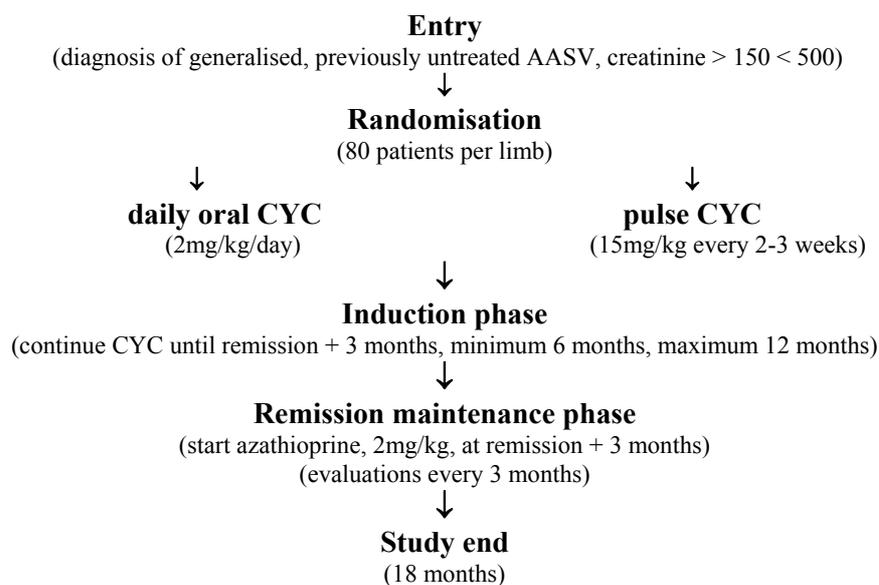


CLINICAL TRIAL PROTOCOL - CYCLOPS

Randomised trial of daily oral versus pulse Cyclophosphamide as therapy for ANCA-associated Systemic Vasculitis

Summary

The primary, ANCA-associated systemic vasculitides (AASV), including Wegener's granulomatosis and microscopic polyangiitis, are progressive, multisystem, autoimmune diseases which respond to immunosuppressive therapy. Their treatment with corticosteroids and cytotoxic drugs has been standardised in a first wave of studies (ECSYVASTRIAL project), but limitations of such regimens include only partial efficacy and appreciable treatment-related toxicity. The present trial, CYCLOPS, aims to reduce the cumulative exposure to immunosuppressive drugs by administering cyclophosphamide (CYC) as intermittent pulses. The potential benefit of using CYC in this way for AASV has been demonstrated in preliminary, smaller studies. Patients with previously untreated AASV and, "generalised", but not life threatening, disease with renal involvement, will be randomised to either continuous oral CYC or intermittent pulse CYC. CYC will be continued until three months after remission has been achieved, with a minimum CYC total duration of six months and maximum duration of twelve months; both limbs will then receive the same maintenance regimen of azathioprine and prednisolone. The study will last 18 months. The primary end-point is the disease-free period, taken as the period of time from remission until relapse or study end; secondary end-points are adverse effects, cumulative damage and immunosuppressive drug exposure. 160 patients will be required.



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1. Introduction to the trials

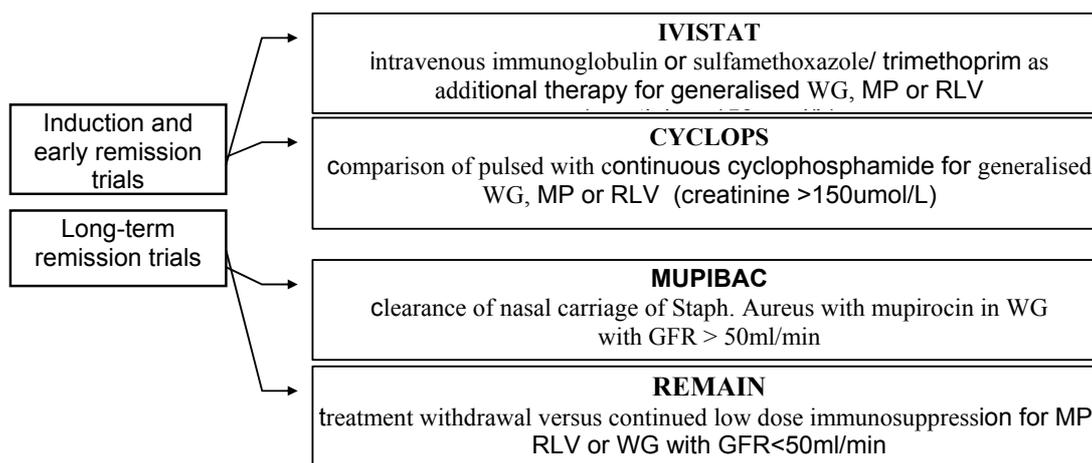
1.1. ECSYSVASTRIAL

The ECSYSVASTRIAL project started in January 1994 under the European Community (EC) BIOMED-1 concerted action programme. It aimed to design and standardise disease scoring and data collection methodology, facilitate therapeutic trials and harmonise the treatment of vasculitis within the EC. A first wave of clinical trials for ANCA-associated systemic vasculitis (AASV), (Wegener's granulomatosis, WG, microscopic polyangiitis, MP, and its renal-limited variant, renal-limited vasculitis, RLV), was launched in 1995, based on the extent and severity of disease (NORAM - early systemic disease; CYCAZAREM - generalised disease and MEPEX for severe renal disease) [1]. Four second wave protocols have subsequently been prepared which aim to improve outcome in AASV by introducing newer drugs and optimising long-term treatment regimens.

