Population Health Sciences Institute
Biostatistics Research Group

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.

Statistical Analysis Plan
SAP Version number: 2.0
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This statistical analysis plan is based on protocol version 4.0 [17/11/2021]

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This current version of the SAP and all preceding versions will be stored in the Statistical Section of the Trial Master File held by the PHSI Biostatistics Research Group.

This statistical analysis plan (SAP) provides a framework and guidelines for the statistical analysis and reporting of the BIOVAS trial.

Any deviation from the methods outlined in this SAP will be documented in the statistical end of trial report. Example Tables, Figures and Listings are for illustrative purposes only and are subject to change.

Revision history

Version	Date	Changes made	Justification for change	Timing of change
1.0	05-02-2024	First version	NA	
2.0	16-04-2024	Change made to Table 8, 13, 14: combining INF and Placebo groups	Only one patient received the placebo. The placebo group was combined with the corresponding IMP	16/04/2024
		Changes made to Table 10 and section 5.1	Only one patient received placebo. Comparisons will be made between IMP	
		Changes made to Table 15	Patients tabulated by steroid dose and treatment first IMP in sequence	
		Changes made to Table numbering	Tables 16, 17, 18	
		Changes made Table 16 and section 6.1	AEs reported by severity	

Abbreviations

Ab	Antibody
AESIs	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ANCA	Antineutrophil cytoplasmic antibody
BVAS	Birmingham Vasculitis Activity Score
CCTU	Cambridge Clinical Trials Unit
CHU-9D	Child Health Utility 9D Index
CPAN	Cutaneous polyarteritis nodosa
CRP	C-reactive Protein
DADA2	Deficiency of adenosine deaminase type 2
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol five-dimension scale
ESR	Erythrocyte Sedimentation Rate
GCA	Giant Cell Arteritis
GIACTA	An Efficacy and Safety Study of Tocilizumab (RoActemra/Actemra) in Participants with Giant Cell Arteritis
HB	Hepatitis B
HIV	Human Immunodeficiency Virus
IgA	Immunoglobulin A
IgAV	IgA vasculitis
IL-6	Interleukin 6

IMP	Investigational Medicinal Product
INF	Infliximab
ITAS	Indian Takayasu's Arteritis Activity Score
NAAV	Non-ANCA associated vasculitis
NICE	The National institute for Health and Care Excellence
NIHR	National Institute for Health Research
PACNS	Primary angiitis of the central nervous system
PAN	Polyarteritis Nodosa
PBO	Placebo
PGA	Physician's Global Assessment
PVAS	Paediatric Vasculitis Activity Score
PVDI	Paediatric Vasculitis Damage Index
RP	Relapsing Polychondritis
RPDAI	Relapsing Polychondritis Disease Activity Index
RTX	Rituximab
SAE/SAR	Serious Adverse Event/Serious Adverse Reaction
SAP	Statistical Analysis Plan
TA	Takayasu's Arteritis
TCZ	Tocilizumab
TNF	Tumour Necrosis Factor
TTF	Time to Treatment Failure
VDI	Vasculitis Damage Index

Contents

1. INTRODUCTION

1.1 Background and rationale

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
Acronym	BIOVAS
Summary of 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
Summary of Participant Population	Aged at least 5 years, diagnosis of NAAV, refractory disease
Planned Sample Size	140 eligible participants with refractory NAAV will be enrolled
Planned Number of Sites	Approximately 17 sites
Intervention Duration	720 days
Follow Up Duration	4 weeks
Final Follow Up Visit	16 weeks end of trial follow-up
Planned Trial Period	42 months
Intervention	Infliximab, Rituximab, Tocilizumab, and matched placebo
Primary Outcome:	Primary outcome is time to treatment failure (TTF)
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).

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 Antineutrophil 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 Classification of Primary Systemic Vasculitis

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

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 IL-6 receptor inhibitor for remission induction in giant cell arteritis (Villiger et al. 2016; Stone et al. 2017). In this study 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 patients that do not achieve remission with tocilizumab (44% of the patients 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 study (Hoffmann et al. 2007). In this study 44 adult patients 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 study 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. The clinical trial team has 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. The clinical team has reported secondary failure of biologics in a related secondary vasculitis, Behcet's syndrome (Furuta et al. 2012).

1.2 Original Objectives

The following text represents the original objectives of BIOVAS prior to the premature discontinuation of the trial.

BIOVAS will test the hypothesis that biologics are superior to placebo in the control of refractory NAAV. Each of the three biologics 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 (as shown in Table 1). 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).

1.2.1 Primary objective

To determine the clinical efficacy of each of the 3 investigational medicinal products (IMPs) in comparison to placebo in the treatment of refractory NAAV as 1 disease group (primary group as shown in Table 1).

