Clinical Trial Protocol

Trial Title:	Biologics in refractory vasculitis (BIOVAS): A pragmatic, randomised, double-blind, placebo-controlled, modified-crossover trial of biologic therapy for refractory primary non-ANCA associated vasculitis in adults and children
Protocol Number:	BIOVAS
EudraCT Number:	2019-003964-30
Investigational Products:	Infliximab, rituximab and tocilizumab
Protocol Version:	4.0

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Cambridge University Hospitals NHS Foundation Trust

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1. Protocol Signatures:

I give my approval for the attached protocol entitled "Biologics in refractory vasculitis (BIOVAS): A pragmatic, randomised, double-blind, placebo-controlled, modified-crossover trial of biologic therapy for refractory primary non-ANCA associated vasculitis in adults and children" Version 4.0 dated 17th November 2021

Chief Investigator

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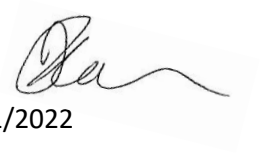
Signature: 

Date: 12/01/2022

Site Signatures

I have read the attached protocol entitled "Biologics in refractory vasculitis (BIOVAS): A pragmatic, randomised, double-blind, placebo-controlled, modified-crossover trial of biologic therapy for refractory primary non-ANCA associated vasculitis in adults and children" Version 4.0, dated 17th November 2021, and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and 2005/28/EC, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and any subsequent amendments of the clinical trial regulations, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

Principal Investigator

Name: David Jayne

Signature: 

Date: 19/04/2022

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3. Abbreviations

Ab	Antibody
ACR	American College of Rheumatology
ADR	Adverse Drug Reaction
AE/AR	Adverse event/Adverse Reaction
AESIs	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCA	Antineutrophil cytoplasmic antibody
BVAS	Birmingham Vasculitis Activity Score
BVAS-BIOVAS	Birmingham Vasculitis Activity Score modified for BIOVAS
CCTU	Cambridge Clinical Trials Unit
CA	Competent Authority
CHCC 2012	Chapel Hill Consensus Conference 2012
CHF	Congestive Heart Failure
CHU-9D	Child Health Utility 9D Index
CNS	Central Nervous System
CPAN	Cutaneous polyarteritis nodosa
CRF	Case Report Form
CRP	C-reactive Protein
CSS	Churg-Strauss syndrome
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CYP	Cytochrome P450
DADA2	Deficiency of adenosine deaminase type 2
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EoT	End of Trial
EQ-5D-5L	EuroQol five-dimension scale
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
EUVAS	European Vasculitis Study Group
FBC	Full Blood Count
FDA	Food and Drug Administration
GCA	Giant Cell Arteritis
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GIACTA	An Efficacy and Safety Study of Tocilizumab (RoActemra/Actemra) in Participants with Giant Cell Arteritis
GP	General Practitioner
HACA	Human anti-mouse antibody
HAMA	Human anti-chimeric antibody
HB	Hepatitis B
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HRA	Health Research Authority
HSTCL	Hepatosplenic T-Cell Lymphoma

HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
ICF	Informed Consent Form
IgA	Immunoglobulin A
IgAV	IgA vasculitis
IgG	Immunoglobulin G
IL-1	Interleukin 1
IL-6	Interleukin 6
IL6-R	Interleukin 6-receptor
IMP	Investigational Medicinal Product
INF	Infliximab
INF-PBO	Infliximab placebo
ISF	Investigator Site File
ITAS	Indian Takayasu's Arteritis Activity Score
IUD	Intrauterine Device
IV	Intravenous
JIA	Juvenile Idiopathic Arthritis
LFT	Liver Function Tests
LVV	Large Vessel Vasculitis
MHRA	Medicines and Healthcare products Regulatory Agency
MPA	Microscopic Polyangiitis
MPO	Myeloperoxidase
MRA	Magnetic Resonance Angiography
MTX	Methotrexate
NAAV	Non-ANCA associated vasculitis
NHS	National Health Service
NICE	The National institute for Health and Care Excellence
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NIMP	Non Investigational Medicinal Product
NSAIDs	Non-steroidal anti-inflammatory drugs
PACNS	Primary angiitis of the central nervous system
PAN	Polyarteritis Nodosa
PBO	Placebo
PET	Positron Emission Tomography
PGA	Physician's Global Assessment
PI	Principal Investigator
PIS	Participant Information Sheet
PMR	Polymyalgia rheumatica
PR3	Proteinase 3
PRES	Posterior reversible encephalopathy syndrome
PRINTO	The Paediatric Rheumatology International Trials Organisation
PSV	Primary Systemic Vasculitis
PVAS	Paediatric Vasculitis Activity Score
PVDI	Paediatric Vasculitis Damage Index
QALYs	Quality-adjusted life year
QoL	Quality of Life
R&D	Research and Development
RA	Regulatory Agency
REC	Research Ethics Committee
RP	Relapsing Polychondritis

RPDAI	Relapsing Polychondritis Disease Activity Index
RSI	Reference Safety Information
RTX	Rituximab
RTX-PBO	Rituximab placebo
SAE/SAR	Serious Adverse Event/Serious Adverse Reaction
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SoE	Schedule of Events
SUSAR	Suspected unexpected serious adverse reaction
TA	Takayasu's Arteritis
TARGET	Treatment according to Response in Giant Cell Arteritis
TB	Tuberculosis
TCZ	Tocilizumab
TCZ-PBO	Tocilizumab placebo
TMF	Trials Master Folder
TMG	Trial Management Group
TNF	Tumour Necrosis Factor
TSC	Trial Steering Committee
TTF	Time to Treatment Failure
UKGCA	UK Giant Cell Arteritis
VDI	Vasculitis Damage Index
WG	Wegener's Granulomatosis

4. Trial Synopsis

Title of clinical trial	Biologics in refractory vasculitis (BIOVAS): A pragmatic, randomised, double-blind, placebo-controlled, modified-crossover trial of biologic therapy for refractory primary non-ANCA associated vasculitis in adults and children
Sponsor name	Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge
EudraCT number	2019-003964-30
Purpose of the clinical trial	To establish the evidence for clinical and cost effectiveness of three biologics in comparison to placebo in the treatment of refractory primary non-ANCA Associated Vasculitis (NAAV)
Trial Design	A pragmatic, randomised, double-blind, placebo-controlled, modified-crossover phase 2B trial of biologic therapy for refractory primary NAAV in adults and children
Medical condition or disease under investigation	The 8 NAAV diseases listed below will be included in the trial. These will be grouped together and henceforth referred to as primary group. 1. Giant cell arteritis (GCA) 2. Takayasu's arteritis (TA) 3. Polyarteritis nodosa (PAN) or cutaneous polyarteritis (CPAN) unrelated to hepatitis B 4. Relapsing polychondritis (RP) 5. IgA vasculitis (IgAV) 6. Cogan's syndrome 7. Non-infective cryoglobulinaemia 8. Primary angiitis of central nervous system (PACNS) * All analyses (other than secondary Bayesian analysis) will be conducted on the primary group. For Bayesian analyses the primary group will be divided into 2 sub-groups: Group 1 (GCA and TA) and Group 2 (PAN, CPAN, RP, IgAV, Cogan's syndrome, non-infective cryoglobulinaemia, PACNS).
Primary objective	To determine the clinical efficacy of each of the 3 IMPs in comparison to placebo in the treatment of refractory NAAV as 1 disease group (primary group)
Secondary objectives	1. To assess the clinical efficacy of each of the three IMPs compared to placebo using Bayesian hierarchical analyses for 2 groups: Group 1 (GCA & TA) and Group 2 (PAN, CPAN, RP, IgAV, Cogan's syndrome, non-infective cryoglobulinaemia, PACNS) 2. To assess the clinical efficacy of each of the 3 IMPs compared to placebo for each of the 8 NAAV diseases 3. To assess the safety of each of the 3 IMPs compared to placebo 4. To assess the safety and risks associated with sequential use of different IMPs 5. To assess the cost-effectiveness of each of the 3 IMPs compared to placebo 6. To compare the clinical and cost-effectiveness of each IMP compared to other IMPs in the primary group
Trial Outcome Measures	**Primary outcome measures:** Primary outcome is time to treatment failure (TTF).

	TTF for each IMP is the time from the start of IMP treatment, to treatment failure (see definitions below) or the end of trial participation (censored). Primary treatment failure is progressive disease (defined by appearance of ≥1 new/worse severe or ≥3 new/worse non-severe items) on Birmingham vasculitis activity score (BVAS) v3 modified for BIOVAS (BVAS v3-BIOVAS) or paediatric vasculitis activity score (PVAS) within 120 days from the time of IMP commencement; or failure to achieve clinical response (see definitions below) by 120 days from the time of IMP commencement. In such cases, TTF will be recorded as zero. Secondary treatment failure is defined as having achieved response (definition below) by 120 days from the time of IMP commencement, and subsequently relapse after 120 days from IMP commencement. If an adverse reaction to an IMP precludes the participant from receiving further doses of the trial drug, this will also be considered treatment failure. The primary outcome for each active IMP is pooled across all participants in the primary group and compared against placebo. Response is defined by: • Absence of new/worse BVAS v3-BIOVAS (adults)/PVAS(children) items assessed at each 120 day evaluation time point after commencing IMP AND • Prednisolone ≤10mg/day or ≤0.2mg/kg for children (whichever is lower) unless baseline dose is <10mg/day for adults or <0.2mg/kg for children (whichever is lower) in which case it should not be more than the baseline dose* **where baseline dose is the dose of oral prednisolone (mg/day), or equivalent oral steroid, averaged over the 7 days prior to the start of each new IMP*. Relapse is defined by either: • Appearance of ≥ 1 severe (new/worse) or ≥ 3 non-severe (new/worse) BVAS v3-BIOVAS/PVAS items from the time of BVAS response (as defined above) assessed at the 120 day evaluation time points[#] OR • The need to increase the dose of prednisolone to > 20mg/day to treat vasculitis OR • The need to increase the dose of an immunomodulator or immune-suppressive therapy in order to treat vasculitis

	[#] Non-severe items can be upgraded by the investigator to severe based on their potential clinical impact, e.g. headache in GCA, thus could meet failure criteria if only one or two items are present. For an increase in 1 or 2 non-severe new/worse BVAS-BIOVAS/PVAS items which does not meet the relapse definition, the current IMP is continued and the participant may be treated, at the physician's discretion, with a prednisolone dose increase to no more than 20mg/day (or 0.3mg/kg but no more than 20mg/day in children) which will be reduced to the previous dose within next 6 weeks. **Secondary outcome measures:** 1. Bayesian hierarchical analysis to assess treatment effects of each of the IMPs compared to placebo and each IMP against other IMPs in 2 NAAV sub-groups: large vessel vasculitis (GCA/TA) and all other NAAV subgroups enrolled in the trial. 2. Proportion of participants achieving response at the 120 day evaluation time point after the start of each IMP. 3. Proportion of participants achieving response at every 120 day evaluation time point defined by a BVAS v3-BIOVAS/ PVAS of ≤ 1 non-severe (no new/worse) item, prednisolone dose ≤ 50% of the dose at the start of the IMP treatment and ≤ 10mg/day (0.2 mg/kg/day for children, whichever is lower) and an ESR < 30mm/hr or CRP <10 mg/L 4. Increase in disease related damage measured by VDI/PVDI from start to end of an IMP treatment 5. Physician's global assessment (PGA) (Likert scale 0-10) at every 120 day evaluation time point from the time of IMP commencement 6. Serious adverse events/adverse events of special interests (SAEs/AESIs) 7. EQ-5D-5L or Child Health Utility (CHU9D) assessments at every 120 day evaluation time point 8. NHS resource use and out of pocket costs and lost productivity
Randomisation:	After obtaining consent and establishing eligibility, participants are randomised to a fixed sequence of 4 trial IMPs. Each sequence will consist of 3 active IMP treatments and a placebo. The order of the IMPs in each sequence will be randomly allocated (e.g. RTX-INF-TCZ-PBO or INF-PBO-RTX-TCZ) from a list of 24 permutations. Further, the placebo in each sequence will be randomly allocated to mirror the drug administration schedule of 1 of the active IMPs in order to maintain the blind. Of the 72 different permutations possible, the 36 sequences that lead to unblinding will be excluded. Participants with a pre-trial history of failure/contraindication to 1 biologic IMP will have that failed IMP removed from their allocated sequence and will be randomised to a reduced number of IMPs. Participants that have previously failed two or more active trial IMPs will not be eligible to enter the trial.
Modified crossover design	Participants responding to an IMP by the next evaluation will continue the same IMP until relapse or to the end of trial participation. At non-response (primary failure) or relapse (secondary failure), participants will progress to the next IMP in the sequence only at defined time

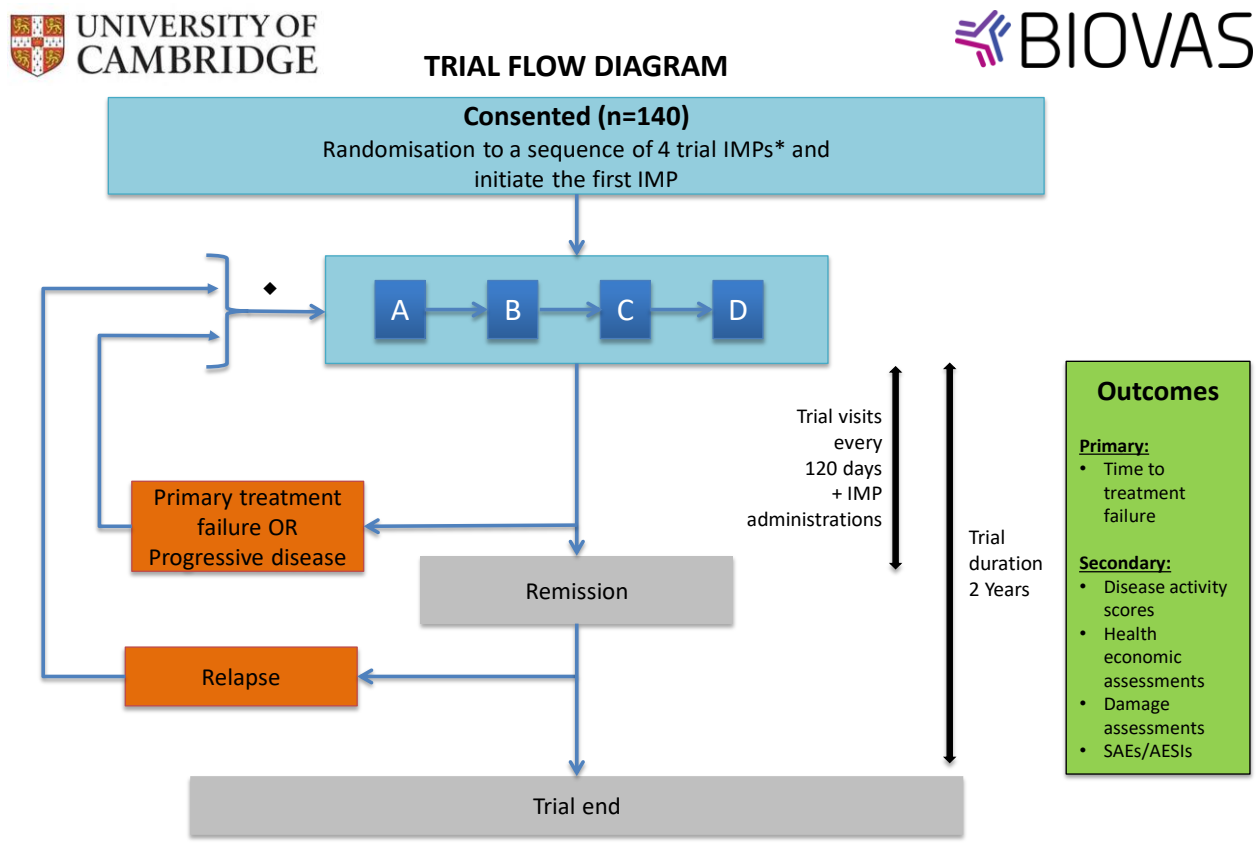
	points of 120, 240, 360, 480 and 600 days from the time of first IMP commencement. In the exceptional circumstance of an IMP not being available due to a general hospital stock issue, moving to the next intervention (IMP/placebo) in the randomised sequence is allowed after discussion with the CI.
Double blind	Participants and investigators are blinded to active-vs-placebo IMP treatment allocation in each block of randomised sequence. The central coordinator and local trial pharmacy will be unblinded to facilitate logistics of drug preparation, administration and to minimise participant risk.
Sample Size	A total of 140 participants (adults and children) with refractory NAAV will be randomised to this trial.
Summary of eligibility criteria	<u>Inclusion Criteria:</u> 1. Aged at least 5 years 2. Have given, or their parent/ legal guardian aged ≥ 16 years old has given, written informed consent 3. Diagnosis of NAAV (Appendix 4) 4. Refractory disease defined by: a) Active disease, BVASv3-BIOVAS/ PVAS with ≥ 1 severe (new/worse) or ≥ 3 non-severe (new/worse) items despite 12 weeks of conventional therapy prior to screening visit <u>OR</u> b) Inability to reduce prednisolone below 15mg/day or (0.2mg/kg/day in case of children) without relapse in the 12 weeks prior to screening visit <u>Exclusion Criteria:</u> 1. Previous treatment failure/contraindication to ≥ 2 active trial IMPs 2. Increase in the dose or frequency of background immunosuppressive (e.g. methotrexate) or anti-cytokine therapy within 30 days of screening visit 3. Use of intravenous immunoglobulins within 30 days (unless required clinically for immunodeficiency), or cyclophosphamide or lymphocyte depleting biologic (e.g. rituximab) within 6 months of initiating trial treatment 4. Concomitant use of any biologic and/or anti-TNF agent other than the trial IMPs during the trial period 5. Have an active systemic bacterial, viral or fungal infection, or tuberculosis 6. Hepatitis B (HB) core antibody (Ab) or HB surface antigen positive or hepatitis C antibody positive or human immunodeficiency virus (HIV) antibody test positive 7. History of malignancy within five years prior to screening visit or any evidence of persistent malignancy, except fully excised basal cell or squamous cell carcinomas of the skin, or cervical carcinoma in situ which has been treated or excised in a curative procedure

