# Plasma exchange and glucocorticoid dosing in anti-neutrophil cytoplasm antibody associated vasculitis: a randomized controlled trial. PEXIVAS

## Short title: PEXIVAS

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# 1 Protocol Synopsis

| | |
|---|---|
| Title | Plasma exchange and glucocorticoid dosing in anti-neutrophil cytoplasm antibody associated vasculitis: a randomized controlled trial. PEXIVAS |
| Short Title | PEXIVAS |
| Clinical Phase | III |
| Principal Investigators | David Jayne<br>Peter A. Merkel<br>Michael Walsh |
| Trial Sponsor | Cambridge University Hospitals NHS Foundation Trust |
| Sample Size | 700 participants |
| Accrual Period | 78 months |
| Study Duration | 90 months |
| Study Design | Multi-centre, international, open label, factorial design, randomized control trial in severe ANCA-associated vasculitis (AAV). Seven hundred participants will be randomized, 1:1, to receive adjunctive plasma exchange (PLEX) in addition to standard immunosuppressive therapy and glucocorticoids (GC) or standard immunosuppressive therapy and GC without PLEX. The same 700 patients will be randomized, 1:1, to receive reduced-dose GC taper or standard-dose GC taper. There will be a minimum duration of follow-up of 1 year. |
| Primary Study Objectives | 1. To determine the efficacy of PLEX in addition to immunosuppressive therapy and GC in reducing death and end-stage renal disease (ESRD)<br>2. To determine the non-inferiority of a reduced-dose GC regimen in reducing death and ESRD |
| Primary Outcome Measures | Composite of i) all-cause mortality or ii) End-stage renal disease |
| Secondary Objectives | For both of i) PLEX in addition to immunosuppressive therapy and GC compared to immunosuppressive therapy and GC alone; and ii) reduced-dose GC compared to standard-dose GC:<br>1. To determine the effect on disease activity<br>2. To determine the effect on mortality<br>3. To determine the effect on ESRD<br>4. To determine safety<br>5. To determine effects on health related quality of life |

| | |
|---|---|
| Secondary Outcome Measures | 1. Sustained Remission<br>2. All-cause mortality<br>3. ESRD<br>4. Serious Adverse Events<br>5. Serious infections<br>6. Medical Outcomes Survey Short Form – 36 (SF-36)<br>7. EuroQoL EQ5D Index Score |
| Exploratory Objectives | For each of i) PLEX in addition to immunosuppressive therapy and GC compared to immunosuppressive therapy and GC alone; and ii) reduced-dose of GC compared to standard-dose GC:<br>1. To determine the cost-effectiveness<br>2. To determine the effects on measures of disease-related damage<br>3. To determine the effects on long-term renal function |
| Exploratory Outcome Measures | 1. Incremental cost-effectiveness ratio<br>2. Combined Damage Assessment Index (CDA)<br>3. Estimated glomerular filtration rate (eGFR) |
| Inclusion Criteria | 1. New or previous relapsing clinical diagnosis of granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis consistent with the Chapel-Hill consensus definitions<br>AND<br>2. Positive test, at any point in the subjects's disease course, by ELISA, for proteinase 3-ANCA or myeloperoxidase-ANCA<br>AND<br>3. Severe vasculitis defined by at least one of the following:<br>a. Renal involvement with both:<br>i. Renal biopsy demonstrating focal necrotizing glomerulonephritis or active urine sediment characterized by glomerular haematuria or red cell casts and proteinuria<br>AND<br>ii. eGFR <50 ml/min/1.73 $m^2$. Patients known to have a stable eGFR <50 ml/min/1.73 $m^2$ for greater than three months prior to enrollment are NOT eligible.<br>b. Pulmonary hemorrhage due to active vasculitis defined by:<br>i. A compatible chest x-ray or CT scan (diffuse pulmonary infiltrates)<br>AND<br>ii. The absence of an alternative explanation for all pulmonary infiltrates (e.g. volume overload or pulmonary infection)<br>AND<br>iii. At least one of the following: |

1. Evidence of alveolar hemorrhage on bronchoscopic examination or increasingly bloody returns with bronchoalveolar lavage
2. Observed hemoptysis
3. Unexplained anemia (<10 g/dL) or documented drop in hemoglobin (>1 g/dL) from less than 10g/dl
4. Increased diffusing capacity of carbon dioxide

4. Provision of informed consent by patient or a surrogate decision maker. In some participating countries permission has also been granted to use deferred consent for enrolling a patient until a legal representative becomes available to consent on their behalf. Please check your national regulations for further guidance.

Exclusion Criteria

1. A diagnosis of vasculitis other than granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis
2. A positive serum test for anti-glomerular basement membrane antibody test or renal biopsy demonstrating linear glomerular immunoglobulin deposition
3. Receipt of dialysis for >21 days immediately prior to randomization or prior renal transplant
4. Age <15 years (age <18 years at centres that do not treat pediatric patients)
5. Pregnant at time of study entry
6. Treatment with >1 IV dose of cyclophosphamide and/or >14 days of oral cyclophosphamide and/or >14 days of prednisone/prednisolone (>30 mg/day) and/or >1 dose of rituximab within the 28 days immediately prior to randomization
7. A comorbidity or condition that, in the opinion of the investigator, precludes the use of cyclophosphamide/rituximab, glucocorticoids, or plasma exchange or absolutely mandates the use of plasma exchange
8. Plasma exchange in 3 months prior to randomization

Treatment Description

<u>Plasma Exchange</u>:

- Seven (7) plasma exchanges of 60 mL/kg, will be performed within 14 days after randomization.
- Plasma exchange may be provided by centrifugation or filter separation according to local practice and availability.
- Anticoagulation may be provided by heparinization or citrate according to local practice.
- Replacement fluid will consist of human serum albumin (3-5% depending on local availability). Albumin may be combined with crystalloid (e.g. saline).
- Patients with active bleeding may receive supplemental plasma to replace clotting factors according to local practice.

*Immunosuppressive and glucocorticoid therapy will be determined by the protocol for the first 12 months after trial entry*

Glucocorticoids:

- All patients will receive between 1 and 3 g of IV methylprednisolone over 1 to 3 days, then daily oral GC.
- Oral GC may consist of prednisone or prednisolone and administered through a weight-based protocol.
- All participants will receive either 50, 60 or 75 mg/day (based on weight) of oral GC for 7 days
    - Participants in the standard-dose group will continue at 50, 60 or 75 mg/day for 7 additional days and taper to between 12.5 and 20 mg/day at 3 months and 5 mg/day at 6 months.
    - Participants in the reduced-dose group will continue at 25, 30 or 40 mg/day for 7 days and taper to between 6 and 10 mg/day by 3 months and 5 mg/day by 6 months.
- All patients will receive 5 mg/day from 6 months to 12 months after randomization.

*Immunosuppressive Remission-Induction Therapy:*
To consist of either cyclophosphamide or rituximab, per preference of site investigators/patients.

Cyclophosphamide:

- Participants may be treated with either intravenous (15mg/kg/pulse) or oral (2mg/kg/day) CYC according to local preferences.
- CYC doses will be reduced for advanced age, poor baseline renal function, or cytopenias.

Rituximab:

- Participants who are prescribed rituximab will receive 4 intravenous doses of 375 mg/m² according to the following schedule:
    - Dose 1 within first 14 days of participation
    - Subsequent doses: should follow the prior dose by 7 days but this may range between 5 and 14 days due to practical considerations for arranging rituximab infusions locally.
    - All doses should be given within 42 days of enrollment in the study.
    - Note: Rituximab will not be given within the 48 hours prior to receiving a PLEX treatment.

*Immunosuppressive Remission-Maintenance Therapy:*

Azathioprine:

- Participants receiving cyclophosphamide will be transitioned to

azathioprine as maintenance immunosuppression no earlier than 3 months and no later than 6 months after starting CYC provided a remission is induced.

- Azathioprine (2 mg/kg/day) will begin immediately after the last dose of oral CYC or 7 days after the last dose of IV CYC with dose reduction for advanced age, cytopenias, or based on TPMT genetic/activity testing (if performed).
- Patients intolerant of azathioprine may use an alternative immunosuppressive agent at the discretion of the local investigator.

Prophylactic Therapies:
Infection prophylaxis such as with low-dose sulfamethoxazole-trimethoprim (i.e. one single strength tablet [480 mg total] daily or one double strength tablet [960 mg total] thrice weekly) and osteoporosis prophylaxis. The use of prophylactic therapies will be left to local practice and the discretion of local investigators.
Other Therapies:
Treatments for AAV not included in the study protocol will not be allowed as adjunctive therapies (e.g. intravenous immunoglobulin, anti-TNF alpha therapy, high-dose sulfamethoxazole-trimethoprim or other immunomodulatory treatments).

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| Sample Size | 700 patients. |
| Primary Analyses | ▪ The primary analysis will be of time to the composite endpoint of all-cause mortality or end-stage renal disease using log-rank test and Cox proportional hazards models, with survival curves generated using the Kaplan-Meier method. |
| Secondary Analyses | 1. Sustained remission will be analyzed by comparing the difference in proportions (and associated 95% confidence intervals) of patients that achieve a sustained remission in each treatment group.<br>2. Death and ESRD will be analyzed separately in an identical manner to the composite primary endpoint.<br>3. Safety analyses will be performed by assessing the 95% confidence interval of the rate difference of serious adverse events between treatment groups.<br>4. The rate of serious infections will be assessing the 95% confidence interval of the rate difference between the treatment groups both for the first year and at trial end..<br>5. Health-related quality of life using the SF-36 Physical Composite, Mental Composite and EQ-5D Index Score will be assessed by constructing repeated measures models. |
| Safety and Monitoring | Adverse events will be assessed at each study visit.<br>Important expected adverse events will be actively surveyed (i.e. must be assessed to complete the case report form). |

An independent Data Monitoring Committee (DMC)/Data Safety Monitoring Board (DSMB) will review adverse event data annually or more frequently if requested by the DMC/DSMB.

## 2 Glossary of Terms

| | |
|---|---|
| Common Closing Date | 12 months after the last patient is enrolled |
| End Stage Renal Disease | The requirement of a renal replacement therapy (hemodialysis or peritoneal dialysis) for at least 12 consecutive weeks or the receipt of a renal transplantation. |
| First Relapse | The first major or minor relapse. |
| Major Relapse | New or recurrent disease activity that occurs after remission has been initially induced and affects a major item of the BVAS/WG (gangrene, scleritis, retinal exudates/haemorrhage, sensorineural deafness, mesenteric ischemia, pulmonary haemorrhage, respiratory failure, red blood cell urinary casts, rise in creatinine >30% or fall in creatinine clearance >25%, meningitis, spinal cord lesion, stroke, cranial nerve palsy, sensory peripheral neuropathy, mononeuritis multiplex, or other manifestation deemed major by the investigator). |
| Minor Relapse | New or recurrent disease activity that occurs after remission has been initially induced but does not constitute a major relapse/does not affect a major item of the BVAS/WG. |
| Remission | The absence of disease activity (BVAS/WG= 0) |
| Resistant Disease | Active AAV that does not improve or worsens despite commencing the allocated induction of remission therapy. |
| Sustained remission | Remission that is obtained within 6 months of randomization and lasts without a first relapse until at least 12 months after randomization. |

## 3 Abbreviations

| | |
|---|---|
| AAV | ANCA-associated vasculitis |
| ANCA | Anti-neutrophil cytoplasm antibody |
| AZA | Azathioprine |
| BCTU | Birmingham Clinical Trials Unit |
| BVAS/WG | Birmingham Vasculitis Activity Score/Wegener's Granulomatosis version |
| CDA | Combined Damage Assessment Index |
| CYC | Cyclophosphamide |
| DMC | Data Monitoring Committee |
| DSMB | Data Safety Monitoring Board |
| eGFR | Estimated glomerular filtration rate |
| EQ5D | EuroQoL 5D Quality of Life Questionnaire |
| ESRD | End-stage renal disease |
| FDA | Food and Drug Administration |
| GC | Glucocorticoids |
| GPA | Granulomatosis with Polyangiitis (Wegener's) |
| MDRD | Modification of Diet in Renal Disease |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MPA | Microscopic Polyangiitis |
| NIAMS | National Institute of Arthritis and Musculoskeletal and Skin Diseases |
| NIH | National Institutes of Health |
| NIHR | National Institutes for Health Research |
| PLEX | Plasma Exchange |
| TMC | Trial Management Committee |
| TPMT | Thiopurine Methyltransferase |
| TSC | Trial Steering Committee |
| SAE | Serious Adverse Event |
| SF-36 | Medical Outcomes Survey Short Form 36 Questionnaire |
| SUSAR | Suspected unexpected Serious Adverse Reaction |

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# 5 Background and Rationale

Granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) are syndromes of primary systemic vasculitis associated with anti-neutrophil cytoplasm antibodies (ANCA). Together, these syndromes are grouped as ANCA-associated systemic vasculitis (AAV). The prevalence of AAV is estimated at 14 - 30 patients per 100 000 in England (1). Left untreated, AAV has a universally poor prognosis with mortality approaching 100% within 5 years (2). The introduction of treatment regimens based on cyclophosphamide (CYC) and glucocorticoids (GC) have transformed AAV from a rapidly fatal disease to one of chronic morbidity and reduced survival often preceded by end-stage renal disease (ESRD).

Plasma exchange (PLEX), a method of rapidly removing potentially pathogenic ANCA and other mediators of inflammation and coagulation, has shown promise as an adjunctive therapy in AAV to improve early disease control and improve rates of renal recovery in severe disease. GC are a standard of care in the treatment of AAV. High doses of GC early in disease although undeniably reduce disease activity due to their anti-inflammatory and immunosuppressive properties also increase the risk of infection particularly in the elderly and in the presence of uremia. There is no randomized trial data to guide GC dosing.

There is a need for therapies with reduced toxicity while improving disease control. Defining the role of therapies that are already in use but that are invasive, expensive, but unproven is a priority in AAV research. PEXIVAS is a randomized controlled trial to test two interventions in a two-by-two factorial design (standard care and PLEX compared to standard care alone and a standard-dose GC compared to a low dose GC regimen) to address these issues.

## 5.1 Target Population

Current standard treatment regimens still have poor outcomes. Unselected cohorts now demonstrate 5 year renal survival (defined as the composite of ESRD or death) of 60 to 70% (3;4). In patients with vital organ threatening disease (e.g. kidneys or lungs), renal survival is worse. Long-term follow-up data from three recently completed RCTs by the European Vasculitis Study Group (EUVAS) with 285 patients with an estimated glomerular filtration rate (eGFR) of less than 50 ml/min/1.73 $m^2$ demonstrated 5 year ESRD-free survival was only 54% and the median time to renal failure or death was 6 years despite the exclusion of patients with lung hemorrhage (Figure 1). In the subgroup of patients with a creatinine of less than 500, a group traditionally thought to have a favorable prognosis, 33% died or developed ESRD by 5 years (Figure 2). Additionally, patients with lung hemorrhage, who were excluded from these studies, have a mortality of up to 50% in the first year.

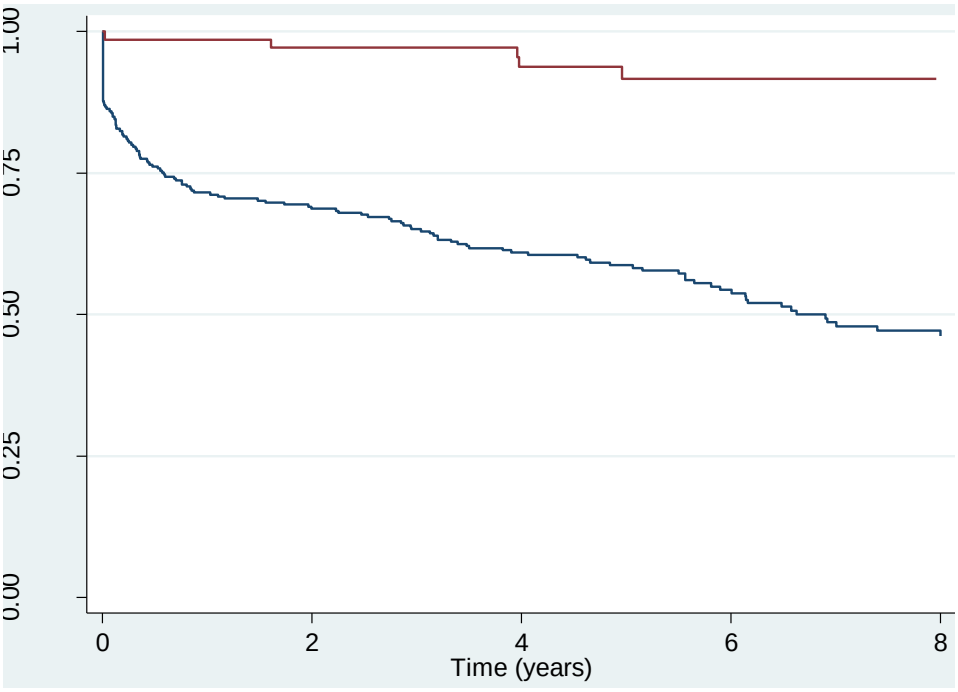


**Figure 1** Differences in long-term renal survival (end-stage renal disease or death) on the basis of estimated glomerular filtration (eGFR) for patients with ANCA-associated vasculitis enrolled in three randomized trials. Blue line represents patients with an eGFR of ≤ 50 ml/min/1.73 $m^2$; red line represents patients with an eGFR of >50 ml/min/1.73 $m^2$.