1.2.2 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 compare the clinical efficacy of each IMP compared to other IMPs in the primary group

1.2.3 Revised objectives

Due to small number of recruited participants when the study was halted, we will not perform the analyses in objectives 1-5. Instead, a descriptive analysis will be conducted for the primary objective.

1.2.4 Exploratory objectives

NA

2. STUDY METHODS

2.1 Trial design

BIOVAS is a multicentre, pragmatic, randomised, double-blinded, placebo-controlled, modified-crossover phase 2B trial of biologic therapy for refractory primary NAAV in adults and children. The study aims 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). Participants will be randomised to a fixed sequence of four trial investigational medicine products (IMPs). Participants with a pre-trial history of failure/contraindication to one biologic IMP will have that failed IMP removed from their allocated sequence and will be randomised to a reduced number of IMPs.

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.

2.2 Study setting and patient population.

Inclusion Criteria:

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 OR
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.

Exclusion Criteria:

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

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 109 cells/l, platelet count < 100 x 109 cells/l, neutrophil count of < 2 x 109 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)

For full details of inclusion and exclusion criteria please refer to section 9.1 and 9.2 of the study protocol (version 4.0, 17/11/2021).

2.3 Randomisation and 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 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.

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). In the case of a known failure/contraindication to a trial IMP, that particular drug was not included in the sequence generation at the time of randomisation.

A web-based randomisation system (Sealed Envelope) performed by 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 occurred, immediate allocation of IMP sequence was performed. A blinded confirmatory email containing a blinded code e.g. CZ7 was sent to the local clinical team and to the Trial Coordinator.

2.4 Definition of outcome measures

2.4.1 Primary endpoint

Primary outcome is time to treatment failure (TTF). TTF for each IMP is the time from the start of IMP treatment to treatment failure 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[1] 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 by 120 days from the time of IMP commencement. In such cases, TTF will be recorded as zero.

Clinical response is defined by:

- Absence of new/worse BVAS V3-BIOVAS (adults)/PVAS (children) items assessed at each 120 days 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[1]

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.

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[2] 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

[1] 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.

[2] 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.

order to treat vasculitis.

2.4.2 Secondary endpoints

1. Proportion of participants achieving response at 120 days evaluation after the start of each IMP.

2.. 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

3.. Increase in disease related damage measured by VDI/PVDI from start to end of an IMP treatment

4.. Physician's global assessment (PGA) (Likert scale 0-10) at every 120-day evaluation time point from the time of IMP commencement

5. Serious adverse events/adverse events of special interests (SAEs/AESIs)

6. EQ-5D-5L or Child Health Utility (CHU9D) assessments at every 120 day evaluation time point

7. NHS resource use and out of pocket costs and lost productivity

Endpoints 6-7 are outside the scope of this analysis plan and will be covered in the Health Economics Analysis Plan.

2.5 Study assessments

Table 2: simplified schedule of assessments

Form	Visit						
	Baseline	120 day (±14 days)	240 day (±14 days)	360 day (±14 days)	480 day (±14 days)	600 day (±14 days)	720 day (±14 days)
Demographics, Medical History, Prior medications	X						
Physical examination	X	X	X	X	X	X	X
Vital signs[a]	X	X	X	X	X	X	X
Routine blood tests	X	X	X	X			
Routine Immunoglobulins blood test	X	X	X	X	X	X	X
BVAS/PVAS	X	X	X	X	X	X	X
PGA	X	X	X	X	X	X	X
ITAS (TA patients only)	X	X	X	X	X	X	X
RPDAI (RP patients only)	X	X	X	X	X	X	X
VDI/PVDI		X	X	X	X	X	X
EQ5-D-L/CHU-9D		X	X	X	X	X	X
Dispense/ review patient steroid diary	X	X	X	X	X	X	X
AESI/SAE review	X	X	X	X	X	X	X
Concomitant medications review	X	X	X	X	X	X	X

a. Vital signs will include body weight (kg), heart rate, body temperature and blood pressure.

