza.

- The **primary endpoint** in this aim will be the time to clinical resolution based on a daily composite score of recorded major influenza symptoms. Study subjects will record a diary of symptom severity, temperature, ability to perform normal activities, and use of relief medication twice daily for 10 days. The diary will be used to create a composite score for each of 5 major symptoms (fever, cough, sore throat, headache, myalgia) ranked from 0 to 3 (none, mild, moderate, severe) for a score ranging from 0 to 15.[80]Clinical resolution of symptoms will be defined as time to alleviation in major symptoms recorded as no more than mild x 24 hours.
- Secondary endpoints will be:
  1.) Change in severity of illness (APACHE II) from enrollment to 24-hour follow-up
  2.) Hospital and ICU lengths of stay
  3.) Rates of progression to vasopressor-dependent shock
  4.) In-hospital mortality

Specific Aim 3(Exploratory): To determine the effect of influenza on host metabolic response to disease.

- The first **exploratory endpoint** (3a) will be to determine if influenza host response consists of a unique metabolic fingerprint for diagnostic or prognostic purposes. We will obtain a "metabolomic" fingerprint of all patients at baseline which will consist of over 250 metabolites. We will evaluate the association of the metabolic profiles to outcome measures including need for hospital or ICU admission and mortality. We will then evaluate the metabolomic profile as a prognostic indicator in comparison to other biomarker indices and severity of illness scoring.
- The second **exploratory endpoint** (3b) will be to identify metabolic derangements and deficiencies that can serve as adjunctive therapies. Specifically, we will examine whether CoQ10 and other metabolic derangements may lead to adjunctive interventional therapies in influenza infection.

B. Statistical Considerations

We will create a master randomization list of 174 randomized assignments, with 87 for the treatment group, and 87 for the control group. However, our total enrollment target for the study will be 1200 subjects to account for RAT screen-out subjects. In the first year of the study, 139 subjects were RAT tested for study eligibility; 15 of the 31 subjects who tested positive for influenza were enrolled into the main study. With the total enrollment target at 1200 subjects, this number will allow us to RAT test approximately 240 patients each year over the course of five years in order to reach target enrollment of 174 patients over 5 years.

Sample Size and Power Calculation, Aim #1: Sample size calculation is based on IL-6 data from our septic shock population. At the 72-hour time point, we found a change in IL-6 levels of (-964.3 ± 1501.2) in the statin group and (-471.9 ± 620.0) in the placebo group. Based on these numbers, we need 87 patients in each group to detect a change in biomarker levels between the statin and placebo groups at alpha 0.05 and 80% power.
Data Analysis, Aim #1: We will first summarize data and examine the distribution of demographics and potential clinical confounding variables to ensure that the randomization scheme works. We will use 2-sample t-test or the Wilcoxon Rank Sum test to evaluate for the difference between groups for continuous variables and the chi-square or Fisher's exact test for categorical variables. Next, IL-6, TNF alpha and VegF levels will be compared between the two groups at multiple time points using a two-sample t-test or Wilcoxon Rank sum test. Initially, we will use a univariate test to see if there is a difference between the mean (median) values between the two groups at each time point. We will then use a linear mixed-effects model with several covariance structures to account for the correlation from the within-subject measurements. In this model we will include an interaction factor between time and group and also control for any potential confounders. We will obtain the estimated mean difference and standard error for the effect of the treatment for each of the biomarkers. We will also report 95% confidence intervals around important parameter estimates.

Sample Size and Power, Aim #2:
Time to clinical resolution: Based on pooled analyses of past influenza antiviral efficacy studies, patients with laboratory confirmed influenza had a 1.5 day reduction in time to alleviation of symptoms as compared to control; the sample size (87 per group) obtained in Aim 1 will achieve 90% power at 5% level of significance
Data Analysis, Time to Clinical Resolution: If there are no censored observations and the data indicate normality (with or without transformations) then t-test will be used in the univariate setting and linear regression to adjust for covariates and their possible interactions. For censored observations, we will use Kaplan-Meir method in the univariate analysis. To adjust for the possible effect of covariates we will use Cox regression.

Severity of Illness Score: We recorded APACHE II scores for patients with confirmed influenza and found that non-statin users had a score of 7.3±3.5. Clinically, we consider a 25% reduction in APACHE II significant; using an absolute score reduction of 1.8 points, assuming the same standard deviation and a 75% admission rate, we will have 90% power to detect a difference between groups with a one-sided Type 1 error of 0.05.
Data Analysis, Severity of Illness Score: Similar to Aim 1, we will make use of all data points and fit a linear mixed-effects model where the within-subject correlation of the APACHE II score is incorporated into the model via an error term which allows for missing APACHE II data.