	8. Pregnant or breastfeeding, or inability/unwillingness to use a highly effective method of contraceptive if a woman of childbearing potential (WOCBP;see section 11.9) 9. Severe disease, which in the opinion of the physician prevents randomisation to placebo 10. Recent or upcoming major surgery within 45 days of screening visit 11. Leukocyte count < 3.5 x 10^9 cells/l, platelet count < 100 x 10^9 cells/l, neutrophil count of < 2 x 10^9 cells/l 12. ALT or AST > 3 times the upper limit of normal 13. Symptomatic congestive heart failure (NYHA class III/IV) requiring prescription medication within 90 days of screening visit 14. Demyelinating disorders 15. History or presence of any medical condition or disease which, in the opinion of the Investigator, may place the participant at unacceptable risk because of trial participation 16. Administration of live or live attenuated vaccines within 45 days of screening 17. Have received an investigational medicinal product (IMP) within 5 half-lives or 30 days prior to screening 18. Diagnosis of adenosine deaminase type 2 (DADA2) 19. Hypersensitivity to the active IMP substance or to any of the formulation excipients
Investigational medicinal products being studied	1. Infliximab (INF) – anti-tumour necrosis factor (TNF) agent 2. Rituximab (RTX) – B cell depleting agent 3. Tocilizumab (TCZ) – anti-interleukin 6-receptor (IL6-R) agent Each IMP will be individually compared to placebo (PBO).
Investigational medicinal product and dosage	All IMPs will be administered intravenously. Bio-similar agents are permitted. 1. Infliximab 5mg/kg on days 1, 15(+/- 3d), 43 (+/-3d), 70 (+/-3d) then every 56 days (+/-14d) thereafter. 2. Rituximab 1g on IMP Days 1, 15 (+/-3d), 180 (+/-14d), 360 (+/-14d) and 540 (+/-14d). (Children, 750mg/m^2/dose, maximum 1 g per dose). 3. Tocilizumab 8mg/kg (maximum 800mg) every 30 days (+/- 7d); 10 mg/kg (maximum 800 mg) for children < 30 kg. In the case of a known contraindication to/failure of a trial IMP, that particular drug will not be included in the sequence generation at the time of randomisation.
Comparator product	One of the agents in the sequence will be a placebo (Sodium Chloride 0.9%), the dosing schedule of which will be randomly allocated to match one of the other active IMP in the sequence in order to maintain the blind. A minimum washout period of 30 days is mandatory between two interventions.
NIMPs	Steroids. Prednisolone dose before entry or during relapse waiting for

	the next IMP initiation is unrestricted. Once on an IMP treatment, physicians are recommended to reduce the steroid dose as per best medical practice. Recommended dose weaning templates provided in appendix 5.
Route(s) of administration	Infliximab, rituximab, tocilizumab and matched placebo will be administered intravenously
Maximum duration of treatment of a participant	Screening period: up to 28 days Treatment period: 720 days
Procedures: Screening & enrolment	IMP will be administered within 28 days of the start of the screening period once eligibility has been confirmed and randomisation performed. 1. Clinical evaluation of participants by trial investigators to ensure the participants meet all of the inclusion criteria and none of the exclusion criteria 2. Screening laboratory 3. Serum pregnancy test
Procedures: Baseline	Baseline procedures can be conducted during the screening period once eligibility confirmed, or on the day of first IMP administration. 1. Clinical assessment of disease activity 2. BVAS-BIOVAS or PVAS (and Indian Takayasu Clinical Activity Score (ITAS)/ Relapsing polychondritis disease activity index (RPDAI) where applicable) 3. Damage assessment (VDI or PVDI) 4. PGA 5. EQ-5D-5L/ Child Health Utility (CHU9D) 6. Health resource use 7. Concomitant medications 8. Baseline blood tests 9. Steroid review
Procedures: Treatment period	Each participant is assessed every 120 days +/-14 days (Days 120, 240, 360, 480, 600 and 720) to establish response to therapy. Additional unscheduled visits may also occur to capture relapse data. The following procedures will take place at each visit during the course of treatment phase 1. Clinical assessment of disease activity 2. BVAS-BIOVAS/PVAS (and ITAS or RPDAI where applicable) 3. Damage assessment VDI/PVDI 4. PGA 5. EQ-5D/ CHU9D 6. Health resource use 7. Concomitant medications 8. Blood tests 9. Patient steroid diary review 10. Safety review 11. Urine pregnancy test (as part of monthly safety monitoring) IMPs are administered as detailed above.
as above Procedures: End of trial	The trial will end when the last participant has completed their day 720 trial clinic visit.
Procedures for safety monitoring during trial	Monthly safety assessments (AE/SAE review, routine clinical bloods review, urine pregnancy testing for WOCBP).

	Furthermore, a Data Monitoring Committee (DMC) will provide independent oversight of this trial.
Criteria for withdrawal of participants	Participants will be withdrawn from the trial and no further follow-up procedures carried out if a participant withdraws consent. Participants will be withdrawn from trial treatment (but follow-up encouraged) for any of the following reasons: 1. Participant withdrawal of consent 2. Physician decision to withdraw participant from trial either due to uncontrolled disease or drug related toxicity 3. Pregnancy during the trial period 4. Life threatening infections 5. Lack or loss of response to all of the IMPs within 720 days 6. If an unblinded event occurs

5. Trial Flow Chart



6. Introduction

6.1. Background

The primary systemic vasculitides are rare autoimmune disorders characterised by inflammation and necrosis of blood vessels leading to tissue infarction, organ failure and death. They are classified by the predominant size of blood vessel involved into large, medium and small vessel vasculitis and include a number of different syndromes in each group (Jennette et al. 2012). Vasculitis syndromes other than Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) have been grouped under the term non-ANCA associated vasculitis (NAAV), shown in Table 1 are the diseases being studied in this trial. These diseases will be collectively referred to as the primary group.

Table 1 NAAV diseases under investigation in this trial

Classification*	**Disease**
Large vessel vasculitis	Giant cell arteritis Takayasu's arteritis
Medium vessel vasculitis	Polyarteritis nodosa Cutaneous polyarteritis nodosa
Small vessel vasculitis	Cryoglobulinaemic vasculitis IgA Vasculitis
Other vasculitis	Cogan's syndrome Primary angiitis of the central nervous system Relapsing polychondritis

*Adapted from the Chapel Hill Consensus Conference 2012

ANCA associated vasculitis has well evidenced therapy and rituximab, a monoclonal antibody directed against B cells was licensed by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2011 and 2013 respectively, and National Institute of Clinical Excellence (NICE) approved in 2013 (Stone et al. 2010; Jones et al. 2010). NAAV, with a combined incidence of ~20/million/year (Table 2) are less well studied and have no licensed therapies except for glucocorticoids, and more recently, Tocillizumab for GCA, as described below. Currently, treatment strategies in NAAV mirror ANCA associated vasculitis treatments due to similarities in disease pathogenesis and manifestations (Mukhtyar et al. 2009; Mukhtyar et al. 2009a).

Table 2 Incidence and prevalence of NAAV

Disease	**Incidence**	**Prevalence**
Giant cell arteritis	63/million	900/million
Takayasu's arteritis	1-2/million	4.7/million
Polyarteritis nodosa (Hepatitis negative)	4-10/million	30/million
Relapsing polychondritis	0.7/million	10/million
IgA Vasculitis in children	60-200/million (children)	33/million (children)
IgA Vasculitis in adults	13/million	25/million
Cryoglobulinaemia	1-2/million	10/million
Cogan's syndrome	1-2/million	10/million
Primary CNS vasculitis	2.4/million	24/million

Clinical presentations, treatment responses and the disease course of NAAV are heterogeneous, but there are major overlaps in pathogenesis and treatment. Current therapies are only partially effective and

commonly result in side effects. Over one third of patients pursue a course marked by repeated disease flares and/or progressive disease with high risks of vital organ damage, high cumulative exposure to glucocorticoids and immunosuppressive agents with attendant chronic morbidity and mortality. There is a three-fold increase in direct medical costs for refractory vasculitis when compared to patients in remission (Trieste et al. 2012). Based on 2014 US health costs, refractory vasculitis at $88,000/year/patient cost more than double the health costs of non-refractory disease at $30,000/year/patient. In marked contrast to ANCA associated vasculitis, patients with NAAV lack standardised treatment pathways and there is wide variance in practice and outcomes. The introduction of evidence-based therapies will help to harmonise therapy, improve patient quality of life and long-term outcomes, and reduce current levels of drug-associated toxicity. It has the potential also to reduce the societal and economic burden of vasculitis.

Biological therapy plays a major role in the treatment of single organ autoimmune diseases, e.g. asthma, rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease. For multi-system autoimmunity, belimumab has been licensed and NICE approved for systemic lupus erythematosus, rituximab for ANCA-associated vasculitis and tocilizumab has been licensed and NICE approved for short-term use in refractory giant cell arteritis (Jones et al. 2010; Villiger et al. 2016; Stone et al. 2017). There is considerable trial and observational data supporting a useful role for the three biologics in this trial in vasculitis. Refractory patients have the greatest need for better treatment with potentially preventable morbidity and mortality. Advances in trial design in ANCA associated vasculitis have been translated to giant cell arteritis but have not been exploited in the other syndromes where the low incidence has been a major barrier to research. The lack of evidence in children is more acute as they are often excluded from trials, but there is also clinical experience with the biologics in this trial [i]in children where tocilizumab and infliximab are licensed for other indications (Akamine & Punaro 2019) in the EU and rituximab is currently licenced for AAV by the FDA. Although tocilizumab has been approved for giant cell arteritis, some patients are not responsive and alternative biologics may be cheaper and as effective.

6.2. Clinical Data

6.2.1. Efficacy

Biologics targeting pathogenic pathways, such as tumour necrosis factor-inhibitors, anti-interleukin 6-receptor (anti-IL6r) or anti-B cells have been used to treat refractory NAAV. Robust evidence in the form of randomised controlled trial evidence in the treatment of NAAV mainly comes from studies in GCA and a few small clinical trials in TA. Such evidence is lacking for other forms of NAAV.

Two randomised controlled trials have shown efficacy of tocilizumab, an anti-IL6 receptor, for remission induction in giant cell arteritis (Villiger et al. 2016; Stone et al. 2017). In An efficacy and safety trial of Tocilizumab in participants with GCA (GIACTA) trial (Stone et al. 2017), tocilizumab combined with a 26-week prednisolone taper was shown to be superior to either a 26-week or 52-week prednisolone taper in maintaining sustained remission at 52 weeks (56% vs. 14%, $p<0.001$). However, this trial does not inform the management of participants that do not achieve remission with tocilizumab (44% of the participants in the GIACTA trial). A recent review by NICE highlights that more evidence is needed in this field not only for tocilizumab but also for other alternatives (NICE 2018). A comparative data between biologics, both for efficacy and safety is of particular importance, and is unlikely to be produced by the pharmaceutical industry, yet is essential for optimal patient care and personalisation of treatment.

A trial of infliximab (TNF inhibitor) failed to show efficacy in a small and underpowered giant cell arteritis trial (Hoffmann et al. 2007). In this trial 44 adult participants with a new diagnosis of GCA were recruited in a 2:1 ratio to either infliximab or placebo. Primary endpoint of being in remission at 24 weeks was similar in both groups (43% vs. 50%, p=NS). This trial suffers from some methodological issues which

include an assumption of large effect size of 50%, small sample size and early termination. Observational data over almost two decades have supported use of TNF inhibitor in giant cell arteritis, Takayasu's arteritis and polyarteritis nodosa (Ferfar et al. 2016). There is preliminary clinical and experimental evidence in GCA that tocilizumab failures may respond to infliximab and vice versa (Muratore et al. 2017; Hernandez-Rodriguez et al. 2003; Visvanathan et al. 2011; Deng et al. 2010; Espígol-Frigolé et al. 2013; Weyand & Goronzy 2013). We believe that the clinical equipoise remains despite the recent tocilizumab approval and clinical trial evidence against TNF inhibitors.

The proven efficacy of rituximab in ANCA associated vasculitis; pathological similarities between ANCA associated vasculitis and NAAV, as well as experience in NAAV (Nakagomi et al. 2018), support further trial of rituximab. We have conducted a systematic literature review (unpublished) that identified 389 cases of NAAV successfully treated with these agents) in line with a meta-analysis of giant cell arteritis /Takayasu's arteritis (Osman et al. 2014). Experience with rituximab in ANCA associated vasculitis (Stone et al. 2010; Jones et al. 2010) has demonstrated improved disease control and reduced costs in refractory subgroups that parallel better disease control, reduced exposure to glucocorticoids and immunosuppression and lower co-morbidity risks. We have reported secondary failure of biologics in a related secondary vasculitis, Behcet's syndrome (Furuta et al. 2012).

6.2.2. Safety and tolerability

All of the IMPs being studied in this trial are licensed therapies for other auto-immune conditions : rituximab is licensed for AAV (FDA and EMA approved in adults and children)), tocilizumab licensed for GCA (FDA and EMA), infliximab licensed for rheumatoid arthritis (FDA and EMA). Tocilizumab is approved for use in paediatric patients with Juvenile idiopathic arthritis (JIA) with well-established safety profiles and tolerability, and recommended as a second line treatment in rare refractory paediatric vasculitides (deGraeff et al, 2019). Rituximab is used in routine practice for ANCA associated vasculitis, and in non-ANCA associated vasculitis of the young. Furthermore, the European SHARE guidance describes recommended use of all three biologics in paediatric populations (deGraeff et al. 2019). The centres that are participating in this trial are well versed with safety and tolerability issues associated with each of the IMPs.

6.2.3. Pharmacokinetics & pharmacodynamics

These are well established and are reflected in the summary of product characteristics (SmPCs) of each IMP.

7. Rationale for Trial

Glucocorticoids remain the standard therapy for remission induction in NAAV and are used with or without immunosuppressive agents depending on the syndrome and severity. Glucocorticoids at high doses control systemic inflammation and reduce acute injury but may not induce long-term treatment free remission and carry a heavy burden of almost universal toxicity (Nesher et al. 1994). Vasculitides are characterised by frequent relapses, which further contribute to disease-related damage and drug-related toxicity.

Steroid use is associated with the risk of diabetes, hypertension, thrombosis, gastro-intestinal haemorrhage, psychosis, insomnia, skin fragility, changed appearance, alopecia, osteoporosis, infections and obesity. The elderly are particularly vulnerable to an increased risk of fragility fractures and cataracts that have major impacts on their mobility and quality of life. Analyses of European Vasculitis Study group (EUVAS) clinical trials have shown that the majority of deaths within the first 12 months are treatment-

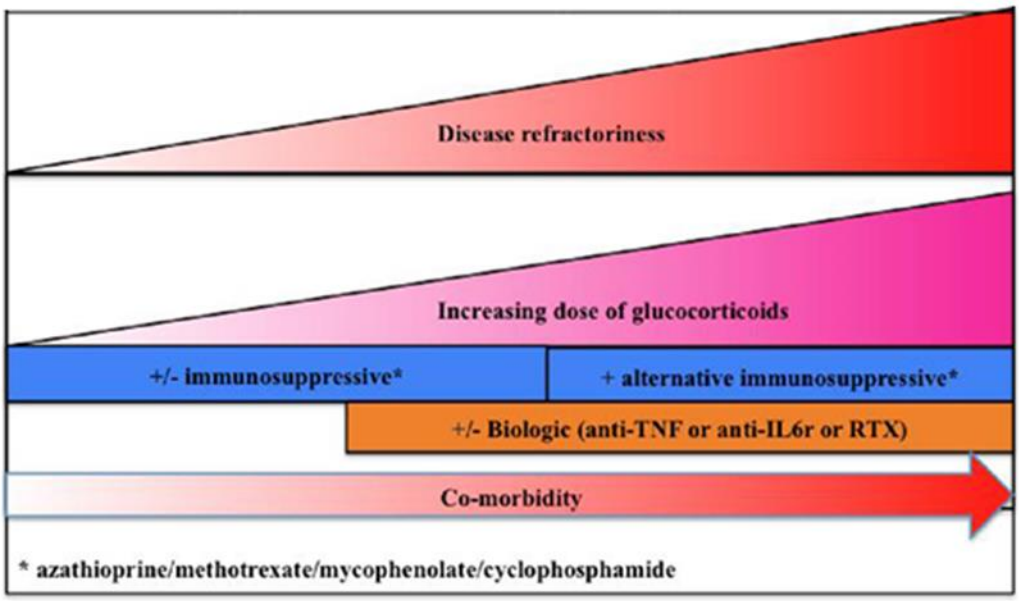
related adverse events, such as infections (48%) (Flossmann et al. 2011). In a French study of AAV participants around 90% of serious infections occurred in relation to glucocorticoids and reduced doses or alternate day dosing regimens were associated with reduced infections (Charlier et al. 2009). Thus, there is a clear and important need to reduce the use of glucocorticoids in NAAV.