2.6 Sample size and power

The study was powered to test the following superiority hypotheses:

a) infliximab vs. placebo,
b) rituximab vs. placebo and
c) tocilizumab vs. placebo

Due to the disease rarity, it was not possible to power the study based on a specified effect size. Instead, simulations were used to explore the power of the design given a realistic number of participants that could be recruited over the course of the trial. The following assumptions were made for power calculations:

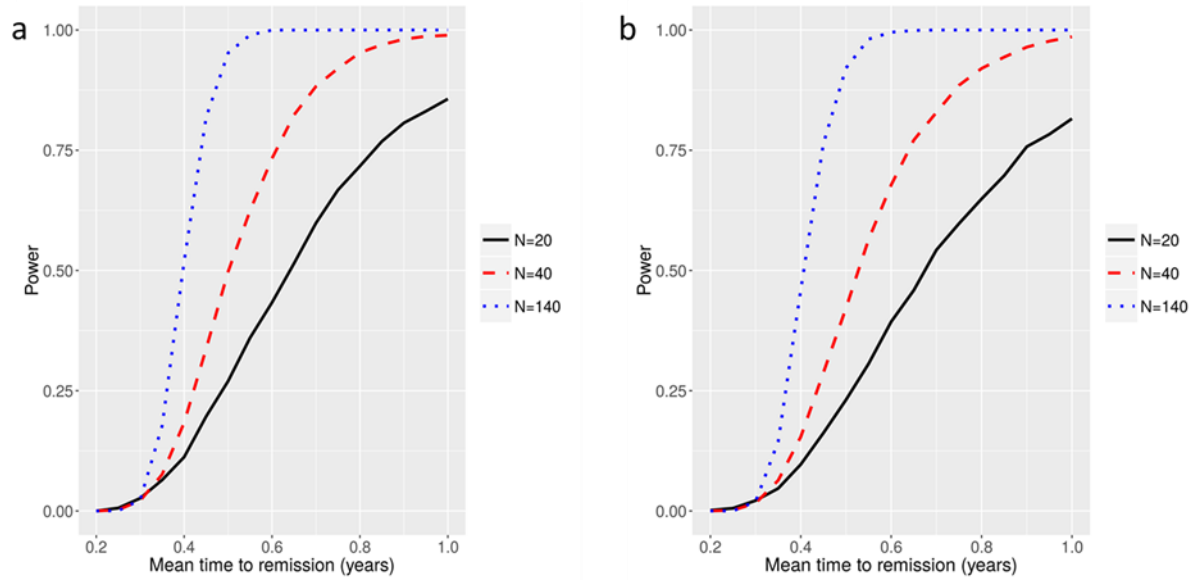
1) Each participant is followed up until they relapse on all four treatments, or two years from the initial randomisation has passed;
2) The final test statistics for the three comparisons (infliximab vs. placebo, rituximab vs. placebo, tocilizumab vs. placebo) were each tested at a nominal two sided 5% type I error rate. Due to sample size constraints, formal multiple testing adjustment was not made. Instead, it was noted that only taking forward treatments that are significantly
better than placebo, the trial design would have 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 was likely to be closer to 5%.

Simulations were performed in R software [2] with 5000 replicates per scenario. The TTF variable was simulated using an exponentially distributed random variable. If the simulated variable was less than four months, then the participant was classified as never having gone into remission, with their TTF included as zero. If the simulated variable was greater than four months, then the TTF was included as the simulated value. To allow for correlation of the TTF outcomes for a particular participant, a random frailty term was used for each participant. In the simulations this was uniformly distributed between 0.5 and 2. The parameter of the exponential distribution used for a participant's TTF outcome was 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 was included as a fixed effect and a random effect for each individual was included. Ties in the outcome were 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 1a (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 1b (shown below). The power for lower sample sizes was 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 was 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 was properly controlled.