Additional Endpoints: Fisher's exact or chi-square test will be used to assess for differences between the statin and placebo groups with regard to development of shock and mortality; for lengths of stay,

we will compare groups using Wilcoxon Rank Sum test.

*Sample size and Power, Aim #*3:
We will perform CoQ10 and metabolomic assessments on the first 50 patients enrolled in the trial. We will compare these results to those of controls in our data repository. A sample size of 50 patients per group will allow us to detect an effect size of 0.5 with 80% power (two-sided alpha 0.1).
Data Analysis, Aim #3: Computational analysis will be performed for the metabolomic analysis and descriptive statistics will be employed for metabolomic profiles and CoQ10 levels.

C. Subject Selection

Inclusion Criteria (all must be present):
1) Adult patient (age > 18 years)
2) Positive influenza DFA/RAT test result
3) <12 hours from positive influenza test result

Exclusion Criteria:
1) Prior statin medication use (within 30 days of positive influenza test result)
2) Comfort measures only designation or anticipated withdrawal of life-support
3) Atorvastatin specific exclusions:
    a. Documented liver cirrhosis or liver dysfunction (AST or ALT greater than 240)
    b. Known allergy or intolerance to statins
    c. Rhabdomyolysis (CPK elevation > 6x normal)
    d. Patients taking the following medications: cyclosporine, HIV protease inhibitors, hepatitis C protease inhibitor telaprevir, fibric acid derivatives (gemfibrozil), niacin, azole antifungals (itraconazole, ketoconazole) clarithromycin and colchicine
4) Patients unable to take oral or nasogastric medications or plan for no oral intake as part of medical course (eg. emergent surgical intervention)
5) Known pregnancy or active breastfeeding
6) Inability to provide written informed consent for any reason

Justification of Inclusion/Exclusion Criteria: We have chosen to include adult patients with confirmed influenza. We will enroll patients immediately after notification of a positive influenza test result and will attempt to capture patients early in their hospital course, as early intervention will likely provide the greatest benefit with respect to modulation of the inflammatory response and clinical resolution. The two potential (though unlikely with short term use) side effects of statin therapy include liver injury and rhabdomyolysis. Therefore, we will exclude patients with liver inflammation (defined by ALT or AST > 6x normal) or muscle inflammation (CPK > 3x normal) at baseline. Moreover, we will exclude patients on medications known to potentiate the effect of statin therapy and therefore potentially increase the chance of adverse effects. We have chosen to exclude patients with recent prior statin use as this would likely confound the interpretation of the results of this investigation.

B4. POSSIBLE BENEFITS

Potential Benefits of the Proposed Research to Human Subjects and Others
It is not known whether statin therapy will benefit patients with acute influenza. Previous reports suggest that statins may attenuate the inflammatory cascade in patients with influenza. However, these reports have been mostly observational in nature and a causal relationship has yet to be established. Our primary hypothesis is that statin therapy will attenuate the inflammatory response in patients with influenza and lead to improved clinical outcomes. We are therefore conducting a randomized placebo controlled clinical trial of atorvastatin versus placebo for adult patients with confirmed influenza. If our hypothesis is correct, patients who receive the statin medication will have an improved clinical course compared to the placebo arm of the study which may include shorter time to hospital discharge and improvement in severity of illness.

Importance of the Knowledge to be Gained
Statin medications are very common for treatment of hyperlipidemia. Our investigation will determine the effects of atorvastatin on the inflammatory cascade and clinical manifestations of the influenza virus. If statins demonstrate a positive result in comparison to placebo we could potentially use statins as an early therapeutic agent for patients with positive influenza. This has significant public health implications as statins are relatively safe in a majority of the population and could potentially impact large numbers of patients who are afflicted with influenza each year in the United States.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Statin risks:
The two potential (though unlikely with short term use) side effects of statin therapy include liver injury and rhabdomyolysis. In general, statins have an excellent safety profile as a recent study of 129,288 patients started on a statin and followed for 4.4 years found a rate of any diagnosed muscle problem to be 4.1/ 10,000 in the first year and no cases in >500,000 person years of observation in rhabdomyolysis.

