

Short-Course Glucocorticoids and Rituximab in ANCA-Associated Vasculitis

I. Background and Significance

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV) affecting small and medium sized vessels. Treatment of systemic AAV with cyclophosphamide and glucocorticoids (GCs) has significantly reduced the previously high mortality rate associated with these diseases. Recently, rituximab, a monoclonal anti-CD20 antibody, was shown to be non-inferior to cyclophosphamide and azathioprine for the treatment for AAV.¹ Based on this trial, rituximab, in combination with GCs, has been approved by the FDA for treatment of GPA and MPA.²

Despite therapeutic advances in AAV, patients continue to be exposed to considerable treatment morbidity from long-term GC use. GCs raise the risk of infection substantially, and this risk increases with higher doses and longer duration of treatment. Moreover, the risk persists even after the discontinuation of GCs.³ GC-induced osteoporosis leads to significant morbidity with a 75% increase in the risk of fracture in the first 3 months of GC therapy and an overall fracture rate of 30-50% in patients treated with long-term GCs.⁴ Gastrointestinal bleeding (GIB) is another common cause of morbidity with a four fold increase in the rate of hospitalization for GIB in patients treated with GCs.⁵ Other adverse events include GC-induced diabetes, cataracts, hypertension and weight gain among others.⁶ Therefore, limiting the duration of GC treatment in this era of biologic therapies for AAV would be an important additional step forward in the treatment of these conditions.

The optimal duration of GC treatment has not been studied in AAV. Previous trials in AAV have used various dosing regimens, lasting 6-24 months.⁷⁻¹⁰ Because the aim of the trials was the investigation of a non-GC therapy, the comparison of GC regimens cannot be made directly. A recent analysis of the data from the registry of the Glomerular Disease Collaborative Network demonstrated that in patients with AAV, GC courses of longer than 6 months were associated with greater risk of infection without a reduction in the risk of relapse.¹¹ In contrast, a meta-analysis performed by Walsh et al demonstrated that longer duration of GC therapy was associated with fewer AAV relapses.¹² However, all of the trials included in the analysis used cyclophosphamide rather than rituximab to induce remission. One course of rituximab depletes circulating B lymphocytes within two weeks of the first infusion and is as effective as prolonged treatment with cyclophosphamide followed by azathioprine at 18 months.¹³ Because of rituximab's ability to deplete circulating B cells entirely for a period of 6 to 18 months (or even longer), treatment regimens that employ this therapy have the potential for substantial GC sparing.

There is evidence to suggest that certain subsets of patients with AAV may be more at risk for flares and severe disease manifestations. Previous studies have shown that

patients with proteinase-3 (PR3) ANCA or diagnosis of GPA are at increased risk for flares as compared to patients with myeloperoxidase (MPO) ANCA or diagnosis of MPA.^{8,10,14,15} Unpublished data from the RAVE trial has demonstrated similar findings.

We hypothesize that an 8 week course of GCs may be sufficient to control disease activity in a subset of patients with AAV who have a more favorable prognosis over a six months. Such an approach would limit the cumulative GC dose by at least 45%, thus limiting GC toxicity.

This protocol will test the hypothesis that short-course GCs in combination with rituximab are effective and safe in the induction of disease remission in a subset of patients with AAV. Close patient follow-up will insure that any patients who require courses of GCs longer than two months will receive longer therapy, if appropriate for their well-being.

II. Specific Aims

The primary aim of this pilot study is to examine whether an 8 week course of GCs in combination with rituximab is effective at inducing and maintaining disease remission through the 6-month timepoint in patients a subset of patients with AAV who have a more favorable prognosis.

III. Subject Selection

A. Inclusion and exclusion criteria

Inclusion criteria:

- Patients ages 18-85 years old
- Diagnosis of GPA or MPA according to the definitions of the Chapel Hill Consensus Conference
- New diagnosis or disease flare with a Birmingham Vasculitis Activity Score/Wegener's granulomatosis (BVAS/WG) of ≥ 3 .