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

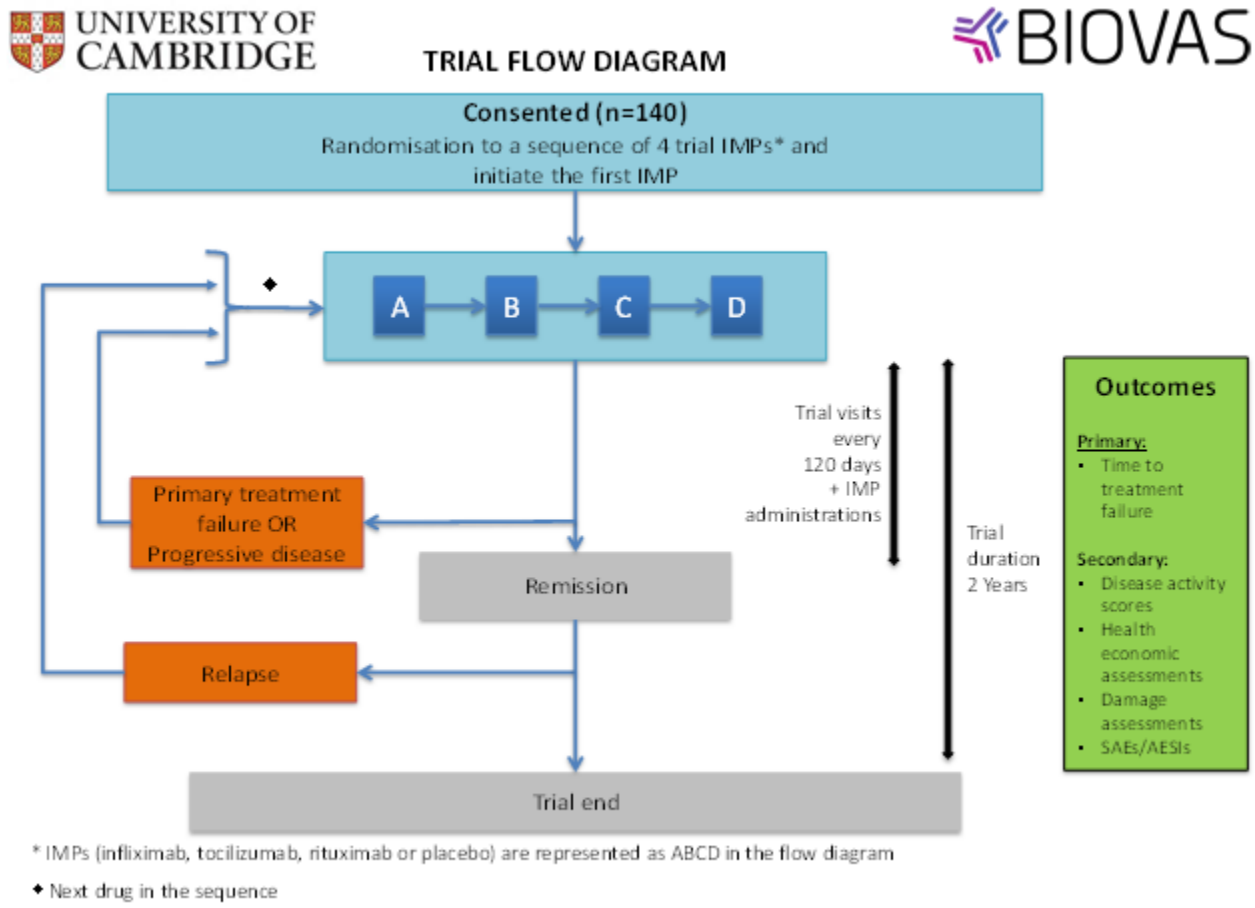
Table 3: Probability of a participant achieving and mean time in remission

	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%

R code used to perform the power calculations is stored in the statistical folder for the trial..

2.7 Study Diagram/Flowchart

Figure 2: Study flowchart



3. STATISTICAL CONSIDERATIONS

3.1 Timing of analyses

The final analysis was planned to take place once the last participant had completed their day 720 trial clinic visit. However, due to the withdrawal of funding by NIHR, the study halted to recruit on the 04/05/2023. The analyses will be mainly descriptive given the small number of recruited patients.
Once all data queries have been resolved (as far as possible) the database will be locked, and the final analysis will commence.

3.2 Interim analyses, data monitoring and stopping guidelines

No interim analyses were planned with regards to the primary endpoint.

3.3 Analysis populations

Intention-to-treat (ITT): This population contains all randomised participants (regardless of whether they were later found to be ineligible, a protocol violator, given the wrong treatment allocation, never treated, switched treatment etc.), analysed according to the treatment sequence they were randomised to receive.

Safety population (SP): This population contains all randomised participants who received at least one dose of trial IMP and will be classified according to the actual treatment received.

