Short title:	Enceph- SAP

Intravenous Immunoglobulin in Autoimmune Encephalitis in Adults – A Randomised Double-Blind Placebo-Controlled Trial

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Draft Plan

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SAP Revision History

Protocol version	Updated Sap version no.	Section number changed	Description and reason for change	Date changed
6.0	1.0	All	First draft	22.07.2022
	1.1	3.3, 3.6		07/12/2023
	1.2	5.1, 5.2, 5.3, 5.4, 5.5, 6.1, 6.3		12/01/2024
6.1	1.3	All	After not meeting targets for site openings and participant recruitment, we were instructed to close the trial prematurely. Thus, our analysis plan was adapted accordingly.	02/09/2024
6.1	1.4	3.7, 4.2.3, 4.2.4, 6.2.1		03/10/2024
6.1	2.1	5.2, 6.5, appendix	Grammatical changes after feedback from the TSC statistician	17/02/2025

ROLES AND RESPONSIBILITIES

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1. INTRODUCTION

This statistical analysis plan (SAP) provides guidelines for the final presentation and analysis for the Intravenous Immunoglobulin in Autoimmune Encephalitis in Adults – A Randomised Double-Blind Placebo-Controlled (Enceph-IG) Trial. This plan, along with all other documents relating to the analysis of this trial, will be stored in the Statistical Analysis Master File electronically within the Trial Master File.

Any deviations from the SAP will be recorded and justified in the SAP deviation log (at the end of this document) and the final report. The analysis will be conducted by an appropriately qualified statistician, who will ensure data integrity by adhering to the guidelines set out in the CTR's (Centre for Trials Research) SOPs (Standard Operating Procedures). This SAP will be reviewed by the senior trial statistician (STS) and approved by the Trial Management Group (TMG) before being signed off by the author (Jennifer Condie), STS (Dr David Gillespie), and the Chief Investigator (Professor Tom Solomon). A copy of the SAP will be sent to the Trial Steering Committee (TSC) and Independent Data Monitoring Committee (IDMC) statisticians for review and amended as appropriate.

2. BACKGROUND

2.1 RATIONALE AND RESEARCH QUESTION

Encephalitis is an acute devastating inflammation of the brain. It can be caused by infections, such as herpes simplex virus (HSV), or by the body's immune system (autoimmune encephalitis). Whilst some forms of autoimmune encephalitis such as acute disseminated encephalomyelitis (ADEM) have been described for many years (Venkatesan et al., 2013), others have been recognised increasingly over the last ten years (Granerod et al., 2010; Graus et al., 2016). These newer forms are characterised by a subacute onset of behavioural change, memory loss, psychiatric features, and seizures.

Although autoimmune encephalitis is relatively rare, its consequences overall are enormous due to the devastating impact on quality of life. For the 94 patients with autoimmune encephalitis in our Enceph-UK cohort, 4% had died by 3 months after discharge and 37% could not live independently. Currently the care of patients with autoimmune encephalitis is hap-hazard, and with no rational basis. Some patients are given steroids only, others are also given intravenous immunoglobulin (IVIG), but there is no clarity over whether it is needed. IVIG has been associated with improved outcomes (Irani et al., 2010; Titulaer et al., 2013); however, it is an expensive blood product (in excess of £7000 per course), with risks of significant adverse events, and there is no trial evidence of efficacy. IVIG is therefore heavily rationed in the NHS. NHS England's Clinical Commissioning Policy Proposition pointed to the lack of definitive evidence to support its use (NHS England, 2016b), prompting alarm among experts, patients and public stakeholder groups who feared its withdrawal (NHS England).

Enceph-IG aimed to determine the effectiveness of early IVIG treatment on time to recovery for autoimmune encephalitis. If IVIG is effective, it could become the standard care for patients with autoimmune encephalitis and improve patient outcomes. In contrast, if it is not effective, this expensive and potentially dangerous treatment can be avoided.

2.1.1 Rationale for current trial/Justification of Treatment Options

The primary hypothesis for the clinical study was that early treatment with IVIG changes the outcome of adult autoimmune encephalitis, as measured by the primary outcome of time to achieve a Glasgow Outcome Scale - Extended (GOSE) of 5 or more; GOSE ranges from 1 (death) to 8 (full recovery), with 5 indicating ability to live independently.

Through the mechanistic studies we planned to test two hypotheses to explain IVIG's therapeutic effects:

1. We hypothesised that patients with autoimmune encephalitis have aberrant IgG Fc glycosylation affecting function, as in other autoimmune diseases, and that IVIG modulates this (Czajkowsky et al., 2015).
2. As a result of the above, we hypothesised that IVIG reduces levels of anti-neuronal antibodies, as well as down regulating pro-inflammatory host pathways, and that these correlate with clinical outcome.