One third of NAAV patients have refractory disease, either failing to achieve remission or relapsing despite relapse prevention strategies. This subgroup experiences the poorest outcomes, the highest drug related toxicity and is most demanding on health resources and is the focus of BIOVAS. Our proposed testing of biologics in BIOVAS concords with the current treatment pathway (see Fig.1) based on European League Against Rheumatism (EULAR) consensus statements supported by low grade evidence, expert opinion and a few small trials (Mukhtyar 2009)

The pathology of vasculitis is characterised by pro-inflammatory cytokines (IL-1, IL-6 and TNF) and infiltration of vessels by neutrophils and lymphocytes. This results in fibrinoid necrosis of the vessel wall and thrombotic occlusion or aneurysmal dilatation or intimal proliferation and stenosis of the vessel lumen. A complex genetic predisposition has been identified for giant cell arteritis and Takayasu's arteritis.

Biologics targeting pathogenic pathways, such as tumour necrosis factor-inhibitors, anti-IL6r or anti-B cells have been used to treat refractory NAAV. Evidence in support of the agents chosen for this trial has been discussed in section 6.2.1.

Figure 1 Current treatment pathway in NAAV



8. Trial Design

8.1. Statement of Design

A multi-centre, pragmatic, randomised double blind, placebo-controlled, modified-crossover phase 2B trial of infliximab, rituximab and tocilizumab for refractory NAAV in adults and children.

8.2. Number of Centres

This multicentre trial will include approximately 17 UK centres.

8.3. Number of Participants

140 eligible participants with refractory NAAV will be enrolled in this trial.

8.4. Participants Trial Duration

The trial comprises a screening period of up to 28 days and a 720 day (+/- 14 days) treatment period. During trial participation, each participant will be required to attend 8 trial related trial clinic visits. Attendance for IMP infusions will vary for each participant dependent on their treatment allocation at any particular time. Each participant will receive a minimum of 5 and a maximum of 24 IMP infusions throughout the 720 day trial treatment period unless withdrawn from the trial. In the exceptional event of a supply issue of hospital stocks of any of the IMPs, patients may be switched to the next IMP in sequence. This should occur even if a patient is allocated the placebo equivalent of the active IMP whose supply is affected: they would still be switched to the next treatment in their randomised sequence. Switching in this exceptional circumstance would not affect the overall trial duration for that patient.

There will be some overlap between IMP administration and trial clinic visits which will mean a minimum of 11 visits and a maximum of 25 visits in total including the screening visit. Trial clinic visits will happen at baseline and every 120 days +/- 14 days following successful screening. For convenience +/- 14 days will not be mentioned when referring to trial visits from hereon.

8.5. Trial Objectives

BIOVAS will test the hypothesis that biologics are superior to placebo in the control of refractory NAAV. Each of the three trial biologics (infliximab, rituximab and tocilizumab) will be compared to placebo in a sequential modified crossover, placebo-controlled design.

All analyses (other than secondary Bayesian analysis) will be conducted on primary group. For Bayesian analysis the primary group will be sub-divided into 2 sub-groups: Group 1 (GCA and TA) and Group 2 (PAN, CPAN, RP, IgAV, Cogan's syndrome, non-infective cryoglobulinaemia, PACNS).

8.5.1. Primary objective

To establish evidence for clinical effectiveness of three different biologics: infliximab, rituximab and tocilizumab in comparison to placebo in the treatment of refractory NAAV as one disease group (primary group).

8.5.2. Secondary objectives

To establish safety, clinical and cost-effectiveness of each of the biologic agents compared to placebo; and to establish the clinical and cost-effectiveness of each biologic agent compared to the other biologic agents studied in the trial.

1. To assess the clinical efficacy of each of the three IMPs compared to placebo using Bayesian hierarchical analyses for 2 groups: Group 1 (GCA & TA) and Group 2 (PAN, CPAN, RP, IgAV, Cogan's syndrome, non-infective cryoglobulinaemia, PACNS)
2. To assess the clinical efficacy of each of the 3 IMPs compared to placebo for each of the 8 NAAV diseases
3. To assess the safety of each of the three IMPs compared to placebo
4. To assess the safety and risks associated with sequential use of different IMPs
5. To assess the cost-effectiveness of each of the three active IMPs compared to placebo
6. To compare the clinical and cost-effectiveness of each IMP compared to other IMPs in the primary group

8.6. Trial Outcome Measures

Primary outcome measures:

Primary outcome is time to treatment failure (TTF).

TTF for each IMP is the time from the start of IMP treatment, to treatment failure (see definitions below) or the end of trial participation (censored).

Primary treatment failure is progressive disease (defined by appearance of ≥1 new/worse severe or ≥3 new/worse non-severe items) on Birmingham vasculitis activity score (BVAS) v3 modified for BIOVAS trial (BVASv3-BIOVAS) or paediatric vasculitis activity score (PVAS) within 120 days from the time of IMP commencement; or failure to achieve clinical response (see definitions below) by 120 days from the time of IMP commencement. In such cases, TTF will be recorded as zero.

Secondary treatment failure is subsequent relapse (see definitions below) after 120 days of IMP commencement in patients who have achieved response by 120 days from the time of IMP commencement,

If an adverse reaction to an IMP precludes the participant from receiving further doses of the trial drug, it will also be considered a treatment failure.

The primary outcome for each active IMP is pooled across all participants in the primary group and compared against placebo.

Response is defined by:

- Absence of new/worse BVAS V3-BIOVAS(adults)/PVAS (children) items assessed at each 120 evaluation time point after commencing IMP AND
- Prednisolone ≤10mg/day or ≤0.2mg/kg for children (whichever is lower), unless the baseline dose is ≤10mg/day or ≤0.2mg/kg for children (whichever is lower), in which case it should not be more than the baseline dose*

*baseline dose is the dose of oral prednisolone, mg/day, or equivalent oral steroid, averaged over the 7 days prior to the start of each new IMP.

Relapse is defined by either:

- Appearance of ≥ 1 severe (new/worse) or ≥ 3 non-severe (new/worse) BVAS v3-BIOVAS/PVAS items from the time of BVAS response (as defined above) assessed at the 120 day evaluation time points[#] OR
- The need to increase the dose of prednisolone to > 20mg/day to treat vasculitis OR
- The need to increase the dose of an immunomodulator or immune-suppressive therapy in order to treat vasculitis

[#] Non-severe items can be upgraded by the investigator to severe based on their potential clinical impact, e.g. headache in GCA, thus could meet failure criteria if only one or two items are present.

For an increase in one or two non-severe new/worse BVAS v3-BIOVAS/PVAS items which does not meet the relapse definition, the current IMP is continued and the participant may be treated, at the physician's discretion, with a prednisolone dose increase to no more than 20mg/day (or 0.3mg/kg but no more than 20mg/day in children) which will be reduced to the previous dose within next 6 weeks.

Secondary outcome measures:

1. Bayesian hierarchical analysis to assess treatment effects of each of the IMPs compared to placebo and each IMP against other IMPs in 2 NAAV sub-groups: large vessel vasculitis (GCA/TA) and all other NAAV subgroups enrolled in the trial
2. Proportion of participants achieving response at 120 days evaluation after the start of each IMP.

3. Proportion of participants achieving response at every 120 day evaluation time point defined by a BVAS v3-BIOVAS/ PVAS of ≤ one non-severe (no new/worse) item, prednisolone dose ≤ 50% of the dose at the start of the IMP treatment and ≤ 10mg/day (0.2 mg/kg/day for children, whichever is lower) and an ESR < 30mm/hr or CRP <10 mg/L
4. Increase in disease related damage measured by VDI/PVDI from start to end of an IMP treatment
5. Physician's global assessment (PGA) (Likert scale 0-10) at every 120 day evaluation time point from the time of IMP commencement
6. Serious adverse events/adverse events of special interests (SAEs/AESIs)
7. EQ-5D-5L or Child Health Utility (CHU9D) assessments at every 120 day evaluation time point
8. NHS resource use and out of pocket costs and lost productivity

9. Selection and withdrawal of participants

9.1. Inclusion Criteria

To be included in the trial the participant must:

1. Aged at least 5 years
2. Have given, or their parent/legal guardian aged ≥ 16 years old has given, written informed consent
3. Diagnosis of NAAV (Appendix 4)
4. Refractory disease defined by:
    - Active disease, BVAS v3-BIOVAS/ PVAS with ≥ 1 severe (new/worse) or ≥ 3 non-severe (new/worse) items despite 12 weeks of conventional therapy OR
    - Inability to reduce prednisolone below 15mg/day or (0.3mg/kg/day in case of children) without relapse in the 12 weeks prior to screening visit

9.2. Exclusion Criteria

Participants are excluded from the trial if any of the following criteria apply:

1. Previous treatment failure/contraindication to ≥ 2 active trial IMPs
2. Increase in the dose or frequency of background immunosuppressive (e.g. methotrexate) or anti-cytokine therapy within 30 days prior to screening visit
3. Use of plasma exchange or intravenous immunoglobulins (unless required clinically for immunodeficiency) within the 30 days, or cyclophosphamide or lymphocyte depleting biologic (e.g. rituximab) within 6 months of initiating trial treatment
4. Concomitant use of any biologic and/or anti-TNF agent other than the trial IMPs for the duration of the trial.
5. Have an active systemic bacterial, viral or fungal infection, or active/latent tuberculosis assessed/documented as per local clinical practice; this includes COVID19 testing if warranted and as per local routine practice.
6. Hepatitis B (HB) core antibody (Ab) or HB surface antigen positive or hepatitis C antibody positive or human immunodeficiency virus (HIV) antibody test positive
7. History of malignancy within five years prior to screening visit or any evidence of persistent malignancy, except fully excised basal cell or squamous cell carcinomas of the skin, or cervical carcinoma in situ which has been treated or excised in a curative procedure
8. Pregnant or breastfeeding, or inability/unwillingness to use a highly effective method of contraceptive if a woman of childbearing potential (WOCBP; Section 11.9)
9. Severe disease, which in the opinion of the physician prevents randomisation to placebo
10. Recent or upcoming major surgery within 45 days of screening visit

11. Leukocyte count < 3.5 x 10^9 cells/l, platelet count < 100 x 10^9 cells/l, neutrophil count of < 2 x 10^9 cells/l
12. ALT or AST > 3 times the upper limit of normal
13. Symptomatic congestive heart failure (NYHA class III/IV) requiring prescription medication within 90 days of screening visit
14. Demyelinating disorders
15. History or presence of any medical condition or disease which, in the opinion of the Investigator, may place the participant at unacceptable risk because of trial participation
16. Administration of live or live attenuated vaccines within 45 days of screening
17. Have received an investigational medicinal product (IMP) within 5 half-lives or 30 days prior to screening
18. Diagnosis of adenosine deaminase type 2 (DADA2)
19. Hypersensitivity to the active IMP substance or to any of the formulation excipients (unless IMP excluded for a particular patient pre-randomisation)

9.3. Treatment Assignment and Randomisation Number

Following informed consent all participants entering screening will be assigned a unique Trial ID number. All eligible participants will be assigned to trial treatment in accordance with the randomisation schedule and randomisation must occur before any investigational product is administered.

Once eligibility has been confirmed, participants will be randomised to a fixed sequence of four different IMPs, each sequence will contain three active IMPs and a placebo. The order of the treatments in each sequence is randomly allocated (e.g. RTX-INF-TCZ-PBO or INF-PBO-RTX-TCZ). Furthermore, the placebo in each sequence is chosen randomly to mirror one of the active IMPs. In the case of a known failure/contraindication to a trial IMP, that particular drug will not be included in the sequence generation at the time of randomisation. This was deemed necessary to maximise the data obtained from a limited number of eligible participants in this rare disease setting.

Access to the web-based randomisation system (Sealed Envelope) will be via individual user accounts provided to the principal investigator (PI) and suitably trained and delegated members of the research team at each site as appropriate. Once randomisation occurs, immediate allocation of IMP sequence will be performed. A blinded confirmatory email containing a blinded code e.g. CZ7 will be sent to the local clinical team and to the Trial Coordinator.

9.4. Method of Blinding

This is a double-blinded trial. The double-blinded period will be the time from start of first IMP in the randomised sequence up to failure on all IMPs (maximum duration 24 months). During this period, neither participants nor local trial team will know whether the participant is on active or placebo IMP. When a participant is on a placebo IMP, they will receive saline with infusion characteristics (duration of administration, frequency and pre-medications) to match one of the active IMPs. There is a small risk of unbinding as tocilizumab can lower ESR and CRP. However this risk is small as any treatment that can induce a response can also lower ESR and CRP.

When participants are randomised to a sequence, the central coordinator and local pharmacy teams will be unblinded to the sequence allocation. This is for practical and safety purposes: the unblinded central coordinator will notify the investigator or delegated member of the trial team which treatment protocol to prescribe, to ensure that the participant is booked for the relevant treatment visits for a particular intervention. Local unblinded pharmacy (and any other authorised site personnel as appropriate) will be able to verify whether they are preparing active or placebo for that particular in IMP the sequence.

For example: if a participant is allocated to the following sequence: RTX-INF-TCZ-RTX-Placebo, the unblinded coordinator would notify investigator that the prescription to prepare for the first IMP in the sequence for this randomised participant would be RTX OR RTX-Placebo. The IMP would be labelled as such (RTX/RTX-Placebo) in order to maintain the blind during this intervention phase of the randomised sequence.

Given that there are three active IMPs plus placebo, 24 permutations are possible. At each placebo position three possibilities (RTX or INF or TCZ placebo) exist, hence there are 72 possible sequences in total. With this design there are 36 sequences where the IMPs can be un-blinded by an educated guess and such sequences are excluded from sequence generation (shown in red in Figure 2). From the design of the trial, it could be inferred that two agents other than the placebo and its matched IMP are active agents. If the placebo and its matched IMP were to be in the first three places of the sequence then it would be easy to guess the IMPs that follow are active agents thus leading to unblinding. Such sequences will be removed.

At or prior to each trial clinic visit, investigators will make a decision to either carry on with the same IMP or switch to the next IMP in the participants' randomised sequence. Central coordinator must be notified of a planned IMP switch, so that they can then provide site delegated members with the next IMP/placebo in the participants' randomised sequence to ensure the correct treatment protocol is prescribed (for example, if a patient with the randomised sequence RTX-INF-TCZ-RTX-Placebo fails first intervention in the sequence, they would be switched to the next, which is INF. The investigator or delegated member of trial team will be notified that the next in sequence is INF OR INF placebo, to ensure the correct IMP protocol is prescribed, whilst maintaining the blind for this intervention period.

In the exceptional event of a supply issue of hospital stocks of any of the IMPs at any point in the study, patients may be switched to the next IMP in sequence, and the reason (I.e. Supply issue) documented. In order to maintain the blind, even if a patient was on the placebo equivalent of the active IMP whose supply is affected, they would still be switched to the next treatment in their randomised sequence, and this would not affect the overall trial duration for that patient. If the active IMP with the supply issue is the one with a placebo match allocated, and the supply issue for the active IMP is subsequently resolved by the time the matched allocation is due (whether for active or placebo), this may go ahead.

Further instructions on randomisation and IMP switching can be found in the Trial Procedures Manual.