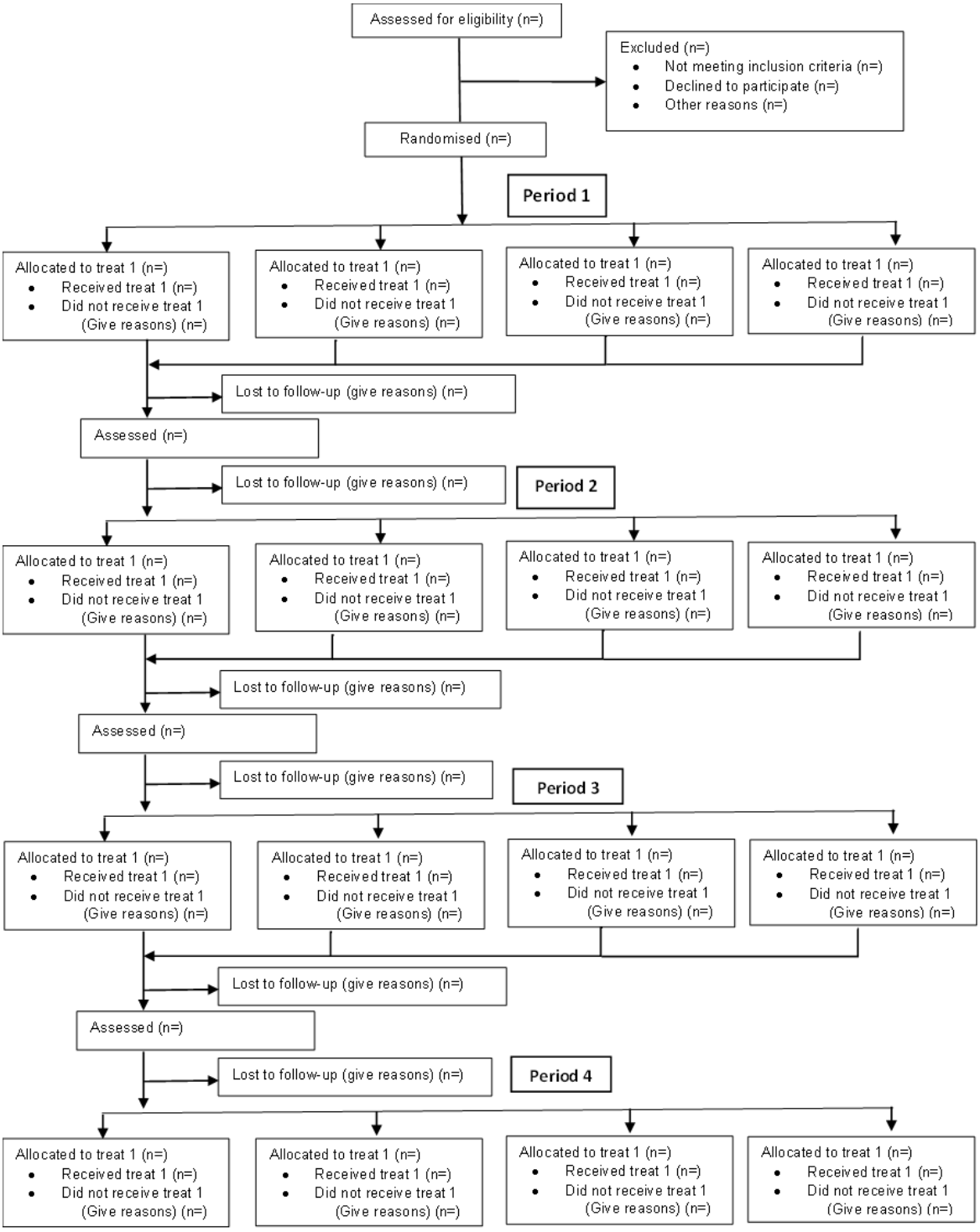
The primary outcome will be analysed in the intention-to-treat population. Safety data will be reported in the safety population.

4. STUDY POPULATION

4.1 Participant flow through trial

Patient flow through the trial will be presented using a CONSORT diagram, see example Figure 3. Information will be provided on numbers and reasons (where available) for: screened patients not being eligible; eligible patients not being randomised; patients found to be ineligible after randomisation; patients deviating from allocated treatment; patients not evaluable for the primary endpoints; discontinuation of trial treatment, withdrawal from follow-up; withdrawal of consent.

Example Figure 3: CONSORT flow diagram



4.1.1 Screening, eligibility and recruitment

Screening and recruitment will be summarised. Reasons for ineligibility and reasons for eligible patients not being recruited will also be summarised (where available).

4.1.2 Protocol deviations

Protocol deviations will be captured on a Deviation Tracking Log which will be held centrally by the Cambridge Clinical Trials Unit (CCTU).
Protocol deviations will be reported overall and by treatment arm. Protocol deviations will include deviations from their allocated treatment strategy, deviations from visit schedule or withdrawal from trial specific follow-up, losses to follow-up and ineligible patients.

Full detail of all protocol deviations will be reported in a line listing, sorted by type. Data will also be summarised by frequency and percentage of the number of patients reporting each type of deviation.

Ineligible patients, those randomised patients who are found to subsequently not adhere to the eligibility criteria of the trial, will be reported in each randomised group by number of ineligible patients and reasons for ineligibility.

Table 4: Line listing of protocol deviations

Trial ID	Randomised sequence	Deviation type	Major/minor	Details
		Ineligible/Consent/Treatment not given as per-protocol/Withdrawal from treatment by investigator/Withdrawal from treatment due to participant choice/Use of prohibited concomitant medication/Study procedures/Visit schedule		

A table listing any randomised participants later found to be ineligible will be presented showing study ID, reason for ineligibility and a summary total number/percentage ineligible.

Table 5: Ineligible participants randomised into trial

Participant ID	**Reason ineligible**	**Number ineligible**
xxxx	reason ineligible	n (%)
xxxx	reason ineligible	n (%)

4.1.3 Follow-Up

The frequency and percentage of patients with data available for each assessment visit will be tabulated overall and in each treatment group.