1.2. AVERT (ANCA-associated Vasculitis European Randomised Trials)

The AVERT project is the subject of a BIOMED-2 grant commencing during 1997. It aims to launch the four second wave trial protocols designed by the ECSYSVASTRIAL study group, identify prognostic markers at presentation and develop three European core facilities: a central serumbank, central histology review and trials database (appendix 6).

1.3. Second Wave trials



2. Aims of CYCLOPS

The aim of this trial is to optimise the treatment of remission induction for patients with generalised, but not immediately life-threatening WG and MP. There is the intent to reduce the toxicity of induction therapy. This will be achieved by reducing the overall dose of cyclophosphamide (CYC) during the induction period by using it in intermittent pulsed form. There is consensus that a regimen containing pulsed CYC will be associated with less toxicity than the current, "gold standard", continuous oral CYC regimen [2,3]. However, there are concerns that less toxicity may be at the expense of reduced efficacy [2-4]. Pulsed or oral continuous CYC will be used for remission induction which must be achieved within the first 9 months after study start. The maintenance medication will be azathioprine (AZA) for both limbs. So far, no formal comparison of the two regimens in a controlled study of efficacy and toxicity in patients with WG or MP has been undertaken.

3. Study design

3.1. Hypothesis

CYC Intermittent pulse therapy is as effective, but less toxic, for remission induction than continuous oral CYC in WG or MP with no immediately life-threatening organ manifestations.

3.2. Inclusion criteria (1,2,3 and 4 are required)

1. **A new diagnosis of WG, MP or renal-limited vasculitis (RLV)** (appendix 5). Patients not previously treated with cytotoxic drugs will be permitted.
2. **Renal involvement attributable to active WG, MP or RLV** with at least one of the following:
 - a) elevated serum creatinine between 150 and 500 $\mu\text{mol/l}$.
 - b) biopsy demonstrating necrotizing glomerulonephritis.
 - c) red cell casts.
 - d) haematuria with >30 red blood cells/high powered field and proteinuria $> 1\text{g}/24\text{hr}$.
3. **ANCA positivity or confirmatory histology or both** (appendix 5). ANCA positivity requires a typical CANCA pattern by indirect immunofluorescence (IIF), (preferably confirmed by anti-PR3 ELISA), or the presence of PR3-ANCA or MPO-ANCA determined by ELISA, PANCA requires confirmation by anti-MPO ELISA [6]. (Central review of ANCA serology and histology will be performed).
4. **Age 18-80 years.**

3.3. Exclusion criteria

1. More than two weeks treatment with cyclophosphamide (CYC) or other cytotoxic drug within previous year or with oral corticosteroids (OCS) for more than 4 weeks. If the patient has received $>1.0\text{g}$ of methyl-prednisolone prior to the study start, discuss with trial co-ordinator.
2. Co-existence of another multisystem autoimmune disease, e.g. SLE.
3. Hepatitis Be antigen positive or Hepatitis C antibody positive.
4. Known HIV positivity (HIV testing will not be a requirement for this trial).
5. Serum creatinine $> 500\mu\text{mol/l}$ (consider MEPEX trial).
6. Immediately life-threatening organ manifestations (e.g. lung haemorrhage or dialysis dependence).
7. Previous malignancy (usually exclude unless agreed with trial co-ordinator).
8. Pregnancy or inadequate contraception if female.
9. Anti-GBM antibody positivity.

3.4. Interventions

1. **Drug regimens**
 - a) At entry, patients who fulfil the inclusion criteria will be randomised to continuous oral CYC or pulsed CYC oral/ intravenous (initially strictly intravenous (I.V.) then oral or I.V.) for remission induction (appendix 3).
 - b) All patients will receive the same daily OCS regimen and will proceed to the same remission maintenance medication (appendix 3).
2. **Evaluations**
 - a) Study assessments will be performed at entry 1.5, 3, 4.5, 6, 7.5, 9, 12, 15 and 18 months and at the time of relapse (appendix 5).
 - b) Blood will be drawn at the same time points as above, apart from additional monitoring of the blood count under CYC or AZA treatment ("notes for drug regimens", appendix 3).
 - c) Birmingham Vasculitis Activity Score (BVAS) will be done at each assessment and at relapse; the Short form-36 patient functional questionnaire (SF-36) and the Vasculitis Damage Index (VDI) will be done every 3 months [6-8]. The disease extension index (DEI) will be computed from the BVAS data [4,9].
3. The study ends at 18 months.

3.5. End-points

1. The primary end-point is the "disease free period" (DFP). The DFP is the period between the achievement of remission and the first relapse or study end.
2. Secondary end-points are:
 - a) time to remission and percentage in remission ($BVAS \leq 1$) at six months.
 - b) relapse rate.
 - c) intolerance to study medications and adverse effects.
 - d) cumulative damage (VDI) and SF-36 rates.
 - e) cumulative doses of CYC and corticosteroids.
 - f) cumulative ANCA and CRP levels.
 - g) glomerular filtration rate at 18 months.

3.6. Adverse-effects

1. The presence of adverse-effects will be actively sought and will be recorded on standardised forms
2. Adverse-effects sufficient to withdraw a medication will be determined after discussion with a trial co-ordinator.

3.7. Withdrawal

1. Patients may withdraw from the trial at their or their physician's request without explanation; where possible the reason for withdrawal will be noted in the Patient Record Book.
2. Patients not achieving remission within 9 months are considered as failures and withdrawn from the trial drug regimen and their treatment will follow local practice, but they will remain under follow-up in the trial (appendix 3).

4. Statistical analysis (supervised by Dr J Hermans)

1. Patients will be stratified at entry by diagnosis (WG or MP/RLV)(appendix 5).
2. The combined outcome measure of the remission rate and the early relapse rate, deemed the "disease free period", (DFP), will be used. DFP is taken from time of remission to the time of relapse; for patients that do not reach remission within 9 months DFP will be taken to be zero. Assuming in the oral continuous CYC limb a remission rate of 90% by 9 months and a rate of early relapse of 15 %, there will be 75% of patients with a DFP of 9 months. Should the percentage with a DFP of 9 months in the pulse CYC limb be 55% or less, this will be detected. With a significance level of 0.05, a power of 0.8 and a one-sided design, 160 patients are needed.