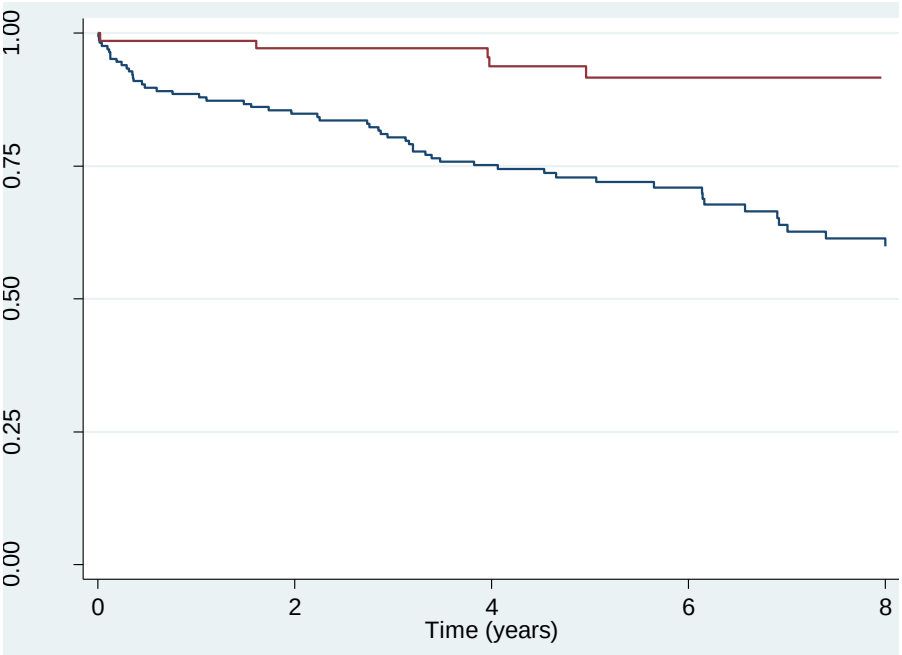


**Figure 2** Differences in long-term renal survival (end-stage renal disease or death) on the basis of estimated glomerular filtration (eGFR) for patients with ANCA-associated vasculitis enrolled in two randomized trials with baseline creatinines < 500 µmol/L. Blue line represents patients with an eGFR of ≤ 50 ml/min/1.73 $m^2$; red line represents patients with an eGFR of >50 ml/min/1.73 $m^2$.

Poor outcomes in AAV are attributed both to ineffective therapies and complications of standard treatments, CYC and GC. Approximately 20% of patients either do not have adequate disease control or are intolerant of their induction of remission treatment (5-7). An additional 50% of patients will have relapsing AAV over the subsequent five years. Inadequate disease control is associated with increased immunosuppressive medication and thus increased risk for treatment related toxicity and progressive organ scarring and death. Additionally, between 25 and 50% of patients with severe AAV experience a severe infection within the first 12 months of treatment and the most frequently cited causes of death are infection or uncontrolled vasculitis (8;9). Treatment regimens that minimize toxicity and infections while providing adequate disease control are therefore needed.

## 5.2 Plasma Exchange for Treatment of ANCA-Associated Vasculitis

PLEX removes potentially pathogenic antibodies as well as mediators of coagulation and inflammation from the circulation and has been advocated as a method of rapidly controlling AAV. Early studies of PLEX in rapidly progressive glomerulonephritis due predominantly to AAV have had mixed results (10-12). These studies had heterogeneous treatment regimens, small sample sizes, and short follow-up periods.

MEPEX examined the effect of PLEX on renal recovery for patients with renal failure due to AAV (8). This trial compared PLEX to IV methylprednisolone as an addition to standard therapy in 137 incident patients with severe AAV manifested by a creatinine >500 μmol/L or dialysis dependency at presentation and demonstrated an absolute reduction in the development of ESRD by 24% (95% CI 6.5 – 41%) after 12 months for patients treated with PLEX. There was no demonstrable difference in mortality at 12 months between those treated with PLEX compared to IV methylprednisolone (mortality of 25% in both groups). Long-term results from MEPEX, however, did not demonstrate a statistically significant difference between the treatment groups in terms of ESRD or death (p=0.57) (Figure 3).

The role of PLEX in patients with less severe renal dysfunction at the time of presentation is even less clear. Exploratory work from Jayne et al found patients with a renal biopsy demonstrating active lesions were the most likely to have a benefit from PLEX. In patients who do not have advanced, chronic renal injuries, the rapid disease control afforded by PLEX may prevent renal (or other vital organ) scarring and thus the cascade of glomerulosclerosis and hyperfiltration that perpetuates renal injury.

PLEX is also widely used for patients with lung hemorrhage due to AAV. This practice comes from cohort data in AAV and experience with anti-glomerular basement membrane disease but has never been rigorously tested and in contemporary cohort data appears effective only in selected subgroups of patients with lung hemorrhage (13). However, PLEX has the potential to exacerbate haemorrhage through removal of clotting factors and increase the risk of infection through antibody removal. Its use in this indication demands critical appraisal.

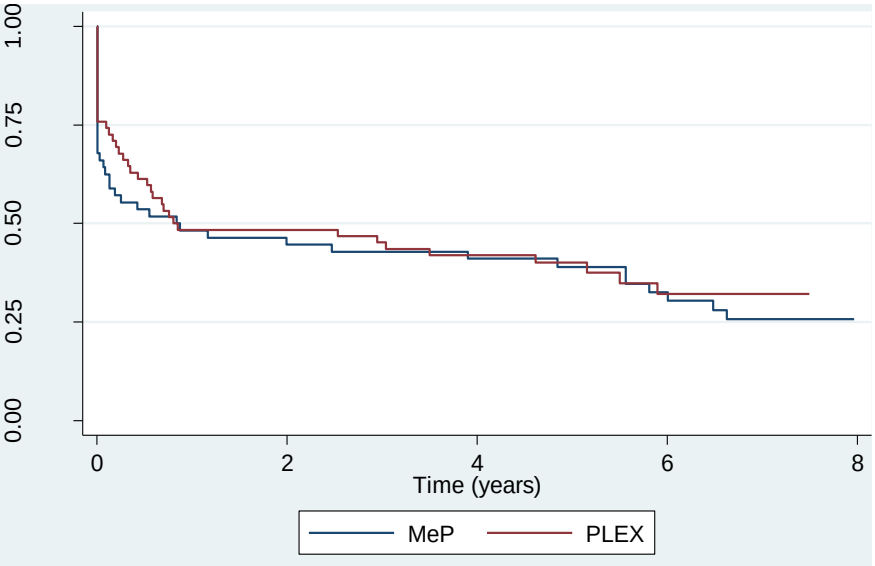


**Figure 3** Results of long-term follow-up of the MEPEX study. Renal survival is defined as the composite of end-stage renal disease or all-cause mortality.

A systematic review of PLEX in AAV identified nine randomized studies. The study populations were skewed towards severe renal dysfunction and often included diseases other than AAV. A meta-analysis of the nine trials that reported death and ESRD outcomes showed a benefit at reducing dialysis dependency (relative risk [RR] 0.64; 95% confidence interval [CI] 0.47 to 0.88) but no benefit at reducing mortality (RR 1.01; 95% CI 0.71 to 1.43). When considering the composite endpoint of death or dialysis the relative risk was 0.81 (95% CI 0.66 to 1.00) (Figure 4).

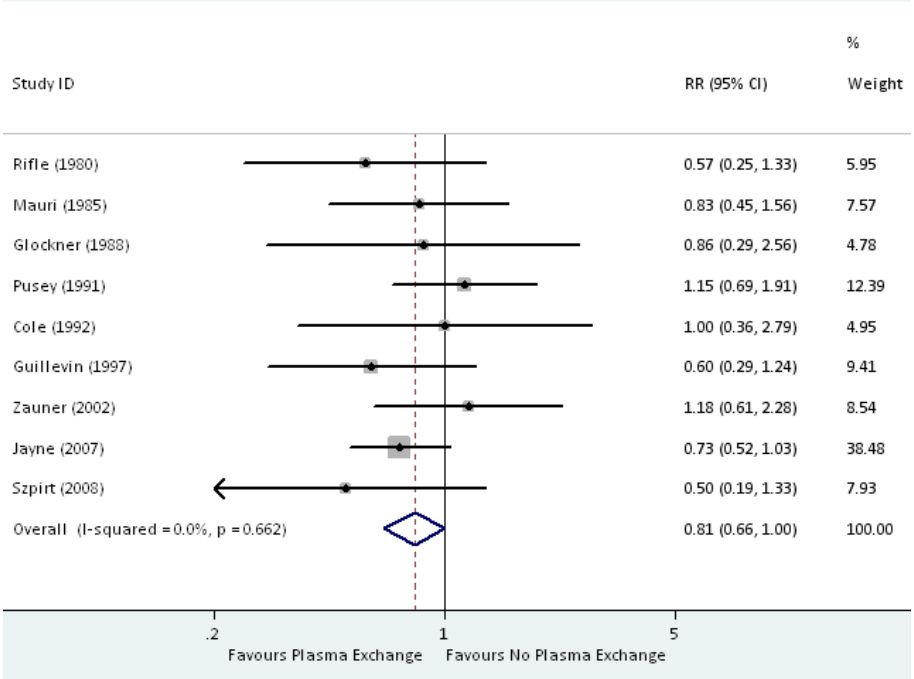

**Figure 4** Meta-analysis 9 studies including 387 patients examining the effect of adjunctive plasma exchange on the endpoint of end-stage renal disease or death in patients with rapidly progressive glomerulonephritis.

### 5.3 The treatment of ANCA-Associated Vasculitis with Glucocorticoids

High dose oral GC are the standard of care for the treatment of AAV on the basis of cohort data prior to the widespread use of cytotoxic medications and strategies for earlier diagnosis with ANCA testing. There is a complex relationship between GC dose and its effects on the immune system as an immunosuppressive versus an anti-inflammatory (14). There is also an increasing trend to reduce GC doses to mitigate their toxicity while maintaining efficacy, a trend supported by laboratory evidence of a ceiling effect of GC dosing with respect to anti-inflammatory properties (15). When combined with cytotoxic medications, high dose GC may significantly increase treatment related toxicity while adding little to therapeutic efficacy.

Infections in AAV are most common in the first two months of treatment when GC doses are highest. Although this relationship is confounded by disease activity and co-treatment with CYC, it is important to note that infection rates fall in parallel with decreasing GC dose despite the maintenance of constant immunosuppression. Dose dependent increases in infections are also observed in rheumatoid arthritis and lupus nephritis (16;17). Furthermore, high cumulative doses of GC are associated with osteoporosis, infections, cardiovascular disease and gastrointestinal bleeding (18). Despite the association between higher GC doses and adverse events and despite their widespread use, there is a paucity of literature to guide the optimal exploitation of GC in AAV.

## 6 Trial Objectives

### 6.1 Primary Objectives

1. To determine the efficacy of PLEX in addition to immunosuppressive therapy and glucocorticoids with respect to death and end-stage renal disease (ESRD)
2. To determine whether a reduced-dose glucocorticoids regimen is non-inferior to a standard-dose regimen with respect to death and ESRD

### 6.2 Secondary Objectives

Secondary objective are limited to those of direct relevance to the assessment of the efficacy and safety of the investigational treatments.
For both of PLEX in addition to immunosuppressive therapy and glucocorticoids compared to immunosuppressive therapy and glucocorticoids alone and for a reduced-dose of glucocorticoids compared to a standard-dose of glucocorticoids:

1. To determine the effect on disease activity
2. To determine the effect on death
3. To determine the effect on ESRD
4. To determine safety
5. To determine effects on serious infections
6. To determine effects on health related quality of life

### 6.3 Exploratory Objectives

For each of PLEX in addition to immunosuppressive therapy and glucocorticoids compared to immunosuppressive therapy and glucocorticoids alone and for a reduced-dose of glucocorticoids compared to a standard-dose of glucocorticoids:

1. To determine the cost effectiveness
2. To determine the effects on measures of disease related damage
3. To determine the effects on long term renal function

## 7 Trial Design

### 7.1 Overview

This trial will randomize patients with AAV in a two-by-two factorial design. Randomization to each intervention will be in a one-to-one ratio stratified by the other intervention. Patients will be randomized to receive either adjunctive PLEX or no PLEX and randomized to receive either a standard GC dose or a low GC dose. All patients will receive standard immunosuppressive induction therapy. The primary outcome of the trial will be the composite endpoint of all-cause mortality or end-stage renal disease.

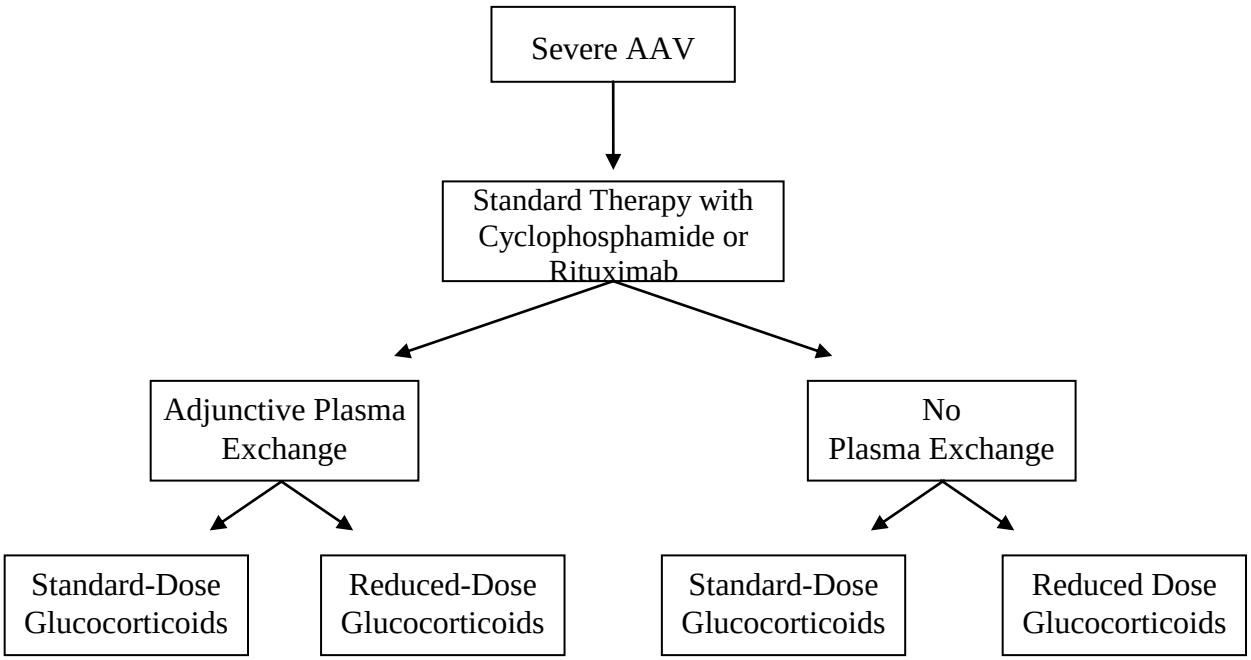


**Figure 5** General schema of randomization**.**

## 7.2 Number of Centres

PEXIVAS will occur in multiple centres internationally including Europe, North America and Australia/New Zealand. Over 90 centres are planned to recruit patients.

## 7.3 Number of Participants

This study will aim to recruit 700 patients with AAV over six and half years (6.5) years.

## 7.4 Methods to Protect Against Bias

Participants will be allocated to the interventions in a one-to-one ratio by a central randomization facility utilizing a computerized minimization algorithm. The algorithm will not be made available to investigators. 350 patients will receive PLEX and be compared to 350 patients that do not. 350 patients will receive reduced-dose GC and be compared to 350 patients that receive standard-dose GC. Allocation will follow a minimisation scheme (see 7.13.3) based on the following prognostic factors in AAV: severity of renal disease at presentation (requiring dialysis or creatinine ≥ 500 µmol/L vs. <500 µmol/L), age (<60, ≥ 60 years old), ANCA subtype (PR3-ANCA vs. MPO-ANCA), severity of lung hemorrhage (no hemorrhage, lung hemorrhage with an oxygen saturation of ≤85% on room air or ventilated, or lung hemorrhage with an oxygen saturation of >85% on room air), and planned induction immunosuppressive therapy to be used (oral CYC vs. intravenous CYC vs. rituximab).