Table 6: Participant follow-up by visit and treatment received

	Visit window	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Total
Randomisation		n (100%)	n (100%)	n (100%)	n (100%)	n (100%)
Day 1	Day –14 to day -1	n (% of randomised)	n (% of randomised)	n (% of randomised)	n (% of randomised)	n (% of randomised)
120 days	+/- 14 days	n (% of randomised)	n (% of randomised)	n (% of randomised)	n (% of randomised)	n (% of randomised)
240 days	+/- 14 days	n (% of randomised)	n (% of randomised)	n (% of randomised)	n (% of randomised)	n (% of randomised)
360 days	+/- 14 days	n (% of randomised)	n (% of randomised)	n (% of randomised)	n (% of randomised)	n (% of randomised)
480 days	+/- 14 days	n (% of randomised)	n (% of randomised)	n (% of randomised)	n (% of randomised)	n (% of randomised)
600 days	+/- 14 days	n (% of randomised)	n (% of randomised)	n (% of randomised)	n (% of randomised)	n (% of randomised)
720 days	+/- 14 days	n (% of randomised)	n (% of randomised)	n (% of randomised)	n (% of randomised)	n (% of randomised)

Reasons for withdrawal, where available, will be tabulated by first treatment group.

Table 7: Line listing of withdrawals from the study

Participant ID	**Treatment group**	**Days from randomisation to withdrawal**	**Reason for withdrawal**	**Completion status**

4.2 Baseline characteristics

Demographic, clinical and baseline characteristics at randomisation will be summarised across treatment arms descriptively. We will report the number and percentage in each treatment arm for all categorical variables (sex, race/ethnicity, disease group) and mean, SD or median, IQR and range, as appropriate, for all continuous variables (age, weight). No significance testing will be carried out due to the randomised nature of the study.
Details of characteristics to be reported are given in Example Table 8 below.

Table 8: Baseline characteristics

	INF+INF-Placebo (n=)	***RIT (n=)***	***TOC (n=)***	***Overall (n=)***
Age (years) Median (IQR); Mean (SD) Range (min, max)				
Sex Male (n; %) Female (n; %)				
Weight (kg) Median (IQR) Mean (sd) Range (min, max)				
Heart rate Median (IQR) Mean (sd) Range (min, max)				
Body temperature Median (IQR) Mean (sd) Range (min, max)				
Race/Ethnicity White (n; %) Asian (of Indian, Pakistani, Bangladeshi ancestry) (n; %) Other Asian (n; %) Black or Afro-Caribbean (of African or Caribbean ancestry) (n; %) Other ethnic origin (n; %)				
Disease group				
GCA (n; %) TA (n; %) PAN (n; %) CPAN (n; %) RP (n; %) IgAV (n; %) Cogan's syndrome (n; %) Non-infective cryoglobulinaemia(n; %) PACNS (n; %)				
Steroid dose (n; %)				
Previous immunosuppression (n; %)				

4.3 Treatment compliance

No dose modifications are permitted for Infliximab, and Rituximab during the treatment period.
For each individual participant, the potential treatment duration (ie the number of days the participant could have potentially taken the IMP) will be calculated from the day after their first injection was issued to the day before their last visit (as per treatment instructions), or to the date treatment was discontinued early, or to date of withdrawal from trial or to date of death. This duration will be summarised as the median, IQR and range in each treatment arm.

Example Table 9: Summary of allocated treatment received

	Treatment 1 (n=)	Treatment 2 (n=)	Treatment 3 (n=)	Treatment 4 (n=)
Received at least one dose of allocated treatment				
Completed treatment				
Discontinued treatment prematurely *If Yes, due to* *AE* *Patient choice* *Other**				
Median duration of treatment (days)				
Median dose intensity (%)				