IVIG was chosen as the drug of choice because it is available to all patients and is frequently given as a first-line treatment option despite a lack of evidence for its usage. Furthermore, IVIG is currently rationed in the NHS due to its high cost. The dosing regime was selected because it is commonly used in neuro-inflammatory conditions, including in Guillain-Barré syndrome, and is the dose we used in a pilot study of IVIG in encephalitis.

2.2 OBJECTIVES

The original aim of this trial was to determine whether treating adults with autoimmune encephalitis with IVIG early changes time to recovery and outcomes compared to standard of care. The trial also aimed to understand the mechanism by which IVIG may change recovery time.

The trial was instructed to close following the target number of sites and participants not being met. Therefore, the objective of this trial switched to describing feasibility outcomes (e.g. recruitment, retention, adherence to trial treatment, use of concomitant medication) and describing clinical outcomes including differences between trial arms.

2.2.1 PRIMARY OBJECTIVES

The original primary objective was to determine if early treatment with IVIG changes the time to recovery as measured on the GOSE.

For the revised objectives, see 2.2.

2.2.2 SECONDARY OBJECTIVES

The original secondary objectives were to:

1. To determine the effect of IVIG on the clinical condition, GOSE, health utility and self-rated health of all patients at 3 and 12 months, and to follow up a subset of patients annually.

2. To determine the effect of IVIG on the modified Rankin Scale, Liverpool Outcome Score and neuropsychological outcomes at 12 months.
3. To determine the effect of IVIG on the rate of adverse events, time to hospital discharge, use of further immunotherapy, rate of relapse and rate of mortality.

For the revised objectives, see 2.2.

3. STUDY MATERIALS

3.1 TRIAL DESIGN

Enceph-IG is a multicentre, double-blind, two-arm, placebo-controlled, randomised superiority trial of IVIG in adults with autoimmune encephalitis, which had planned to incorporate an internal pilot study. The patients, their families, health care workers and the study team will all be blinded to protect against performance and ascertainment bias. In the original plan, a total of 356 adult participants with a diagnosis of autoimmune encephalitis, were planned to be randomised from 50 UK based secondary and tertiary care centres in a ratio of 1:1 to receive either IVIG (2g/kg ideal body weight over 5 days) or placebo treatment (0.9% saline solution). All participants will also receive methylprednisolone 1g daily intravenously for 5 days, followed by 60mg oral prednisolone daily for two weeks, and then taper regime.

The planned trial duration was 73 months, and the end of trial will be defined as last participant, last visit. We planned to conduct an internal pilot study comprising of 50 participants and several stop/go decision points at study month 10 and then at 6-, 12-, 18-, and 24-months recruitment.

Data collected comprised of clinical data, questionnaires, and samples. GOSE assessments were planned to occur fortnightly for the first 3 months and then monthly until 12 months post randomisation. Clinical assessments were planned to occur at 2 weeks, 3 months and 12 months post randomisation, and annually. Participants were planned to be followed up post study completion through the use of data linkage via NHS digital. This would have been funded and reported separately.

Cerebrospinal fluid (CSF) and serum IgG Fc glycosylation will be measured at baseline for all patients and compared with CSF and serum samples from up to 40 controls - patients who had a lumbar puncture for non-inflammatory causes such as migraine and idiopathic intracranial hypertension. Serum IgG glycosylation samples were planned to be taken again at 3 months.

3.2 RANDOMISATION

Participants were individually randomised 1:1 to IVIG or placebo using random permuted blocks stratified by site type, and time from symptom onset. The final randomisation lists, which contained investigational medicinal product identifications and corresponding allocations (IVIG/placebo), were generated by a statistician otherwise not involved in the trial and were supplied to the manufacturing and site pharmacy for appropriate labelling, as well as the CTR safety team. Randomisation took place online using Vanilla, a system created by the CTR. It was available 24 hours a day. On randomisation, a participant was allocated to the next available treatment. The research team, treating healthcare

professionals, participants and their families will remain blind to allocated treatment for the duration of the study.

3.3 SAMPLE SIZE

The initial recruitment target included in the protocol was 356 patients (178 per arm). This was based on a two-sided alpha of 0.05, 85% power, and a median time to recovery in our placebo arm of 87 days (based on analysis of patients in the Enceph-UK study) with 20% of participants not having recovered by the 12-month follow-up period for the primary outcome), and a hazard ratio of 1.43 (i.e. a 30% relative improvement in the median time to recovery – translating into an absolute difference of 26 days). Our extensive discussions with doctors, patients and their families indicated that this would be considered a clinically significant improvement in recovery time. There are considerable data in autoimmune and other forms of encephalitis that early recovery leads to better outcomes overall (Ooi et al., 2008; Raschilas et al., 2002; Titulaer et al., 2013); for example, in a retrospective study of 577 patients with anti-NMDA receptor encephalitis, patients who responded to first line immunotherapy had a better outcome at 24 months than those who did not respond and required second line therapy (Titulaer et al., 2013). In our unpublished analysis of Enceph-UK data, 80% of autoimmune encephalitis patients had recovered (as assessed by GOSE ≥5) within 12-months, which is comparable to published series (Titulaer et al., 2013). Our sample size was inflated to account for 5% drop-out. As our outcome was time-to-event based, and participation in the trial following the initial five-day treatment period revolves around providing follow-up data, we expected drop-out and missing data to be low.