Exclusion criteria:

- Renal disease in patients with PR3-ANCA as defined by any of the following:
 - Urinary red blood cell casts
 - Biopsy-proven glomerulonephritis
 - Increase in serum creatinine of $>30\%$ over baseline
- Severe renal disease in patients with MPO-ANCA as defined by both of the following:
 - Urinary red blood cell casts or biopsy-proven glomerulonephritis
 - Estimated glomerular filtration rate < 30 ml/min/1.73m²
- Diffuse alveolar hemorrhage requiring ventilatory support
- GC treatment for longer than 14 days prior to enrollment unless patient has been on a stable maintenance dose of prednisone at the time of the flare

- Daily oral cyclophosphamide within 1 month prior to enrollment
- Completed a remission induction course of cyclophosphamide or rituximab within 4 months of enrollment
- Current or past HBV infection (e.g., HBsAg positive, regardless of antibody status, HBsAg negative but anti-HBcAb positive).
- HIV infection
- History of anti-GBM disease
- Other uncontrolled disease, including drug and alcohol abuse, that may interfere with the study
- Pregnancy or breastfeeding
- History of severe allergic reactions to human or chimeric monoclonal antibodies

B. Source of subjects and recruitment methods

Subjects will be recruited via one of the following:

- New diagnosis or flare of previously diagnosed disease in patients followed in the Massachusetts General Hospital (MGH) Rheumatology or Nephrology Units.
- New diagnosis or flare of previously diagnosed disease in patients hospitalized at MGH.
- Referrals from subspecialty colleagues who are aware of our interest in AAV.

IV. Subject Enrollment

A. Methods of enrollment and procedures for obtaining informed consent.

- Drs. Stone, Miloslavsky, Unizony or Niles will discuss various treatment modalities with patients meeting the inclusion criteria. In addition to the study treatment protocol, the following treatment options will be discussed: Rituximab and conventional duration of GC therapy (6-12 months); cyclophosphamide and conventional duration of GCs, followed by azathioprine or methotrexate. Patients will be given adequate time to ask questions related to various treatment options and to discuss the study procedures in detail.
- Informed consent will be discussed with all potential study subjects by Drs. Stone, Miloslavsky, Unizony or Niles. In addition to the physicians, a nurse or coordinator will be available to answer patient's questions.
- Patients will be given up to seven days to consider treatment options.

V. Study Procedures

A. Study visits and data collection

1. Screening visit
 - a. Diagnosis of new onset AAV or flare with BVAS/WG ≥ 3 will be confirmed by a complete history and physical examination performed by one of the investigators.
 - b. Treatment options will be discussed with the patient and informed consent for study participants will be obtained by one of the investigators.
 - c. The following laboratory values will be obtained – complete blood count (CBC), complete metabolic panel (CMP), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ANCA, chronic hepatitis B infection panel, HIV antibody, B-cell flow cytometry, immunoglobulin levels (IgG, IgM and IgA), urinalysis and urine pregnancy test if applicable.
 - d. Imaging as deemed necessary by the investigator
 - e. Patients will begin GC therapy at a dose selected by the investigator or the treating physician with oral prednisone 60mg or 1mg/kg (if weight less than 60kg) or intravenous methylprednisolone, up to 1g/day for three days.
 - f. Patients will be started on omeprazole 20mg daily, trimethoprim-sulfamethoxazole one single strength tablet daily, calcium citrate 500mg twice daily and vitamin D 400 units twice daily.
 - g. Prior clinical assessment (labs) within one year can be used to determine screen eligibility.
2. Study visit 1 (no later than 14 days after the screening visit)
 - a. Treatment options will be discussed with the patient and informed consent for study participants will be obtained by one of the investigators.
 - i. All screening laboratory values must be completed
 - b. First dose of rituximab 375mg/m² administered (premedication with hydrocortisone 100mg IV, diphenhydramine 25-50mg IV or PO, acetaminophen 650mg PO)
 - c. Prednisone 60mg daily continued
 - d. Focused history and physical exam performed by one of the investigators
 - e. BVAS/WG and Vasculitis Damage Index (VDI) assessed by one of the investigators
 - f. Adverse events assessed by one of the investigators
3. Study visit 2 – one week after first study visit
 - a. Second dose of rituximab 375mg/m² administered (premedication with hydrocortisone 100mg IV, diphenhydramine 25-50mg IV or PO, acetaminophen 650mg PO)
 - b. Prednisone 60mg daily continued
4. Study visit 3 – two weeks after first study visit
 - a. Third dose of rituximab 375mg/m² administered (premedication with hydrocortisone 100mg IV, diphenhydramine 25-50mg IV or PO, acetaminophen 650mg PO)
 - b. Prednisone decreased to 40mg daily