5. Ethical Considerations

1. CYCLOPS aims to reduce toxicity of induction therapy in vasculitis through the use of pulsed CYC. The control limb will be treated with a standard induction regimen designed by consensus.
2. Approval for the study will be sought from local ethical committees.
3. Patients will only be entered after they have given written, informed consent.
4. Details of patients' identities will be restricted to the local investigator only .
5. Data will be coded prior to any computer entry and study databases will be independent from computer networks. Confidentiality of patient data will be respected.
6. Participation in this study should not require additional tests or clinic attendances above normal practice, apart from the drawing of an additional 10ml of blood (appendix 4).

6. Trial administration

The AVERT Trial Management Subcommittee (TRIM) has overall responsibility for the trials. The trial co-ordinators are available to give advice on patient management and drug administration.

6.1 Trial administration office (TAO)

1. Patient registration forms (P.4) will be faxed to the TAO.
2. The TAO will register and randomise patients and dispatch a Patient Record Book.
3. Patient activity will be monitored by three monthly data returns from participating centres.
4. Trial data will be entered by the TAO into the central database.
5. The TAO will submit three monthly reports of trial progress to the trial management subcommittee.

6.2 Data Collection

1. Patient Record Book: either solely by entry into the Patient Record Book, or by use of the VITAL software programme for scoring tools (BVAS, VDI and SF-36) and laboratory variables supported by the Patient Record book for trial specific data. Three monthly postal returns of data.
2. Histology Review: following patient entry central review of renal and respiratory tract histology will be performed. Histology images will be computer archived and slides returned.
3. Central serumbank: 5ml of sera to be taken at entry and three monthly until the study end. Sera will be batched and shipped frozen to the serumbank.

6.3. National networks

1. Participating centres will be organised into national networks, co-ordinated by an AVERT member.
2. The national co-ordinator will be responsible for local supervision and data collection.

6.4. Independent Review Board

1. An Independent Review Board has been appointed (Prof. Stewart Cameron, UK; Prof. Claudio Ponticelli, Italy and Dr Geert Schou, Denmark).
2. Annual reports will be submitted by the trial co-ordinators to the Independent Review Board concerned with recruitment rate, adverse effects and data returns.
3. After 50% of patients have been recruited there will be a review of primary end-point data, which will be blinded to the participants, and will allow early identification of unexpected variations in therapeutic response between limbs.

6.5. Finances

1. Trial administrative costs will be provided by the AVERT project.
2. There will be no contribution to other medical costs which should not be influenced by participation into the trial.

6.6. Trial Duration

1. Trial launch in February 1998.
2. Recruitment by 2000 - 2002 (24-48 months).
3. Follow-up complete by 2002-2004 (24 months).
4. Data analysis and results by late 2002-2004 (6 months).

Appendix 1. Background

A.1.1. The diseases

The primary systemic vasculitides are multisystem autoimmune disorders of unknown cause which are potentially fatal and often result in long-term morbidity and incapacity. The presence of circulating autoantibodies to neutrophil cytoplasmic antigens (ANCA) has helped to define those systemic vasculitides predominantly affecting small blood vessels, Wegener's granulomatosis (WG) and microscopic polyangiitis (MP), as ANCA-associated vasculitides (AASV) [10-12]. This grouping is supported by similarities in histological appearance and response to therapy of these syndromes; also, the existence of early and organ-limited forms, such as renal-limited vasculitis (RLV) is now clearly recognised. Their annual incidence exceeds 20 per million per year and they account for at least 5 % of causes of end stage renal failure [10]. They have been presumed to have an autoimmune basis due to their association with ANCA, the abnormal behaviour of immune reactants in the circulation and at sites of injury, and by their response to immunosuppressive medication [13,14]. However, no immunogenetic predisposition has been clearly demonstrated, and in some cases these diseases have been causally linked with certain drugs, infections, or occupational exposures.

A.1.2. Their treatment

Untreated, generalised WG and MP follow a progressive course with a fatal outcome due to vital organ failure; but with the empirical introduction of corticosteroids and cytotoxic agents, five year survival was increased from under 20% to over 60% [15-18]. Although unsupported by controlled study, the combination of oral corticosteroids (OCS) and cyclophosphamide (CYC) has become established as standard therapy for WG and MP, and is effective at controlling disease progression in up to 90% of patients [17,18]. Their limitations are: firstly, disease remission may only be partial or despite absence of objective vasculitic activity the restoration of health is delayed or incomplete; secondly, 25-40% of patients relapse within the first two years, as therapy is reduced, and many pursue a chronic, grumbling course; thirdly, this combination of drugs has a narrow therapeutic index and treatment-related morbidity and mortality rivals that caused by the underlying disease [18]. Of particular concern has been the late damage resulting from high cumulative exposure to OCS and CYC such as osteoporosis, infertility and cancer.