Figure 2 Randomisation permutations and placebo matched possibilities

Sq.No	Allocated sequence	Placebo possibilities			
		1st Drug	2nd Drug	3rd Drug	4th Drug
1	RTIP	R	T	I	R-P
		R	T	I	T-P
		R	T	I	I-P
2	RIPT	R	I	I-P	T
		R	I	R-P	T
		R	I	T-P	T
3	RPIT	R	I-P	I	T
		R	R-P	I	T
		R	T-P	I	T
4	RTPI	R	T	R-P	I
		R	T	T-P	I
		R	T	I-P	I
5	RITP	R	I	T	R-P
		R	I	T	T-P
		R	I	T	I-P
6	RPTI	R	R-P	T	I
		R	I-P	T	I
		R	T-P	T	I
7	IPRT	I	I-P	R	T
		I	R-P	R	T
		I	T-P	R	T
8	IRTP	I	R	T	R-P
		I	R	T	T-P
		I	R	T	I-P
9	ITPR	I	T	T-P	R
		I	T	I-P	R
		I	T	R-P	R
10	IPTR	I	T-P	T	R
		I	I-P	T	R
		I	R-P	T	R
11	IRPT	I	R	R-P	T
		I	R	I-P	T
		I	R	T-P	T
12	ITRP	I	T	R	R-P
		I	T	R	T-P
		I	T	R	I-P

Sq.No	Allocated sequence	Placebo possibilities			
		1st Drug	2nd Drug	3rd Drug	4th Drug
13	TIPR	T	I	I-P	R
		T	I	T-P	R
		T	I	R-P	R
14	TPRI	T	T-P	R	I
		T	R-P	R	I
		T	I-P	R	I
15	TRIP	T	R	I	R-P
		T	R	I	T-P
		T	R	I	I-P
16	TIRP	T	I	R	R-P
		T	I	R	T-P
		T	I	R	I-P
17	TPIR	T	T-P	I	R
		T	I-P	I	R
		T	R-P	I	R
18	TRPI	T	R	R-P	I
		T	R	T-P	I
		T	R	I-P	I
19	PRTI	R-P	R	T	I
		T-P	R	T	I
		I-P	R	T	I
20	PTIR	R-P	T	I	R
		T-P	T	I	R
		I-P	T	I	R
21	PIRT	R-P	I	R	T
		T-P	I	R	T
		I-P	I	R	T
22	PRIT	R-P	R	I	T
		T-P	R	I	T
		I-P	R	I	T
23	PTRI	R-P	T	R	I
		T-P	T	R	I
		I-P	T	R	I
24	PITR	R-P	I	T	R
		T-P	I	T	R
		I-P	I	T	R

Legend: R: RTX, I: INF, T: TCZ, P: Placebo, T-P: TCZ placebo, I-P: INF placebo, R-P: RTX placebo. Sequences containing red shading will be excluded from sequence generation due to the possibility of unblinding

9.5. Participant Withdrawal Criteria

Participants may withdraw from the trial treatment or from the trial completely, at any time at their request, or they may be withdrawn at any time at the discretion of the investigator.

9.5.1. Withdrawal from protocol treatment

Participants may be withdrawn from trial treatment for any of the following reasons:

1. Participant withdrawal of consent
2. Physician decision to withdraw participant from trial either due to uncontrolled disease or drug related toxicity
3. Pregnancy during the trial period
4. Life threatening infections
5. Lack or loss of response to all of the IMPs within 720 days
6. If an unblinded event occurs

Participants who discontinue trial treatment will be encouraged to continue to participate in trial visits in accordance with the schedule of events (SoE). With ongoing consent, the trial participants should remain in the trial and data will continue to be collected.

A participant's trial visit non-compliance will not automatically lead to withdrawal from the trial. The participant will be encouraged to attend a clinic visit at their earliest convenience in case of a missed trial

clinic visit. If the investigator decides to continue the same IMP then the participant can continue to receive the same IMP.

Withdrawal is anticipated to be a rare occurrence. Pregnant patients will be treated with best medical practice, and continue in long term follow up. Non-compliant patients will be helped to return to protocol compliance, and continue in long term follow up.

Any decision to withdraw the patient from the trial MUST be discussed with the chief investigator in order not to adversely affect the conduct of the trial. Patients will continue to be followed up, and data collected and documented as set out in the protocol, unless they withdraw their consent for this.

9.5.2. Withdrawal of consent

If the participant explicitly states they no longer wish to contribute further data to the trial, the investigator should inform the BIOVAS co-ordinating centre in writing and the withdrawal of consent should be documented by the in the participant's medical records and in the electronic Case Report Form (eCRF). No further trial procedures will be undertaken and the only data that will be collected following withdrawal will be resolution/stability of adverse reactions. However, data and samples collected up to the time of consent withdrawal will be included in the data reported for the trial. These participants' subsequent management will follow standard of care.

10. Trial Treatments

10.1. Treatment Summary

For the purpose of this trial, infliximab, rituximab, tocilizumab and placebo to match (Sodium Chloride 0.9%) are all considered Investigational Medicinal Products (IMP) conducted with a Clinical Trial Authorisation. The use of bio-similar agents are permitted as per local policy (with the brand in use and batch number being recorded, in such a manner that unblinding does not occur). Also allowed is any bio-similar non-UK stock which has received interim MHRA approval for clinical use, for example, interim non-UK supply of Tocilizumab.
In the case of a known failure/contraindication to one of the trial IMPs, that particular drug will not be included in the sequence generation at the time of randomisation.

In the exceptional event of a supply issue of hospital stocks of any of the IMPs at any point in the study, patients may be switched to the next IMP in sequence, and the reason (I.e. Supply issue) documented. In order to maintain the blind, even if a patient was on the placebo equivalent of the active IMP whose supply is affected, they would still be switched to the next treatment in their randomised sequence, and this would not affect the overall trial duration for that patient. If the active IMP with the supply issue is the one with a placebo match allocated, and the supply issue for the active IMP is subsequently resolved by the time the matched allocation is due (whether for active or placebo), this may go ahead.

Since immunosuppressive therapy can impair response to vaccines, please ensure that there is at least 4 weeks between last vaccine dose andinitiating trial IMP. Investigators should follow the most up-to-date JCVI advice regarding further vaccine doses in immunosuppressed patients, paying close attention to any further guidelines and recommendations relating to time windows between vaccine and rituximab dosing for trial participants if they are due to receive rituximab as their randomised IMP.

A minimum washout period of 30 days is mandatory between any 2 IMPs. This interval reflects current clinical practise and our understanding of the mode of action of biologics. It is assumed that the biologic

'switch off' after withdrawal in non-responding patients will not influence propensity to respond to the next IMP. The biologic half-life of TNF inhibitor and anti-IL6r is 10 days, and 22 days for rituximab. As drug switching occurs due to progressive disease or a relapse, it will be assumed that the previous IMP was ineffective, and the benefit seen from the subsequent IMP (which is assessed 120 days after starting the IMP) is not associated with exposure to the first drug or due to a synergistic effect. However, rituximab has a prolonged effect on B cell counts; while experience in AAV suggests a delayed therapeutic response after four months is unlikely, the possibility of a synergy between prior B cell depletion and anti-cytokine agent remains. Sensitivity analyses will be performed on the primary end-point to investigate this possibility. We will also be employing analytical washouts (5) to counteract the effect of the preceding drug on patient-reported outcomes.

For further information on treatments, the pharmacy manual and Trial Procedures Manual should be consulted.

10.1.1. Infliximab

A human/mouse chimeric TNF Inhibitor monoclonal antibody.

10.1.1.1. Legal Status

Infliximab IV is licensed in the UK, US, Canada and Australia. It is used to treat the following indications: rheumatoid arthritis, adult Crohn's disease, paediatric Crohn's disease, ulcerative colitis, paediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis. The Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) Initiative recommends infliximab as a second-line therapy in rare refractory vasculitides in children (deGraeff et al. 2019).

10.1.1.2. Supply

Infliximab IV is available commercially and will be supplied from local hospital stock for the duration of the trial. There is no requirement to ring-fence. For detailed instructions on how to prepare and handle infliximab, please refer to the most recent version of the SmPC for the brand of drug used at the participating site.

10.1.1.3. Packing and Labelling

The IMP will have a blinded label at the point of treatment.

10.1.1.4. Storage Conditions

Infliximab should be kept in a secure place under appropriate storage conditions as stated in the current version of the SmPC of the brand being used within the trial.

10.1.1.5. Maximum duration of treatment of a participant

The maximum dose received will be 15 infusions of Infliximab over the 2 year trial period.

10.1.1.6. Dose

Participants will receive infliximab IV 5mg/kg at days 1, 15(+/-3d), 43 (+/-3d), 70, (+/- 3d) followed by dosing every 56 days (or 8 weeks, +/-14d). Doses will be on days 1,15,43,70, 126, 182, 238, 294, 350, 406, 462, 518, 574, 630, 686, or until treatment failure.
Dose calculations for adult participants will be based on actual body weight as measured during the Screening period (if first IMP in sequence) or preceding trial assessment visit. Dose calculations for paediatric patients will be based on body weight as measured during the screening visit (if first IMP in sequence) or in the preceding trial assessment visit.

10.1.1.7. Administration

Infliximab should be administered IV as per local practice including any pre-medication protocols.

10.1.1.8. Known drug reactions

Known Infliximab reactions are summarised in section 4.8 of Remsima SmPC approved by the MHRA for use in this trial. Concomitant use of anakinra, etanercept or abatacept with Infliximab is not recommended. Investigators should refer to the SmPC to review any other prohibited concomitant therapy use with infliximab.

10.1.1.9. Dose modifications

No dose modifications will be made.

10.1.1.10. Procedures for monitoring treatment compliance

Infliximab will be administered IV to participants. Administration of the blinded IMP will be documented in the source documents i.e. participant hospital records and CRFs.

10.1.1.11. Placebo for infliximab

Infliximab-placebo will consist of a matched volume of Sodium Chloride 0.9% and be administered IV to participants according to the infliximab schedule of events.

10.1.2. Rituximab

Rituximab is a human/mouse chimeric anti-CD20 monoclonal antibody.

10.1.2.1. Legal status

Rituximab IV is approved for the treatment of adult participants with AAV in the United States, Canada, Switzerland, Australia, Japan and the European Union. Rituximab IV is approved by the FDA for the treatment of ANCA associated vasculitis in children over the age of 2 years. Furthermore, the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) Initiative recommends rituximab as a second-line therapy in rare refractory vasculitides in children (deGraeff et al. 2019). For further information, please refer to the SmPC for rituximab for the brand used.

10.1.2.2. Supply

Rituximab IV is available commercially and will be supplied from local hospital stock for the duration of the trial with no requirement to ring-fence. For detailed instructions on how to prepare and handle Rituximab, please refer to the most recent version of the SmPC for the brand of drug used at the participating site.

10.1.2.3. Packing and Labelling

The IMP will have a blinded label at the point of treatment.

10.1.2.4. Storage conditions

Rituximab should be kept in a secure place under appropriate storage conditions as stated in the current version of the SmPC of the brand being used within the trial.

10.1.2.5. Maximum duration of treatment of a participant

The maximum dose received will be 5 x 1g over the 2 year trial period.

10.1.2.6. Dose

Adult participants will receive rituximab IV 1000mg in an appropriate volume of 0.9% sodium chloride solution on Days 1 , 15 (+/-3d), then 180 (+/-14d), 360 (+/-14d) and 540 (+/- 14 d) (i.e. first 2 doses 14 days apart followed by infusions every 180 days).

Children will receive 750mg/m^2/dose (maximum 1g per dose) at the same time intervals, with BSA to be calculated using body weight measured at screening visit (if first IMP in sequence) or preceding trial assessment visit, as per the modified Boyd formula provided in the children's British National formulary (https://bnfc.nice.org.uk/guidance/body-surface-area-in-children-image.html) (Sharkey et al, 2001).

Children who reach 16 years old will be dosed as per the adult regimen.

10.1.2.7. Administration

Before each infusion all participants should receive premedication including antipyretic (e.g. paracetamol) and antihistamine (e.g. chlorphenamine) and 100mg IV methyl-prednisolone as per local practice. Rituximab should be administered IV as per local practice.

10.1.2.8. Known drug reactions

Known Rituximab reactions are summarised in section 4.8 of Mabthera SmPC approved by the MHRA for use in this trial. Currently there are limited data on possible drug interactions with rituximab.

10.1.2.9. Dose modifications

No dose modifications will be made.

10.1.2.10. Procedures for monitoring treatment compliance

Rituximab will be administered IV to participants, following administration of the pre-medication regimen. Administration of the pre-medication regimen and the blinded IMP will be documented in the source documents i.e. participant hospital records and CRFs.

10.1.2.11. Placebo/Active comparator products

Rituximab-placebo will consist of a matched volume of Sodium Chloride 0.9% and be administered IV to participants according to the rituximab schedule of events.

10.1.3. Tocilizumab

Tocilizumab is an anti-IL6 receptor humanised monoclonal antibody.

10.1.3.1. Legal status

Tocilizumab is licenced to treat adults with Giant Cell Arteritis. Whilst the solution for subcutaneous administration and not the solution for infusion is indicated for GCA, this trial will use the solution for infusion due to easier preparation of a comparable placebo and for consistent mode of administration across all three IMPs. The Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) Initiative recommends tocilizumab as a second-line therapy in rare refractory vasculitides in children (deGraeff et al. 2019).

10.1.3.2. Supply

Tocilizumab IV is available commercially and will be supplied from local hospital stock (including non-UK MHRA-approved interim supplied stock) for the duration of the trial. There is no requirement to

ring-fence. For detailed instructions on how to prepare and handle tocilizumab, please refer to the most recent version of the SmPC for the brand of drug used at the participating site.

10.1.3.3. Packing and Labelling

The IMP will have a blinded label at the point of treatment.

10.1.3.4. Storage conditions

Tocilizumab should be kept in a secure location under appropriate storage conditions as stated in the current version of the SmPC of the brand being used within the trial.

10.1.3.5. Maximum duration of treatment of a participant

The maximum dose received will be 24 x 800mg every 30 days over the 2 year trial period.

10.1.3.6. Dose

Participants will receive tocilizumab IV 8mg/kg (maximum 800mg) on Days 1, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510, 540, 570, 600, 630, 660 and 690 (i.e. every 30 days, +/-7d) of IMP schedule or until treatment failure. Dosing is based on weight measured at most recent trial visit prior to start of IMP.

Children <30kg will receive tocilizumab IV 10mg/kg (maximum 800mg) on Days 1, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510, 540, 570, 600, 630, 660 and 690 (i.e. every 30 days, +/- 7d) of IMP schedule or until treatment failure. Children >30kg would receive the adult dosing regimen.

10.1.3.7. Administration

Tocilizumab will be administered IV as per local practice.

10.1.3.8. Known drug reactions

Known Tocilizumab reactions are summarised in section 4.8 of RoActemra SmPC approved by the MHRA for use in this trial. Investigators should refer to the SmPC for details on permitted/prohibited concomitant medication use with Tocilizumab, and ensure patients are monitored appropriately during treatment.

10.1.3.9. Dose modifications

Dose modifications are as per section 4.2 of RoActemra SmPC.

<u>Dose adjustments due to laboratory abnormalities.</u>

• Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 x Upper Limit of Normal (ULN)	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, reduce Tocilizumab dose to 4 mg/kg or interrupt Tocilizumab until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalised Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate
> 3 to 5 x ULN	Interrupt Tocilizumab dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN

(confirmed by repeat testing).	For persistent increases > 3 x ULN, discontinue Tocilizumab
> 5 x ULN	Discontinue Tocilizumab

• Low absolute neutrophil count (ANC)

In patients not previously treated with Tocilizumab, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/l. Investigators should discuss this with the CI prior to treatment start.

Laboratory Value (cells x 10^9/ l)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt Tocilizumab dosing When ANC increases > 1 x 10^9/ l resume Tocilizumab at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC < 0.5	Discontinue Tocilizumab

• Low platelet count

Laboratory Value (cells x 10^3/ µL)	Action
50 to 100	Interrupt Tocilizumab dosing When platelet count > 100 x 10^3/ µ resume Tocilizumab at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
< 50	Discontinue Tocilizumab

10.1.3.10. Procedures for monitoring treatment compliance

The blinded IMP will be administered IV to participants and will be documented in the source documents i.e. participant hospital records and CRFs.

10.1.3.11. Placebo for tocilizumab

Tocilizumab-placebo will consist of a matched volume of Sodium Chloride 0.9% and be administered IV to participants according to the tocilizumab, schedule of events.

10.2 Non Investigational Medicinal Products

10.2.1 Glucocorticoids

For the purpose of this trial, glucocorticoids will be considered a Non Investigational Medicinal Product (NIMP). Prednisolone or an equivalently dosed steroid (e.g. hydrocortisone) may be used.

Steroid dosing is not protocolised, however recommended steroid weaning templates have been provided in the appendix (See appendix 5).

Steroid dose prior to trial entry and during treatment of a relapse, prior to next IMP initiation, is unrestricted.

Once an IMP has been initiated, physicians are recommended to reduce the steroid dose as per best medical practice.

Steroid doses will be captured using a participant steroid diary.

See section 10.3 for details of Steroid dosing during treatment of a relapse.

10.3 Treatment of relapse

10.3.1 Minor Relapse

A minor relapse is defined as the appearance of one or two non-severe BVAS items. A minor relapse does not require a change in IMP. The participant may be treated, at the physician's discretion, with a transient steroid increase to no more than 20mg/day reduced to previous dose within 6 weeks.

10.3.2 Major Relapse

A relapse prompting change to next IMP is defined by worsening of BVAS v3-BIOVAS/PVAS by either:

1. ≥ 1 severe (new/worse) items OR
2. ≥ 3 non-severe (new/worse)* items OR
3. The need to increase the dose of prednisolone to > 20mg/day (or ≥0.25mg/kg/day for children) to treat vasculitis OR
4. An increase in the dose of immunomodulator or immune-suppressive therapy

* Non-severe items can be upgraded by the investigator to severe based on their potential clinical impact, e.g. headache in GCA, thus could meet failure criteria if only one or two items are present.