- c. Laboratory tests – CBC, CMP, ESR, CRP, urinalysis
5. Study visit 4 – three weeks after first study visit
 - a. Final dose of rituximab 375mg/m² administered (premedication with hydrocortisone 100mg IV, diphenhydramine 25-50mg IV or PO, acetaminophen 650mg PO)
 - b. Prednisone 40mg daily continued
6. Study visit 5 – four weeks after first study visit
 - a. Patient assessed for disease response defined as:
 - i. no new disease manifestations
 - ii. no worsening of existing disease
 - iii. stable or improved BVAS/WG score
 - b. Focused history and physical exam performed by one of the investigators
 - c. Adverse events assessed by one of the investigators
 - d. Prednisone decreased to 30mg daily if disease response is achieved
 - e. Laboratory tests – CBC, CMP, ESR, CRP, ANCA, urinalysis, B-cell flow cytometry
7. Phone call – five weeks after first study visit
 - a. Phone assessment for any new or ongoing symptoms performed by one of the physicians, research nurse or study coordinator
 - b. Prednisone decreased to 20mg if no new symptoms
 - c. Schedule urgent visit if new or worsening symptoms
8. Phone call – six weeks after first study visit
 - a. Phone assessment for any new or ongoing symptoms performed by one of the physicians, research nurse or study coordinator
Prednisone decreased to 10mg if no new symptoms
 - b. Laboratory tests – BMP, ESR, CRP, urinalysis
 - c. Schedule urgent visit if new/worsening symptoms or worsening laboratories
9. Phone call – seven weeks after first study visit
 - a. Phone assessment for any new or ongoing symptoms performed by one of the physicians, research nurse or study coordinator
Prednisone decreased to 5mg if no new symptoms
 - b. Schedule urgent visit if new or worsening symptoms
10. Study visit 6 – eight weeks after first study visit
 - a. Patient assessed for partial disease remission defined as:
 - i. no new disease manifestations
 - ii. no worsening of existing disease
 - iii. BVAS/WG < 3
 - b. Adverse events assessed by one of the investigators

- c. Prednisone discontinued (or reduced to patient's stable chronic dose of prednisone in order to avoid adrenal insufficiency) if patient meets partial disease remission criteria Omeprazole discontinued
 - d. Laboratory tests – CBC, CMP, ESR, CRP, ANCA, urinalysis, B-cell flow cytometry
11. Phone call – nine weeks after first study visit
- a. Phone assessment for any new or ongoing symptoms performed by one of the physicians, research nurse or study coordinator Laboratory tests – CBC, CMP, ESR, CRP
 - b. Schedule urgent visit if new/worsening symptoms or worsening laboratories
12. Study visit 7– twelve weeks after first study visit
- a. Focused history and physical exam performed by one of the investigators
 - b. BVAS/WG assessed by one of the investigators
 - c. Adverse events assessed by one of the investigators
 - d. Laboratory tests – CBC, CMP, ESR, CRP, ANCA, urinalysis
13. Phone call – sixteen weeks after first study visit
- a. Phone assessment for any new or ongoing symptoms performed by one of the investigators
 - b. Laboratory tests – CBC, CMP, ESR, CRP, ANCA, and urinalysis
 - c. Schedule urgent visit if new/worsening symptoms or worsening laboratories
14. Study visit 8 – twenty weeks after first study visit
- a. Focused history and physical exam performed by one of the investigators
 - b. BVAS/WG assessed by one of the investigators
 - c. Adverse events assessed by one of the investigators
 - d. Laboratory tests – CBC, CMP, ESR, CRP, ANCA, urinalysis
15. Study visit 9 – twenty-four weeks after first study visit
- a. Focused history and physical exam performed by one of the investigators
 - b. BVAS/WG and VDI assessed by one of the investigators
 - c. Primary outcome measured - defined as BVAS/WG = 0 and prednisone dose = 0 (or maintained at patient's stable chronic dose of prednisone in order to avoid adrenal insufficiency) with no preceding flares.
 - d. Adverse events assessed by one of the investigators
 - e. Laboratory tests – CBC, CMP, ESR, CRP, ANCA, urinalysis, B-cell flow cytometry, immunoglobulin levels (IgG, IgM and IgA).

Following the completion of six months on protocol, subjects will be treated according to the best medical judgment of their treating physician and will continued to be followed for six additional months.