Appendix 2. Study Medications

A.2.1. Cyclophosphamide

Cyclophosphamide is an inactive pro-drug, converted by the mixed function oxidase system in the liver to the alkylating agents 4-hydroxy-cyclophosphamide and phosphoramidate mustard, which alkylate guanine nucleotides, thus blocking cell division [19]. Bioavailability after oral administration is greater than 75%, but there are large variations between individuals in the rate of production of active metabolites. A phenotypic variation in carboxylase activity affects the production of the inactive metabolite carboxyphosphoramidate from 4-hydroxy-cyclophosphamide, which may influence efficacy and toxicity. The relation of renal and hepatic failure to the production and elimination of active metabolites has not been fully determined. Bladder toxicity is caused by renal excretion of the metabolite acrolein which can cause haemorrhagic cystitis and a markedly increased risk of bladder cancer [18,20,21]. Other adverse-effects include nausea and vomiting, myelosuppression with neutropaenia, infections due to immunosuppression, alopecia and infertility [22,23]. Permanent ovarian failure occurs in over 50% of women after one year's exposure and is age-related; male infertility has been less well studied. The incidence of leukaemia and lymphoma is increased tenfold with prolonged administration; less common adverse-effects include pulmonary fibrosis, hepatitis and inappropriate ADH secretion.

A.2.2. Azathioprine

After hepatic conversion to 6-mercaptopurine, the cytotoxic effects of azathioprine are mediated by the impairment of purine synthesis and incorporation of purines into DNA, and of the endonuclease repair activity of DNA polymerase [19]. The drug is well absorbed after oral administration and elimination requires hepatic metabolism by xanthine oxidase; an important drug interaction is with xanthine oxidase inhibitors, such as allopurinol. Lymphocyte function is reduced, and there is suppression of the cellular component of the inflammatory response. The major adverse effects are nausea and vomiting, dose-dependent myelosuppression and reversible, cholestatic, hepatic toxicity. There is an increased incidence of skin cancers and lymphomas following administration for more than two years after organ transplantation.

A.2.3. Prednisolone

Prednisolone is a synthetic derivative of cortisone with widespread influences on metabolism and organ function. Desirable effects in vasculitis relate to the suppression of acute and chronic inflammatory processes and immune cell function. The major short-term adverse-effects of OCS are salt and water retention, hypertension, hyperglycaemia, central nervous system stimulation, peptic ulceration and immunosuppression. While such effects are reversible, if the use of OCS is prolonged additional adverse-effects including osteoporosis, subcapsular cataracts, skin fragility, myopathy, Cushingoid facies, hirsutism, alopecia, fat re-distribution and striae may occur [19]. Of note in vasculitis has been the correlation of the cumulative OCS dosage with the total incidence of adverse-effects, and with infections.

Appendix 3. Drug Regimens

A.3.1. Induction/consolidation regimen for daily oral CYC

	Time	dosage ²
Induction:	month 0 - 3 ¹	2.0 mg/kg/day
Consolidation:	following remission for 3 months	1.5 mg/kg/ day

Note:

1. If remission is not achieved by 3 months, continue 2mg/kg/day, until remission is achieved, then reduce CYC dose to 1.5 mg/kg/day for a further 3 months after remission (consolidation phase). Remission must be achieved by 9 months, so that the longest total treatment period with CYC is 12 months (appendix 3.3.).
2. CYC dose reduction for age > 60 years (appendix 3.8.1.).

A.3.2. Induction/consolidation regimen for pulsed CYC:

Time (weeks) ¹	pulse no. ²	route	dosage ³
0	1	intravenous (I.V.)	15 mg/kg
2	2	I.V.	15 mg/kg
4	3	I.V.	15 mg/kg
7	4	I.V. or oral	15 mg/kg I.V. or 5 mg/kg orally for 3 days
10	5	I.V. or oral	15 mg/kg I.V. or 5 mg/kg orally for 3 days
13	6	I.V. or oral	15 mg/kg I.V. or 5 mg/kg orally for 3 days
16	7	I.V. or oral	15 mg/kg I.V. or 5 mg/kg orally for 3 days
19	8	I.V. or oral	15 mg/kg I.V. or 5 mg/kg orally for 3 days
22	9	I.V. or oral	15 mg/kg I.V. or 5 mg/kg orally for 3 days
25	10	I.V. or oral	15 mg/kg I.V. or 5 mg/kg orally for 3 days

Note:

1. The first 3 pulses are given at intervals of 2 weeks and must be given I.V.. If it is decided to give the subsequent pulses orally, which is recommended, the dose of CYC should be divided over 3 days giving 5 mg/kg each day. If it is decided to give the subsequent pulses I.V., the entire dose of CYC (15 mg/kg) can be given on one day.
2. This regimen implies remission within 3 months and a further 3 months of pulse CYC after entry into remission (i.e. 6 months in total). Should remission not be achieved by 3 months, continue CYC pulses at 3 week intervals until remission is reached, then give another 3 months of CYC pulse therapy before you proceed to the remission maintenance regimen. Remission must be reached by 9 months and the total duration of CYC must not exceed 12 months as above (appendices 3.1. and 3.3.).
3. CYC dose reduction for age > 60 and for creatinine 300-500umol/l (appendix 3.8.2.).

A.3.3. Failure to achieve remission by 9 months

1. The trial co-ordinators should be informed.
2. Treatment should follow local practice in consultation with the trial co-ordinators.
3. Trial data collection should continue and the patient remains in the trial.
4. See appendix 3.6. below.

A.3.4. Remission maintenance regimen - all groups: azathioprine

1. Switch CYC to azathioprine (AZA), 3 months after remission achieved.
2. AZA dose is 2mg/kg/day from 3 months after remission to the end of the trial (18 months).
3. AZA dose reduced for age > 60 years (appendix 3.8.3.).