PLEX is an invasive procedure requiring the placement of a large central venous catheter and the use of a large, complex device with additional monitoring and nursing care. As such, it is not feasible to blind either patients or treating physicians to this treatment allocation. There is the potential for treating physicians to alter their treatment on the basis of knowing whether the patient will receive PLEX. This will partially be controlled by randomly determining their GC regimen. Although CYC dosing will be protocol driven, the route of administration will not. The

route of CYC administration, determined before randomization, will therefore be used as a stratification variable thus removing some potential for confounding (see 7.13.3 below).

## 7.5 Study Duration

Each patient will be followed until study close with a minimum duration of follow-up of 1 year. Patient recruitment is anticipated to require 6.5 years. Therefore, the maximum duration of follow-up is 7.5 years. Patients will be followed more frequently when they begin the trial when the interventions are most intense and treatment is designed to induce remission of disease (Induction of Remission Period) and follow-up will be less intense after this period (Maintenance of Remission Period). The patient follow-up schedule is provided below (Table 4).

## 7.6 Trial Endpoints

### 7.6.1 Primary Endpoint

The primary endpoint for this trial is a composite of all-cause mortality or end-stage renal disease. End-stage renal disease is defined as the requirement of a renal replacement therapy (hemodialysis or peritoneal dialysis) for at least 12 consecutive weeks or the receipt of a renal transplantation. Endpoints will be ascertained at study assessments. In the event a patient does not attend an assessment, investigators will attempt to contact any or all of the following: (in order) the patient, the patient's family physician/general practitioner, the patient's next of kin, and the patient's listed contacts in order to ascertain their endpoint status. In countries with vital status registries, we will use the registry to ascertain missing patient's endpoint status.

### 7.6.2 Secondary Endpoints

The secondary objectives will be assessed using the following outcome measures:

- Sustained remission (remission that occurs before 6 months after randomization and lasts without a first relapse until at least 12 months after randomization)
- All-cause mortality
- End stage renal disease (ESRD) as described above
- Serious adverse events defined as any medical occurrence that results in permanent disability, hospitalization or the prolongation of a hospitalization, is life threatening or results in death (Section 8.1.4).
- Serious infections defined as an infectious syndrome that requires intravenous antibiotics or hospitalization for treatment.
- Medical Outcomes Survey Short Form 36 (SF-36) Physical Composite Score and Mental Composite Score.
- EuroQoL EQ5D Index score.

### 7.6.3 Tertiary Endpoints

The tertiary objectives will be assessed using the following outcome measures:

- Estimated glomerular filtration rate (Modification of Diet in Renal Disease four variable formula)
- Combined Damage Index
- Cost-Effectiveness Ratios

## 7.7 Treatments

### 7.7.1 Adjunctive Plasma Exchange Induction Therapy

PLEX therapy will only be prescribed in addition to standard induction therapy. PLEX will consist of 7 exchanges within 14 days of randomization, of at least 60 ml/kg (based on actual body weight) per session using albumin (3% to 5% depending on local availability, with or without crystalloid) as a replacement solution. The minimum replacement solution volume is 3000 mL. Intravenous immunoglobulin should not be used after PLEX.

The following parameters may be determined according to local practice: 1) PLEX may be performed by centrifugation or filter separation technique, double filtration apheresis (DFA) is not permitted 2) Anticoagulation may be provided by citrate or by heparin but it is suggested that in patients with active bleeding regional citrate anticoagulation be utilized, 3) PLEX may be performed via a central venous catheter if patient is deemed unsuitable for peripheral venous access, the latter is strongly recommended, and 4) monitoring of coagulation parameters or immunoglobulin levels, and 5) PLEX dose may be reduced for PLEX related complications according to local best medical practice and indication and dose alteration noted for future analysis.

#### 7.7.1.1 Patients with Bleeding Risks

Renal biopsy the day of PLEX should be avoided, to minimize the risk of bleeding from dilutional coagulopathy.

Local practice should be followed for patients with active bleeding including patients with known pulmonary hemorrhage or a bleeding episode from any source within the 24 hours prior to PLEX treatment. This may include fresh frozen plasma at the end of the exchange. This information will be recorded in the case report form.

#### 7.7.1.2 Additional Plasma Exchange Treatments

Patients will not receive additional PLEX treatments for ongoing signs or symptoms of AAV (unless they imminently threaten vital organ function – see Major Relapses section 7.9), serological markers of disease (e.g. elevated ANCA titres), elevated markers of inflammation, or histologic evidence of disease activity. Any PLEX treatments considered outside of the treatment protocol should be discussed with the trial medical monitor and the details must be recorded in the patient's trial case report form.

### 7.7.2 Glucocorticoids Therapy

#### 7.7.2.1 Patients Who Have Not Received Any Glucocorticoid Therapy Prior To Randomization

GC therapy shall commence with intravenous (IV) methylprednisolone irrespective of the GC group the patient is allocated to. IV methylprednisolone shall be given as three daily pulse doses (minimum 1g maximum 3g, total dose). Each pulse dose may be between 0.5 g and 1 g at the local investigators discretion. The day following the last IV methylprednisolone dose, patients will commence the randomized oral GC regimen (see 7.7.2.5 below).

#### 7.7.2.2. Patients Who Have Received <3 g IV Methylprednisolone Within 14 days Prior To Randomization

IV methylprednisolone administered within 14 days prior to randomization will contribute to the maximum allowable dose of 3g. If <3 g of IV methylprednisolone were given within 14 days prior to randomization, participants may receive additional IV methylprednisolone over 3 days after randomization to reach a minimum of 1 g and a maximum of 3 g (including all IV methylprednisolone given within 14 days prior to randomization). The day following the last IV methylprednisolone dose, patients will commence the randomized oral GC regimen (see 7.7.2.5 below).

#### 7.7.2.3. Patients Who Have Received Oral GC But No IV Methylprednisolone Within 14 Days Prior to Randomization

Oral GC given prior to randomization do not impact on the protocol GC regimen in terms of either IV methylprednisolone or oral GC. These patients should be treated as if they had not received any GC prior to randomization (see 7.7.2.1 above).

#### 7.7.2.4 Patients Who Have Received ≥3 g Of IV Methylprednisolone Within 14 Days Prior to Randomization

Patients that have received ≥3 g IV methylprednisolone within 14 days prior to randomization should begin the oral GC regimen according to their randomized group within 24 hours of randomization (see 7.7.2.5 below)

#### 7.7.2.5. Randomized Oral GC Therapy

Oral GC therapy shall commence according to previously received IV methylprednisolone as detailed in sections 7.7.2.1 through 7.7.2.4 above. Oral GC therapy will consist of non-enteric coated prednisone or prednisolone at equivalent mg to mg doses. Dosing will depend on patient weight with three possible weight categories. All oral GC will be given as a single daily dose. Patients intolerant of oral medications or for whom oral medications are contraindicated may be given an equivalent daily IV dose. Pre-printed prescriptions for oral GC therapy will be provided for each patient in the trial after randomization to ensure adherence to the allocated GC regimen. The standard-dose regimen and reduced-dose regimen are summarized in Table 1. The reduced-dose regimen will expose patients to approximately 50% of the standard oral dose over the first 3 months and 53% over the first 6 months of treatment. Oral GC therapy will continue at a dose of 5 mg/day until at least week 52 of the study after which GC therapy will revert to local practice. Alternate day dosing regimens (i.e. those that use two different doses on alternate days) may be used to achieve the appropriate average daily dose required by the protocol but differences in alternative day doses may not be >5 mg. For example, a dose of 12.5 mg/day may be achieved by alternating daily doses of 15 mg/day and 10 mg/day.

Table 1 **Dosing for oral Glucocorticoids in the standard and reduced-dose limbs from trial start**

| Week | Standard | | | Reduced-dose | | |
|---|---|---|---|---|---|---|
| | <50 kg | 50-75 kg | >75 kg | <50 kg | 50-75 kg | >75 kg |
| | pulse | pulse | pulse | Pulse | pulse | pulse |
| 1 | 50 | 60 | 75 | 50 | 60 | 75 |
| 2 | 50 | 60 | 75 | 25 | 30 | 40 |
| 3-4 | 40 | 50 | 60 | 20 | 25 | 30 |
| 5-6 | 30 | 40 | 50 | 15 | 20 | 25 |
| 7-8 | 25 | 30 | 40 | 12.5 | 15 | 20 |
| 9-10 | 20 | 25 | 30 | 10 | 12.5 | 15 |
| 11-12 | 15 | 20 | 25 | 7.5 | 10 | 12.5 |
| 13-14 | 12.5 | 15 | 20 | 6 | 7.5 | 10 |
| 15-16 | 10 | 10 | 15 | 5 | 5 | 7.5 |
| 17-18 | 10 | 10 | 15 | 5 | 5 | 7.5 |
| 19-20 | 7.5 | 7.5 | 10 | 5 | 5 | 5 |
| 21-22 | 7.5 | 7.5 | 7.5 | 5 | 5 | 5 |
| 23-52 | 5 | 5 | 5 | 5 | 5 | 5 |
| >52 | Investigators' Local Practice | | | Investigators' Local Practice | | |

### 7.7.3 Cyclophosphamide Remission-Induction Immunosuppressive Therapy

Standard induction therapy with CYC will be prescribed for at least 13 weeks and no more than 26 weeks. As the experience of using either oral or intra-venous routes of administration varies between centres and there is no apparent difference in efficacy or safety, the study protocol will allow the use of either oral or IV CYC. The CYC regimens will be identical for all treatment groups.

A starting dose of 15 mg/kg/pulse will be used for pulse CYC (maximum 1.2 g/dose) or 2 mg/kg/day for oral CYC (maximum 200 mg/day) with reductions made for age and renal function in each group according to previous trials conducted in Europe. Oral CYC will be administered daily with the recommendation for morning administration of full dose, if tolerated. Pulse CYC will be administered IV at a frequency of every two weeks for the first 3 doses then every three weeks thereafter (Table 2). Modifications to dose and frequency will be made in the case of leucopenia.

For patients undergoing PLEX, PLEX will not occur for at least 24 hours following an IV dose of CYC.

**Table 2.** Pulse **i**ntravenous cyclophosphamide schedule. Doses may be modified for age and renal function. After week 13, patients in remission may be transitioned to remission-maintenance therapy.

| Time (weeks) | Pulse number | Dose |
|---|---|---|
| 0 | 1 | 15 mg/kg |
| 2 | 2 | 15 mg/kg |
| 4 | 3 | 15 mg/kg |
| 7 | 4 | 15 mg/kg |
| 10 | 5 | 15 mg/kg |
| 13 | 6 | 15 mg/kg |
| 16 | 7 | 15 mg/kg |
| 19 | 8 | 15 mg/kg |
| 22 | 9 | 15 mg/kg |
| 25 | 10 | 15 mg/kg |

For patients receiving PLEX and daily CYC (oral or IV), on days when PLEX is performed, CYC will be given following PLEX. PLEX will not be performed for at least 12 hours following a dose of oral CYC.

Full (complete) blood counts will be performed according to local protocol but the following minimum is recommended: patients receiving oral CYC should have their blood count monitored weekly for the first four weeks and weekly for four weeks after any dose adjustment and every other week thereafter. Patients receiving pulse CYC should have their blood count monitored 10 to 14 days after each dose and within 1 day prior to each dose.

Concomitant use of mesna is optional and left to the discretion of the investigator and local practice.

#### 7.7.3.1 Dosage Modifications

##### 7.7.3.1.1 Renal Function and Age

Starting doses of CYC should be adjusted for advanced age or reduced renal function. Renal function may change over the course of the trial and medication dosages may be adjusted to reflect these changes (Table 3.)

##### 7.7.3.1.2 Leucopenia

Oral cyclophosphamide

Oral CYC should be held if the total WBC count is $<4x10^9$/L. Oral CYC may be restarted at a dose at 25 mg/day less than previous once the WBC count is $>4x10^9$ on two consecutive tests or $>5x10^9$ on at least 1 test. After an episode of leucopenia, WBC counts should be monitored at least weekly for at least four weeks.

In the case of severe (WBC < $1x10^9$/L) or prolonged (< $4x10^9$/L for >2 weeks) leucopenia, oral CYC should be restarted at a dose at least 50 mg/day lower than the previous dose once the weekly WBC count permits. In cases of severe leucopenia, consideration should also be given to granulocyte-colony stimulating factor (G-CSF), fungal prophylaxis, and other precautions for patients with severe leucopenia.

Patients with a declining WBC count but no overt leucopenia (i.e. WBC count <$6x10^9$ and at least $2x10^9$/L lower than previous) should have their WBC count rechecked within 1 week and have their oral CYC reduced by at least 25 mg/day if the WBC count continues to fall.

Pulse cyclophosphamide

The WBC count should be determined within 1 day prior to an IV pulse CYC. If the WBC count is <$4x10^9$/L, the CYC dose should be postponed until the WBC count is >$4x10^9$/L and the dose should be reduced to 75% of the planned dose (planned dose x 0.75).

The WBC count nadir should also be determined 10 to 14 days after the pulse dose is given. If the nadir is <$3x10^9$/L, the next pulse should be reduced even if the next pre-dose WBC count is >$4x10^9$/L. For a nadir <$2x10^9$/L, the next dose should be 60% of the previous dose (previous dose x 0.6). For a nadir of 2-$3x10^9$/L, the next dose should be 80% of the previous dose (previous dose x 0.8).

#### 7.7.3.1.3 Other Dose Modifications

Similar dose reductions to those made for leucopenia may be made for thrombocytopenia and anemia at the investigator's discretion. Dose alterations should also be made in the event of infectious complications.

**Table 3.** Oral and intravenous cyclophosphamide dose adjustments (mg/kg) for age and renal impairment. NOTE: dose reductions for renal impairment should reflect renal function at the time the dose is given rather than baseline renal function.

| | Oral Cyclophosphamide eGFR (ml/min/1.73 $m^2$) | | IV Cyclophosphamide eGFR (ml/min/1.73 $m^2$) | |
|---|---|---|---|---|
| Age | >30 | ≤30 | >30 | ≤30 |
| <60 | 2 | 1.5 | 15 | 12.5 |
| 60-70 | 1.5 | 1.25 | 12.5 | 10 |
| >70 | 1.25 | 1 | 10 | 7.5 |

### 7.7.4 Rituximab Remission-Induction Therapy

Rituximab may be prescribed to patients as induction remission therapy. Rituximab will be prescribed as 4 intravenous doses of 375 mg/m² according to the following schedule:

1. Dose 1 within first 14 days of participation
2. Subsequent doses should occur 7 days after the previous dose. Doses may, however, occur 5 to 14 days to accommodate practical considerations of administering rituximab and to accommodate plasma exchange. All doses must be given within 42 days of the

first dose. PLEX should not be given within the first 48 hours after administering rituximab.

Prophylaxis against infusion reactions must be given as 100 mg of intravenous hydrocortisone or equivalent with or without an anti-histamine agent immediately preceding the first rituximab infusion, and local guidelines should be followed before subsequent infusions of rituximab.

*The use of rituximab will not be allowed in Germany for this trial.*

### 7.7.5 Remission-Maintenance Immunosuppressive Therapy

Patients who have completed at least 13 weeks of CYC treatment and achieved a clinical remission of disease will be converted to maintenance therapy. A clinical remission is defined as the absence of disease activity that causes symptoms or signs of active vasculitis and has a BVAS/WG of 0. Symptoms or signs of disease that are due to the effects of scarring or damage caused by vasculitis or are a side-effect of therapy are not considered active disease (e.g. isolated persistent proteinuria or some cases of isolated microscopic hematuria or healing lung cavitations). Patients will remain on CYC therapy for no longer than 26 weeks.

Azathioprine

Maintenance therapy consists of azathioprine at a target dose of 2 mg/kg/day (rounded to the nearest 25 mg/day) and will begin immediately after the last dose of oral CYC or 7 days after the last dose of IV CYC. Patients intolerant of azathioprine will be permitted to be maintained on either a lower dose or on an alternative agent such as methotrexate or mycophenolate mofetil at their physician's discretion. TPMT activity or polymorphism assessments may be performed according to local availability and practice. Bone marrow and hepatotoxicity should be assessed according to local practice but as a minimum we suggest checking full blood counts and aminotransferases every two weeks for the first month of azathioprine therapy and then every two months for the first year of therapy and every three months thereafter.

#### 7.7.5.1 Azathioprine Dosage Modifications

The starting dose of azathioprine may be reduced to 1.5 mg/kg/day in patients >60 years old and to 1 mg/kg/day in patients >75 years old.

Patients with a WBC count $<4x10^9$/L should have their azathioprine temporarily held and have their WBC count checked weekly. Once the WBC count is $>4x10^9$/L, azathioprine should be restarted at a dose of at least 25 mg/day less than the previous dose with continued weekly monitoring for at least one month.

Patients with a declining WBC count but no overt leucopenia (i.e. WBC count $<6x10^9$ and at least $2x10^9$/L lower than previous) should have their WBC count rechecked within 1 week and have their oral azathioprine reduced by at least 25 mg/day if the WBC count continues to fall.

## 7.8 Guidelines for the Treatment of Resistant Disease

Resistant disease is active AAV that does not improve or worsens despite administration of the allocated induction of remission therapy.