16. Study visit 10 – 9 months after first study visit
 - a. Focused history and physical exam performed by one of the investigators
 - b. BVAS/WG assessed by one of the investigators
 - c. Adverse events assessed by one of the investigators
 - d. Laboratory tests – CBC, CMP, ESR, CRP, ANCA, urinalysis, B-cell flow cytometry
17. Study visit 11 – 12 months after first study visit
 - a. Focused history and physical exam performed by one of the investigators
 - b. BVAS/WG and VDI assessed by one of the investigators
 - c. Adverse events assessed by one of the investigators
 - d. Sustained remission assessed – defined as BVAS/WG = 0, prednisone dose = 0 (or maintained at patient’s stable chronic dose of prednisone in order to avoid adrenal insufficiency) and no disease flares during the study period.
 - e. Laboratory tests – CBC, CMP, ESR, CRP, ANCA, HACA, urinalysis, B-cell flow cytometry, immunoglobulin levels (IgG, IgM and IgA)

Additional visits may be required at the discretion of the investigator.

Missed visits

- If a subject is unable to attend a scheduled visit they may reschedule within 10 days of the time specified by the protocol.
- If a subject cannot attend a scheduled visit within 10 days of the date specified by the protocol a phone call and laboratory testing may be substituted on up to two occasions over the one year study period. The phone call will include a focused history and BVAS/WG scoring.

Mechanistic study

Subjects may be asked to give a blood sample for mechanistic studies, not to exceed 40ccs at the beginning of the study, at the 6 month timepoint, at the completion of the study and during disease flares.

Reimbursement

- Subjects will be given a \$40.00 echeck for each study visit.

Treatment of flares

Limited flares - having a new occurrence or worsening of one or more minor BVAS/WG items with a total BVAS/WG score < 3.

- First limited flare - prednisone increase up to 40 mg/day for one week followed by 4 week taper (30mg, 20mg, 10mg, 5 week per week). Lower starting

prednisone dose and shorter taper can be instituted at the discretion of the investigator.

- Second limited flare - treatment according to best medical judgment of the investigator.

Severe flares – BVAS/WG ≥ 3 or experiencing one of the major BVAS/WG items.

- Patients with severe flares will be treated according to best medical judgment of the investigator.

Termination of protocol

The following pre-defined events will lead to subject's treatment according to best medical judgment:

- Two limited flares - defined as having a new occurrence or worsening of one or more minor BVAS/WG items.
- One severe flare - defined as BVAS/WG ≥ 3 or experiencing one of the major BVAS/WG items)
- Failing to achieve disease response at 4 weeks following the first rituximab infusion - defined as no new disease manifestations, no worsening of existing disease and stable or improved BVAS/WG score
- Failing to achieve partial remission at 8 weeks following the first rituximab infusion - defined as no new disease manifestations, no worsening of existing disease and BVAS/WG < 3 .

Subjects treated according to best medical judgment will continue to be followed according to a modified visit schedule of no less than once every three months for 12 months from study entry.

Data Collection

Data, including BVAS/WG scores, blood and urine test results, relevant radiology and pathology findings will be kept on data collection sheets and on Partners workstations or encrypted mobile devices using unique patient identifiers. Drs. Stone, Miloslavsky, Unizony, Niles as well as Karen Laliberte, Andrew Murphy, Katherine Cosgrove and study staff will have access to coding sheets linking patient names and their unique identifiers. The data collection sheets will be kept in a locked file cabinet in the Rheumatology Unit.

Drs. Stone and Miloslavsky will review data on the number of subjects having limited or severe flares, achieving disease response, achieving partial remission and achieving remission after the first ten patients have been followed for six months. Dr. Stone will be responsible for determining whether the research should be altered or stopped.

PI's intention is to maintain the subject files electronically through utilizing a Redcap database as well as accessing additional information from LMR. The current Redcap

project has developed CRFs for almost all of the visits, and they are labeled by visit number (Screening visit, Visits 1-11). Specific visits may have multiple CRFs depending on the protocol-specific study procedures. With the exception of the laboratory CRF, the remaining data will be entered into the Redcap system by the clinician seeing the subjects. The plan is to have no paper worksheets and the data will be entered from the LMR clinical note by the clinicians.