A.3.5. Prednisolone regimen (same for both limbs)

time from entry (weeks)	prednisolone dosage¹ (mg/kg/day)	prednisolone dosage (mg/day for 60 kg)
0	1	60
1	0.75	45
2	0.5	30
3	0.4	25
6	0.33	20
8	0.25	15
	prednisolone dosage (mg/day)	
reduce at end of month 3	12.5	12.5
reduce at end of month 5	10	10
during months 12 - 15	7.5	7.5
during months 15 - 18	5	5

Note:

1. Flexibility in prednisolone dose of +/- 12.5% allowed in the first 12 weeks and 25% thereafter.

A.3.6. Failure to control disease activity or to achieve remission

1. Either treatment limb: for failure to control progressive disease activity during the remission induction period: (rising serum creatinine or progression of disease activity in other vital organs), additional treatment is recommended with I.V. methyl-prednisolone, 15 mg/kg/day for 3 days (maximum 1 g/day) and/or to follow local practice. Preliminary data also suggest, that any patient who fails on methyl-prednisolone pulse treatment may do better on continuous oral CYC; so if a patient is in the pulse CYC limb the trial co-ordinator should be contacted. All patients should remain in the trial for the purposes of data follow-up even if they depart from the trial drug regimen.
2. If remission is not achieved after 9 months: In pulse limb, switch to continuous OCS and CYC. For continuous limb, consider adjunctive treatment and discuss with trial co-ordinator.

A.3.7. Changes to drug regimens for relapse

These are non-obligatory guidelines, additional or alternative regimens may follow local practice. Relapsing patients should remain in the trial with protocol departures (drugs and doses etc.) noted in the Patient Record Book, despite the fact that relapse is a primary end-point.

A.3.7.1. Major relapse (appendix 4)

1. For daily oral CYC regimen: increase, or start, CYC at 2mg/kg/day. Increase OCS to 0.5mg/kg/day, reduce to 20mg/day by four weeks.
2. For pulse CYC regimen: increase CYC pulse frequency to two week intervals for three pulses or until remission achieved, then three week intervals for three pulses and then return to the protocol. Increase OCS to 0.5mg/kg/day, reduce to 20mg/day by four weeks.
3. If ineffective after 2 months, or if life-threatening, follow local preference or discuss with trial co-ordinator.
4. When remission achieved return to 3 month point on drug regimen.

A.3.7.2. Minor relapse (appendix 4)

1. Increase OCS to 0.5mg/kg/day, reduce to 15mg/day by four weeks.
2. If relapse occurs during remission maintenance phase, increase AZA to 2mg/kg/day.
3. If the relapse occurs remission induction or consolidation phases:
 - a) For daily oral CYC regimen: increase, or start, CYC at 2mg/kg/day.
 - b) For pulse CYC regimen: give next CYC pulse after two weeks and then return to the protocol.
4. When remission achieved return to drug regimen at 3 month point.

Relapsing patients will remain in the study and all changes in drugs and doses should be recorded in the patient record book.

A.3.8. Notes for drug regimens

A.3.8.1. Daily oral cyclophosphamide

1. Maximum dose is 200mg.
2. Round dose down to nearest 25mg (may vary alternate day dosage, e.g. 100 and 150mg).
3. Age > 60 years, reduce dose by 25%, > 75 years by 50%.
4. Administer dose in the morning and maintain good hydration.
5. Check full blood count (FBC):
 - a) weekly for first month.
 - b) two-weekly for second and third month.
 - c) monthly thereafter.
6. Mesna is optional. The dose is the same as the cyclophosphamide dose, either from the I.V. vial orally or in form of tablets.

A.3.8.2. Pulsed Cyclophosphamide

Pulsed CYC dose reductions for renal function and age		
age (years)	creatinine (umol/l)	
	150-300	300-500
< 60	15 mg/kg/pulse	12.5 mg/kg/pulse
> 60 and < 70	12.5 “ “ “	10 “ “ “
> 70	10 “ “ “	7.5 “ “ “

1. Reductions for renal function and age according to table above.
2. Maximum CYC pulse is 1.2g.
3. Dissolve cyclophosphamide in water for injection, then dilute in saline 0.9% 500 ml and administer as I.V. drip over one hour.
4. Mesna is optional and will be administered orally in the same dose in mg as CYC in mg either from I.V. vials or in the form of tablets on days when CYC is administered. (If it has to be administered I.V., reduce mesna dose to 60% of the CYC dose).
5. Prevention of emesis: the choice of antiemetic drugs to cover the CYC pulses should follow local practice. Ondansetron is suitable for this indication.
6. Check FBC on day of pulse or previous day. If WBC prior to pulse < $4 \times 10^9/L$, then postpone pulse until WBC > $4 \times 10^9/L$, while checking WBC at least weekly. Reduce dose of pulse by 25%. With any further episodes of leucopenia, make equivalent dose reduction.
7. Check FBC between days 10 and 14 after a pulse. If the leucocyte nadir (i.e. the lowest leucocyte count between two CYC pulses) is < $3 \times 10^9/L$, even if the WBC just previous to the next pulse is > $4 \times 10^9/L$, then reduce the dose of the next pulse by:
 - a) leucocyte nadir 1 - $2 \times 10^9/L$ reduce CYC dose of last pulse by 40 % of previous dose.
 - b) leucocyte nadir 2 - $3 \times 10^9/L$ reduce CYC dose of last pulse by 20 % of previous dose.

A.3.8.3. Azathioprine

1. Maximum dose is 200mg.
2. Round dose down to nearest 25mg (may vary alternate day dosage, e.g. 100 and 150mg).
3. Age > 60 years, reduce dose by 25%, > 75 years by 50%.
4. Check full blood count (FBC) and ALT or AST (for hepatotoxicity):
 - a) two-weekly for one month.
 - b) two monthly for first year, then three monthly.

A.3.8.4. Leucopaenia

1. Stop oral CYC/AZA if white blood cells (WBC) < $4 \times 10^9/L$.
2. Restart with dose reduced by 25% when WBC > $4 \times 10^9/L$. Monitor weekly for four weeks.
3. If severe (< $1 \times 10^9/L$) or prolonged (< $4 \times 10^9/L$ for > 2 weeks), restart CYC/AZA at 50mg/day, increasing to target dose as weekly WBC permits. *Pneumocystis carinii* pneumonia and fungal prophylaxis are recommended, G-CSF may be considered.
4. For falling WBC (< $6 \times 10^9/L$ and fall of > $2 \times 10^9/L$ over previous count), reduce dose by 25%.