For failure to improve or worsening of nephritis, lung hemorrhage, or other major organ threatening disease (neurological, gastrointestinal, cardiac, eye) within the first two weeks from

entry, we recommend a repeated course of IV methyl prednisolone (1-3g total dose) or high dose oral prednisone/prednisolone (1 mg/kg for 1 week) according to local practice. Oral prednisone/prednisolone dosing should return to the allocated tapering regimen at that regimen's starting dose (i.e. restart tapering regimen). Consideration of other therapies must be discussed with the medical monitor.

### 7.9 Guidelines for the Treatment of Major Relapses

A major relapse is new or worsened disease activity that occurs after remission has been initially induced and affects a major item of the BVAS/WG. New or worsening disease activity which occurs while the patient is on ≥20 mg/day of prednisone is considered resistant disease (Section 7.8).

For patients who received cyclophosphamide at the start of the study, major relapses may be treated with the reintroduction of cyclophosphamide (if it occurs during the maintenance of remission phase), an increase in the dose of cyclophosphamide if tolerated, rituximab, additional doses of IV methylprednisolone (up to 3 g), an increase in oral prednisone/ prednisolone to the same doses used during the initial induction of remission.

For patients who received rituximab at the start of the study, major relapses may be treated with the reintroduction of rituximab, introduction of cyclophosphamide, additional doses of IV methylprednisolone (up to 3 g), an increase in oral prednisone/ prednisolone to the same doses used during the initial induction of remission.

The use of plasma exchange to treat a major relapse must be discussed with the medical monitor.

### 7.10 Guidelines for the Treatment of Minor Relapses

A minor relapse is new or worsening disease activity that occurs after remission has been initially induced that does NOT affect a major item of the BVAS/WG. New or worsening disease activity which occurs while the patient is on ≥20 mg/day of prednisone is considered resistant disease.

Minor Relapses may be treated with up to 20 mg/day of prednisone or prednisolone for a maximum of 14 days. Following this, if disease activity is controlled, patients will resume their GC regimen starting at the next dose below 20 mg/day. If disease activity is not controlled within 14 days, patients will be regarded as having a major relapse.

### 7.11 Prophylactic Therapies

Consideration should be given to therapies to prevent the complications of treating AAV. This includes, but is not limited to, the use of prophylaxis against glucocorticoid induced osteoporosis, prophylaxis of *Pneumocystis jiroveci* (formerly *P. carinii*) pneumonia infections for at least 6 months. Appropriate prophylactic therapy includes sulfamethoxazole-trimethoprim as a single strength tablet daily (i.e. 480 mg daily) or a double strength tablet every other day thrice weekly (i.e. 960 mg Monday, Wednesday, and Friday). The use of prophylactic therapies will be left to local practice and the discretion of local investigators. Care should also be taken by the investigators to ensure the non-immunologic sequelae of AAV are also treated (e.g. hypertension, proteinuria).

## 7.12 Criteria for Discontinuation

### 7.12.1 Individual Subject

Patients will be withdrawn if they withdraw consent. All other patients will be followed until trial termination or death.

### 7.12.2 Trial

Either factor of the trial may be discontinued in the event of clear evidence of harm or benefit for one treatment regimen on the recommendation of the DMC/DSMB and in conjunction with the Trial Management Committee. The Haybittle-Peto approach will be used whereby all interim analyses use a difference of 3 standard errors (approximately p=0.002) as a stopping guideline (19;20). Efficacy and safety data will be reviewed by the DMC/DSMB on an annual basis. The trial is planned to stop 12 months after the last patient is enrolled (common closing date).

## 7.13 Patient Selection

### 7.13.1 Inclusion Criteria

Patients must meet all of the following criteria:

1. New or previous relapsing clinical diagnosis of granulomatosis with polyangiitis (Wegener's), or microscopic polyangiitis consistent with the Chapel-Hill consensus definitions (see 7.13.5) AND
2. Positive test, at any point in the subjects's disease course, by ELISA, for proteinase 3-ANCA or myeloperoxidase-ANCA AND
3. Severe vasculitis defined by at least one of the following manifestations:
    a. Renal involvement characterized by <u>both</u> of the following:
        i. Evidence of glomerulonephritis by either of the following:
            1. Renal biopsy demonstrating focal necrotizing glomerulonephritis or
            2. Active urine sediment characterized by glomerular haematuria/cellular casts and proteinuria

        AND
        ii. An estimated glomerular filtration (eGFR) rate of <50 ml/min/1.73 $m^2$. Patients known to have a stable eGFR <50 ml/min/1.73 $m^2$ for greater than three months prior to enrollment are NOT eligible.
    b. Pulmonary hemorrhage due to active vasculitis defined by the following:
        i. A compatible chest x-ray or CT scan (diffuse pulmonary infiltrates)
        AND
        ii. The absence of an alternative explanation for all pulmonary infiltrates (i.e. volume overload or pulmonary infection)
        AND
        iii. At least one of the following:
            1. Evidence of alveolar hemorrhage on bronchoscopic examination or increasingly bloody returns with bronchoalveolar lavage
            2. Observed hemoptysis
            3. Unexplained anemia (<10 g/dL) or documented drop in hemoglobin (>1 g/dL) from less than 10g/dl
            4. An increased diffusing capacity of carbon dioxide

4. Provision of informed consent by patient or a surrogate decision maker. In some participating countries permission has also been granted to use deferred consent for enrolling a patient until a legal representative becomes available to consent on their behalf. Please check your national regulations for further guidance.

### 7.13.2 Exclusion Criteria

Patients must have none of the following:

1. A diagnosis of vasculitis other than granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis
2. A positive serum test for anti-glomerular basement membrane or a renal biopsy demonstrating linear glomerular immunoglobulin deposition
3. Receipt of dialysis for greater than 21 days immediately prior to randomization or prior renal transplant
4. Age <15 years. In centres that do not routinely treat patients <18 years or if no local investigator routinely treats patients <18 years, enrollment may be restricted to patients 18 years or older*
5. Pregnant at time of study entry
6. Treatment with >1 IV dose of cyclophosphamide and/or >14 days of oral cyclophosphamide and/or >14 days of prednisone/prednisolone (>30 mg/day) and/or treatment with >1 dose of rituximab within the last 28 days
7. A comorbidity or condition that, in the opinion of the investigator, precludes the use of cyclophosphamide/rituximab, glucocorticoids, or plasma exchange or absolutely mandates the use of plasma exchange
8. Plasma exchange in 3 months prior to randomization

** Patients < 18 years of age will be excluded in Germany*

### 7.13.3 Randomization

Allocation will occur according to a minimization scheme. Minimization allows the allocation of treatments to be balanced for known prognostic risk factors and is particularly useful in small trials (<1000 participants) in diseases with many prognostic risk factors (>3).
The prognostic factors that will serve as minimization strata in PEXIVAS are:

- severity of renal disease at presentation (requiring dialysis or creatinine ≥ 500 µmol/L (5.6 mg/dL) vs. <500 µmol/L)
- age (<60, ≥ 60 years old)
- ANCA binding specificity (PR3 vs. MPO)
- severity of lung hemorrhage (no hemorrhage, hemorrhage with blood oxygen saturation >85% on room air, or hemorrhage with blood oxygen saturation ≤ 85% on room air or ventilated)
- induction immunosuppression therapy to be used (IV CYC vs. oral CYC vs. rituximab).

Participants will be minimized in a one-to-one ratio to each intervention or control group by a central facility utilizing a computerized randomization algorithm. Randomization will be performed using an internet/world wide web based secure program from the Birmingham Clinical Trials Unit. This program will provide the investigator with the patient's unique trial identification number and the allocated interventions. The randomization program will also

inform the responsible PLEX centre, the study pharmacy and the trial coordinator of the patient's identification number and treatment allocation by email. The minimization sequence will not be shared with any investigator.

### 7.13.4 Subject Withdrawal Criteria

Subjects will be withdrawn from the trial at any time that they withdraw consent to participate. Patients will otherwise be followed to either the trial end or until death. In the event that consent to participate is withdrawn, we will request that we be allowed to collect vital status information from the patient and/or their family physician or general practitioner. Subjects who are withdrawn will not be replaced.

### 7.13.5 Disease definitions

Granulomatosis with polyangiitis (Wegener's) is characterised by granulomatous inflammation of the respiratory tract, together with necrotizing vasculitis affecting small to medium-sized vessels (21). A C-ANCA pattern by IIF with ANCA specific for antibodies to PR3, is found in over 90% of untreated patients, a minority have MPO-ANCA. Diagnosis requires the presence of chronic inflammation, with a history of at least four weeks affecting the upper and/or lower respiratory tract and not attributable to another cause. The diagnosis may be supported by characteristic histology, such as a focal, necrotizing, pauci-immune glomerulonephritis; or non-renal biopsies with an inflammatory exudate dominated by polymorphonuclear leucocytes with at least one of (1) necrotizing vasculitis affecting small to medium-sized vessels; (2) epithelioid granulomata; or (3) giant cells; and the exclusion of other causes.

Microscopic polyangiitis is characterised by a chronic inflammatory process with non-granulomatous vasculitis of small vessels (i.e. capillaries, venules, arterioles or small arteries) (22). In contrast to granulomatosis with polyangiitis (Wegener's), granulomatous vasculitis of the respiratory tract and/or lung nodules/cavities are absent. Renal involvement is usual and is reflected by a focal, necrotizing, pauci-immune glomerulonephritis. Arteritis of medium-sized vessels may also occur. Microscopic polyangiitis is associated with MPO-ANCA or PR3-ANCA; minorities are ANCA negative or recognise other ANCA autoantigens. Diagnosis of microscopic polyangiitis requires the exclusion of secondary causes of vasculitis, including drugs, infections and malignancy, and vasculitis mimics, such as, anti-phospholipid syndrome and atheroembolic disease.

## 8. Study Procedures and Assessments

**Table 4** Summary of PEXIVAS trial assessments and data collected at each assessment.

| | Induction of Remission | | | | | | | | Maintenance of Remission | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Visits** | **Screen** | **Baseline** | | **WK 2** | **WK 4** | **WK 8** | **WK 12** | | **WK 26** | **WK 39** | **WK 52** | **Every 26 WKs until Study Termination** | **Relapse Visit *or* Termination Visit** |
| **Study Drug** | | | | | | | | | | | | | |
| Glucocorticoid Dose | X | X | | X | X | X | X | | X | X | X | X | X |
| PLEX Type/Details | | | | X | | | | | | | | | |
| **Data Forms** | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | |
| Eligibility | X | | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | |
| Clinical Data | X | | | X | X | X | X | | X | X | X | X | X |
| Weight | | X | | X | X | X | X | | X | X | X | X | X |
| Medications | X | X | | X | X | X | X | | X | X | X | X | X |
| BVAS/WG | X | X | | X | X | X | X | | X | X | X | X | X |
| CDA | | X | | | | | X | | X | | X | X | X |
| SF-36 and EQ5D | | X | | | | | X | | X | | X | X | X |
| Adverse Event Report | | | | X | X | X | X | | X | X | X | X | X |
| **Clinical Labs** | | | | | | | | | | | | | |
| ANCA | X | | | X | | | X | | X | X | X | X | X |
| Anti-GBM | X | | | | | | | | | | | | |
| Creatinine | X | X | | X | X | X | X | | X | X | X | X | X |
| Pregnancy Test* | X | | | | | | | | | | | | |
| **Research Specimens** | | | | | | | | | | | | | |
| DNA** | | X | | | | | | | | | | | |
| RNA | | X | | | | | X | | | | X | | |
| Serum | | X | | X | | | X | | | | X | | |
| Plasma | | X | | X | | | X | | | | X | | |
| Renal pathology[§] | | X | | | | | | | | | | | |

*Only performed on women who have child-bearing potential
** Sites may opt out of this during informed consent
[§] Separate consent for use of renal pathology specimen for research; only applies to patients who have undergone renal biopsy as part of clinical care

### 7.14 Screening Evaluation and Informed Consent

Potential participants will undergo a screening evaluation by a study physician or qualified study nurse to determine if the patient meets all of the inclusion criteria and none of the exclusion criteria. The screening visit requires documentation of ANCA results, organ manifestations of active AAV, serum creatinine/eGFR result, assessment of treatment with cyclophosphamide and glucocorticoids in the last 14 days, assessment of use of dialysis within the last 21 days, a pregnancy test where applicable, documentation of pulmonary hemorrhage if applicable, anti-glomerular basement membrane antibody result, and available pertinent histology results.

Informed consent will be sought from all potentially eligible patients. Detailed study information will be reviewed with eligible patients or the family or legal guardians of eligible patients that are unable to understand the consent process due to medical or mental illness. After disclosure of the study details and potential risks and benefits of participating in the study, patients will be given adequate time to consider consenting to participate. Patients that participate will undergo a baseline visit as soon as possible and will then be randomized.
Therapy with IV methylprednisolone and/or cyclophosphamide may begin during screening.

### 7.15 Baseline Data

Baseline data will include basic demographic information, laboratory data, and clinical data and will be collected prior to receiving study therapy. This information will include:

- Date of birth, sex, limited medical history
- Medications
- Height/Weight
- Disease activity assessment (BVAS/WG)
- Disease related damage assessment (CDA)
- Serum creatinine/dialysis status
- Patient self-reported Short Form 36 questionnaire and EQ-5D questionnaire
- Biological specimens for biobank

### 7.16 Randomization

Before randomization, the investigator or treating physician must decide on induction treatment (i.e., IV cyclophosphamide, oral cyclophosphamide, or rituximab). Randomization may be performed by the local investigator or other qualified local research staff. Patients will be randomized by logging in to an internet based website provided by the Birmingham Clinical Trials Unit (https://www.trials.bham.ac.uk/PEXIVAS). After logging in the investigator will confirm the eligibility criteria and specify the intended route of cyclophosphamide. The randomization algorithm will then assign the patient to either PLEX or no PLEX and to either reduced-dose glucocorticoids or usual dose glucocorticoids and will assign the patient a unique trial identification number to be used on all trial related material for the patient. Notification of the treatment allocation and trial identification number will be forwarded to the trial coordinator, the local investigator and local plasma exchange provider, and the local pharmacy via electronic mail (email) upon randomization. In the event access to the internet is unavailable, the investigator may call the Birmingham Clinical Trials Unit (BCTU), Tel: 0800 953 0274 (toll free in UK, available 9am to 5pm UK time), or +44 (0)121 415 9137 (from outside the UK, available 9am to 5pm UK time) who will access the paper randomization system and inform the

investigator of the treatment allocation and ensure randomization information reaches the appropriate study personnel.

### 7.17 Induction of Remission

During remission induction (up to 6 months) patients will be seen at weeks 2, 4, 8, 12. During these study visits, basic clinical and laboratory data will be collected and will include:

- Medications (including glucocorticoid dose)
- Disease activity assessment (BVAS/WG) and CDA (week 12)
- Serum creatinine
- Adverse Events
- Patient self-reported Short Form 36 questionnaire and EQ-5D questionnaire (week 12)

### 7.18 Maintenance of Remission

During the maintenance of remission phase patients will be seen at 26, 39, 52 weeks and then every 26 weeks. During these study visits, basic clinical and laboratory data will be collected and will include:

- Medications
- Disease activity assessment (BVAS/WG, and CDA)
- Serum creatinine
- Patient self-reported Short Form 36 questionnaire and EQ-5D questionnaire (each visit except week 39)
- Adverse events

### 7.19 Termination of Study

Follow-up for all patients will end on the common Termination of Study date. If a patient has not been reviewed in the last 3 months, they be seen for a final study visit. At the termination of study visit, basic clinical and laboratory data will be collected and will include:

- Medications
- Disease activity assessment (BVAS/WG and CDA)
- Serum creatinine
- Patient self-reported Short Form 36 questionnaire and EQ-5D questionnaire
- Adverse events

## 8 Assessment of Safety

### 8.1 Definitions

#### 8.1.1 Adverse event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product

#### 8.1.2 Adverse reaction of an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any

dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship

### 8.1.3 Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on patient/event outcome or action criteria.

### 8.1.4 Serious adverse event or serious adverse reaction

Any untoward medical occurrence or effect that:

- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect.