B. Drugs to be used

- a. Rituximab - patients will receive rituximab according to the regimen that the FDA has approved to treat AAV (375mg/m²). They will also receive hydrocortisone 100 mg, acetaminophen 650 mg, and diphenhydramine 25 mg at the time of each infusion. These medications are administered according to Rheumatology Infusion Center or the Nephrology Infusion Center protocols to decrease the likelihood of infusion reactions. Common side effects include infusion reactions, cytopenias, and infection.
- b. Glucocorticoids – prednisone will be tapered off over eight weeks from a starting dose of 60mg or 1mg/kg, whichever is lower. At the discretion of the investigators, patients can receive methylprednisolone 1g daily via intravenous infusion for three days at the onset of treatment. For patients on stable chronic doses of prednisone (4 months or greater) prior to entering the trial, prednisone will be reduced to the chronic stable dose in order to avoid adrenal insufficiency due to rapid prednisone withdrawal.
- c. Trimethoprim-sulfamethoxazole will be prescribed for prophylaxis against pneumocystis infection. Dapsone or atovaquone can be substituted for trimethoprim-sulfamethoxazole in case of allergy or at the investigator's discretion.
- d. Omeprazole will be prescribed to prevent gastrointestinal ulceration.
- e. Calcium and vitamin D will be prescribed to prevent bone loss.

Toxicity Grading Scale

All adverse events will be recorded and classified according to the most recent version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), published June 10, 2003. Adverse events will include those associated with glucocorticoid therapy, including hypertension, diabetes, osteoporosis, fractures, weight gain, adrenal insufficiency and others. Adverse events should be recorded and graded 1 to 5 according to the CTCAE grades provided below:

- Grade 1 = Mild adverse event
- Grade 2 = Moderate adverse event
- Grade 3 = Severe and undesirable adverse event
- Grade 4 = Life-threatening or disabling adverse event
- Grade 5 = Death

VI. Statistical Analysis

The following variables will be collected during the study:

- Baseline variables
 - o Age
 - o Sex
 - o Disease type (GPA or MPA)
 - o ANCA type
 - o New or relapsing disease
 - o If relapsing disease - treatment prior to flare
 - o BVAS/WG
 - o VDI
- BVAS/WG at visits 1 and 5-11
- VDI at visits 9 and 11
- Laboratory data at baseline and at visits 3, 5, 6, 7, 8, 9, 10 and 11 and after phone calls at 6,9 and 16 weeks of the study
 - o CBC
 - o CMP
 - o ESR
 - o CRP
 - o ANCA
 - o Urinalysis
 - o Flow cytometry for B-cells (measured at visits 1, 5, 9, 10, 11)
 - o HACA (measured at visits 1, 9, 11)
 - o Quantitative immunoglobulins (measured at visits 1, 9 and 11)
 - o Mechanistic studies (optional) (visit 1, 9, 11)
- Prednisone dose at each visit
- Adverse events

Study endpoints

Primary endpoint (assessed at 24 weeks) - Number of patients entering remission defined as BVAS/WG = 0 and prednisone dose = 0 (or maintained at patient's stable chronic dose of prednisone in order to avoid adrenal insufficiency).

Secondary endpoints (assessed at 24 weeks)

- Number of early treatment failures defined as patients who have new or worsening disease manifestations assessed at 4 weeks after study entry
- Number of severe flares defined as flare with BVAS/WG ≥ 3 or experiencing one of the major BVAS/WG items
- Number of limited flares defined as having a new occurrence or worsening of one or more minor BVAS/WG items
- Number of patients having a disease response
- Number of patients entering partial remission
- Number of patients entering sustained remission defined as BVAS/WG = 0, prednisone dose = 0 (or maintained at patient's stable chronic dose of prednisone in order to avoid adrenal insufficiency) and no disease flares during the study period.
- Area under the curve BVAS/WG

- Total GC dose

Statistical Methods

Continuous data will be summarized using descriptive statistics (e.g., mean, standard deviation, median, minimum, and maximum). Categorical data will be assessed using the Chi-square and the Fisher exact tests as appropriate. Descriptive statistics and two-sided 95% confidence intervals will be calculated to assist in the interpretation of efficacy outcomes.

Power Analysis

We plan to enroll a convenience sample of 20 patients for this pilot study. This is based on the number of patients that we anticipate being able to enroll in one calendar year.

VII. Risks and Discomforts

Rituximab has been FDA approved for the treatment of AAV (April, 2011).