Blood draw risk
In addition, we will collect blood samples from study participants which the risk of pain during needle insertion, and hematoma at the site of needle insertion. We will minimize the highly unlikely side effects of a blood draw by conforming with standard phlebotomy techniques including drawing blood while patients are supine or sitting, the site of the blood draw will be cleansed prior to the draw, and direct pressure will be held post-blood draw. All research assistants performing phlebotomy will have formalized training and oversight. Infection, excess bleeding, and fainting are also possible, although unlikely. .

Rapid Antigen Test and Viral Swabs collection
The currently known mild effects that have been seen with the rapid antigen test procedure and viral swab collection are listed below.

Swab Collection: Generally, the side effects have been mild. The most common side effects have been as follows:

- Sneezing
- Runny nose
- Watery eyes
- Soreness where the nose is swabbed

There are not known risks associated with the viral swab collection.

Pregnancy and Breastfeeding Risks:
The risks to the unborn baby include birth defects, premature delivery or death. Atorvastatin may pass through the breast milk and harm the baby. All women of child bearing potential will be given a pregnancy test to confirm they are not pregnant prior to the first dose of study medication.

We do not anticipate any psychological risks of participating in the study. There will be no financial risks associated with study participation

We have carefully evaluated the risk: benefit ratio and feel that the potential benefits of a positive trial significantly outweigh the potential risks for participation in the investigation. As described above, the potential risks to subjects are minimal and we have carefully considered a plan to ensure that risks are minimized throughout the interventional period.

Adverse Events
An Adverse Event (AE) is defined by any symptom, illness or disease that commences or worsens during the 5 day study duration and is confirmed to be the result of study intervention. We have an advantage in studying a drug with well documented safety profile. Though rare, the known side-effects of atorvastatin include the potential for liver toxicity and skeletal muscle effects (myopathy and rhabdomyolysis). For all patients enrolled in this trial liver function tests (LFTs) including AST and ALT as well as creatine kinase (CPK) will be measured at the time of enrollment and at the 72-hour follow-up. Of note, we will exclude patients from this investigation if at the time of enrollment they have LFTs or CPK above 6x the normal range as described in the Inclusion/Exclusion section above.

Safety Monitoring Plan
The study will undergo regular data safety monitoring to ensure the safety of the intervention in this patient population. We will include a Data Safety Monitoring Board (DSMB) comprised of an emergency physician, a specialist in influenza research investigations and a biostatistician. The DSMB will meet at regular intervals as follows: the DSMB will convene initially when 30 subjects are enrolled into the trial to ensure no obvious safety concerns for the investigational protocol. Subsequent to the initial meeting, the DSMB will convene when the trial reaches 1/3 and 2/3 enrollments and those subjects have completed the intervention.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

Screening: Our research team provides in-house coverage 24 hours a day. We have successfully developed and utilized an electronic screening mechanism through the ED patient registry system that allows for nearly 100% capture of all potentially eligible patients. Primary screening for eligible patients with acute influenza will occur in the emergency department as our data show that over 92% of patients admitted with influenza present through the ED. In addition, any positive influenza test in the hospital laboratory generates an automatic email alert to the investigative team enabling for further identification of hospitalized, non-ED patients.

Consent

Verbal RAT consent for Influenza A and B confirmation: Patients will first be approached to undergo the Rapid Antigen Screening for influenza confirmation before they are presented with the main written informed consent form. The research assistant will provide the patient information regarding the background and significance of the RAT test, eligibility criteria, and a brief description of the main protocol. Verbal consent will be obtained from the study subject or legal authorized representative prior to undergoing the RAT test. IF the subject is flu positive, the subject will be presented with the main written informed consent form.

Main Consent and Enrollment: Patients who meet all inclusion criteria and none of the exclusion criteria will be approached for written informed consent. The research assistant will provide to the patient information regarding the background and significance of the study, eligibility criteria, and a description of the protocol. Written informed consent will be obtained from the study subject or legal authorized representative prior to performing any procedures solely for the purpose of research.

For the verbal RAT consent, research staff will document that subject gave permission. The subject will be provided with an information sheet.

For the Main ICF, if the patient / LAR agrees to participate, he / she will sign and date (and a witness if applicable) the inform consent form. The name of the study investigator obtaining consent will be clearly documented, and this person will sign the informed consent document and provide the date of their signature and time. Signed copies of the consent form will be given to the participant/LAR, and the original consent document will be stored in the secure study file. A copy of the consent form will also be placed in the subject's medical record.