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

## 8.2 Expected adverse drug reactions

Plasma exchange is associated with the following adverse reactions, in 5-10% of procedures (details in section (8.6)):

- Respiratory: dyspnea
- Cardiac: arrhythmias, hypotension
- Metabolic: hypocalcemia, metabolic alkalosis
- Hematologic: coagulation abnormalities, bleeding
- Infection: bacterial infections, catheter related blood stream infections, transmission of viral infections via blood products
- Dermatologic: urticaria
- Neurologic: paresthesia

Plasma exchange is also associated with the following Serious Adverse Events, in 0.5% of procedures:

- Respiratory: acute respiratory distress syndrome, non-cardiogenic pulmonary edema (TRALI or transfusion-related acute lung injury), pneumothorax, hemothorax
- Cardiac: arrhythmias, hypotension, arterial dissection, air embolism
- Hematological: bleeding, bleeding diathesis, venous thrombosis

- Infection: blood stream infections, sepsis

Prednisone and prednisolone are associated with the following adverse drug reactions (details in section 8.6):

- >10%:
  Central nervous system: Insomnia, nervousness
  Gastrointestinal: Increased appetite, indigestion
- 1% to 10%:
  Central nervous system: Dizziness or lightheadedness, headache
  Dermatologic: Hirsutism, hypopigmentation
  Endocrine & metabolic: Diabetes mellitus, glucose intolerance, hyperglycemia
  Neuromuscular & skeletal: Arthralgia
  Ocular: Cataracts, glaucoma
  Respiratory: Epistaxis
  Miscellaneous: Diaphoresis
- <1% (Limited to important): Cushing's syndrome, edema, fractures, hallucinations, hypertension, muscle-wasting, osteoporosis, pancreatitis, pituitary-adrenal axis suppression, seizures

Prednisone and Prednisolone are also associated with the following Serious Adverse Events:

- Musculoskeletal: insufficiency fractures, avascular osteonecrosis
- Cardiovascular: premature atherosclerosis, myocardial infarction
- Gastrointestinal: ulceration and bleeding
- Central nervous system: psychosis
- Endocrine: hyperosmolar non-ketotic state, Addisonian crisis
- Miscellaneous: Bacterial infections, fungal infections, viral infections, ocular herpes zoster

## 8.3 Recording and evaluation of adverse events

Non-serious expected or unexpected adverse events, with the exception of infections, will not be collected or reported as part of this trial.

Infections are defined as episodes, which require treatment with intravenous (IV) or oral antibiotics or hospitalization, or infections that are commonly understood to be opportunistic**.**

## 8.4 Recording and evaluation of serious adverse events

Individual serious adverse events need to be recorded by the investigator and reported to the Cambridge central study coordinator for evaluation immediately, and within 24 hours of the investigator becoming aware of the event. This includes the evaluation of its seriousness and the causality between the investigational medicinal product(s) and/or concomitant therapy and the adverse event.

The sponsor has to keep detailed records of all SAEs reported to him by the investigator(s´) and to perform an evaluation with respect to seriousness, causality and expectedness.

### 8.4.1 Assessment of seriousness

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated

Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity

Severe: Significant impairment of functioning; the subject is unable to carry out usual activities and / or the subject's life is at risk from the event.

### 8.4.2 Assessment of causality

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product.

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible.

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible.

## 8.5 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested investigations medical products and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting.

### 8.5.1 Who should report and whom to report to?

The chief investigator and central study coordinator (not the sponsor) should report all the relevant safety information previously described to the concerned competent authorities and to the Ethics Committee concerned. The chief investigator and central study coordinator (not the sponsor) shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

### 8.5.2 When to report?

#### 8.5.2.1 Fatal or life-threatening SUSARs

The MHRA and the Research Ethics Committee should be notified within 24 hours of knowledge of the event but no later than 7 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting.
In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the MHRA and the Ethics Committee within an additional eight calendar days.

#### 8.5.2.2 Non fatal and non life-threatening SUSARs

All other SUSARs and safety issues must be reported to the competent authority and the Ethics Committee in the concerned Member States as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting.
Further relevant follow-up information should be given as soon as possible.

### 8.5.3 How to report?

#### 8.5.3.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:

a) a suspected investigational medicinal product,
b) an identifiable subject (e.g. study subject code number),
c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
d) an identifiable reporting source, and, when available and applicable:
- an unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)
- an unique case identification (i.e. sponsor's case identification number).

#### 8.5.3.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. The sponsor should report further relevant information after receipt as follow-up reports.
In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

#### 8.5.3.3 Format of the SUSARs reports

Electronic reporting should be the expected method for expedited reporting of SUSARs to the MHRA. In that case, the format and content as defined by the Guidance 1 should be adhered to. The CIOMS-I form is a widely accepted standard for expedited adverse reactions reporting. However, no matter what the form or format used, it is important that the basic information/data elements described in annex 3 of the EU directive, when available, be included in any expedited report (some items may not be relevant, depending on the circumstances).

## 8.6 Reporting adverse events

The sponsor is responsible for the prompt notification to all concerned investigator(s), the Research Ethics Committee and competent authority (e.g. MHRA) of each concerned Member State of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority’s authorisation to continue the trial in accordance with Directive 2001/20/EC.

## 8.7 Known Potential Risks

### 8.7.1 Plasma Exchange

Mortality: PLEX has a reported fatality rate of 1 death per 20,000 exchanges (Canadian Apheresis Group, unpublished data). The dominant causes are respiratory or cardiac complications, often attributable to underlying diagnoses such as TTP. Respiratory complications include acute respiratory distress syndrome, and noncardiacogenic pulmonary edema (TRALI),

while cardiac complications include arrhythmias and hypotension. Both respiratory and cardiac complications are more common with plasma replacement than albumin replacement fluids.

Coagulation Abnormalities: PLEX with albumin as a replacement fluid decreases clotting factors. Prothrombin time may increase 30% and partial thromboplastin time may double. These changes tend to normalize within 4 hours after PLEX but may become more long lasting with repeated PLEX procedures over a short period. The bleeding risk from the depletion of coagulation factors may be increased by the use of systemic anticoagulation (e.g. heparin).

Infection Risks: PLEX reduces immunoglobulin levels and may therefore increase the risk of infection. This risk is increased by the placement of central venous catheters and concomitant renal failure. Viral transmission from plasma products may also occur. The risks are largely dependent on the local plasma donor population and screening procedures used.

Metabolic: PLEX procedures utilizing citrate anticoagulation may induce severe hypocalcemia due to the binding of free calcium by citrate. PLEX with citrate anticoagulation may also induce metabolic alkalosis when there is concurrent renal impairment, especially if plasma is the sole replacement fluid.

Drug Removal: Highly protein bound drugs are significantly removed during PLEX. Drugs such as prednisone and prednisolone are largely unaffected but cyclophosphamide (10-60% protein bound) and azathioprine (30% protein bound) may be removed by PLEX. The administration of drugs particularly antibiotics and cyclophosphamide after a PLEX treatment may minimize this removal.

Complications of Central Line Placement: CVC placement may be complicated by discomfort, bleeding, perforation or dissection of an arterial vessel, air embolism, pneumothorax, hemothorax, local infection, or a blood stream infection, or thrombosis.

Hypotension: PLEX may result in a reduction in blood pressure due to a diminished intravascular volume. This risk may be slightly higher in machines utilizing discontinuous blood flow technology. Vasovagal reactions, hypocalcemia, and ACE inhibitors may also contribute to hypotension.

Dyspnea: PLEX procedures, particularly in patients with renal disease, may be complicated by dyspnea due to volume overload. Dyspnea may also occur from allergic bronchospasm or non-cardiogenic pulmonary edema (TRALI) in patients that receive fresh frozen plasma as replacement fluid, or from complement activation in machines that utilize bio-incompatible membranes.

### 8.7.2 Glucocorticoids

From post-marketing experience, the following side-effect incidences are commonly quoted. The occurrence of drug reactions is generally dose dependent. Table 5 lists additional major reactions to prednisolone.

- >10% of patients experience:
  Central nervous system: Insomnia, nervousness
  Gastrointestinal: Increased appetite, indigestion

- 1% to 10% of patients experience:
  Central nervous system: Dizziness or lightheadedness, headache
  Dermatologic: Hirsutism, hypopigmentation
  Endocrine & metabolic: Diabetes mellitus, glucose intolerance, hyperglycemia
  Neuromuscular & skeletal: Arthralgia
  Ocular: Cataracts, glaucoma
  Respiratory: Epistaxis
  Miscellaneous: Diaphoresis

<1% of patients experience (Limited to important): Cushing's syndrome, edema, fractures, hallucinations, hypertension, muscle-wasting, osteoporosis, pancreatitis, pituitary-adrenal axis suppression, seizures

**Table 5** Commonly recognized adverse reactions to oral glucocorticoids.

| | |
|---|---|
| Dermatologic and soft tissue | Renal |
| Skin thinning and purpura | Hypokalemia |
| Cushingoid appearance | Fluid volume shifts |
| Alopecia | Genitourinary and reproductive |
| Acne | Amenorrhea/infertility |
| Hirsutism | Intrauterine growth retardation |
| Striae | Bone |
| Hypertrichosis | Osteoporosis |
| Eye | Avascular necrosis |
| Posterior subcapsular cataract | Muscle |
| Elevated intraocular pressure/glaucoma | Myopathy |
| Exophthalmos | Neuropsychiatric |
| Cardiovascular | Euphoria |
| Hypertension | Dysphoria/depression |
| Perturbations of serum lipoproteins | Insomnia/akathisia |
| Premature atherosclerotic disease | Psychosis |
| Arrhythmias with pulse infusions | Pseudo tumor cerebri |
| Gastrointestinal | Endocrine |

| | |
|---|---|
| Gastritis | Diabetes mellitus |
| Peptic ulcer disease | Hypothalamic-pituitary-adrenal insufficiency |
| Pancreatitis | Infectious disease |
| Steatohepatitis | Heightened risk of typical infections |
| Visceral perforation | Opportunistic infections |
| | Herpes zoster |

### 8.7.3 Cyclophosphamide

Serious side effects include infertility, carcinogenesis, mutagenesis and an increased risk of bacterial, viral and fungal infections.

Digestive System: Nausea and vomiting commonly occur with Cyclophosphamide therapy. Anorexia and, less frequently, abdominal discomfort or pain and diarrhea may occur. There are isolated reports of hemorrhagic colitis, oral mucosal ulceration and jaundice occurring during therapy. These adverse drug effects generally remit when cyclophosphamide treatment is stopped.

Skin and Its Structures: Alopecia occurs commonly in patients treated with Cyclophosphamide. The hair can be expected to grow back after treatment with the drug or even during continued drug treatment, though it may be different in texture or color. Skin rash occurs occasionally in patients receiving the drug. Pigmentation of the skin and changes in nails can occur. Very rare reports of Stevens-Johnson syndrome and toxic epidermal necrolysis have been received during postmarketing surveillance; due to the nature of spontaneous adverse event reporting, a definitive causal relationship to Cyclophosphamide has not been established.

Hematopoietic System: Leukopenia occurs in patients treated with Cyclophosphamide, is related to the dose of drug, and can be used as a dosage guide. Leukopenia of less than 2000 cells/$mm^3$ develops commonly in patients treated with an initial loading dose of the drug, and less frequently in patients maintained on smaller doses. The degree of neutropenia is particularly important because it correlates with a reduction in resistance to infections. Fever without documented infection has been reported in neutropenic patients. Thrombocytopenia or anemia develop occasionally in patients treated with Cyclophosphamide. These hematologic effects usually can be reversed by reducing the drug dose or by interrupting treatment. Recovery from leukopenia usually begins in 7 to 10 days after cessation of therapy.

Urinary System: Cystitis and urinary bladder fibrosis. Hemorrhagic ureteritis and renal tubular necrosis have been reported to occur in patients treated with Cyclophosphamide. Such lesions usually resolve following cessation of therapy.

Infections: Patients have a reduced resistance to all infections.

Respiratory System: interstitial pneumonitis has been reported as part of the postmarketing experience. Interstitial pulmonary fibrosis has been reported in patients receiving high doses of Cyclophosphamide over a prolonged period.

Other: Anaphylactic reactions have been reported; death has also been reported in association with this event. Possible cross-sensitivity with other alkylating agents has been reported. SIADH (syndrome of inappropriate ADH secretion) has been reported with the use of Cyclophosphamide. Malaise and asthenia have been reported as part of the postmarketing experience.

### 8.7.4 Azathioprine

The principal and potentially serious toxic effects of azathioprine are hematologic and gastrointestinal. The risks of secondary infection and neoplasia are also significant. The frequency and severity of adverse reactions depend on the dose and duration of azathioprine as well as on the patient's underlying disease or concomitant therapies. The incidence of hematologic toxicities and neoplasia encountered in groups of renal homograft recipients is significantly higher than that in studies employing azathioprine for rheumatoid arthritis. The relative incidences in clinical studies are summarized below and in Table 6:

**Table 6** Adverse side effects associated with azathioprine in patients treated to prevent rejection of a renal transplant or treated for rheumatoid arthritis.

| Toxicity | Renal Transplant | Rheumatoid Arthritis |
|---|---|---|
| Leucopenia (any degree) | >50% | 28% |
| <2.5x109 cells/L | 16% | 5.3% |
| Infections | 20% | <1% |
| Neoplasia/Lymphoma | 0.5% | Unknown |
| Other Adverse Events | 2.8% | |

Hematologic: Leukopenia and/or thrombocytopenia are dose-dependent and may occur late in the course of therapy with azathioprine. Dose reduction or temporary withdrawal may result in reversal of these toxicities. Infection may occur as a secondary manifestation of bone marrow suppression or leucopenia, but the incidence of infection in renal transplantation is 30 to 60 times that in rheumatoid arthritis. Macrocytic anemia and/or bleeding have been reported.

Thiopurine S-methyl transferase (TPMT) genotyping or phenotyping can help identify patients with low or absent TPMT activity (homozygous for non-functional alleles) who are at increased risk for severe, life-threatening myelosuppression from azathioprine. Death associated with pancytopenia has been reported in patients with absent TPMT activity receiving azathioprine. Gastrointestinal: Nausea and vomiting may occur within the first few months of therapy with azathioprine, and occurred in approximately 12% of 676 rheumatoid arthritis patients. The frequency of gastric disturbance often can be reduced by administration of the drug in divided doses and/or after meals. However, in some patients, nausea and vomiting may be severe and may be accompanied by symptoms such as diarrhea, fever, malaise, and myalgias. Vomiting with abdominal pain may occur rarely with a hypersensitivity pancreatitis. Hepatotoxicity manifest by elevation of serum alkaline phosphatase, bilirubin, and/or serum transaminases is known to occur following azathioprine use, primarily in allograft recipients. Hepatotoxicity has

been uncommon (less than 1%) in rheumatoid arthritis patients. Hepatotoxicity following transplantation most often occurs within 6 months of transplantation and is generally reversible after interruption of azathioprine. A rare, but life-threatening hepatic veno-occlusive disease associated with chronic administration of azathioprine has been described in transplant patients and in one patient receiving azathioprine for panuveitis. Periodic measurement of serum transaminases, alkaline phosphatase, and bilirubin is indicated for early detection of hepatotoxicity. If hepatic veno-occlusive disease is clinically suspected, azathioprine should be permanently withdrawn.

Others: Additional side effects of low frequency have been reported. These include skin rashes, alopecia, fever, arthralgias, diarrhea, steatorrhea, negative nitrogen balance, reversible interstitial pneumonitis and hepatosplenic T-cell lymphoma.

Serious Side Effects:
Severe leucopenia, thrombocytopenia, macrocytic anemia, and/or pancytopenia may occur in patients being treated with IMURAN. Severe bone marrow suppression may also occur. Patients with intermediate TPMT activity may be at an increased risk of myelotoxicity if receiving conventional doses of azathioprine. Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity if receiving conventional doses of azathioprine. TPMT genotyping or phenotyping can help identify patients who are at an increased risk for developing azathioprine toxicity. Hematologic toxicities are dose-related and may be more severe in renal transplant patients whose homograft is undergoing rejection. Bone marrow and hepatotoxicity should be assessed according to local practice but as a minimum we suggest checking full blood counts and aminotransferases every two weeks for the first month of azathioprine therapy and then every two months for the first year of therapy and every three months thereafter. Delayed hematologic suppression may occur. Prompt reduction in dosage or temporary withdrawal of the drug may be necessary if there is a rapid fall in or persistently low leukocyte count, or other evidence of bone marrow depression. Leucopenia does not correlate with therapeutic effect; therefore the dose should not be increased intentionally to lower the white blood cell count.

Serious infections are a constant hazard for patients receiving chronic immunosuppression, especially for homograft recipients. Fungal, viral, bacterial, and protozoal infections may be fatal and should be treated vigorously. Reduction of azathioprine dosage and/or use of other drugs should be considered.

Azathioprine is mutagenic in animals and humans, carcinogenic in animals, and may increase the patient's risk of neoplasia. Renal transplant patients are known to have an increased risk of malignancy, predominantly skin cancer and reticulum cell or lymphomatous tumors. The risk of post-transplant lymphomas may be increased in patients who receive aggressive treatment with immunosuppressive drugs. The degree of immunosuppression is determined, not only by the immunosuppressive regimen, but also by a number of other patient factors. The number of immunosuppressive agents may not necessarily increase the risk of post-transplant lymphomas. However, transplant patients who receive multiple immunosuppressive agents may be at risk for over-immunosuppression; therefore, immunosuppressive drug therapy should be maintained at the lowest effective levels. Information is available on the spontaneous neoplasia risk in

rheumatoid arthritis, and on neoplasia following immunosuppressive therapy of other autoimmune diseases. It has not been possible to define the precise risk of neoplasia due to azathioprine. The data suggest the risk may be elevated in patients with rheumatoid arthritis, though lower than for renal transplant patients. However, acute myelogenous leukemia as well as solid tumors have been reported in patients with rheumatoid arthritis who have received azathioprine.