A. Complications of peripheral intravenous line insertion

The insertion of a peripheral intravenous line is associated with a mild degree of discomfort at the insertion site for a short period of time. Small degrees of bleeding or bruising may occur at the site. Skin irritation and rarely cellulitis can result at the site of intravenous catheter insertion.

We have experienced infusion nurses who are expert in the insertion of peripheral intravenous catheters.

B. Potential side-effects of rituximab

Infusion reactions occur in a minority of patients treated with rituximab. These reactions are normally treated effectively by stopping the infusion and when the symptoms resolve, restarting the infusion at one-half the rate of the previous dose.. In addition, such reactions are often prevented by the administration of hydrocortisone (100 mg), acetaminophen (650 mg), and diphenhydramine (25 mg) before the infusion. Rituximab will be administered by an experienced infusion nurse who oversees up to two patient infusions at any given time.

Other known risks of rituximab treatment are:

Common but mild and transient side effects:

- Within 24 hours of the 1st infusion - chills, itching, hives, sneezing, swelling, throat irritation or tightness

- Headache
- Nausea
- Upper respiratory tract infections
- Joint pain

Possible serious side effects or reactions:

- Serious infusion reaction with hives, low blood pressure, breathing difficulties, irregular heartbeat and chest pain are very rare. Infusion reactions occur more commonly during the first infusion but can occur during any administration of rituximab. Medications given with the infusion can prevent them and the infusion can be stopped immediately if a reaction occurs. Resuming the infusion at half the rate after the symptoms has resolved is frequently effective at preventing further infusion reactions.
- Infections are a concern with all drugs that affect the immune system. Rituximab has been associated with reactivation of hepatitis B virus and progressive multifocal leukoencephalopathy infection, in addition to other common viral and bacterial pathogens. Rituximab may decrease immunoglobulin levels. In the event of a severe infection immunoglobulins will be checked in order to determine whether the administration of intravenous immunoglobulin is indicated.
- Skin reactions, painful sores, ulcers, blisters and peeling skin (rare).
- Decreased white blood cell counts.

We anticipate that the risk of many of the infections which patients treated with the combination of rituximab and GCs are prone to will be attenuated by the shorter GC courses prescribed in this protocol.

There may be other risks of rituximab that are currently unknown.

VIII. Potential Benefits

Benefits to participating individuals

Individual patients may benefit from effective control of their disease with decreased toxicity from GC therapy.

Benefits to society

Results of this study may elucidate the optimal dose of GCs in the treatment of severe autoimmune disease such as AAV. Decreasing administration of GCs may decrease their side effects and thus decrease the cost burden on society associated with treatment of severe autoimmune disease.

IX. Monitoring and Quality Assurance

Drs. Stone and Miloslavsky will monitor study data to ensure the safety of patients. A formal compilation of safety and efficacy data will be performed after ten patients have been enrolled in the study and followed for six months.

Specific elements related to the safety of study subjects that will be examined include:

- Deaths
- Flares
- Failure to achieve disease response, partial remission or remission.
- Hospitalizations from any cause
- Infections
- Infusion reactions
- Status of peripheral B cell pool with regard to reconstitution
- Other unexpected and serious adverse events

Specific elements of efficacy that will be examined include:

- Decrease in disease activity as assessed by the BVAS/WG score
- Ability to discontinue GCs

The study will be terminated if 60% of subjects fail the primary endpoint. This includes patients who have one severe flare, two limited flares or discontinue the study medication due to an adverse event.

Adverse event reporting guidelines:

Taking into account the nature, size, and complexity of the research protocol, the expected risks of the research, and the type of subject population being studied, an independent medical monitor has been identified to assess the ongoing safety of this study. Dr. Paul Monache, BU medical center rheumatologist, who specializes in vasculitis, will serve in this role. The Independent Medical Monitor will regularly review adverse events; reports from these reviews by the Medical Monitor should be submitted to the IRB, upon receipt. The medical monitor will review adverse events on a quarterly basis. The medical monitor will issue a written report for each quarterly review, which will include: subject study ID number for adverse events that were reviewed, and the monitor's overall determination as to whether there are any safety concerns, and if so, recommendations. This quarterly report from the medical monitor will be submitted to the IRB as an Other Event, upon receipt.

Adverse events and unanticipated problems involving risks to subjects or others will be reported to the PHRC in accordance with PHRC adverse event and unanticipated problems reporting guidelines.

X. References

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