*Other reasons will be provided in a line listing

Data are n; % or median (IQR); range, unless otherwise stated

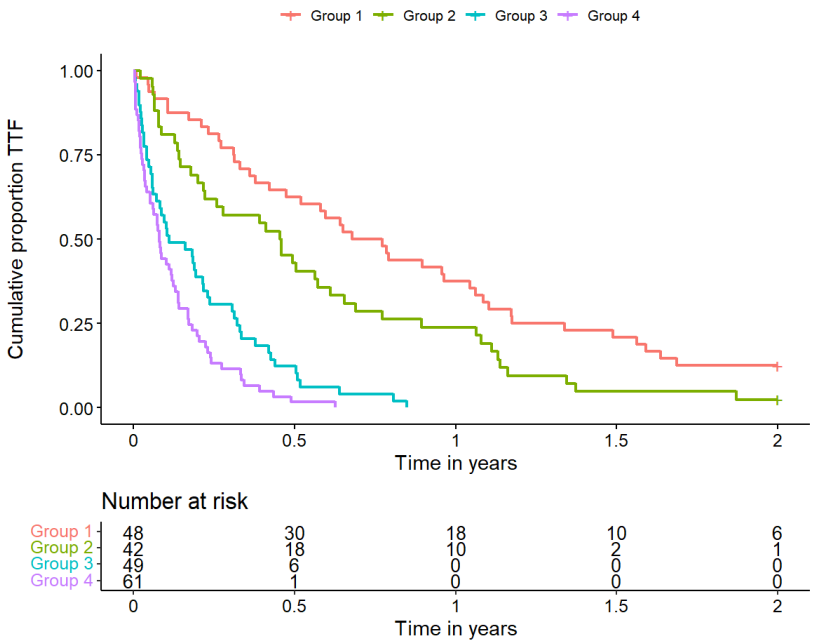
5. ANALYSIS METHODS

5.1 Analysis of primary outcome

The ITT population will be used for the analysis. Due to small number of recruited patients at the time the recruitment was halted, the analyses will mainly be descriptive. Graphical displays and summary statistics will be presented. If appropriate 95% confidence intervals will be reported.

Primary outcome is time to treatment failure (TTF). TTF for each IMP is the time from the start of IMP treatment to treatment failure or the end of trial participation (censored). If the data allows, a Kaplan-Meier comparing time to first treatment failure will be produced. Example Figure 1 depicts such plot.

Example Figure 4: Kaplan-Meier plot of time to first failure



As an exploratory analysis, a frailty model (i.e. a Cox regression model with shared frailty) will be fitted to the time to treatment failure. The treatment assignment will be included as a fixed effects and patient as a shared frailty term. Shared frailty terms will be assumed to follow a normal distribution. . From this model we will obtain the hazard ratio (HR) for the treatment effect comparing RIT and INF, TOC and INF. P values will not be reported given the small sample size. In case there will be convergence issues with the Frailty model, a standard Cox proportional hazard model will be fitted.
The exploratory model will be:

$$\lambda_{ij}(t) = \lambda_0(t)\exp(\beta_1 Trt_i + b_{0i})$$
$$b_{0i} \sim N(0, \sum)$$

Where λ_0 is an unspecified baseline hazard function, Trt_i is a treatment allocation indicator (Trt_i =1 for allocated treatment in the sequence is Placebo, Trt_i =2 allocated treatment in the sequence is Infliximab (INF), Trt_i =3 allocated treatment in the sequence Rituximab (RTX), and Trt_i =4 allocated treatment in the sequence is Tocilizumab (TCZ).
The model will be fitted using the R codes below (as implemented by the 'coxme' package in R). Ties in the outcome will be handled using the method of Efron:

```
model<- coxme(Surv(time=TTF, status=failure) ~ Trt + (1 | patient), data=Biovas)
```

No assumptions will be made regarding missing outcome. The output from the above model will be reported in Example Table 10

Example Table 10: Frailty / Cox model of time to treatment failure

Time to Treatment Failure		Events/N	HR	95% CI
	INF		Reference	
	RIT			
	TCZ			

5.2 Analysis of secondary outcomes

5.2.1 Bayesian hierarchical analyses

Not to be performed because of small sample.

5.2.2 Proportion of participants achieving response at 120 days

The response status (Response, non-response/relapse), at 120 days after the start of each IMP will be tabulated by the first treatment in the sequence.

Example Table 11: Number of responders at 120 days

	Placebo	INF	RIT	TCZ
120 days	n(%)			

5.2.3 Proportion of participants achieving response at every 120 day evaluation

Proportion of participants achieving response at every 120 day evaluation time point will be tabulated using Example Table 12. The response status will be 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

Example Table 12: Number of responders at 120 days

	Placebo	INF	RIT	TCZ
120 days	n (%)			
240 days				
360 days				
480 days				
600 days				
720 days				

5.2.4 Increase in disease related damage

The increase in disease related damage is as measured by Vasculitis Damage Index (VDI/PVDI) from start to end of an IMP treatment.
The VDI/PVDI score will be summarised descriptively by visit. The number with data, mean, standard deviation and the median, IQR and range will be summarised at each visit. Data will also be presented graphically by patient each visit. In case there are less than 5 patients for one of the form, their individual data will be listed.

Example Table 13: VDI/PVDI summary scores at every 120 days visit and by treatment.