Azathioprine has been reported to cause temporary depression in spermatogenesis and reduction in sperm viability and sperm count in mice at doses 10 times the human therapeutic dose; a reduced percentage of fertile matings occurred when animals received 5 mg/kg.11

# 9 Study Risk Assessment

Data from this trial will be handled by the Birmingham Clinical Trials Unit (BCTU), a full time research facility dedicated to, and with substantial experience in, the design and conduct of randomized clinical trials. The BCTU is an experienced clinical trials unit that has participated in numerous large, multinational studies in the areas of hematology, oncology and renal medicine. The BCTU recognizes the responsibilities of a data management centre with respect to the ethical practice of research and the adequate protection of human subjects. All BCTU staff members are trained and certified in Good Clinical Practice standards. Additionally, all staff and investigators in this study who contact patients or their data or have the potential to handle patient data are required to complete and provide documentation of Good Clinical Practice certification.

## 9.1 Risks to the Subjects

a. Human Subjects Involvement and Characteristics:
The proposed research project will involve 700 adult patients with systemic vasculitis of all health statuses. Inclusion criteria includes having a diagnosis of ANCA-associated vasculitis (AAV, granulomatosis with polyangiitis, microscopic polyangiitis) with at least one severe manifestation that is either nephritis or lung hemorrhage. Patients with anti-glomerular basement membrane disease, other forms of vasculitis, or who are pregnant will be excluded. A patient who subsequently becomes pregnant during the trial does not have to be excluded provided that she remains consented for the trial and that all teratogenic medications are switched to safer alternatives, as per clinical practice. Two interventions are planned in this study in addition to standard care; with 50% of patients exposed to each intervention: 1) adjuvant plasma exchange; and 2) low-dose oral glucocorticoids.

b. Sources of Materials:
Medical records will be reviewed for all subjects. Routine physical examinations will be performed. The extent of data collection are contained in the protocol. One hundred and twenty millilitres in total of extra blood will be taken for research purposes at the same time as routine blood tests during the first year of the study. .These biomarker samples will be sent on a regular basis to the international coordinating PEXIVAS centre at Cambridge. Only local investigators will have access to any identifiable information on study subjects.

c. Potential Risks:
The hazards of this trial to patient safety are low-moderate given the experience of the investigators with the proposed interventions. These hazards for plasma exchange include the risk of adverse events related to central line placement (some patients may be able to have this procedure performed using peripheral intravenous access), the risks of infectious diseases due to receipt of a blood product, the risk of hypomagnesemia or hypocalcemia with citrate anti-coagulation, and the risk of a coagulopathy/bleeding diathesis (Section 8.2 and 8.6.1). Of note, the serious adverse event rate in a previous trial of plasma exchange in severe AAV was not greater than in the group not receiving plasma exchange.

For the reduced-dose GC regimen, these hazards include the theoretical risk of precipitating a flare of AAV or delay in the time to remission of their AAV.

In addition, all subjects will experience the potential inconvenience of study appointments. Lost school or work time for both patients and their family members is unavoidable in performing this study. However, every effort will be made to perform study visits in an efficient manner and to have them coincide with appointments that would be made with standard care to minimize the excess burden of the study. The medical interviews are not anticipated to be psychologically harmful or stressful.

## 9.2 Adequacy of Protection Against Risks

a. Recruitment and Informed Consent:
Recruitment will occur through the investigators' clinical practices and from referring physicians. The Ethics Committee/Institutional Review Board of each participating center will approve this protocol as well as the consent forms to be used prior to study start or enrollment. Details of the goals of the research and the risk and benefits of the protocol will be reviewed with each potential study subject. Recruitment will occur by physicians, study nurses, and research coordinators.

Patients who decline to participate in any or all parts of the study will still have available the opportunity of evaluation by a vasculitis expert if they or their physician feels this is appropriate.

Strict patient confidentiality will be observed throughout all aspects of the study. While medical records will be reviewed by members of the research team, no individually identifiable patient data will be distributed to non-research or care-giving team members. BUT the onsite monitor could have access to identifiable patient info during inspections.

In the event of adverse effects from the study, the full resources of the hospital will be available to intervene as medically necessary. Licensed physicians expert in the care of patients with vasculitis are available at all times at each study site.

## 9.3 Potential Benefits of the Proposed Research to the Subject and Others

As described above, the potential risks to the study subjects in participating in this study are low-moderate. Participants in this study are unlikely to gain direct benefit from participation. If the study leads to higher quality care or therapeutic trials for vasculitis then study patients could

theoretically benefit in the future. All subjects will potentially have the satisfaction of helping to contribute to medical knowledge of vasculitis. Further understanding of both the clinical and molecular aspects of vasculitis is of great medical importance and because progress in understanding these diseases is expected from this study it is felt that the potential benefits of this research outweigh the risks of participation.

### 9.4 Importance of the Knowledge to be Gained

Knowledge to be gained from this study will be highly important. The optimization of treatment strategies for patients with severe AAV has the potential to dramatically and directly affect clinical practice and patient outcomes. This is underscored by the current widely varied practice patterns regarding use of plasma exchange technology and the consistently poor outcomes of the AAV patient population. Furthermore, the relative rarity of patients with AAV has traditionally made it difficult to collect high quality data on interventions that affect hard, clinical endpoints. This trial would also allow a unique perspective on the pathogenesis of AAV given the novel mechanism of action of the plasma exchange therapy.

## 10 Study Monitoring

PEXIVAS will employ central statistical monitoring of data. This monitoring process will be applied by the Birmingham Clinical Trials Unit. Trial sites identified by the central statistical monitoring process as having outlying data or that have extensive quality control issues will undergo on-site monitoring. Additional sites will undergo random on-site monitoring on a periodic basis.

## 11 Data and Safety Monitoring Plan

An independent Data Monitoring Committee/Data and Safety Monitoring Board (DMC/DSMB) will be established for this trial and will include at least one member from each of the following designations: a statistician, an expert in vasculitis and an expert in trial methodology. The DMC/DSMB will meet annually to review all collected data and may meet more frequently if required after analysis of the available data. The DMC/DSMB will advise the Trial Management Committee and the independent Trial Steering Committee on the safety of continuing this clinical trial. A report from each meeting of the DMC/DSMB will be forwarded to each Institutional Review Board at each participating center.

All unexpected serious adverse events will be reported to the Trial Management Committee and the trial Sponsors (the Cambridge University Hospitals NHS Foundation Trust) by facsimile within 24 hours of knowledge of their occurrence by local investigators. The receipt of all serious adverse events must be acknowledged by the Sponsor and the Sponsor must forward notification of all serious events to the responsible authorities of participating countries within 7 days of the initial notification. All other serious adverse events must be reported to the Sponsor and the Trial Management Committee within 14 days of knowledge of their occurrence by the local investigator. The Sponsor will process, record and report these serious adverse events and a report will be forwarded to the responsible regulatory agency of each participating country and the local institutional review boards of each participating center in the United States annually. A listing of all suspected serious adverse reactions will also be made available globally as per

European law. All data regarding the occurrence of serious adverse events will be made available to the DMC/DSMB for review.

# 12 Statistical Considerations

## 12.1 Sample Size Estimation

The sample size for this trial is event driven in order to detect a hazard ratio of 0.64 (PLEX versus no PLEX) with 80% power and a two sided alpha of 0.05. Protocol versions 1.0 and 2.0 estimated a required sample size of 500 predicting 164 events over the study period equivalent to a 12% absolute risk reduction of the primary endpoint at five years - 44% in the control group vs. 32% in PLEX group (overall 38%). This sample size estimate assumed a five year median time to ESRD or death on the basis of previous extended follow-up studies in randomized trials of AAV of a similar severity to those targeted in this study (Figure 1). Review of PEXIVAS event rates in 2014 indicates a two year event rate of 24% and predicted overall five year event rate of 30-35%. Improvements in death and ESRD have been recently reported in registry studies. In order to obtain the required number of events the sample size needs to be increased to 675-725 patients allowing a 10% loss to follow-up in or cross over between treatment groups. The trial now plans to enroll 700 patients over a six and a half year period with a minimum of one year of follow-up and therefore a maximum follow-up of seven and a half years in order to observe at least 160 events. These calculations assume no significant interaction between the two treatment factors. Although this absolute risk appears larger than is often clinically significant, the expensive and invasive nature of the primary intervention, PLEX warrants a relatively large effect size. Additionally, this effect size is close to the estimated effect of PLEX in the meta-analysis of prior studies (80% power to detect a relative risk reduction of 27% with our sample size compared to a relative risk reduction of 20% in the meta-analysis).
While this effect size appears reasonable to detect for PLEX, it is unlikely a reduction in GC will result in a 12% absolute risk reduction of death or dialysis. However, we expect approximately 25% of patients to experience a severe infection based on prior studies. A sample size of over 700 patients will allow 80% power to detect at least a 10% absolute risk reduction in severe infections (relative risk reduction of severe infection by 40%), a finding of clinical significance. In terms of the non-inferiority hypothesis, a sample size of 700 patients would allow >80% power to ensure that the reduced-dose GC regimen results in an increase in ESRD or death by no more than 11% (one-sided alpha of 0.05).

## 12.2 Planned Analyses

### 12.2.1 Interim Analyses

Interim analyses of efficacy and safety are planned annually. The Haybittle-Peto approach will be used whereby all interim analyses use a difference of 3 standard errors (approximately p=0.002) as a stopping guideline. Safety data will be reviewed by the DMC/DSMB on an annual basis or more frequently if required by the DMC/DSMB or Trial Management Committee.

### 12.2.2 Primary Endpoint Analyses

The final analysis of all trial data will occur one years after the final patient is enrolled.
The primary analysis for this study will be a comparison between groups of time-to the development of ESRD or death by any cause. The primary comparison groups will be composed of those treated with PLEX to those not treated with PLEX (comparison 1) and those treated with

a reduced-dose GC regimen to those treated with a standard-dose (comparison 2). A test for interaction between treatments will be performed but will be interpreted cautiously. It is anticipated that the randomization/minimization strategy will be successful and the primary analysis can be conducted with a simple log-rank test. Kaplan-Meier survival curves will be constructed for visual analysis of time-to-event comparisons. In the event that important co-variables are unbalanced between groups, a Cox proportional hazards or an extended Cox model to account for any differences. The primary analysis will be based on the intention to treat principle, with all patients analysed in the arms to which they were allocated irrespective of compliance with the allocated treatment. For all tests, 95% confidence intervals will be constructed where appropriate and a p-value of <0.05 will be considered significant. No corrections for multiple tests will be made.

There is a risk of cross-over of patients randomized to not receive PLEX to the PLEX arm, although this practice will be discouraged and any such decision on protocol-defined parameters. The primary intention to treat analysis will deal with this cross-over in a conservative manner (bias to the null). To explore the potential that this cross-over may reduce the true magnitude of effect of PLEX, secondary analyses will be performed. Secondary analyses will therefore also include a per protocol analysis where patients are classified with respect to the intervention they ultimately received rather than the intervention they were randomized to. For the purpose of this analysis, patients will be regarded as having received PLEX if they received at least one complete exchange. Patients will be regarded as receiving the standard-dose of GC if they receive at least 70% of the cumulative dose of the standard regimen in the first 6 months of therapy. Patients will be regarded as receiving the reduced-dose of GC if they receive no more than 130% of the cumulative doses of the reduced-dose regimen in the first 6 months of therapy. Secondary analyses will not, irrespective of their differences from primary analyses, supplant the planned primary analyses.

### 12.2.3 Secondary Endpoint Analyses

#### 12.2.3.1 Sustained Remission

Disease activity will be analyzed in terms of sustained remissions. Patients will have obtained a sustained remission if they achieve a BVAS/WG of zero (complete remission) within 26 weeks of randomization and maintain a BVAS/WG of zero from complete remission until at least 52 weeks after randomization. The proportion of patients that achieve a sustained remission will be calculated and an absolute risk difference and relative risk with the associated 95% confidence interval will be calculated.

#### 12.2.3.2 Death and ESRD

Death and ESRD will be analyzed as separate endpoints in a manner identical to primary composite endpoint.

#### 12.2.3.3 Quality of Life Measures

Quality of life data will be analyzed using mixed effect repeated measures with the interventions specified as independent variables.

#### 12.2.3.4 Serious Adverse Events

The proportion of patients that experience at least one serious adverse event will be analyzed as a categorical variable by intervention utilizing a Fisher's exact test. If appropriate, a more complex

model of serious adverse event occurrences will be constructed utilizing adverse events as count variables.
An analysis of major subgroups of adverse events will be performed separately but in an identical manner as the overall adverse events analyses (e.g. infections, malignancy, cardiovascular complications).

### 12.2.4 Tertiary Endpoint Analyses

#### 12.2.4.1 Renal Function

Renal function will be compared between groups using serial estimated glomerular filtration rates as the outcome in longitudinal panel data analysis with the intervention as an independent variable. Patients who reach ESRD will be considered to have an estimated glomerular filtration rate of zero.

#### 12.2.4.2 Economic Analyses

An economic evaluation will be conducted in order to estimate whether it is cost-effective to provide PLEX, in addition to standard care, for severe AAV. Additionally, the cost-effectiveness of low dose GC, compared to high dose GC, will also be estimated.

The health care costs for each patient will be estimated by monitoring the resource use for each patient and assigning appropriate unit costs to these resource items. This will enable the total treatment cost to be identified for each patient, along with the mean cost of each of the treatment regimes.

The main measures of effectiveness within the economic analysis will be the level of mortality and ESRD, along with the EQ-5D. This will enable the overall treatment effect to be estimated for each patient as well as the mean level of effectiveness for each treatment regime. Cost effectiveness will be determined by estimation of incremental cost-effectiveness ratios and cost effectiveness acceptability curves.

#### 12.2.4.3 Planned Subgroup Analyses

Several a priori subgroup analyses are planned with respect to both primary and secondary outcomes. The subgroups will be each strata included for minimization. Subgroup analyses will employ a test of interaction to explore whether there is evidence that the treatment effect differs across subgroups.

## 13 Biomedical Substudies

Biomedical substudies are anticipated for the PEXIVAS Trial. Study sites will not all participate in all substudies. The organization of Biomedical Substudies will be coordinated by the Biomedical Substudy Committee. Consent for the procurement of biological specimens for use by an international team will be obtained during the consent procedure for the trial. Sites may opt out of participating in biomedical substudies but still participate in the clinical trial. Biological specimens considered may include DNA, RNA, plasma, and renal biopsy specimens.

# 14 Ethical Considerations

## 14.1 Evaluation of Risks to Patients

Medical records will be reviewed for all subjects and routine physical examinations will be performed. No specimens will be collected that are not considered the current standard of care. Specimens will be handled locally unless otherwise indicated. Only local investigators will have access to any identifiable information on study subjects.

The hazards of this trial to patient safety are low-moderate given the experience of the investigators with the proposed interventions. These hazards for plasma exchange include the risk of adverse events related to central line placement (some patients may be able to have this procedure performed using peripheral intravenous access), the risks of infectious diseases due to receipt of a blood product, the risk of hypomagnesemia or hypocalcemia with citrate anti-coagulation, and the risk of a coagulopathy/bleeding diathesis (See Section 8 above for details). Of note, the serious adverse event rate in a previous trial of plasma exchange in severe AAV was not greater than in the group not receiving plasma exchange.

For the reduced-dose GC regimen, these hazards include the theoretical risk of precipitating a flare of AAV or delay in the time to remission of their AAV. In the event of excess disease activity, the trial protocol allows for additional glucocorticoid treatment in order to regain control of the patient's disease.

In addition, all subjects will experience the potential inconvenience of study appointments. Lost school or work time for both patients and their family members is unavoidable in performing this study. However, every effort will be made to perform study visits in an efficient manner and to have them coincide with appointments that would be made with standard care to minimize the excess burden of the study. The medical interviews are not anticipated to be psychologically harmful or stressful.

## 14.2 Protection Against Risks

Recruitment will occur through the investigators' clinical practices and from referring physicians. The Institutional Review Board of each participating center will provide ethical review and approval for this protocol as well as the consent forms to be used prior to study start or enrollment. Details of the goals of the research and the risk and benefits of the protocol will be reviewed with each potential study subject. Recruitment will occur by physicians, study nurses, and research coordinators.

Patients who decline to participate in any or all parts of the study will still have available the opportunity of evaluation by a vasculitis expert if they or their physician feels this is appropriate.

Strict patient confidentiality will be observed throughout all aspects of the study. While medical records will be reviewed by members of the research team, no individually identifiable patient data will be distributed to non-research or care-giving team members.

In the event of adverse effects from the study, the full resources of the hospital will be available to intervene as medically necessary. Licensed physicians expert in the care of patients with vasculitis are available at all times at each study site.

### 14.3 Potential Benefits to Participants

As described above, the potential risks to the study subjects in participating in this study are low-moderate. Participants in this study are unlikely to gain direct benefit from participation. If the study leads to higher quality care or therapeutic trials for vasculitis then study patients could theoretically benefit in the future. All subjects will potentially have the satisfaction of helping to contribute to medical knowledge of vasculitis. Further understanding of both the clinical and molecular aspects of vasculitis is of great medical importance and because progress in understanding these diseases is expected from this study it is felt that the potential benefits of this research outweigh the risks of participation.