Participants experiencing a major relapse of vasculitis will have achieved their primary endpoint for that IMP. In this situation, the current IMP should be halted and the participant may be treated with steroids at a dose and regimen as per local Investigator decision until the next IMP is initiated. Investigators must inform central coordination team of IMP discontinuation and decision to move to the next IMP in sequence as soon as the decision is made. The next IMP will only be administered at the subsequent pre-specified scheduled trial clinic visit (i.e. only on Days 120, 240, 360, 480 and 600 (+/- 14 days)).

10.4 Concomitant Therapy

Steroids will be tapered (Section 10.2.1) and stable adjunctive immunosuppressive therapy (such as methotrexate/azathioprine/mycophenolate/leflunomide) will be given as per local Investigator decision. Adjunctive immunosuppressive therapy may be initiated and the dose increased once the primary end-point (treatment failure) is reached. However no dose modification or commencement of adjunctive immunosuppressive therapy is allowed within the 30 days prior to initiation of the next IMP. Prophylaxis against infections and bone protection will be given as per local practice. Investigators should note any prohibited/permitted conmeds as specified in each IMP SmPC at the time the patient is receiving that particular IMP or IMP-placebo

10.5 Emergency unblinding

In the event of a valid medical or safety reason (e.g. in the case of an SAR where it is necessary for the investigator or treating health care professional to know which treatment the participant is receiving before the participant can be treated), the responsibility to break the treatment code resides solely with the treating clinician (i.e. investigator or sub-investigator). Investigators should note that the occurrence of an SAE should not routinely precipitate the immediate unblinding.

The online Sealed Envelope randomisation system will be used for emergency unblinding. Appropriately trained and delegated site staff will be given the necessary access rights and permissions to access this

facility. The name, contact details of the unblinder and reason for unblinding will be recorded within the Sealed Envelope system.

The unblinder will not be shown the treatment allocation sequence on-screen. Instead, the allocation will be sent to the unblinder by email and should be printed and retained confidentially within the Investigator Site File. An email stating that an unblinding has taken place will be automatically sent to the coordination team for oversight purposes. It is the responsibility of the treating physician to promptly document and explain the necessity for unblinding to the CI and the Sponsor. The IMPs in use are licenced biologic drugs and the trial physicians will have knowledge of their effects and risks, and the trial teams will know which IMP treatment protocol a participant is on at any one time; therefore in the event of the online unblinding system being unavailable, or in an emergency setting, it should be assumed that a participant is on active IMP and treated accordingly and IMP stopped. The central trial coordinator should be notified immediately by email that unblinding is needed and the system is unavailable, and that IMP has been stopped. Unblinding should occur as soon as the online system is reavailable. If an unblinding event occurs the participant will be withdrawn from the trial. Further details are provided in the trial procedures manual.

10.6 Accountability and dispensing

10.6.1 Drug accountability

Accountability records will be maintained by the site pharmacy, detailing which treatment was dispensed at each treatment visit, including batch number. Refer to pharmacy manual for further details.

10.6.2 Returns and destruction

Sites must maintain a full accountability record for the IMPs which may include receipt, storage, dispensing, administration, return of unused IMP and destruction of returned/unused trial medication. Template accountability forms will be supplied to sites. However, sites are permitted to use their own drug accountability records as long as these are available to the Sponsor. Refer to pharmacy manual for further details.

11 Procedures and assessments

All procedures and assessments will be conducted in the hospital setting by suitably trained medical professionals. Procedures and assessments are summarised in both the Clinic Visit SoE (Section 11.6) and IMP SoE (Section11.7).

11.1 Participant identification

Participants will be identified by the trial team during their attendance to outpatient clinics or during the course of an inpatient admission. Participants and/or their guardians (for paediatric participants) will be approached by the investigator or researchers who are part of the clinical care team. However, if the trial team are not involved in the participant's clinical care, verbal consent from the participant and/or their guardian (for paediatric participants) will be sought by the clinical care team to allow them to be approached by the trial team. Once contact has been made with the participant and/or their guardians, the trial team will outline and explain the aims of the trial. A copy of the Participant Information Sheet will be provided to interested participants and/or their guardians, who will then be given the opportunity to consider the information with relatives and then to discuss the trial with trial staff and have any queries answered before consenting to participate in the trial.

11.2 Consent

The Informed Consent Form and Assent form will be approved by the REC and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator or designee must ensure that each trial participant, or his/her legally acceptable representative where appropriate, is fully informed about the nature and objectives of the trial and possible risks associated with their participation.

The investigator or designee will obtain written informed consent from each participant or legal guardians of participants under the age of 16 before any trial-specific activity is performed. Written informed assent will also be sought from participants aged 5-15 years old. Any paediatric participant that turns 16 during the trial will be re-consented using the adult PIS and ICF.

The informed consent and assent form used for this trial and any change made during the course of this trial, must be prospectively approved by the REC. The investigator will retain the original of each participant signed informed consent form.

Should a participant require a verbal translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators.

Any new information which becomes available, which might affect the participant's and/or their guardians' willingness to continue participating in the trial will be communicated to the participant and/or their guardians as soon as possible. This information will be provided verbally over the telephone and/or at their next visit.

Participants will be encouraged to enrol in the UK and Ireland Vasculitis Rare Disease Group (UKIVAS) registry at the time of enrolment in to the BIOVAS trial if not already registered. The UKIVAS registry is collaboration between patients, clinicians and scientists to create the first comprehensive database of vasculitis patients in the UK and Ireland. By collecting longitudinal data, the UKIVAS aims to provide an evidence base to enhance diagnosis and treatment of patients with vasculitis. Furthermore, participants are provided with the option to consent to having their data collected for registration into Public Health Englands' National Congenital Abnormality and Rare Disease Registration Service (NCARDRS), which forms part of the UK Rare Diseases Strategy. Participating sites are requested to collect data such as NHS number/full name/Date of Birth/Diagnosis and Date of Diagnosis for those patients who have provided optional consent, which is sent every 6 months via secure (i.e. nhs.net to nhs.net) email to the NCARDRS.

11.3 Screening evaluation

11.3.1 Screening Assessments

Trial specific assessments will only be conducted after participants have given written informed consent. After consent has been obtained, participants will be reviewed to ensure they meet all of the inclusion criteria and none of the exclusion criteria of the trial.

Consented participants will enter a screening period of up to 28 days. During the screening period the following procedures and assessments will be performed:

- Demographics: date of birth, sex, race
- Medical history/investigations/medication will be assessed in relation to eligibility
- Physical exam
- Vital signs
- Tuberculosis (latent/active) screening as per local Investigator's clinical practice
- Urine dipstick test as per local investigator's clinical practice
- The following laboratory tests:

  - Biochemistry: CRP, LFT, U&E, Lipid profile
  - Haematology: FBC, ESR
  - Immunology: Immunoglobulins
  - Virology: HIV, HBV, HCV (as per local practice). COVID19 test is recommended if this is part of local practice.
  - Serum pregnancy test for WOCBP only
- Birmingham Vasculitis Activity Score v3 modified for BIOVAS(BVASv3-BIOVAS)/Paediatric Vasculitis Activity Score (PVAS) and physicians global assessment (PGA).
- Indian Takayasu's Arteritis Activity Score (ITAS) (TA participants only)
- Relapsing polychondritis disease activity index (RPDAI) (RP participants only)
- Participants will start recording their daily steroid use from date of informed consent.

11.3.2 Participant Registration/Randomisation

Once a participant has been confirmed eligible for the trial, the participant may be randomised and a unique trial ID will be allocated.

Randomisation can occur at any point during the screening period after all eligibility criteria have been met. Please ensure that there is at least 4 weeks between COVID-19 vaccine dose and baseline (D1) visit and receiving first dose of IMP.
Details on randomisation using Sealed Envelope are provided in the Randomisation Manual.

11.4 Treatment Period

11.4.1 Clinic Visits

The treatment period comprises Trial Clinic Visits 2 to 8 (Days 1, 120, 240, 360, 480, 600 and 720). All clinic visits will occur within a +/- 14 day window of the scheduled visit, unless under exceptional circumstances and first discussed with the central BIOVAS coordinator. The following procedures will be performed:

- Physical examination
- Vital signs
- Urine dipstick test as per local investigator's clinical practice
- Standard of care bloods: CRP, LFT, FBC, ESR, U&E, immunoglobulins, lipid profile
- Birmingham Vasculitis Activity Score (BVAS) v3 modified for BIOVAS (BVAS v3-BIOVAS)/ Paediatric Vasculitis Activity Score (PVAS)
- Physician global assessment (PGA)
- Indian Takayasu Clinical Activity Score (ITAS) for TA participants only
- Relapsing polychondritis disease activity index (RPDAI) for RP participants only
- Vasculitis Damage Index (VDI)/ Paediatric Vasculitis Damage Index (PVDI)
- EuroQol (EQ-5D-5L)/Child Health Utility Index 9D (CHU-9D)
- Health resource use (NHS resource use/out of pocket costs/lost productivity)
- Review of participant steroid diary
- Serious Adverse Event (SAE)/ Adverse Event of Special Interest (AESI) review
- Concomitant medications review
- Administration of allocated IMP treatment if applicable

If a participant is assessed to be experiencing a relapse, the current IMP may be halted and the participant switched to the next IMP in their allocated sequence. The participant IMP record CRF should be updated and the central coordination office in Cambridge and local pharmacy teams informed as soon as possible if there is a change in IMP. Day 1 of the next IMP in the sequence will only be administered at the subsequent pre-specified scheduled trial clinic visit (i.e. only on Days 120, 240, 360, 480 and 600 (+/- 14 days).

In the exceptional event of an IMP hospital stock/supply issue of an IMP at the time of a patient either starting IMP1, during the trial, or switching to next in sequence, the IMP in question (or its placebo equivalent) can be skipped to the following IMP in sequence, and the reason for additional switching documented. It is recommended to discuss with the CI any potential hospital IMP stock supply issues as they arise. If the active IMP with the supply issue is the one with a placebo match allocated, and the supply issue for the active IMP is subsequently resolved by the time the matched allocation is due (whether for active or placebo), this may go ahead.

An example of this is a Tocilizumab hospital stock shortage due to increased demand as a COVID treatment globally. In such a circumstance, if a patient was randomised to a sequence where IMP1 was either Tocilizumab or Tocilizumab placebo, and there was a hospital shortage of this, the patient can immediately be switched to the next IMP in sequence. If the IMP shortage was encountered during the trial or at the time of a planned IMP switch due to relapse the patient can switch IMP at the next scheduled visit, due to supply issue, and treated with steroid accordingly until next scheduled visit. If the active IMP with the supply issue is the one with a placebo match allocated, and the supply issue for the active IMP is subsequently resolved by the time the matched allocation is due (whether for active or placebo), this may go ahead.

Urinary pregnancy testing will be performed monthly from day 1 through to 1 month after the last dose of IMP in the trial. Patients can perform these tests at home if they do not have a treatment or trial visit scheduled at the time the monthly test is due to be performed; see section 11.4.4.

A telephone call to the participant 2 weeks prior to their scheduled four monthly trial clinic visits is recommended to be made by the local trial team to try and gauge the disease activity. This may aid the logistics of drug administration, assist pharmacy and ward teams in case of a potential switch in IMP.

11.4.2 Unscheduled Visit

An unscheduled visit will be arranged for participants experiencing a relapse. The following assessments and procedures should be performed:

- Physical examination
- Vital signs
- Urine dipstick test as per local investigator's clinical practice.
- Standard of care bloods: CRP, LFT, FBC, ESR, U&E, immunoglobulins.
- Birmingham Vasculitis Activity Score (BVAS)v3-BIOVAS/ Paediatric Vasculitis Activity Score (PVAS)
- Physician global assessment (PGA)
- Indian Takayasu Clinical Activity Score (ITAS) for TA participants only
- Relapsing polychondritis disease activity index (RPDAI) for RP participants only
- Vasculitis Damage Index (VDI)/ Paediatric Vasculitis Damage Index (PVDI)
- EuroQol (EQ-5D-5L)/Child Health Utility Index 9D (CHU-9D)
- Health resource use (NHS resource use/out of pocket costs/lost productivity)
- Serious Adverse Event (SAE) review
- Concomitant medications review

11.4.3 IMP Visits

IMP administration will follow the scheduled visits listed in the IMP SoE (Section 11.7). The initiation of IMP administration will begin at IMP Day 1, which occurs at pre-specified scheduled trial clinic visit (i.e. only on Days 120, 240, 360, 480 and 600 (+/- 14 days)). Where an IMP visit coincides with a monthly pregnancy test, this can be performed in clinic on the same day as the treatment visit, as well as

conducting AE/SAE review with the patient. Most recent clinical blood tests (within 30 days of treatment visit) should also be reviewed prior to administering IMP.

11.4.4. Safety monitoring visits

Additionally, safety reviews will be conducted monthly, either remotely by telephone with the patient, or in person if coinciding with a treatment visit. Safety monitoring will include: AESI/SAE review, routine clinical blood review (for patients on Tocilizumab/Tocilizumab dosing schedule, routine blood FBC/WBC/ESR/CRP/LFT and lipid results available within past 30 days; for Infliximab/infliximab placebo and rituximab/rituximab placebo schedules, review of FBC/WBC and LFT at a minimum; results available within past 30 days), review of urine pregnancy test result (for WOCBP participants).

11.5 Trial assessments

Procedures and assessments at the scheduled visits are listed in the Clinic Visit SoE (Section 11.6) whilst IMP infusion activity is listed in a separate IMP SoE (Section 11.7)

For the purposes of this trial, a month will be deemed to have 30 days and a year 360 days. The total duration of the trial will be 720 days (2 years).

11.5.1 Timing of assessments

Participants will be seen every 120 days (+/-14days) for clinic visits. Upon randomisation, participants will be allocated a sequence of 4 IMP treatments. The first allocated IMP will be given on Day 1 of the treatment period and the participant will continue to follow the first IMP treatment dosing schedule as in the first IMP SoE (Section 11.7) until the investigator deems the participant to have met the treatment failure criteria as previously defined.

If the treatment failure criteria have been met, the second IMP in the randomisation sequence will then be initiated at the next scheduled clinic visit (i.e. Days 120, 240, 360, 480 or 600). The first dose of the second IMP will be given beginning at Day 1/Visit 1 of the second IMP SoE (Section 11.7) and continue following the second IMP SoE schedule until treatment failure.

Upon treatment failure of the second IMP, the third IMP will then be initiated at the next scheduled clinic visit (i.e. Days 240, 360, 480 or 600). The first dose of the third IMP will be given beginning at Day 1/Visit 1 of the third IMP SoE (Section 11.7) and continue following the third IMP SoE schedule until treatment failure.
Upon treatment failure of the third IMP, the fourth IMP in the randomisation sequence will then be initiated at the next scheduled clinic visit (i.e. Days 360, 480 or 600). The first dose of the fourth IMP will be given beginning at Day 1/Visit 1 of the fourth IMP SoE (Section 11.7) and continue following the fourth IMP SoE schedule.

The clinic visit schedule (Section 11.6) will remain as per the schedule assigned at randomisation and will not be affected by change in IMP.

Additional unscheduled visits will also occur to capture relapse data.