A.3.8.5. Prednisolone

1. Maximum dose in first week is 80mg/day.
2. Round dose to nearest 5mg above 20mg, and nearest 2.5mg below 20mg.
3. Single daily dose (may vary alternate day dosage by up to 5mg, i.e. 10 and 15 mg on alternate days).
4. Use either prednisone or prednisolone, avoid enteric coated or soluble forms.
5. Patients intolerant of oral medication may receive any I.V. steroid at an equivalent dose as a daily injection.
6. A flexibility in dose of $\pm 12.5\%$ from the protocol will be allowable in the first 12 weeks and $\pm 25\%$ thereafter.
7. Minimum dose in first three months is 10mg/day.

A.3.8.6. Prophylaxis (suggested only):

1. Gastric protection: ranitidine or omeprazole, not cimetidine or misoprostol, for 6 months
2. *Pneumocystis carinii* pneumonia: avoid unless strong local preference, sulfamethoxazole/trimethoprim 480mg three times a week or monthly aerosolised pentamidine may then be used, stop at 3 months
3. Fungal infection: oral fluconazole, nystatin or amphotericin, for 12 weeks
4. Bone protection: calcium and vitamin D tablets to those > 50 years.

Appendix 4. Study Evaluations

Minimum information required for the study. Additional tests to follow local practice.

A.4.1. Entry

1. VITAL Scores¹:
 - a) Birmingham Vasculitis Activity Score: (BVAS) [6].
 - b) Vasculitis Damage Index: (VDI) [8].
 - c) Short form 36 score: (SF-36) [7].
2. Haematology
 - a) Full blood count (FBC): haemoglobin (Hb), white cell count (WBC), neutrophil, lymphocyte and platelet counts.
 - b) ESR.
3. Biochemistry
 - a) Serum creatinine and GFR (creatinine clearance or isotope study).
 - b) ALT or AST, alkaline phosphatase, albumin, glycated haemoglobin (such as, HbA1c).
 - c) C-reactive protein (CRP).
4. Immunology
 - a) IgG, IgA and IgM levels.
 - b) ANCA (IIF, PR3 and MPO ELISA).
 - c) ANA, rheumatoid factor, cryoglobulins, complement (C3 and C4).
 - d) Hepatitis BsAg (if positive, check HBeAg), Hepatitis C Antibody.
5. Other
 - a) 5ml serum saved.
 - b) Urine microscopy for red cells and red cell casts .
 - c) Urine dipstick for protein (24hr quantification if present).

A.4.2. 1.5, 3, 4.5, 6, 7.5, 9, 12, 15 months and at relapse

1. BVAS score.
2. VDI and SF-36 scores every 3 months .
3. FBC: Hb, WBC, neutrophil, lymphocyte and platelet counts, ESR.
4. Serum creatinine and CRP.
5. ANCA, urine dipstick², and 5ml serum saved.

A.4.3. Study end (18 months)

1. VITAL scoring (BVAS, VDI and SF-36).
2. Hb, WBC, neutrophil, lymphocyte and platelet counts, ESR.
3. Serum creatinine and GFR (creatinine clearance or isotope study).
4. AST or ALT, alkaline phosphatase, albumin, HbA1, CRP.
5. ANCA, urine dipstick, and 5ml serum saved.

Note:

1. VITAL is a composite of the Birmingham Vasculitis Activity Score (BVAS), the Vasculitis Damage Index (VDI), the Short-Form-36 (SF-36) functional assessment score [6-8]. BVAS and VDI have been validated and BVAS will contribute to definition of remission and relapse in this study. The disease extension index (DEI) score will be computed from the BVAS data [4].
2. If there is occurrence of new macroscopic haematuria, a cystoscopy should be performed. Consider cystoscopy for new microscopic haematuria. If haemorrhagic cystitis is confirmed, 6-monthly surveillance cystoscopies should be performed.

Appendix 5. Disease Definitions

A.5.1. Wegener's granulomatosis

Generalised WG is characterised by granulomatous inflammation of the respiratory tract, together with necrotizing vasculitis affecting small to medium-sized vessels; necrotizing glomerulonephritis is common and reflects renal involvement [12]. A CANCA pattern by IIF, with specificity for proteinase 3 (PR3-ANCA) by ELISA, is found in over 90% of untreated patients with generalised WG; some studies have found a minority of cases to have ANCA with specificity for myeloperoxidase (MPO-ANCA) instead of PR3-ANCA. In WG with disease localised to the respiratory tract, ANCA positivity is less frequent.

For the purposes of this study, a diagnosis of WG requires the presence of chronic inflammation, with a history of at least four weeks and not attributable to another cause, supported by characteristic histology on biopsy and/or detectable CANCA by IIF, or PR3-ANCA or MPO-ANCA by ELISA. In cases of diagnostic doubt the trial co-ordinator should be consulted.

Characteristic or confirmatory histology for non-renal biopsies requires the exclusion of other causes and an inflammatory exudate dominated by polymorphonuclear leucocytes with at least one of the following:-

1. necrotizing vasculitis affecting small to medium-sized vessels.
2. epithelioid granulomata.
3. giant cells.

Generalised WG requires the involvement of an extra-respiratory tract organ (e.g. kidney, skin, nervous system) in addition to respiratory tract disease. Constitutional symptoms (e.g. fever, headache, myalgia, arthralgia, tiredness, weight loss of >2 kg) themselves do not constitute extra-respiratory involvement but indicate that the disease is active and systemic. Disease only involving one non-vital organ (usually the upper respiratory tract) with less than two constitutional symptoms is defined as localised disease.