### 14.4 Trial Ethical Approval

Each national coordinator or local coordinator will apply for national or regional ethics approval as well as regulatory approval (e.g. MHRA, Health Canada etc).
International sponsorship will be provided by the Cambridge University Hospitals NHS Foundation Trust upon signing of the site agreement with each trial site. Site agreements will be contingent upon the provision of evidence that study personnel have completed Good Clinical Practice training.

### 14.5 GCP Statement

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and all applicable regulatory requirements.

## 15 Trial Organization

### 15.1 Principal Investigators

David Jayne
Peter Merkel
Michael Walsh

### 15.2 Data Management and Analysis Centre

Birmingham Clinical Trials Unit
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College of Medical & Dental Sciences
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B15 2TT
Telephone 0121 415 9131
Fax 0121 415 9135
Email: PEXIVAS-trial@contacts.bham.ac.uk

### 15.3 Trial Communications

Trial communication will be provided in the form of twice yearly electronic newsletters, annual investigator's meetings, site monitoring visits, and electronic mail (emerging issues).

A medical monitor will be available on-call for the trial at all times to advice investigators on issues surrounding the interface between clinical practice and trial protocol. Contact information for the medical monitor is available on the investigator's area of the trial website (website address) or from the Trial Coordination Centre.

### 15.4 Trial Publication Policy

The Writing Committee will approve all publications using PEXIVAS data and the authorship. The Writing Committee will be composed of the PI's, BCTU statistical and data analysis staff, and investigators with expertise in clinical and basic science related to AAV.

## 16 Funding

This trial is currently funded by the Medical Research Council of the United Kingdom, the National Institutes of Health Research (UK), the United States Food and Drug Administration Office for Orphan Product Development, the US National Institutes of Health (National Institute of Arthritis and Musculoskeletal and Skin Diseases), the Canadian Institutes of Health Research, and the National Health and Medical Research Council (Australia).

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# 18 Appendices

## 18.1 Birmingham Vasculitis Activity Score for WG Vasculitis (BVAS/WG)

**Instructions:**
**Mark only if abnormality is ascribable to the presence of active ANCA-Associated Vasculitis. Mark "Persistent" or "New/Worse" depending upon if the abnormality is persistent disease activity since the last assessment and not worse within the previous 28 days or if the abnormality is newly present or worse within the previous 28 days correspondingly. If no items are present in any section, tick "none". Major items are in bold and marked with *. All WG-related clinical features need to be documented on this form if they are related to active diseases. Use "OTHER" category as needed.**

| | Persistent | New/Worse | None |
|---|---|---|---|
| **1. GENERAL** | | | ( ) |
| a. arthralgia/arthritis | ☐ | ○ | |
| b. fever (≥ 38 degrees C) | ☐ | ○ | |
| **2. CUTANEOUS** | | | ( ) |
| a. purpura | ☐ | ○ | |
| b. skin ulcer | ☐ | ○ | |
| c. ***gangrene** | ☐ | ○ | |
| **3. MUCOUS MEMBRANES/EYES** | | | ( ) |
| a. mouth ulcers | ☐ | ○ | |
| b. conjunctivitis/episcleritis | ☐ | ○ | |
| c. retro-orbital mass/proptosis | ☐ | ○ | |
| d. uveitis | ☐ | ○ | |
| e. ***scleritis** | ☐ | ○ | |
| f. ***retinal exudates/haemorrhage** | ☐ | ○ | |
| **4. EAR, NOSE & THROAT** | | | ( ) |
| a. bloody nasal discharge / nasal crusting / ulcer | ☐ | ○ | |
| b. sinus involvement | ☐ | ○ | |
| c. swollen salivary gland | ☐ | ○ | |
| d. subglottic inflammation | ☐ | ○ | |
| e. conductive deafness | ☐ | ○ | |
| f. ***sensorineural deafness** | ☐ | ○ | |
| **5. CARDIOVASCULAR** | | | ( ) |
| a. pericarditis | ☐ | ○ | |
| **6. GASTROINTESTINAL** | | | ( ) |
| a. ***mesenteric ischemia** | ☐ | ○ | |
| **7. PULMONARY** | | | ( ) |
| a. pleurisy | ☐ | ○ | |
| b. nodules or cavities | ☐ | ○ | |
| c. other infiltrate secondary to WG | ☐ | ○ | |
| d. endobronchial involvement | ☐ | ○ | |
| e. ***alveolar hemorrhage** | ☐ | ○ | |
| f. ***respiratory failure** | ☐ | ○ | |

**DETERMINING DISEASE STATUS:**
**Severe Disease / Flare:** ≥ 1 new/worse Major item
**Limited Disease / Flare:** ≥ new/worse Minor item
**Persistent Disease:** Continued (but not new/worse) activity
**Remission:** No active disease, including either new /worse or persistent items

| | Persistent | New/Worse | None |
|---|---|---|---|
| **8. RENAL** | | | ( ) |
| a. hematuria (no RBC casts) (≥ 1 + or ≥ 10 RBC/hpf) | ☐ | ○ | |
| b. ***RBC casts and / or glomerulonephritis** | ☐ | ○ | |
| c. ***rise in creatinine > 30% or fall in creatinine clearance > 25%** | ☐ | ○ | |
| Note: If both hematuria and RBC casts are present, score only the RBC casts (the major item). | | | |
| **9. NERVOUS SYSTEM** | | | ( ) |
| a. ***meningitis** | ☐ | ○ | |
| b. ***cord lesion** | ☐ | ○ | |
| c. ***stroke** | ☐ | ○ | |
| d. ***cranial nerve palsy** | ☐ | ○ | |
| e. ***sensory peripheral neuropathy** | ☐ | ○ | |
| f. ***motor mononeuritis multiplex** | ☐ | ○ | |

**10. OTHER** (describe all items and * items deemed major) ( )

*Major*

☐ _____ ☐ ○
☐ _____ ☐ ○
☐ _____ ☐ ○
☐ _____ ☐ ○

**11. TOTAL NUMBER OF ITEMS:** ( )

| a. | b. | c. | d. |
|---|---|---|---|
| ___ ___ | ___ ___ | ___ ___ | ___ ___ |
| Major New / Worse | Minor New / Worse | Major Persistent | Minor Persistent |

**12. CURRENT DISEASE STATUS** (check only one)

Severe Disease/Flare ☐
Limited Disease/Flare ☐
Persistent Disease ☐
Remission ☐

**Remission** 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 ○ **Maximum activity**

## Birmingham Vasculitis Activity Score Modified for Wegener's Granulomatosis (BVAS/WG)

## An Introduction and Glossary of Terms

### Purpose of assessment

**BVAS/WG is designed to document clinical features that are directly due to active WG or MPA (AAV).** In addition, the instrument separates the features that represent new or worse disease activity from those that represent persistent activity. In scoring BVAS for WG, it is very important not to confuse *activity* with *damage*. Damage, defined as the presence of non-healing scars, and is a concept distinct from current disease activity. Damage will be scored separately in PEXIVAS using another index, the Combined Damage Assessment (CDA), which is not the subject of this exercise.

### Recording disease activity

The list of items in BVAS/WG includes clinical symptoms and signs, as well as information obtained from additional tests (e.g., chest x-rays) or subspecialty consultations. When using the BVAS/ WG evaluation form, one scores only these items attributable to currently active WG (after the exclusion of obvious causes such as infection, hypertension, and treatment toxicity). BVAS scores may vary rapidly, and reflect the need for therapy.

### New Patients

If the patient is being evaluated for the first time and has not been treated, all of the abnormalities noted should be recorded as NEW/WORSE (○) regardless of their duration. After going through the entire items list, also remember to consider adding any other significant items to the "Other" section, if relevant. A list of "Other" items that might be included in these sections is displayed at the end of the glossary. If a section has no items present, check the "none" box.

### Follow-up Patients

If the patient is being evaluated in follow-up, there may be some abnormalities that are NEW or WORSE (○) within the previous 28 days. Other abnormalities may have been present on the previous assessment and are neither new nor worse, but rather still present (PERSISTENT □). By making this distinction, one differentiates new, acute disease activity from persistent disease activity. It is important to remember that *persistent* activity is *activity*, not damage. Thus, persistent purpura should be scored as activity. In contrast, weakness from mononeuritis multiplex of 4 months duration is damage, and should not be scored in BVAS. Sometimes (admittedly), it is difficult to be certain whether a symptom or sign is due to persistent activity or to damage. As in caring for real patients, in evaluating such cases one relies on clinical judgement to make this distinction.

### Checking the boxes

Check **one** of the boxes for each item (○ or □) only if the abnormality is ascribed to the presence of active WG. If no abnormalities ascribable to WG are present in a given organ system, check the "none" box. In this way, we can be certain that you did not overlook an organ system on the scoring

sheet. Sometimes you will have patients in whom abnormalities are present that are not due to AAV (e.g., hematuria due to urinary infection or cyclophosphamide toxicity). In these cases, you should NOT record them in the BVAS/WG list, even though they are present, because they cannot be ascribed to active AAV. In some patients, abnormalities that were due to previous episodes of WG may still be evident, even though the disease is entirely inactive (e.g., stroke). These features should also NOT be recorded on BVAS/WG, since they represent non-healing scars (damage).

○ Check this box only if the abnormality is NEW/WORSE within the **previous 28 days** (unless this is the first presentation of untreated disease).
□ Check this box only if the abnormality is PERSISTENT since the last assessment and not worse within the **previous 28 days.**
( ) Check this space if there is not a single major or minor item that is new/worse within a particular organ system.

**Necessity for "Judgement Calls"**

As in clinical practice, one must sometimes make "judgement calls" in scoring BVAS/WG. For example, persistent sinus symptoms are often notoriously difficult to classify with certainty as either active disease or permanent damage. Similarly, small amounts of hematuria (usually with RBC casts) may persist for months in patients whose disease is otherwise quiescent. In both such cases, the physician is unlikely to intensify treatment in the absence of other indications of active disease. For this reason, these findings (and analogous findings in other organ systems) should not be scored in BVAS/WG. If subsequent events cause you to re-consider your judgement call, you may go back and change your initial decision regarding a particular finding.

You will note that for some features (e.g., sensorineural deafness, most of the neurological items) there is no persistent box. This reflects the fact that if these features are present, they are new/worse by definition. If the feature is still present at subsequent assessments — as mononeuritis multiplex is likely to be — the feature is (by definition) damage, and should not be scored.

**Recording Major and Minor Items**

Individual items are defined as Major by the presence of an asterisk (*). All other items are defined as Minor. If you list additional items in the "Other" section, you should indicate whether the item is "Major" or "Minor". <u>In general, a Major item is one whose presence would have traditionally prompted the use of cyclophosphamide.</u> Minor items are those more likely to be treated with methotrexate or an increase in prednisone.

If you decide that a particular abnormality is due to the presence of active WG, you must distinguish problems that are new/worse from those problems that are persistent. For each item where there is an abnormality, you need to check either the NEW/WORSE box or the PERSISTENT box, but not both.

## Summing Up BVAS/WG

Now add up all of the Major (*) items marked in the New/Worse column, and enter the sum in the appropriate box on the right side of the page. Repeat this for the Minor items in the NEW/WORSE column, and then do the same for the Major and Minor items in the Persistent column.

### Defining disease status

**Severe disease/flare:** If any Major item is recorded, the patient has a "Severe Flare".
**Limited disease/flare:** If any Minor item is recorded, the patient has a "Limited Flare".
**Persistent Disease:** Persistent disease indicates the presence of 1 or more persistent items attributed to active disease.
**Remission:** Remission indicates no active disease (i.e., no new/worse and no persistent items present).

### Physician's Global Assessment

Finally, use the 10 point likert scale to record your assessment of the overall disease activity in this case. Remember that you should not be influenced by the presence of any accumulated damage, complication of treatment, social/emotional problems, or other issues not related to active vasculitis.

## BVAS/WG

## GLOSSARY OF TERMS

**GENERAL RULE: Disease features are scored only when they are attributable to active WG/MPA, after exclusion of other obvious causes (e.g., infection, hypertension, toxicity of treatment, etc.). THIS IS THE MOST IMPORTANT ASPECT OF SCORING TO REMEMBER!**

If the patient is presenting for the first time and has not been treated, then all items due to WG that is currently active are defined as NEW/WORSE, regardless of how long the patient has had them.

If an item is new or represents a deterioration of status occurring in the previous 28 days, it is scored in the NEW/WORSE box.

If the feature was present at the previous evaluation and is not new or worse but still represents ongoing disease activity, record it as PERSISTENT.

Check box (○ or □) only if the abnormality is ascribable to the presence of active WG.

○ Check this circle only if the abnormality is NEW/WORSE within the **previous 28 days.**
□ Check this box only if the abnormality is PERSISTENT since the last assessment and not worse within the **previous 28 days.**

For some features, further information (e.g., a chest radiograph or subspecialty consult) may be required to determine if an abnormality is new or worse.

**Glossary definitions used in BVAS/WG**

Remember that for most patients, you will be able to complete the BVAS evaluation form on the same day you evaluate the patient. However, on other occasions, you may require further information before entering some items. For example, if the patient has new onset of stridor, you would usually ask an ENT colleague to investigate this further to determine whether or not it is due to active WG. We suggest that you leave such items blank temporarily, but complete them once the information is available.

| **1. General** | |
|---|---|
| **Arthralgia:** | Joint pain without obvious swelling. |
| **Arthritis:** | Joint inflammation. |
| **Fever:** | Documented temperature elevation. The value refers to oral temperatures (38.0ºC). |

| **2. Cutaneous** | |
|---|---|
| **Purpura:** | Petechiae (small red spots), palpable purpura, or ecchymoses (large plaques) in skin or oozing (in the absence of trauma) in the mucous membranes. |
| **Ulcer:** | Open sore in a skin surface. |
| ***Gangrene:** | Extensive tissue necrosis (e.g., digit). Gangrene refers not to superficial infarction (e.g., a nailbed infarct), but rather to severe ischemia affecting the viability of a substantial portion of tissue, such as an entire fingertip. |
| ** If new/worse, this denotes a major item for assessment of flares.* | |

| **3. Mucous Membranes and Eyes** |
|---|

| | |
|---|---|
| **Mouth ulcers:** | Ulcers localized in the mouth. Exclude other causes, such as drugs, Crohn's disease, pemphigus, etc. |
| **Conjunctivitis:** | Inflammation of the conjunctivae (exclude infectious causes). |
| **Episcleritis:** | Inflammation of the superficial sclera. |
| **Retro-orbital mass/ Proptosis:** | Protrusion of the eye caused by an inflammatory mass behind the globe. This may be associated with diplopia due to infiltration of extra-ocular muscles. |
| **Uveitis:** | Inflammation of the uveal tract (iris, ciliary body, choroid) confirmed by ophthalmologist. |
| ***Scleritis** | Inflammation of the deep sclera (specialist opinion usually required). |
| ***Retinal exudates:** | Any area of soft retinal exudates (exclude hard exudates) seen on ophthalmoscopic examination. |
| ***Retinal haemorrhages:** | Any area of retinal hemorrhage seen on ophthalmoscopic examination. |
| ** If new/worse, this denotes a major item for assessment of flares.* | |

| | |
|---|---|
| **4. ENT** | |
| **Bloody nasal discharge:** | Blood stained secretions from the nose, irrespective of severity or frequency, occurring since the last visit. |
| **Nasal crusting:** | Discharge of large serous or serosanguinous crusts. |
| **Nasal ulceration:** | Nasal mucosal lesions (not due to trauma). |
| **Sinus involvement:** | Tenderness or pain over paranasal sinuses or X-ray evidence of sinusitis. If nasal bridge collapse is observed, this may be recorded separately (in the section for "Other" items). |
| **Swollen salivary glands** | Tender swelling of one or more major salivary glands not due to an infection, stone, or other non-WG cause. |
| **Subglottic inflammation:** | Inspiratory stridor with significant narrowing of subglottic space confirmed by further examination (usually by an ENT specialist). |
| **Conductive deafness:** | Any hearing loss due to middle ear involvement, preferably confirmed by audiometry. |
| ***Sensorineural deafness:** | Deafness caused by damage to the auditory nerve or cochlea. |
| ** If new/worse, this denotes a major item for assessment of flares.* | |

| |
|---|
| **5. Cardiovascular** |

| | |
|---|---|
| **Pericarditis:** | Pericardial pain and/or friction rub on clinical assessment. |

| | |
|---|---|
| **6. Abdominal** | |
| **Mesenteric ischemia:** | Defined as severe abdominal pain, bloody diarrhea, gut perforation/ infarction due to WG. |
| ** If new/worse, this denotes a major item for assessment of flares.* | |