11.6 Trial clinic visit Schedule of Events (SoE)

		SCR	Treatment Period																																				
Clinic Visit Number		**1**	**2**					**3**						**4**					**5**					**6**						**7**					**8**	**Unscheduled [i]**
Study Timepoint[a]	**Day**	**-14 to -1**	**1**	**15**	**30**	**60**	**90**	**120**	**135**	**150**	**180**	**210**	**225**	**240**	**270**	**300**	**315**	**330**	**360**	**390**	**405**	**420**	**450**	**480**	**495**	**510**	**540**	**570**	**585**	**600**	**630**	**660**	**675**	**690**	**720**	
	Month				**1**	**2**	**3**	**4**	**4.5**	**5**	**6**	**7**	**7.5**	**8**	**9**	**10**	**10.5**	**11**	**12**	**13**	**13.5**	**14**	**15**	**16**	**16.5**	**17**	**18**	**19**	**19.5**	**20**	**21**	**22**	**22.5**	**23**	**24**	
Informed Consent		X																																				
Randomisation[b]		X																																				
Demographics, Medical History, Prior Medications		X																																				
Physical Examination[c]		X	X					X						X					X					X						X					X	X
Vital Signs[d]		X	X					X						X					X					X						X					X	X
Routine blood tests[e]		X						X						X					X					X						X					X	X
Virology screening[f]		X																																				
Routine Immunoglobulins blood test		X						X						X					X					X						X					X	X
Tuberculosis screening[g]		X																																				
Serum pregnancy test (WOCBP only)[h]		X																																				
BVAS/PVAS		X	X					X						X					X					X						X					X	X
PGA		X	X					X						X					X					X						X					X	X
ITAS (TA patients only)		X	X					X						X					X					X						X					X	X
RPDAI (RP patients only)		X	X					X						X					X					X						X					X	X
VDI/PVDI			X					X						X					X					X						X					X	X
EQ5D-L/CHU-9D			X					X						X					X					X						X					X	X
Resource use questionnaire		X	X					X						X					X					X						X					X	X
Dispense / review patient steroid diary		X	X					X						X					X					X						X					X	X
AESI/SAE review		X	X					X						X					X					X						X					X	X
Concomitant medications review		X	X					X						X					X					X						X					X	X

11.7 IMP Schedule of Events (SoE)

Treatment Period (as per patient schedule)

From start of IMP																																						
IMP	**Day**	**1**	**15**	**30**	**43**	**60**	**70**	**90**	**120**	**126**	**150**	**180**	**182**	**210**	**238**	**240**	**270**	**294**	**300**	**330**	**350**	**360**	**390**	**406**	**420**	**450**	**462**	**480**	**510**	**518**	**540**	**570**	**574**	**600**	**630**	**660**	**686**	**690**	**720**
Timepoin	**Month**	**0**		**1**		**2**		**3**	**4**		**5**	**6**		**7**		**8**	**9**		**10**	**11**		**12**	**13**	**14**	**14**	**15**		**16**	**17**		**18**	**19**		**20**	**21**	**22**		**23**	**24**
Safety monitoring-ALL IMPs includes: monthly urine pregnancy test & review, AE/SAE review, clinlab results review		X		X		X		X	X		X	X		X		X	X		X	X		X	X		X	X		X	X		X	X	X		X	X
IMP Visit Number for Infliximab		**1**	**2**		**3**		**4**			**5**			**6**		**7**			**8**			**9**			**10**			**11**			**12**			**13**		**14**		**15**		
INFLIXIMAB/ INFLIXIMAB-PLACEBO infusion (Days 1,15,43,70, then every 56 days)		X	X		X		X			X			X		X			X			X			X			X			X			X		X		X		
IMP Visit Number for rituximab		**1**	**2**									**3**										**4**									**5**								
RITUXIMAB/ RITUXIMAB-PLACEBO infusion (Day 1 and 15, followed by every 180 days)		X	X									X										X								X								
IMP Visit Number for Tocilizumab		**1**		**2**		**3**		**4**	**5**		**6**	**7**		**8**		**9**	**10**		**11**	**12**		**13**	**14**		**15**	**16**		**17**	**18**		**19**	**20**		**21**	**22**	**23**		**24**	
TOCILIZUMAB/ TOCILIZUMAB-PLACEBO infusion (every 30 days)		X		X		X		X	X		X	X		X		X	X		X	X		X	X		X	X		X	X		X	X		X	X		X	X	

a. Trial clinic visits must occur within a +/- 14 day window of the scheduled trial clinic visit.
b. Randomisation must occur after all screening procedures have been performed and the participant has been confirmed eligible to enter the trial.
c. Physical examination
d. Vital signs will include body weight (kg), heart rate, body temperature and blood pressure.
e. Standard of care bloods will include: CRP, LFT, FBC, U&E, lipid profile and ESR.
f. Virology screening bloods will include: HIV, HBV and HCV as per local practice.
g. Tuberculosis screening as per local practice.
h. Serum pregnancy test at screen only. Urine pregnancy tests monthly thereafter as part of monthly safety review.
i. , Infliximab up to D70 and Rituximab D15 visits should occur within a +/-3d window, with subsequent doses occurring within a +/-14d window. All Tocilizumab visits should occur within a +/-7d window
j. Infliximab infusions will be administered at days 1, 15 (+/-3d), 42 (+/-3d) and 70 (+/-3d), then every 56 days (+/-14d) thereafter (ie days 126, 182, 238, 294, 350, 406, 462, 518, 630 and 686.
k. Rituximab infusions will be administered on IMP Days 1 and 15 (+/-3d),, Days 180 (+/-14d),, 360 (+/-14d), and 540 (+/-14d),
l. Tocilizumab infusions will be administered every 30 days (+/-7 d), on IMP Days 1, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510, 540, 570, 600, 630, 660 and 690.

11.8 End of Trial Participation

Participants are considered to have completed the trial once they have completed 2 years of treatment phase i.e. completed their Day 720 trial clinic visit.
If a participant is withdrawn from trial treatment early, they will still be encouraged to attend the remaining clinic visits and undergo the trial assessments as detailed in the schedule of events.

11.9 Trial restrictions

Participants should not receive live or live attenuated vaccines within 45 days of screening or throughout the trial, or within 12 months of the last dose of Rituximab.
A serum pregnancy test will be performed on women of childbearing potential (WOCBP) during the screening period. At the time of an investigator-initiated switch to next IMP in the randomised sequence, a urine pregnancy test is required, as per standard clinical practice for initiation of a biologic. Furthermore, for safety monitoring purposes, monthly urine pregnancy tests will be carried out. These can be performed by the patient at home if the monthly tests do not match the patient's randomised IMP dosing schedule.
A women is considered of childbearing potential if she is fertile, following menarche, and until becoming post-menopausal* unless is permanently sterile**.

*Post-menopausal is defined as: No menses for 12 or more months without an alternative medical cause. FSH laboratory value can be used to confirm post-menopausal status in women not using hormonal contraception or homone replacement therapy.
**Permanently sterile is defined as: hysterectomy, bilateral salpingectomy, bilateral oophorectomy.

Women of childbearing potential are required to use a highly effective method of contraception for the duration of the trial and for 12 months after the completion of the trial/last treatment. This includes:

- Combined hormonal contraception (pill, contraceptive injection or implant)
- Progesterone only hormonal contraception (pill, contraceptive injection or implant)
- Intrauterine device (IUD)
- Intrauterine hormone releasing system (IUS)
- Bilateral tube occlusion
- Vasectomised partner
- True abstinence (where this is in accordance with the particpants preferred and usual lifestyle)

12 Assessment of Safety

12.1 Definitions

12.1.1 Adverse event (AE)

Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
An adverse event can therefore be any unfavourable 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.
Due to the underlying clinical conditions of the trial populations, it is not practicable to record all adverse events in this trial. Therefore, only adverse events of special interest (AESIs) as described in section 12.3 will be reported from the point of informed consent until the end of participation in the

trial for each participant.

12.1.2 Adverse reaction to 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.

12.1.3 Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the applicable reference safety information (RSI) (Section 12.1.6).

When the outcome of the adverse reaction is not consistent with the applicable RSI 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 participant /event outcome or action criteria.

12.1.4 Serious adverse event or serious adverse reaction (SAE / SAR)

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing in participants´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect.
- is an important medical event - Some medical events may jeopardise the participant or may require an IMP to prevent one of the above characteristics/ consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious'

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant 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.

When reporting a SAE, causality and expectedness should be assessed for each IMP.

12.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the Reference Safety Information.

Any potential SUSARs will be assessed by an unblinded central safety officer.

12.1.6 Reference Safety Information (RSI)

A list of medical events that defines which reactions are expected for the IMP within a given trial and thus determining which Serious Adverse Reactions (SARs) require expedited reporting.

The RSI is contained in a clearly identified section of the Summary of Product Characteristics (SmPC).

For this trial the Reference Safety Information is:

Section 4.8 of the following SmPCs approved by the MHRA for use in this trial:

- Mabthera (rituximab) 100 mg concentrate for solution for infusion, Roche Products Limited Table 4 dated 27/02/2020
- RoActemra (tocilizumab) 20mg/ml concentrate for solution for infusion, Roche Products Limited Table 1 dated 17/10/2019
- Remsima (infliximab) 100mg powder for concentrate for solution for infusion, Napp Pharmaceuticals Limited, Table 1 dated 12/12/2019

12.2 Expected Adverse Reactions/Serious Adverse Reactions (AR /SARs)

All expected Adverse Reactions are listed in the latest MHRA approved version of the RSI as specified in section 12.1.6. This must be used when making a determination as to the expectedness of the adverse reaction. If the adverse reaction meets the criteria for seriousness, this must be reported as per section 12.6.

12.3 Expected Adverse Events/Serious Adverse Events (AE/SAE)

Any pre-planned or elective surgery that necessitates hospital admission will not be considered a SAE and does not need expedited reporting, however details will be collected in the CRF.

All serious adverse events should be reported according to guidance in section 12.6.

In addition to all SAEs, all infections requiring antimicrobial, antiviral or antifungal treatment are being collected as adverse events of special interest (AESIs) as part of the BIOVAS trial.

Each Principal Investigator must report all AESIs to the CI using the CRF in a timely manner. If the AESI is deemed to be serious, then the reporting procedure for an SAE should be followed as detailed in section 12.6.

12.4 Pregnancy Reporting

All pregnancies within the trial should be reported to the Chief Investigator and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification.
Details of all pregnancies in female participants will be collected after the start of trial treatment and until 12 months after the last dose of IMP.
Pregnancy is not considered an SAE unless a negative or consequential outcome (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, and ectopic pregnancy) is recorded for the mother or child/foetus.
Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the participant has completed the trial and considered by the investigator as possibly related to the trial treatment, should be reported to Sponsor within 24 hours.

12.5 Evaluation of adverse events

The Sponsor expects that reportable adverse events (i.e. AESI, SAEs, Pregnancies) are recorded from the point of Informed Consent regardless of whether a participant has yet received a medicinal product. Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, and any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event (causality).

12.5.1 Assessment of seriousness

Seriousness is assessed against the criteria in section 12.1.4.This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction

12.5.2 Assessment of causality

Definitely: A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**
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. **This is therefore an Adverse Reaction.**
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. **This is therefore an Adverse Reaction.**
Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**
Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unlikely and Unrelated causalities are considered NOT to be trial drug related
Definitely, Probable and Possible causalities are considered to be trial drug related

A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the trial and meets the criteria for reporting or recording in the appropriate section of the CRF.

12.5.3 Clinical assessment of severity

Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated
Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity
Severe: Significant impairment of functioning; the participant is unable to carry out usual activities and / or the participant's life is at risk from the event.

12.5.4 Recording of adverse events

Adverse events of special interest (AESI) should be recorded on the AESI reporting form as described in section 12.3. Serious Adverse Events and Serious Adverse Reactions should be reported to the sponsor as detailed in section 12.6

12.6 Reporting serious adverse events

Each Principal Investigator must report all serious adverse events to the Chief Investigator using the trial specific SAE form within 24 hours of their awareness of the event.

The Chief Investigator is responsible for ensuring the assessment of all SAEs for expectedness and relatedness is completed and the onward notification of all SAEs to the Sponsor immediately but not more than 24 hours of first notification. The Sponsor has to keep detailed records of all SAEs reported to them by the trial team.

The Chief Investigator is also responsible for prompt reporting of all serious adverse event findings to the competent authority (e.g. MHRA) of each concerned Member State if they could:

- adversely affect the health of participants
- impact on the conduct of the trial
- alter the risk to benefit ratio of the trial
- alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC

The completed SAE form should be emailed. Details of where to report the SAE's can be found on the BIOVAS SAE form and the front cover of the protocol.

12.7 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. Please see section 12.1.6 for the Reference Safety Information to be used in this trial.

12.7.1 Who should report and whom to report to?

The Sponsor delegates the responsibility of notification of SUSARs to the Chief Investigator. The Chief Investigator must report all the relevant safety information previously described, to the:

- Sponsor
- competent authorities in the concerned member states (e.g. MHRA)
- Ethics Committee in the concerned member states

The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

12.7.2 When to report?

12.7.2.1 Fatal or life-threatening SUSARs

The CI must inform the Sponsor of any fatal SUSAR immediately but not more than 24 hours of first notification. The MHRA and Ethics Committee must be notified as soon as possible but no later than **7 calendar days** after the trial team and 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 all parties within an additional **8 calendar days**.

12.7.2.2 Non-fatal and non-life-threatening SUSARs

All other SUSARs and safety issues must be reported to the Sponsor immediately but not more than 24 hours of first notification. The MHRA and Ethics Committee should be notified as soon as possible but no later than **15 calendar days** after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

12.7.3 How to report?

12.7.3.1 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 participant (e.g. trial participant 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:

- A unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)
- A unique case identification (i.e. sponsor's case identification number)

12.7.3.2 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. Further available relevant information should be reported as follow-up reports.
In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

12.7.3.3 Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to.
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Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

13 Toxicity – Emergency Procedures

For this trial, any dose of infliximab in excess of 5mg/kg (adults and children); tocilizumab in excess of 800mg (adults and children); rituximab in excess of 1000 mg IV within a 24 hour period (children: maximum 1000mg/dose)will be considered an overdose. There is no specific recommended treatment for overdose of infliximab, tocilizumab or rituximab.

In the event of an infliximab, rituximab or tocilizumab overdose, the investigator should:

- Contact the Trial Physician immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Trial Physician based on the clinical evaluation of the participant.

14 Evaluation of Results (Definitions and response/evaluation of outcome measures)

Timings and details of efficacy assessments are shown in the Clinic Visit SoE (section 11.6).

Trial objectives are shown in section 8.5.

14.1 Response criteria

14.1.1 Time to treatment failure

Primary treatment failure is defined as progressive disease (worsening of Birmingham vasculitis activity score v3.0 modified for BIOVAS (BVAS v3-BIOVAS) or paediatric vasculitis activity score (PVAS) compared

to baseline) within 120 days or failure to achieve response (see definition below) by 120 days. In such cases, TTF will be zero.

Secondary treatment failure is defined as having achieved response (definition below) by 120 days from the time of IMP commencement, and subsequently relapse after 120 days from IMP commencement.

Response is defined by:

- Absence of new/worse BVAS v3-BIOVAS (adults) / PVAS (children) items assessed at the 120 days evaluation time point after commencing IMP AND
- Prednisolone ≤ 10mg/day or ≤ 0.2 mg/kg for children (whichever is lower), unless the baseline dose is ≤ 10mg/day or ≤ 0.2 mg/kg children (whichever is lower) in which case it should not be more than the baseline dose*

* Baseline dose is the dose of oral prednisolone, mg/day, or equivalent steroid, averaged over the 7 days prior to the start of each new IMP.

Relapse is defined by either:

1. Appearance of ≥ 1 severe (new/worse) or ≥ 3 non-severe (new/worse) BVAS v3-BIOVAS/PVAS items from the time of BVAS response (as defined above) assessed at 120 day evaluation time points # OR
2. The need to increase the dose of prednisolone to > 20mg/day to treat vasculitis OR
3. The need to increase the dose of an immunomodulator or immune-suppressive therapy in order to treat vasculitis.

Non-severe items can be upgraded by the investigator to severe based on their potential clinical impact, e.g. headache in GCA, thus could meet failure criteria if only one or two items are present.

For an increase in one or two non-severe new/worse BVAS/PVAS items, which does not meet the relapse definition, the current IMP is continued and the participant may be treated, at the physician's discretion, with a prednisolone increase to no more than 20mg/day (or 0.3mg/kg but no more than 20mg/day in children) which will be reduced to the previous dose within 6 weeks.

A minor relapse is defined as an increase in one or two non-severe BVAS items. A minor relapse does not require a change in IMP. The participant may be treated, at the physician's discretion, with a transient steroid increase of no more than 20mg/day reduced to previous dose within 6 weeks.

Storage and Analysis of Samples

No samples will be stored as part of the BIOVAS trial. All specimens will be analysed at each participating site via standard of care processes.

15 Statistics

15.1 Statistical methods

Data analysis:

A full Statistical Analysis Plan (SAP) will be developed and finalised prior to the final database lock.

For the primary analysis, we will include all participants who were entered and randomised. For the TTF outcome we will use a mixed-effects Cox regression model (as implemented by the 'coxme' package in R). The unit of analysis will be each allocation to a treatment (so that a participant may contribute up to four data points). Fixed effects are treatment assignment; a normally distributed random effect for each individual is included. Ties in the outcome are handled using the method of Efron. The effect of each experimental treatment vs. placebo will be estimated from this model, with Wald tests performed.

If a participant drops out of the trial during a treatment period, then their TTF will be censored at the time of dropout. The only exception to this will be if a participant drops out before the first remission assessment is done (so that it is not clear whether they went into remission or not) – in that case, their outcome will be imputed with a multiple imputation procedure. We expect dropout to be low, so it is possible there will be no such issues with the analysis.

As a secondary analysis, we will repeat the above for each of the eight disease subgroups. As an exploratory analysis we will also use a Bayesian hierarchical model that will allow information to be borrowed between the different disease subgroups if there is evidence the effect size is similar (37). A full analysis plan will be developed with sensitivity analyses proposed to ensure results are robust.

Secondary outcomes will be analysed in the pooled set of all participants, in a similar way to the primary outcome, but with a suitable regression model used for the type of data. Time-to-event outcomes will be analysed in the same way as the primary outcome; binary outcomes will use a mixed-effects logistic regression model.

15.2 Interim analyses

No interim analyses are planned with regards to the primary endpoint, but the Trial Management Group and Trial Steering Committee will review efficacy and safety data, and will advise on the need for any additional analyses or alterations to the conduct or even continuation of the trial if there are major safety concerns.

15.3 Number of Participants to be enrolled

15.3.1 Sample size determination

There are three primary hypotheses of the trial – superiority of:

1. infliximab vs. placebo,
2. rituximab vs. placebo and
3. tocilizumab vs. placebo

They will be evaluated on the time to treatment failure (TTF) outcome. The primary analysis is in the entire group of participants. Secondary analyses involve testing for a difference in individual diseases either using frequentist or Bayesian hierarchical methods depending on the sample size. Where some clinical experience exists we will elicit priors for Bayesian analyses before the start of the trial (36). We present here the power for the main (pooled) analysis and for various samples sizes.