	N; Mean (SD)	Median (IQR)	Range
Baseline			
120 days			
240 days			
360 days			
480 days			
600 days			
720 days			

5.2.5 Physician's global assessment (PGA)

The Physician's global assessment (PGA) is a visual analogue scale from 0-10, where 0 is no disease activity and 10 is maximum disease activity.
Frequencies and percentage of patients having a given score will be tabulated at every 120 day visit.

Example Table 14: PGA scores tabulation at every 120 days visit and by treatment

	N; Mean (SD)	Median (IQR)	Range
Baseline			
120 days			
240 days			
360 days			
480 days			
600 days			
720 days			

5.2.6 Steroid dosing

Frequencies and percentage of patients on a given steroid dose at each evaluation will be tabulated for each treatment group.

Example Table 15: Number of patient receiving steroid doses at each evaluation and by treatment

Dose	INF+INF-Placebo	RIT	TOC	Total
Baseline				
0	n(%)			
3				
5				
10				
11.3				
15				
17.5				
20				
25				
Mean (sd)	X1(Y1)	X2(Y2)	X3(Y3)	X4(Y4)
Day 120				
0				
3				
5				
⋮				
Mean (sd)	X1(Y1)	X2(Y2)	X3(Y3)	X4(Y4)
⋮	⋮	⋮	⋮	⋮
Day 720				
0				
3				

Dose	INF+INF-Placebo	RIT	TOC	Total
5				
Mean (sd)	X1(Y1)	X2(Y2)	X3(Y3)	X4(Y4)

5.3 Missing data

The extent of missing data for the primary endpoint will be summarised by the first treatment in the sequence. However, due the small sample size, we will not perform any imputations.
Missing items from a partially completed validated questionnaire will be handled as described in the relevant scoring manual.

6. SAFETY

6.1 Adverse events

Expected adverse events/ serious adverse events (AE/SAE) were reported from the point of informed consent until the end of participation in the trial for each participant. In addition to all SAEs, all infections requiring antimicrobial, antiviral or antifungal treatment were collected as adverse events of special interest (AESIs) as part of the BIOVAS trial.
Any pre-planned or elective surgery that necessitates hospital admission were not considered a SAE and does not need expedited reporting, however details will be collected in the CRF.

The severity of symptoms are graded using the Common Terminology Criteria for Adverse Events (CTC) 4.0.

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.

Adverse events will be coded using the MedDRA dictionary (version 24.0 released in March 2021) and presented by preferred term, grouped by system organ class.

Data will be presented separately for related (possibly, probably, definitely) and unrelated (unrelated, unlikely) events. The occurrence of non-serious adverse events will be tabulated, as required for EudraCT reporting. All data will be presented in the safety population by randomised treatment group.

6.1.1 Adverse events

Example Table 16: Adverse events by type severity

	Treatment 1 (n=)	Treatment 2 (n=)	Treatment 3 (n=)	Treatment 4 (n=)
System Organ Class 1				
Event 1 Mild Moderate Severe				
Event 2 Mild Moderate Severe				
System Organ Class 2				
Event 1 Mild Moderate Severe Total number with at least one AE				

Example Table 17: Number of subjects affected by non-serious adverse events – for EudraCT

	Treatment 1 (n=)	Treatment 2 (n=)	Treatment 3 (n=)	Treatment 4 (n=)
System Organ Class 1				
Event 1 Participants affected Occurrences (all)				
Event 2 Participants affected Occurrences (all)				
System Organ Class 2				
Event 1 Participants affected Occurrences (all)				
Participants affected by non-serious adverse events				

6.1.2 Serious adverse events

Serious adverse events will be reported in a line listing. A summary of the number of SAEs reported per participant will also be tabulated by randomised treatment group.

Example Table 18: Line listing of all SAEs

ID	SAE no.	Trt group	Trt start	Trt end	Onset date	Description	Severity [A]	Seriousness criteria [B]	Causality [C]	Expected [D]	Outcome [E]	Outcome date

A: Mild / Moderate / Severe

B: Death / Life-threatening / Hospitalisation or prolongation of hospitalisation / Persistent or significant disability or incapacity / Congenital anomaly or birth defect / Other significant medical event

C: Related / Unrelated / Indeterminate

D: Expected / Unexpected

E: Recovered / Condition improved / Condition deteriorated / Condition unchanged / Recovered with sequalae / Condition stable and no change anticipated / Participant died

7. STATISTICAL SOFTWARE

Data will be exported from the electronic Clinical Data Management System (CDMS) into a CSV format by the CCTU Data(base) Manager at time points agreed by the Trial Management Group. Statistical analyses will be carried out by the Trial Statistician at the Biostatistics Research Group predominately using R software. All programs and output will be stored in the School Statistics folder on the PHIS server.

REFERENCES

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