- In the event that a physician Investigator is not physically present in the hospital to perform the consent process, a research assistant will introduce the study and obtain preliminary consent from the patient or LAR. We anticipate that this will occur predominantly on weekends and/ or nights.
- The research assistant will then coordinate a video or phone conference with physician investigator or co-investigator such that any additional questions can be addressed by the physician investigator who will confirm consent directly with the patient or LAR.
- The research assistant will sign the consent, in addition to the patient or LAR, and that signed copy will be included in the patient's medical record and as well as be provided to the study subject.
- The research assistant will place a note to file documenting the physician investigator's role in the consent (via phone or video conference).

Remote recruitment and consent from proxy:
Patients who qualify for this study may be intubated or confused due to the disease process that impairs their ability to provide informed consent. In our experience, the patient's proxy is sometimes not present in the ICU or the ED when the patient is intubated to provide written consent. The enrollment

criteria for this study create a short time window when the patients can be enrolled (12 hours from a positive influenza test result).. In such a circumstance, the study staff will send the informed consent document to the subject's surrogate electronically (email, facsimile, etc.) and a licensed physician investigator, or a co-investigator will conduct the consent discussion by video or telephone. Once the surrogate has had time to review the consent form, if he/she agrees to participation he/she will sign the consent and return the signed document to the investigator electronically (email, facsimile, etc.).

All email correspondence will occur in accordance with BIDMC guidelines. Once the signed consent form has been received by the investigator, he/she will then sign, date, and time the form. No study procedures will occur before the consent form has been signed by both the surrogate and the investigator. The surrogate will be instructed to return the original signed consent form to BIDMC which will be kept in the subject's research record with the electronically transmitted copy and a detailed note to file.

The research assistant will record demographic data (including age, sex, race, and ethnicity), vital signs and laboratory data and perform venipuncture to collect approximately 30mL of blood at the time of enrollment. During this process, confidentiality will be strictly maintained.

Subject Protection

There will be no undue influences on the potential study subjects to participate.

There is a DSMB comprised of an independent group sponsored by the NIGMS who will make recommendations in general about the efficacy of study intervention, the benefit/risk ratio of procedures and participant burden, selection, recruitment and retention of participants, amendments, safety and referral for abnormal findings.

Dr. Chase will also periodically review the data to evaluate subjects' safety and data integrity. The purpose is to determine whether study subjects are exposed to unreasonable risk because of study participation, and to monitor study progress and integrity. Dr. Chase will review all adverse events to the CCI according to the adverse event reporting policy of the CCI.

All biological material will be stored in a locked refrigerator within a locked facility, which is under hospital security surveillance at all times. All electronic records will be maintained on BIDMC IS compliant computers.

B7. STUDY LOCATION

Privacy

Standard clinical protocols regarding protecting patient confidentiality will be followed during the course of this study. Consideration is given to their privacy when discussing their condition. In order to maintain privacy, the investigators will discuss the study and consent the subjects in a private area. Once consent is obtained, blood samples and patient information is obtained at the bedside. For the 14 day follow up phone call, the phone calls will be made through a secure hospital land line.

Physical Setting

Patients (or their legally authorized representatives) will be approached, recruited and enrolled in the Beth Israel Deaconess Medical Center's Emergency Department, inpatient floor and intensive care units.

The follow-up phone calls will take place in the Emergency Department research offices.

No patient information will be provided to the sponsor. Additionally, no one other than the research team, the patient's physicians and family will be apprised of the patient's participation in the study.

B8. DATA SECURITY

Data will be stored in electronic form on computer hard drive. The computer will be password protected behind the BIDMC firewall, making the data available only to study personnel. Only the principal investigator, co-investigators and research staff will have access to the database. Patient data will be accessible only to study personnel. All efforts to protect patient confidentiality will be strictly enforced.

Data Management: Clinical, laboratory and safety data for this trial will be stored in the REDCap electronic data management system. The online database ensures confidentiality through the use of a patient ID number. In order to ensure accuracy and protection of the data, we will maintain an electronic and hard copy of the master list with identifiers. The computer list will be maintained on the hard-drive of two separate computers in password-protected files kept in a locked research office used only by study investigators. The online database has the capacity for generating periodic reports for the Data Safety and Monitoring Board (DSMB).

Frozen blood specimens will have only the study ID as the identifying information.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☒ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☒ No

B10 Dissemination of Research Results

We will plan to disseminate the results after completion of data analysis through a peer-reviewed scientific publication as appropriate and through oral presentations at seminars and scientific conferences.

A description of the study will be available on clinicaltrials.gov as required by U.S. law. The website will not include information that can identify the participant. The website will include a summary of the results. The participant can search this website at any time.