Because the diseases are rare, we cannot necessarily choose the sample size based on a specified effect size. Instead we investigate the power of the design given a realistic number of participants that could be recruited over the course of the trial. Since the trial design is novel, there are no sample size formulae available. Instead we use simulations to explore the power of the trial design. For the power calculation we make these assumptions: 1) Each participant is followed up until they relapse on all four treatments,

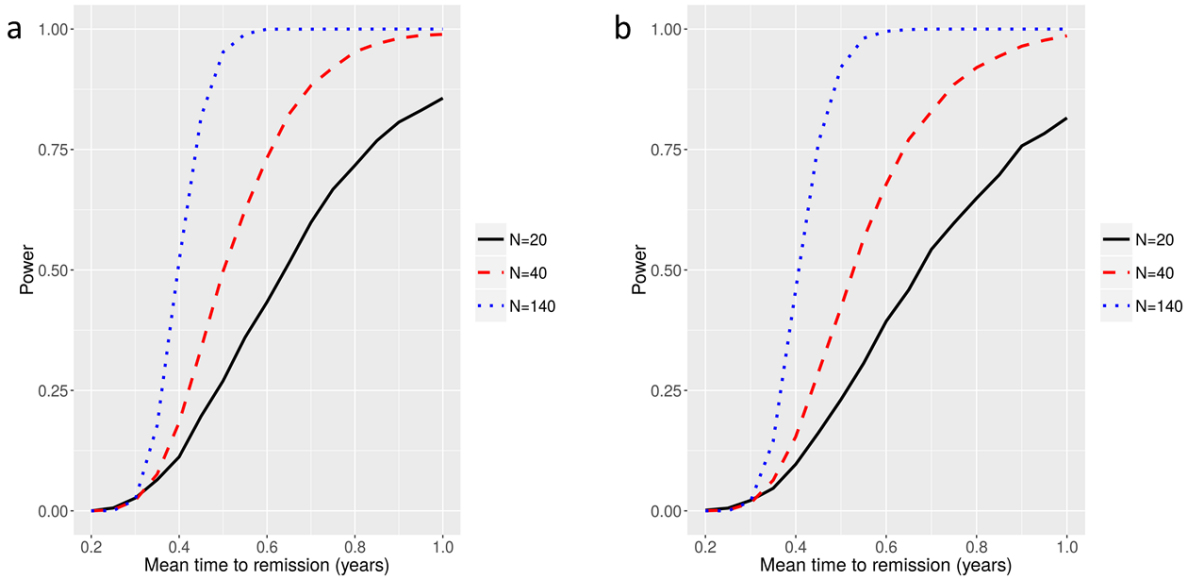
or two years from the initial randomisation has passed; 2) the final test statistics for the three comparisons (infliximab vs. placebo, rituximab vs. placebo, tocilizumab vs. placebo) are each tested at a nominal two-sided 5% type I error rate. Due to sample size constraints, we do not make a formal adjustment for multiple testing. Instead we note that since we would only take forward treatments that are significantly better than placebo, the trial design has a maximum chance of incorrectly recommending an ineffective treatment of 7.5% (each hypothesis is 2.5% one-sided). Due to the correlation between tests, the actual maximum chance is likely to be closer to 5%.

Simulations were performed in R with 5000 replicates per scenario. The TTF variable is simulated using an exponentially distributed random variable. If the simulated variable is less than four months, then the participant is classified as never having gone into remission, with their TTF included as zero. If the simulated variable is greater than four months, then the TTF is included as the simulated value. To allow for correlation of the TTF outcomes for a particular participant, we use a random frailty term for each participant. In the simulations this is uniformly distributed between 0.5 and 2. The parameter of the exponential distribution used for a participant's TTF outcome will then be the overall hazard parameter for the treatment allocated multiplied by the frailty of the participant. In more mathematical language, let λ_j be the overall hazard parameter for arm j and θ_k be the frailty term for participant k; then if participant k is allocated arm j the hazard parameter for the TTF will be $\lambda_j\theta_k$. The analysis used in the simulations is a mixed-effects Cox regression model (as implemented by the 'coxme' package in R). Treatment assignment is included as a fixed effect and a random effect for each individual is included. Ties in the outcome are handled using the method of Efron.

We explored the power of the trial for pooled sample and different sample sizes. This involved specifying the TTF parameters for the four arms and exploring in what proportion of simulation replicates was each IMP (infliximab, rituximab & tocilizumab) significantly superior to placebo. We first considered the situation where two experimental treatments had the same effect as placebo (mean TTF of 0.3 years), and the other one varied in effect. The power of the trial to find the latter was significantly better than placebo is shown in Figure 3a (shown below). The power of the trial is 90% for the sample size of 140 when the mean TTF is 6 months.

We also examined the power to conclude significance of the second experimental treatment, for different effect sizes, when the first experimental treatment had a mean TTF of 0.6 years. The power is shown in Figure 3b (shown below). The power for lower sample sizes is notably lower in this case. However, the trial would still have high power for realistic treatment effects in the pooled analysis and larger disease subgroups. The lower power is because when one experimental treatment has a positive effect it will result in fewer participants being allocated to the other one (as they stay longer on the effective treatment). Again, the type I error rate is properly controlled.

Figure 3 Simulations used to explore the power of the trial to conclude significance of experimental treatments as their mean time to remission varies. 3a Experimental treatments 1, 2 and placebo have their mean time to remission set to 0.3 years. 3b Experimental treatment 1 has mean time to remission set to 0.6 years; placebo set to 0.6 years.



We finally looked at the power of the trial design to find significant treatment effects of infliximab, rituximab & tocilizumab when they had mean TTF of 8 months. Table 5 shows the probability of a participant not going into remission, the mean time in remission (conditional on going into remission) and the power for testing infliximab vs. placebo and tocilizumab vs. placebo in the different subgroups and the overall sample. There will be a cap on recruitment, a maximum of 50 participants in each disease group, in order to prevent the 'easy to recruit group', for e.g. giant cell arteritis, dominating the total sample.

Table 1 Probability of a participant achieving and mean time in remission

	Placebo	Infliximab	Rituximab	Tocilizumab
Probability of not going into remission	67%	39.3%	39.3%	39.3%
Mean time in remission	3.6 months	8 months	8 months	8 months
Power: n=20	N/A	47.9%	49.0%	47.5%
Power: n=40	N/A	77.3%	77.6%	77.8%
Power: n=140	N/A	>99.9%	>99.9%	>99.9%

15.4 Criteria for the premature termination of the trial

. The trial may be terminated prematurely in the event of:

1) a significant safety signal indicating harm of one of the treatment regimens as determined by the DSMB in conjunction with the TSC and sponsor, or
2) the funder (NIHR) terminating support for the trial.

15.5 Procedure to account for missing or spurious data

For the primary outcome, if a participant drops out of the trial during a treatment period, then their TTF will be censored at the time of dropout. The only exception to this will be if a participant drops out before the first remission assessment is done (so that it is not clear whether they went into remission or not) – in that case, their outcome will be imputed with a multiple imputation procedure.

Secondary endpoints will be analysed with mixed-effects models which account for missing data under a Missing At Random (MAR) assumption.

15.6 Economic evaluation

15.6.1 Data Collection

Quality of life (QoL) and cost effectiveness will be assessed in all randomised participants via the following validated research questionnaires:

- EQ-5D-5L (EuroQol) or Child Health Utility Index 9D (CHU-9D)

QoL and health economic questionnaire packs will be administered to trial participants at the following time points, regardless of whether the participant is receiving treatment or not:

- Day 1 post randomisation
- 120 days post randomisation (+/- 14 days)
- 240 days post randomisation (+/- 14 days)
- 360 days post randomisation (+/- 14 days)
- 480 days post randomisation (+/- 14 days)
- 600 days post randomisation (+/- 14 days)
- 720 days post randomisation (+/- 14 days)
- Any unscheduled visits

Research staff will provide the participant with the questionnaires in clinic where the participants and/or participant's guardians will be asked to complete the questionnaires. If possible, all questionnaires should be completed prior to the participant's clinical consultation as this aids objectivity and compliance.

The baseline questionnaires must be completed after consent has been obtainedand prior to first dose of IMP. The health resource use questionnaires should be completed prior to clinical assessment.

15.6.2 Within trial cost effectiveness analysis

The within trial economic evaluation will estimate the incremental cost effectiveness ratio (ICER) for each of treatment permutations compared to placebo over a period of 24 months from the perspective of the NHS and social care sector. A secondary analysis will be undertaken from the societal perspective. The analyses will use trial data collected to 24 months follow up.

The primary outcome measure of the trial is TTF. The trial economic evaluation will, for consistency, use the same primary outcome measure. However, economic evaluations are designed to inform resource allocation decisions, so evaluations will also be produced using overall survival and quality adjusted life years (QALYs) outcome measures. The estimation of QALYs requires the production of utility weights for each health state observed in the trial population. We will use the EQ-5D-5L (EuroQol) or Child Health Utility 9D (CHU-9D) instruments for this purpose.

Measurement of resource use: NHS resource use associated with each treatment modality will be collected. Data will also be collected on hospital admissions, extra outpatient visits, and use of supportive drugs to contribute to a health economics analysis of additional health costs related to treatment and the trial. Data collection will be through trial CRFs (investigations, drugs, referrals for other services), participant completed health economic questionnaires (the resource use questionnaire; contact with participant, community and social care services plus additional costs mentioned below) and use of hospital episode statistics (HES). Participant out of pocket expenditure will include travel costs to attend clinics and other miscellaneous expenditure. Lost productivity will be estimated based on employment status of the participant/and/or guardians (for paediatric participants). We will also measure and value the time contribution of carers (applicable to adult and paediatric participants). These data will be extracted from participant completed health economic questionnaires. Costs and outcomes will be discounted at 3.5% in line with current recommendations.

Incremental cost effectiveness ratios will be presented. Analyses will combine crossover data to predict the expected cost-effectiveness of each treatment alone. Parameter uncertainty will be quantified using non-parametric bootstrapping techniques. Outputs will be presented as ICERs, cost effectiveness acceptability curves and expected net benefit. The permutation with the highest expected net benefit (mathematically identical to identifying the most cost-effective option with an incremental cost-effectiveness ratio below the threshold using the NICE threshold of £20,000 per QALY) will be highlighted as the preferred treatment choice. Given the number of permutations there will be very small numbers of participants under each permutation and so the impact of missing data will be examined using imputation methods. Sensitivity analyses will explore the impact of key cost drivers and factors that might affect the outcomes measured on decision uncertainty.

15.6.3 Modelling long-term cost effectiveness

A long-term cost effectiveness analysis is required to capture the full impact of any therapy where it is possible that there is a difference in morbidity or mortality between IMPs. The exact structure of the cost effectiveness model will be established in discussions with the clinicians on the trial team and after analysis of any adverse event data observed in the trial. It is likely that the model will be a Markov or semi-Markov state model. As far as possible the initial transition rates for the model will be estimated from the trial data – this will include data up to 24 months. For all model parameters for which data could not be collected within the trial e.g. longer term outcomes, recommended best practice will be followed in identifying and synthesising evidence in the published literature.

The long term modelling will adopt strategies for addressing issues of perspective and discounting as the within trial analysis. The incremental cost effectiveness ratios and expected net benefit will be estimated. To address uncertainty, probabilistic sensitivity analyses will be undertaken using Monte Carlo simulation techniques.

15.7 Definition of the end of the trial

The competent authority and Ethics Committee must be notified of the end of a clinical trial within **90 days** of its completion. The end of the trial will be the date of the last participant's Day 720 Clinical Trial Visit.

16 Data handling and record keeping

16.1 CRF

All data will be recorded on electronic CRF (eCRF), which will be identified by trial ID. Full date of birth is also required for the purposes of randomisation. In the event of technical difficulty or unavailability of eCRF, paper CRF will be used as back up and the data will be entered into the database at a later date. All trial data in the CRF/eCRF must be extracted from and be consistent with the relevant source documents. The CRFs must be completed, dated and signed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness, legibility and accuracy of the CRF pages. The CRF/eCRF will be accessible to trial coordinators, data managers, the investigators, Clinical Trial Monitors, Auditors and Inspectors as required.

Copies of the hand-written CRF pages (if used) should be returned by email or post to the trial coordinating centre at Cambridge within 2 weeks of the evaluations. The investigator at each participating site will retain the original of each completed CRF in the relevant sections of their Investigator Site File. The investigators must ensure that the CRFs and other trial related documentation sent to the trial coordination centre does not contain any patient identifiable information.
All hand-written CRF pages must be clear, legible and completed in black ink. Any errors should be crossed with a single stroke so that the original entry can still be seen. Corrections should be inserted and the change dated and initialled by the investigator or designee. If it is not clear why the change has been made, an explanation should be written next to the change. Typing correction fluid must not be used. Changes must not be made to the CRF pages once the original has been returned to the trial coordination centre.

The participant steroid diary should be copied at each trial visit, and used to calculate average steroid use since last visit, which will be recorded in the CRF/eCRF.

16.2 Source Data

To enable peer review, monitoring, audit and/or inspection the investigator must agree to keep records of all participating participants (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.

Data sources will include participant medical records, signed consent forms, physician assessment forms including BVAS, ITAS, RPDAI and participant questionnaires and diary, laboratory results, prescriptions. Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

16.3 Data Protection & Participant Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection ACT 2018 and Trust Policy with regards to the collection, storage, processing, transfer and disclosure of personal information and will uphold the Act's core principles.

Participants will be assigned a unique identifier by the trial team upon enrolment to the trial.

17 Data Monitoring Committee/Trial Steering Committee

17.1 Independent Data Monitoring Committee

A Data Monitoring Committee will provide oversight of this trial. In line with NIHR guidelines the composition of the IDMC will be reviewed by the NIHR Programme Director and will include independent members only. The BIOVAS IDMC will consist of, at a minimum, two independent clinicians with experience in vasculitis trials and a statistician.

A comprehensive charter for this trial will be drafted and implemented prior to the start of the trial. It is anticipated that the IDMC will receive summary safety reports and meet approximately 6 monthly to discuss the trial progress and review safety data. Ad hoc meetings of the IDMC can also be requested as needed to review reported safety events.

17.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will monitor the progress of the trial and maximise the chances of completing the trial within the agreed time scale and budget. In line with NIHR guidelines the composition of the TSC will be reviewed by the NIHR Programme Director and will include a minimum of 75% independent members. The BIOVAS TSC will include an independent UK based Chair, independent clinician(s) and an individual able to represent a patient and/or wider public perspective. In addition, they will receive a summary of all SAEs to ensure that there are no major safety concerns. The TSC will meet regularly via teleconference.

17.3 Trial Management Group (TMG)

The members of the TMG will meet via teleconference on a regular basis and are responsible for the design, conduct and overall management of the trial.

18 Ethical & Regulatory considerations

18.1 Ethical committee review

Before the start of the trial or implementation of any amendment we will obtain approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and GP information letters from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

18.2 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Development Safety Update Reports (DSURs) will be submitted to the MHRA in accordance with national requirements. It is the Chief Investigators responsibility to produce the annual reports as required.

18.3 Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the HRA, REC and/or MHRA.

The only circumstance in which an amendment may be initiated prior to HRA, REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the HRA, REC and/or MHRA approval has been obtained.

18.4 Peer Review

The trial protocol has been designed by the Trial Management Committee, which includes representatives from Cambridge University and Cambridge University Hospitals NHS Foundation Trust. The trial design has been reviewed by external reviewers and by the funding panel as part of the application process for a HTA grant from NIHR.

18.5 Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

18.6 GCP Training

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with your Trust's policy.

19 Sponsorship, Financial and Insurance

The trial is sponsored by Cambridge University Hospitals NHS Foundation Trust and University of Cambridge. The trial is funded by the National Institute for Health Research (NIHR) HTA programme (award 17/83/01). The views expressed are those of the authors and not necessarily those of the NIHR of Department of Health

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

20 Monitoring, Audit & Inspection

The investigator must make all trial documentation and related records available should an MHRA Inspection occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the Sponsor's representative. All participant data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of

the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

Remote monitoring will be conducted for all participating sites. The scope and frequency of the monitoring will be determined by the risk assessment and detailed in the Monitoring Plan for the trial.

21 Protocol Compliance and Breaches of GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach.

Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor without any delay.

22 Publications policy

Ownership of the data arising from this trial resides with the trial team. On completion of the trial the data will be analysed and tabulated and a Final Trial Report prepared.

The aim of this trial is to establish the clinical and cost-effectiveness of biologics in refractory NAAV. The data will also help to establish the much needed evidence in the treatment of these conditions. Evidence generated from this trial will inform NHS policy development, enhance service provision and optimise resource usage. We also anticipate added value through the collaborative nature of this trial in harmonizing treatment pathways and improving outcomes for NAAV across the UK. The direct comparison of targeted biologics has the potential to offer new insights into the relevant contribution of different pathogenetic pathways, although BIOVAS does not aim to be a mechanistic trial and will not collect biologic samples. Parallel mechanistic studies by BIOVAS participants, such as the TARGET Partnership and UKGCA Consortium will leverage further value from the trial. There is a paucity of detailed phenotype; outcome and health utilisation data on NAAV necessary for the appropriate refinement of clinical services, BIOVAS will contribute valuable data in this regard. A parallel biomarker trial will be developed through participating Biomedical Research Centres to optimize the value and opportunity of the clinical cohort and outcome data.