A.5.2. Microscopic polyangiitis

MP is characterised by a vasculitis predominantly affecting small vessels. In contrast to WG, granulomata are absent, and inflammation of the upper respiratory tract and/or lung nodules are absent. Renal involvement is usual and is reflected by a necrotizing glomerulonephritis. Arteritis of medium-sized vessels may also occur [12]. MP is associated with MPO-ANCA or PR3-ANCA; a minority of MP patients are ANCA negative or recognise other ANCA autoantigens. For the purposes of this study, patients may be entered in the category of MP if they have a chronic inflammatory process with non-granulomatous vasculitis of small vessels (i.e. capillaries, venules, arterioles or small arteries).

A.5.3. Renal-limited vasculitis

Isolated pauci-immune necrotising and crescentic glomerulonephritis, typically known as idiopathic rapidly progressive glomerulonephritis, has many features to suggest that it represents a renal-limited form of WG or MP, including the presence of circulating MPO-ANCA or PR3-ANCA antibodies.

A.5.4. Remission

Full clinical remission is indicated by:

1. complete absence of clinical disease activity using the BVAS item list.
2. The absence of renal disease activity is indicated by stable or falling creatinine and the absence of red cell casts.
3. The absence of pulmonary activity is indicated by.
 - a) resolution of radiological opacities.
 - b) reduction in size existing lesions unless attributable to scarring.
 - c) no new lesions.
4. Diagnosis of complete remission is supported by a normal CRP.

A.5.5. Relapse

1. Major relapse requires the recurrence or new appearance of major organ involvement such as the following, if they are attributable to active vasculitis [24]:
 - a) an increase in serum creatinine of >30% or reduction in creatinine clearance of >25%, within a period of three months or histological evidence of active, focal, necrotizing glomerulonephritis. Biopsy is strongly recommended for recurrent haematuria or unexplained rise in creatinine.
 - b) clinical, radiological or bronchoscopic evidence of pulmonary haemorrhage or granulomata. Biopsy may be appropriate for undiagnosed opacities.
 - c) threatened vision, e.g. increasing orbital granuloma or retinal vasculitis.
 - d) significant subglottic or bronchial stenosis.
 - e) new multifocal lesions on brain MR suggestive of cerebral vasculitis.
 - f) motor mononeuritis multiplex.
 - g) gastro-intestinal haemorrhage or perforation.

2. Minor relapse requires the recurrence of disease activity of less severity, such as the following, if they are attributable to active vasculitis [24]:
 - a) ENT: epistaxis, crusting, pain, new deafness, active nasal ulceration or proliferative mass at nasal endoscopy.
 - b) mouth ulcers.
 - c) rash.
 - d) myalgia, arthralgia, arthritis.
 - e) episcleritis or scleritis.
 - f) pulmonary symptoms without or with minor radiological changes, e.g. cough, wheeze, dyspnoea.

3. Relapse is supported by:
 - a) exacerbation of at least two constitutional symptoms (new malaise, weight loss, fever or night sweats).
 - b) rise in CRP.

4. If in doubt, contact a trial co-ordinator.

Note:

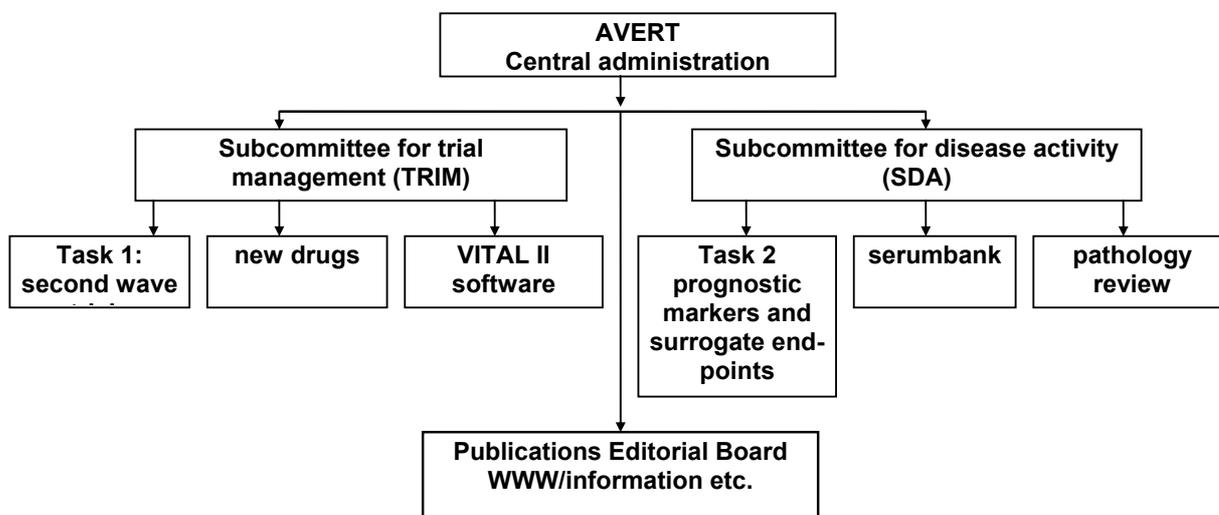
A rising ANCA may signify relapse. Such patients should be watched more closely.

Appendix 6. AVERT Organisation

A.6.1. AVERT study group members

Name	Centre	Fax numbers
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C Feighery	Dublin, Ireland	353 1 4545 609
F Ferrario	Milan, Italy	39 2 4022 2222
G Gaskin	London, UK	44 181 383 2410
G Gregorini	Brescia, Italy	39 30 3995 012
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P Lesavre	Paris, France	33 1 4566 5133
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E Mirapeix	Barcelona, Spain	34 3 227 5444
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A.6.2. AVERT management structure



References

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P.1. CYCLOPS - Summary of Practical Procedures

Potentially suitable ?