| | |
|---|---|
| **7. Chest/Pulmonary** | |
| **Pleurisy:** | Pleural pain and/or friction rub on clinical assessment or new onset of radiologically confirmed pleural effusion. Other causes (e.g., infection, cancer) should be excluded. |
| **Nodules or cavities:** | New lesions, detected by CXR. |
| ***Tracheobronchial involvement:** | Pseudotumour or ulceration of tracheobronchial tree. Requires bronchoscopy to exclude tumor or infection. |
| ***Alveolar haemorrhage:** | Major pulmonary bleeding, with shifting pulmonary infiltrates. Other causes of bleeding should be excluded. |
| ***Respiratory failure:** | Dyspnea requiring artificial ventilation. |
| ** If new/worse, this denotes a major item for assessment of flares.* | |

| | |
|---|---|
| **8. Renal** | |
| ***Hematuria: (no RBC casts)** | ≥1+ on urinalysis; ≥10 rbc/hpf. Infection should be excluded. The hematuria must be considered due to <u>active</u> renal vasculitis, not just prior damage. |
| ***RBC casts and/or Glomerulonephritis** | The appearance of RBC casts in the urinary sediment and/or evidence of <u>active</u> glomerulonephritis on biopsy. RBCs are essentially the "surrogate" for glomerulonephritis. |
| **Rise in creatinine > 30% or creatinine clearance fall > 25%:** | Deterioration in renal function that is attributable to active WG and meets these criteria. |
| ** If new/worse, this denotes a major item for assessment of flares.* | |

| |
|---|
| **9. Nervous System** |

| | |
|---|---|
| ***Meningitis:** | Severe headache +/- neck stiffness, ascribed to inflammatory meningitis after the exclusion of infection, bleeding, and other causes. |
| ***Stroke:** | Cerebrovascular accident resulting in focal neurological signs such as paresis, weakness, etc. |
| ***Cord lesion:** | Transverse myelitis with extremity weakness or sensory loss. |
| ***Cranial nerve palsy:** | Isolated acute cranial nerve palsy (excluding sensorineural hearing loss, which is listed in ENT). |
| ***Sensory Peripheral neuropathy:** | Neuropathy resulting in glove and/or stocking distribution of sensory loss. Other causes should be excluded (e.g., idiopathic, metabolic, vitamin deficiencies, infectious, toxic, hereditary). |
| ***Motor mononeuritis multiplex:** | Neuritis of named peripheral nerve, only scored if motor involvement. On EMG/NCV evaluation, multiple nerve dysfunction may be documented, but clinical involvement of only one named nerve is required to score this item. Other causes should be excluded (diabetes, sarcoidosis, carcinoma, amyloidosis). |
| ** If new/worse, this denotes a major item for assessment of flares.* | |

| | |
|---|---|
| **10. Other:** | Significant features attributable to active WG not listed above. Please provide full details and designate item as Major or Minor items. Potential "Other" items are listed below. |
| *If defined as new/worse, this may denote a major or minor item for assessment of flares.* | |

**Examples of Potential "Other" items:**

- Weight loss (>2 kg over 28 day period)
- Seizures
- Genitourinary involvement
- Cardiac valvular lesions
- Cutaneous infarctions (splinter hemorrhages, digital infarcts)
- Pulmonary infiltrates (not due to alveolar hemorrhage, cavity)
- New loss of pulses / threatened loss of limb
- Angina (ischemic cardiac pain secondary to WG)
- Cardiomyopathy
- Pancreatitis
- Aural D/C
- Many others….

## 18.2 CDA - Combined Damage Assessment Index

***Instructions:*** This is for recording organ damage that has occurred in patients since the onset of vasculitis. Co-morbidity that exists before the onset of vasculitis must not be scored. A new patient should have a CDA of zero unless he has had vasculitis for at least 6 months, and the damage has developed or become worse since the onset of vasculitis. A finding must be present for 6 months to be scored. Damage is irreversible, and only rarely should a scored item not be carried forward.Where applicable, please include the primary data values, in addition to marking the relevant box

**Musculoskeletal** *None:* Δ

- ☐ Osteoporosis/vertebral collapse
- Bone fracture:
- ☐ *Due to renal dystrophy*
- ☐ *Due to osteoporosis*
- ☐ *Due to both*
- Muscle atrophy due to glucocorticoids:
- ☐ *Normal strength, atrophy on exam*
- ☐ *Weak on examination, normal ADLs*
- ☐ *Weak and has difficulty with ADLs*
- ☐ Avascular necrosis
- ☐ Deforming/erosive arthritis
- ☐ Osteomyelitis

**Skin/Membranes** *None:* Δ

- ☐ Alopecia
- ☐ Mouth ulcers
- ☐ Cutaneous scarring
- ☐ Cutaneous ulcers
- ☐ Striae
- ☐ Gangrene with permanent tissue loss
- ☐ Easy bruising

**Ocular** *None:* Δ

- ☐ Proptosis **L R B**
- ☐ Pseudotumor **L R B**
- ☐ Scleral thinning **L R B**
- ☐ Scleral perforation **L R B**
- ☐ Optic nerve edema **L R B**
- ☐ Optic nerve atrophy **L R B**
- ☐ Retinal changes **L R B**
- ☐ Retinal artery occlusion **L R B**
- ☐ Retinal vein occlusion **L R B**
- ☐ Low vision **L R B**
- ☐ Diplopia **L R B**
- ☐ Blindness **L R B**
- ☐ Cataracts **L R B**
- ☐ Glaucoma **L R B**
- ☐ Orbital wall destruction **L R B**

**Ear** *None:* Δ

- ☐ Sensorineural hearing loss **L R B**
- ☐ Conductive hearing loss **L R B**
- ☐ Tympanic membrane perforation or scarring **L R B**
- ☐ Tinnitus **L R B**
- ☐ Eustachian tube dysfunction **L R B**
- ☐ Auricular cartilage deformity **L R B**
- ☐ Cholesteatoma **L R B**

**Nose** *None:* Δ

- ☐ Chronic rhinitis/crusting
- ☐ Nasolacrimal duct obstruction
- ☐ Nasal bridge collapse/saddle nose
- ☐ Nasal septal perforation
- ☐ Anosmia
- ☐ Ageusia

**Sinuses** *None:* Δ

- ☐ Chronic sinusitis
- ☐ Neo-ossification of sinuses

**Subglottic stenosis** *None:* Δ

- ☐ *No intervention required*
- ☐ *Intervention required*

**Pulmonary** *None:* Δ

- ☐ Irreversible loss of lung function
- ☐ Fixed large airway obstruction
- ☐ Pulmonary hypertension
- ☐ Pulmonary fibrosis
- ☐ Pulmonary embolism
- ☐ Pulmonary infarction
- ☐ Vena caval filter
- ☐ Continuous oxygen dependency
- ☐ Chronic asthma
- ☐ Pleural fibrosis
- ☐ Chronic breathlessness

***FEV1*** _____ _____ . _____

***FVC*** _____ _____ . _____

***RVSP*** _____ _____

**Cardiac** ***None:*** Δ

Hypertension: ***BP*** _____ / _____

- ☐ *Pre-HTN: SBP 130-139 or DBP 80-89*
- ☐ *Stage I: SBP 140-149 or DBP 90-99*
- ☐ *Stage II: SBP >149 or DBP >99*
- ☐ Angina
- ☐ Myocardial infarction
- ☐ Percutaneous coronary intervention
- ☐ Coronary artery bypass graft

LV dysfunction: ***EF:*** ___ ____ ***%***

- ☐ *NYHA Class I/II*
- ☐ *NYHA Class III/IV*
- ☐ Third degree AV block
- ☐ Valvular disease:

*Specify:*

- ☐ Pericarditis or pericardectomy

**Vascular Disease** ***None:*** Δ

- ☐ Absent pulses in 1 limb
- ☐ 2nd episode of absent pulses in 1 limb
- ☐ Major vessel stenosis
- ☐ Claudication > 3 months
- ☐ Minor tissue loss
- ☐ Major tissue loss
- ☐ Subsequent major tissue loss
- ☐ Deep venous thrombosis
- ☐ Complicated venous thrombosis
- ☐ Carotid artery disease
- ☐ Renal artery stenosis
- ☐ Arterial thrombosis/occlusion

*Specify:*

**Gastrointestinal** ***None:*** Δ

- ☐ Gut infarction/resection
- ☐ Hepatic fibrosis
- ☐ Mesenteric insufficiency/pancreatitis
- ☐ Esophageal stricture/surgery
- ☐ Chronic peritonitis

**Renal** ***None:*** Δ

- ☐ Estimated/measured GFR<50%
- ☐ Chronic kidney disease
- ☐ End-stage renal disease
- ☐ Dialysis
- ☐ Renal transplant

Proteinuria:

- ☐ *< 3g/24h*
- ☐ *>3g/24h*

**Neurologic** ***None:*** Δ

- ☐ Seizures
- ☐ Transverse myelitis

Sensory polyneuropathy:

- ☐ *Mild*
- ☐ *Moderate*
- ☐ *Severe*
- ☐ Motor neuropathy (mononeuritis)
- ☐ Neuropathic pain
- ☐ Cerebrovascular accident
- ☐ 2nd Cerebrovascular accident
- ☐ Cranial nerve lesion, *specify:*

**Psychiatric** ***None:*** Δ

- ☐ Cognitive impairment
- ☐ Anxiety disorder due to vasculitis
- ☐ Mood disorder due to vasculitis
- ☐ Major psychosis

**Endocrine** ***None:*** Δ

- ☐ Diabetes insipidus
- ☐ Premature ovarian failure
- ☐ Azoospermia
- ☐ Impaired fasting glucose
- ☐ Diabetes mellitus

**Hematology/Oncology** ***None:*** Δ

- ☐ Bladder cancer
- ☐ Cervical cancer
- ☐ Hematopoetic malignancy
- ☐ Solid tumor malignancy

*Specify:*

- ☐ Refractory cytopenia
- ☐ Myelodysplastic syndrome

**Other** ***None:*** Δ

- ☐ Weight gain > 10 lbs/4.4 kg
- ☐ Fibromyalgia

Drug-induced cystitis:

- ☐ *with microscopic hematuria*
- ☐ *with gross hematuria*
- ☐ *requiring transfusion*
- ☐ *requiring cystectomy*
- ☐ Damage requiring surgical intervention

*Specify:*

- ☐ Medications to manage side effects of immunosuppressive agents

*Specify:*

- ☐ Hypogammaglobulinemia

***Physician Global Assessment*: mark line to indicate the total burden of damage in this patient:**

**NONE 0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10 MAXIMUM**

## 18.3 SF-36 (example)

**HEALTH STATUS – SF 36 V2 (as reported by participant) Page 1 of 3**

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

**Your Health and Well Being**

**1. In general, would you say your health is:**

| Excellent | Very Good | Good | Fair | Poor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**2. Compared to in year ago, how would you rate your health in general now?**

| Much better now than one year ago | Somewhat better now than one year ago | About the same as one year ago | Somewhat worse now than one year ago | Much worse now than one year ago |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?**

| | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|---|---|---|
| a) Vigorous Activities, such as running, lifting heavy objects, participating in strenuous sports. | ☐ | ☐ | ☐ |
| b) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf. | ☐ | ☐ | ☐ |
| c) Lifting or carrying groceries | ☐ | ☐ | ☐ |
| d) Climbing several flights of stairs | ☐ | ☐ | ☐ |
| e) Climbing one flight of stairs | ☐ | ☐ | ☐ |
| f) Bending, kneeling, or stopping | ☐ | ☐ | ☐ |
| g) Walking more than a mile | ☐ | ☐ | ☐ |
| h) Walking several hundred yards | ☐ | ☐ | ☐ |
| i) Walking one hundred yards | ☐ | ☐ | ☐ |
| j) Bathing or dressing yourself | ☐ | ☐ | ☐ |

**HEALTH STATUS – SF 36 V2** **Page 2 of 3**

**4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a) Cut down on the amount of time you spent on work or other activities | ☐ | ☐ | ☐ | ☐ | ☐ |
| b) Accomplished less than you would like | ☐ | ☐ | ☐ | ☐ | ☐ |
| c) Were limited in the kind of work or other activities | ☐ | ☐ | ☐ | ☐ | ☐ |
| d) Had difficulty performing the work or other activities (ie, it took extra effort) | ☐ | ☐ | ☐ | ☐ | ☐ |

**5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a) Cut down on the amount of time you spent on work or other activities. | ☐ | ☐ | ☐ | ☐ | ☐ |
| b) Accomplished less than you would like | ☐ | ☐ | ☐ | ☐ | ☐ |
| c) Did work or other activities less carefully than usual | ☐ | ☐ | ☐ | ☐ | ☐ |

**6. During the past 4 week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups?**

| Not at all | Slightly | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**7. How much bodily pain have you had during the past 4 weeks?**

| None | Very Mild | Mild | Moderate | Severe | Very Severe |
|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

**8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

| Not at all | Slightly | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**HEALTH STATUS – SF 36 V2** **Page 3 of 3**

**9. These questions are about how your feel and how things have been with you during the past 4 weeks. For each question please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…**

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a) Did you feel full of life? | ☐ | ☐ | ☐ | ☐ | ☐ |
| b) Have you been very nervous | ☐ | ☐ | ☐ | ☐ | ☐ |
| c) Have you felt so down in the dumps That nothing could cheer you up? | ☐ | ☐ | ☐ | ☐ | ☐ |
| d) Have you felt calm and peaceful? | ☐ | ☐ | ☐ | ☐ | ☐ |
| e) Did you have a lot of energy? | ☐ | ☐ | ☐ | ☐ | ☐ |
| f) Have you felt downhearted and Depressed? | ☐ | ☐ | ☐ | ☐ | ☐ |
| g) Did you feel worn out? | ☐ | ☐ | ☐ | ☐ | ☐ |
| h) Have you been happy? | ☐ | ☐ | ☐ | ☐ | ☐ |
| i) Did you feel tired? | ☐ | ☐ | ☐ | ☐ | ☐ |

**10. During the past 4 week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?**

| All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**11. How TRUE or FALSE is each of the following statements for you?**

| | Definitely true | Mostly true | Don't know | Mostly false | Definitely false |
|---|---|---|---|---|---|
| a) I seem to get sick a little easier than other people | ☐ | ☐ | ☐ | ☐ | ☐ |
| b) I am healthy as anybody I know | ☐ | ☐ | ☐ | ☐ | ☐ |
| c) I expect my health to get worse | ☐ | ☐ | ☐ | ☐ | ☐ |
| d) My health is excellent | ☐ | ☐ | ☐ | ☐ | ☐ |

## 18.4 EQ5D

**EQ-5D HEALTH QUESTIONNAIRE**

By placing a check-mark in one box in each group below, please indicate which statements best describe your own state of health today.

**Mobility**

| | |
|---|---|
| I have no problems in walking about | |
| I have some problems in walking about | |
| I am confined to bed | |

**Self-Care**

| | |
|---|---|
| I have no problems with self-care | |
| I have some problems with washing or dressing myself | |
| I am unable to wash or dress myself | |
| I have no problems with performing my usual activities | |

**Usual Activities** (e.g. work, study, housework, family or leisure activities)

| | |
|---|---|
| I have no problems with self-care | |
| I have some problems with washing or dressing myself | |
| I am unable to wash or dress myself | |
| I have no problems with performing my usual activities | |

**Pain/Discomfort**

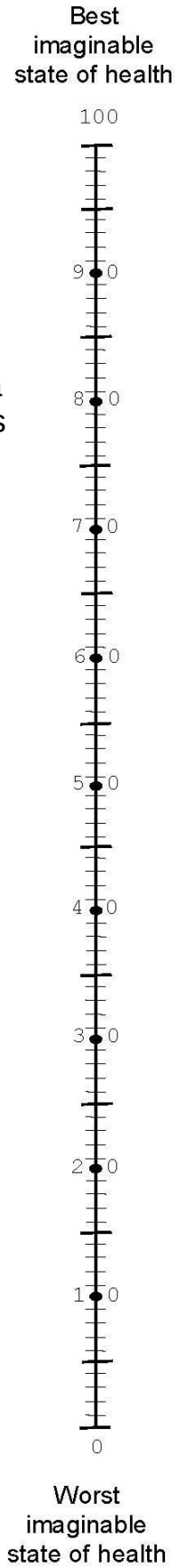
| | |
|---|---|
| I have no problems with self-care | |
| I have some problems with washing or dressing myself | |
| I am unable to wash or dress myself | |
| I have no problems with performing my usual activities | |

**Anxiety/Depression**

| | |
|---|---|
| I am not anxious or depressed | |
| I am moderately anxious or depressed | |
| I am extremely anxious or depressed | |

To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your
own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.



## 18.5 Modification of Diet in Renal Disease (MDRD) Estimated Glomerular Filtration Rate Calculation

The four variable MDRD equation is:

$$GFR = 186 \times Scr^{-1.154} \times age^{-0.203} \times 1.210 \text{ if black} \times 0.742 \text{ if female}$$

Note 1: serum creatinine (Scr) is given in mg/dl (divide by 88.4 to convert to µmol/L) and age is given in years.

Note 2: Use multiplier of 175 instead of 186 if sCr was IDMS-standardized. IDMS = isotope dilution mass spectrometry.

A free on-line calculator (available for serum creatinine in mg/dL or µmol/L) is available at:

http://www.hdcn.com/calcf/gfr.htm