A trial website will contain fields accessible to the general public and health care professionals as well as trial specific functionality. It will also update the wider community on trial progress.

The output from this trial will be presented at national and international specialist conferences, published in peer reviewed international journals. Participants will be made aware of the trial results through our PPI group, in the clinics, by letters to the participants, by advertising in participant magazines, newsletters and participant attended workshops and conferences.

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24 Appendices

24.1 Appendix 1 - Trial Management / Responsibilities

24.1.1 Participant registration/ Randomisation procedure

See section 9.3 of the Trial Protocol.

24.1.2 CRF Completion & Data management

The sponsor or designee is responsible for the data management of this trial including quality checking of the data.

Data entered into the eCRF by authorised site personnel should be accurate, complete, and verifiable from source documents and completed in a timely manner.

24.1.3 Preparation & submission of amendments

The Sponsor has delegated responsibility for preparing and submitting amendments to the trial team.

24.1.4 Preparation and submission of Annual Safety Report/Annual Progress Reports

The Sponsor has delegated responsibility for preparing and submitting amendments to the trial team.

24.1.5 Data protection/ confidentiality

24.1.6 Trial documentation & archiving

Each participating site is responsible for archiving their own trial data including source data, the Investigator Site File (ISF) for the appropriate time period as determined by the regulations governing clinical trials in place at the time of archival. The archiving facility may be at the participating site or at another appropriate location off-site as per local policy. The trial team will advise when the site may commence archiving. The site will need to provide the name and address of the archival facility to the Trial team. In case of audit or inspection following archival, the participating site will be expected to retrieve the relevant documentation within a reasonable timeframe.

24.2 Appendix 2 – Authorisation of Participating Sites

24.2.1 Required Documentation

Prior to initiating a participating site, the following documentation is required;

- PI and other key trial team staff CV (signed and dated) and GCP certificate
- Authority approval (HRA, REC, MHRA)
- Local R & D capability and capacity approval
- Participating Site Agreement executed, including pharmacy participating site agreement
- Participant Information Sheets and consent forms on local headed paper
- Protocol signed and dated by PI
- Delegation of Authority Log
- Confirmation of randomisation system training

24.2.2 Procedure for initiating/opening a new site

When all the regulatory paperwork is in place, prior to site opening, an initiation teleconference will take place. This will be led by the trial physician or clinical trial coordinator with as many of the local team present as is practicable. This initiation meeting constitutes training for the trial and it is therefore imperative that all members of the trial team who will be involved in the trial are represented at the meeting. A log of attendees will be completed during the meeting. The presentation slides will be provided to the site in advance of the meeting. A trial initiation form will be completed for each site initiation meeting. Copies of all initiation documentation must be retained in the Investigator Site File (ISF) and TMF.

The sponsor's regulatory green light procedure will be followed. Following the green light, the site will be opened for recruitment and the randomisation system opened to that site.

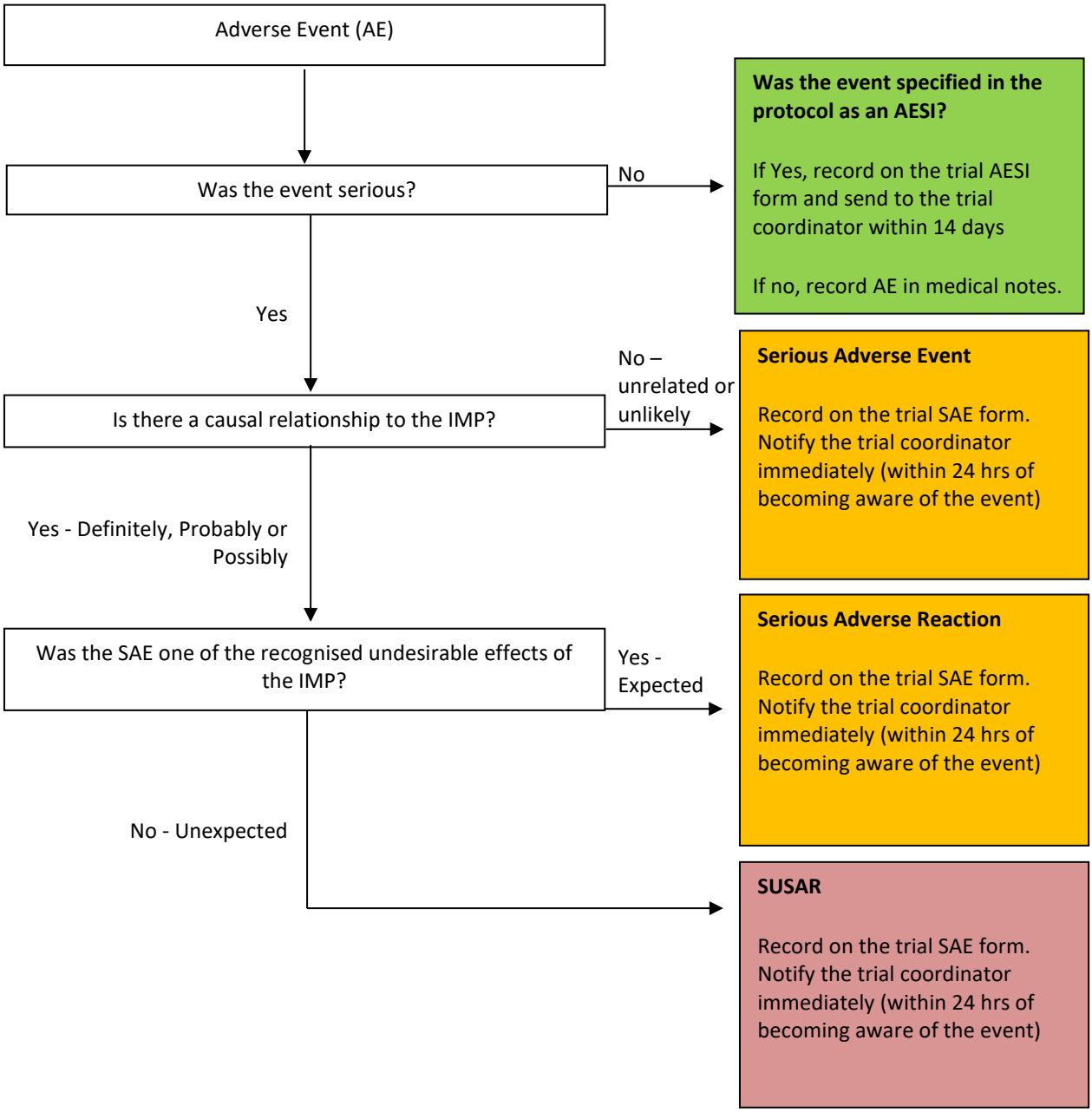
24.2.3 Principal Investigator Responsibilities

The PI has overall responsibility for the conduct of the trial at the participating site.

In particular, the PI has responsibilities which include (but are not limited to):

- Ensuring the appropriate approvals are sought and obtained
- Continuing oversight of the trial
- Ensuring the trial is conducted according to the currently approved protocol
- Ensuring consent is received in accordance with the protocol and national requirements
- Ensuring that the ISF is accurately maintained
- Delegation of activities to appropriately trained staff (this must be documented on the Delegation of Authority Log)
- Providing protocol or specialised training to new members of the trial team and ensuring that if tasks are delegated, the member of staff is appropriately trained and qualified
- Appropriate attendance at the initiation meeting
- Dissemination of important safety or trial-related information to all stakeholders at the participating site
- Safety reporting within the timelines and assessment of causality and expectedness of all SAEs

24.3 Appendix 3 - Safety Reporting Flow Chart



24.4 Appendix 4 – NAAV Classification Criteria

GCA:

1. *AGE > 50 years (mandatory) AND*
2. *Elevated inflammatory markers (mandatory) AND*
3. *Either Imaging (CT/PET/MRA/US) or biopsy (showing current disease activity) OR*
4. *Unequivocal cranial symptoms of GCA or PMR symptoms with historical evidence from either imaging/biopsy confirming a diagnosis of GCA.*

Takayasu's Arteritis: consistent with ACR criteria with mandatory imaging

Takayasu's arteritis 1990 ACR

1. Age at disease onset < 50 years
Development of symptoms or findings related to Takayasu arteritis at age <50 years
2. Claudication of extremities
Development and worsening of fatigue and discomfort in muscles of 1 or more extremity while in use, especially the upper extremities
3. Decreased brachial artery pulse
Decreased pulsation of 1 or both brachial arteries
4. BP difference >10 mm Hg
Difference of >10 mm Hg in systolic blood pressure between arms
5. Bruit over subclavian arteries or aorta
Bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta
6. Arteriogram abnormality
Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental

** For purposes of classification, a participant shall be said to have Takayasu arteritis if at least 3 of these 6 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%. BP = blood pressure (systolic; difference between arms).*

Paediatric diagnosis of Takayasu's Arteritis: consistent with EULAR/PRINTO/PRES 2008 classification criteria.

c-TA EULAR/PRINTO/PRES Ankara 2008 classification definition

Angiographic abnormalities of the aorta or its main branches and pulmonary arteries showing aneurysm/dilation (mandatory criterion) plus one of the five following criteria:

1. *Pulse deficit or claudication*
2. *Four limbs BP discrepancy*
3. *Bruits*
4. *Hypertension*
5. *Acute phase response (ESR >20; or CRP > reference range for laboratory)*

PAN: consistent with EMA criteria (angiographic and/or biopsy evidence of disease) and exclusion of other vasculitides (*Figure 1*).

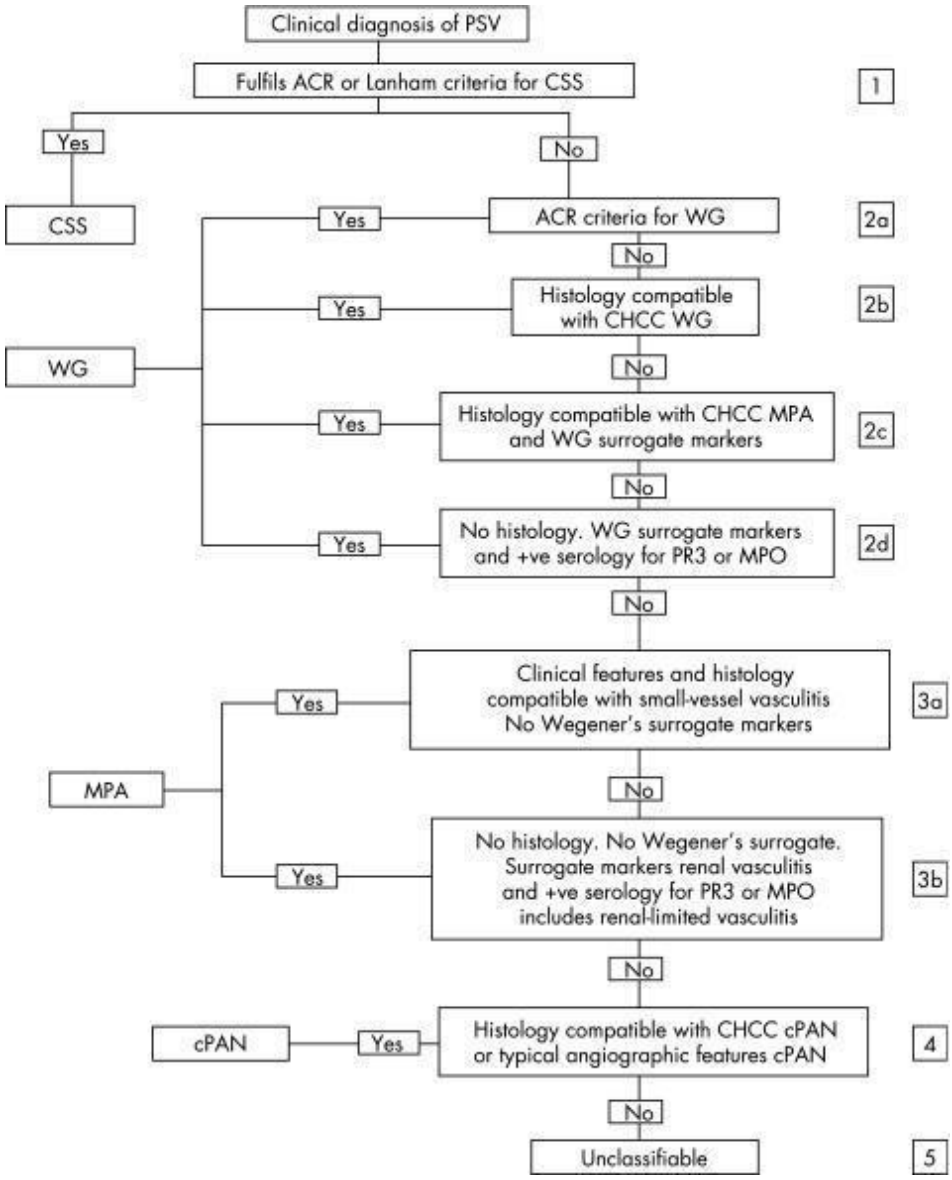


Figure 1: EMA algorithm for diagnosis of PAN

Paediatric diagnosis of PAN: consistent with EULAR/PRINTO/PRES classification criteria.

c-PAN EULAR/PRINTO/PRES Ankara 2008 classification criteria

Histopathology or angiographic abnormalities (mandatory) plus one of the five following criteria:

1. *Skin involvement*
2. *Myalgia/muscle tenderness*
3. *Hypertension*
4. *Peripheral neuropathy*
5. *Renal involvement*

Relapsing polychondritis: consistent with McAdam's criteria – meet at least 3 of 6 McAdam's criteria and/or 1 of 6 with histological confirmation

McAdam's relapsing polychondritis criteria
Histopathology plus one of six of the following criteria OR three of six of the following criteria:

1. *Recurrent chondritis of both auricles*
2. *Nonerosive inflammatory polyarthritis*
3. *Chondritis of nasal cartilages*
4. *Inflammation of ocular structures*
   Conjunctivitis/keratitis/scleritis/uveitis
5. *Chondritis of respiratory tract*
   Laryngeal/tracheal cartilages
6. *Cochlear and/or vestibular damage*
   Neurosensory hearing loss/tinnitus/vertigo

IgA vasculitis: Diagnosis based on typical clinical features and biopsy. Consistent with the following Chapel Hill Consensus Conference 2012 (CHCC2012):

Vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract, and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur.

Paediatrics diagnosis of IgA vasculitis: consistent with the following EULAR/PRINTO/PRES criteria.

HSP EULAR/PRINTO/PRES Ankara 2008 classification criteria
Purpura or petechiae (mandatory) with lower limb predominance and at least one of the following criteria:

1. *Abdominal pain*
2. *Histopathology*
3. *Arthritis or arthralgia*
4. *Renal involvement*

Cogan's syndrome: Consistent with the following Chapel Hill Consensus Conference 2012 (CHCC2012) definition and exclusion of mimics:

Cogan's syndrome characterized by ocular inflammatory lesions, including interstitial keratitis, uveitis, and episcleritis, and inner ear disease, including sensorineural hearing loss and vestibular dysfunction. Vasculitic manifestations may include arteritis (affecting small, medium, or large arteries), aortitis, aortic aneurysms, and aortic and mitral valvulitis.

Non-infective cryoglobulinaemia: Consistent with the following Chapel Hill Consensus Conference 2012 (CHCC2012) definition and exclusion of infective cause:

Vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with serum cryoglobulins. Skin, glomeruli, and peripheral nerves are often involved.

CNS vasculitis: Clinical diagnosis, imaging or biopsy and exclusion of mimics – infection/drugs/malignancy. Peer review process for confirmation of diagnosis.

24.5 Appendix 5: Steroid weaning templates

Patients starting on a baseline dose of 60mg		
Days	Week	Steroid dose in mg
0	0	60
7	1	60
14	2	40
21	3	40
28	4	30
35	5	30
42	6	25
49	7	25
56	8	20
63	9	20
70	10	15
77	11	15
84	12	10
91	13	10
98	14	5
105	15	5
112	16	5
119	17	5

Patients starting on a baseline dose of 40mg		
Days	Week	Steroid dose in mg
0	0	40
7	1	40
14	2	30
21	3	30
28	4	25
35	5	25
42	6	20
49	7	20
56	8	15
63	9	15
70	10	10
77	11	10
84	12	5
91	13	5
98	14	5
105	15	5
112	16	5
119	17	5

Patients starting on a baseline dose of 30mg		
Days	Week	Steroid dose in mg
0	0	30
7	1	30
14	2	25
21	3	25
28	4	20
35	5	20
42	6	15
49	7	15
56	8	10
63	9	10
70	10	5
77	11	5
84	12	5
91	13	5
98	14	5
105	15	5
112	16	5
119	17	5

Patients starting on a baseline dose of 20mg		
Days	Week	Steroid dose in mg
0	0	20
7	1	20
14	2	15
21	3	15
28	4	10
35	5	10
42	6	5
49	7	5
56	8	5
63	9	5
70	10	5
77	11	5
84	12	5
91	13	5
98	14	5
105	15	5
112	16	5
119	17	5