- male or female, 18-80 years with WG, MP or RLV
 - Creatinine > 150 and < 500
 - ANCA positive or confirmed by biopsy
 - informed consent given
-

Ready to enter ?

- fax registration form to trial office for randomisation (P.4.)
 - score BVAS, VDI and SF-36, baseline laboratory data and store sera
 - save histology slides for subsequent central review
-

Entry

- your patient will be randomised to one of two limbs :-
 - continuous oral CYC or pulse CYC
 - commence CYC and OCS according to regimen patient is randomised to:
 - continuous oral (2mg/kg/day) **or** pulse (15mg/kg initially IV every 2 weeks)
 - OCS 1mg/kg/day
-

Remission induction phase (minimum 0-6, maximum 0-12 months)

- at 1.5, 3, 4.5, 6, 7.5, 9 and 12 months
 - score BVAS, laboratory data and store sera
 - every 3 months score VDI and SF-36
 - continue CYC until 3 months after remission achieved
 - if no remission by 9 months
 - withdraw from trial drug regimen and follow local practice
 - patient remains in the trial, continue to collect data
-

Remission maintenance phase (6-12 to 18 months)

- starts 3 months after remission achieved, earliest 6, latest 12 months from entry
 - stop CYC and start AZA
 - taper azathioprine and prednisolone according to regimen
 - every 3 months and at relapse: BVAS, VDI, SF-36, laboratory data and store sera
-

End of the study (18 months)

- complete termination record
 - data to trial database
 - sera to central serumbank
 - slides to central histology review

P.2. Clinical Trial: Patient Information Sheet

(This may be modified to meet local requirements)

Pulsed versus continuous oral cyclophosphamide (CYC) as therapy for Systemic Vasculitis (CYCLOPS)

We would be grateful if you could consider participating in this project investigating which is the best way of giving the drug cyclophosphamide as treatment for your condition. As you know, you are suffering from a form of inflammation of the blood vessels or vasculitis. The standard treatment of this condition consists of a combination of corticosteroids and cyclophosphamide tablets which are usually given every day to control the disease. These tablets are thought to be the best treatment we have available but frequently cause side-effects which can be serious.

Over the past few years some doctors have given cyclophosphamide intermittently every few weeks. This pulse or intermittent dose is given over 3 days in quite a large amount, but over a period of months the TOTAL dose is less than that which would be given if the drug is taken daily. This is thought to reduce the side-effects. This study will examine whether the intermittent regimen is as effective as the daily regimen and whether there will be fewer side-effects.

The side-effects associated with the standard therapy include lowering of the blood count, increased susceptibility to infection, stomach irritation, difficulty sleeping, weight gain, hair loss, nausea, bladder irritation, thinning of the bones (osteoporosis), infertility, liver inflammation, skin rashes, foetal damage and an increased risk of diabetes, high blood pressure and cancer. You will be regularly assessed by a doctor and by blood tests to detect and treat any side-effects, and will also receive tablets to reduce the risk if infection, stomach irritation and bladder irritation. Milder side-effects, which will get better as the drug doses are reduced, occur in nine out of ten patients; while more serious side-effects, such as those needing a hospital admission, occur in one in ten patients. It is essential that women of child-bearing age use efficient contraception to prevent pregnancy during the study.

As part of your routine care, we will perform a number of blood and urine tests which will be repeated initially at weekly intervals, then less frequently as your condition improves. We require, for research purposes, an additional small quantity of blood at your visits, but this will not need an extra needle puncture. All patients will be given the same treatment after 6-12 months (once the condition is under control). This will consist of other tablets called azathioprine combined with a smaller dose of corticosteroids. Azathioprine is a less potent but also less toxic drug and will be given to maintain control of the disease. You will also be asked to complete a questionnaire about how you are feeling at the beginning of the study and after every three months. The trial will last for two years.

Your personal medical information may be scrutinised by properly authorised persons but will be treated as strictly confidential. Details of your case will be stored in an anonymous form on a computer, but will not be available to anyone not directly involved in this trial; the computer will not be connected to any computer networks.

If you do not wish to take part in this study, your treatment will not be affected in any way; you are also free to withdraw from the study at any stage without giving an explanation and without influencing the care you receive from your doctors.

If you have any questions about your treatment or this study please contact:

Dr.

Tel:

P.3. Consent form

(This form may be replaced to meet local requirements)

CYCLOPS clinical trial

(Pulsed versus continuous oral cyclophosphamide (CYC) as therapy for systemic vasculitis)

The details of this study have been explained to me by

.....

I fully understand what is involved and any questions I have about the study have been answered satisfactorily. I also understand that I may withdraw from the study without my care being affected.

Signed (patient)Date

Signed (investigator) Date

Signed (witness) Date

(The witness's duty is to make sure the patient understands what is involved. The witness may not be directly associated with this study, and should indicate his/her status.)

P.4. CYCLOPS TRIAL**PATIENT REGISTRATION**

Copy, complete and fax this form to register patients for entry into CYCLOPS.
A reply will be faxed within 48 hours.

Centre details

From Dr		<input type="text"/>
Centre		<input type="text"/>
FAX		<input type="text"/>
Date	dd/mm/yy	<input type="text"/> / <input type="text"/> / <input type="text"/>

Patient details

Date of entry	dd/mm/yy	<input type="text"/> / <input type="text"/> / <input type="text"/>
Date of birth	dd/mm/yy	<input type="text"/> / <input type="text"/> / <input type="text"/>
Sex	M/F	<input type="text"/>

Please Fax this form to:

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