As a secondary outcome, our study would have been able to detect a difference in the proportion of patients with a GOSE of 5 or more at 3 months follow up from 0.5 (based on our Enceph-UK data) to 0.67 (i.e. 34% relative difference); this was based on the sample size of 354 (allowing for 15% loss to follow up), two-sided alpha of 0.05, and 85% power. At 12 months, we would have been able to detect a difference in the proportion of patients with a GOSE of 5 or more from 0.8 (based on our Enceph-UK data) to 0.94 (i.e 17.5% relative difference); this was based on the sample size of 244 (allowing for 15% loss to follow up) two-sided alpha of 0.05, and 85% power. We expect 30% of patients to be antibody positive, and within this subgroup (approximate 106 patients) we would have had approximately 80% power to detect a hazard ratio of 1.84. This translates into a 46% relative improvement in the median time to recovery for patients allocated to IVIG, or an absolute difference of 40 days (i.e. from 87 to 47 days).

At the time of study close down, 22 participants had been randomised.

3.4 FRAMEWORK

This is now a randomised pilot study and data will be analysed descriptively only. The analysis will include all participants with outcome data. We will provide descriptive statistics for feasibility outcomes and clinical outcomes including the time from randomisation to recovery (defined as two consecutive GOSE scores ≥5 according to the assessment schedule defined in primary outcome section), comparing participants allocated to IVIG and placebo arms.

We will provide descriptive statistics on instances of treatment switching and the use of further immunotherapy (IVIG, steroids plasma exchange, or other). We suspect that the decision to initiate further immunotherapy will be because of a perceived lack of response to treatment or because of a positive anti-neuronal antibody result.

3.5 INTERIM ANALYSES

N/A

3.5.1 PLANNED SAMPLE SIZE ADJUSTMENT

Due to slow recruitment the original sample size was reduced from 356 to 286 participants in total (143 per arm). This was based on a **one-sided** alpha of 0.05, 85% power, and a median time to recovery in our placebo arm of 87 days (based on analysis of patients in the Enceph-UK study) with 20% of participants not having recovered by the 12-month follow-up period for the primary outcome), and a hazard ratio of 1.43 (i.e. a 30% relative improvement in the median time to recovery – translating into an absolute difference of 26 days). This sample size is also inflated to account for 5% drop-out.

3.5.2 STOPPING RULES

We included Stop/Go decision points based on initiating the study at 10 months, and recruitment progress. Recruitment progress was assessed by the number of patients recruited at 6, 12, 18 and 24 months following the commencement of recruitment and the length of time it took to recruit the first 50 patients for the internal pilot. We used a traffic light system to indicate progression onto the remainder of the trial, where GREEN = Proceed with no modification; AMBER = review progress and reasons for failure to meet target; instigate remedial action, and set new target in conjunction with the Trial Steering Committee (TSC), Independent Data Monitoring Committee (IDMC) and Efficacy and Mechanistic Evaluation (EME) Board; RED = Proceed only with major modifications, following discussion and approval from with TSC, IDMC and EME. If two successive review points were RED, then this would indicate that the project would automatically stop.

Table 1: Stop/Go Decision Time Points

Outcome domain	Metric	GREEN	AMBER	RED
Progress with Set Up	Assessment at 10 months after study started	Ready to open first site Ethics approved MHRA Approval HRA approval R&D approval of 1st site	Contracts signed Ethics submitted MHRA Submitted HRA Submitted	Contracts not signed and Ethics, MHRA, HRA not submitted
Recruitment	No. of patients 6 months after recruitment starts (target 2; study month 16)	>1	0-1	-

Recruitment	No. of patients 12 months after start (target 14; study month 22)	>11	7-11	<7
Recruitment	No. of patients 18 months after start (target 35; study month 28)	>28	7-28	<17
Recruitment	No. of patients 24 months after start (target 70; study month 34)	>56	35-56	<35
Recruitment for internal pilot	Time from start of patient recruitment (and start of study) to recruit first 50 patients	21 (30) months	21-26 (30-35) months	> 26 (35) months
Retention	Percentage of randomised patients remaining in the study for primary outcome	> 90%	75-90%	< 75%
Adherence	Percentage of patients commencing treatment within 5 days of randomisation	> 90%	75-90%	< 75%
Contamination	Percentage of patients randomised to placebo arm who receive IVIG within the first 14 days post-randomisation	< 5%	5-10%	> 10%

3.5.3 INTERNAL PILOT

The statistical analysis of the internal pilot data from the placebo arm was planned to be conducted and reported during the closed session of the IDMC by a statistician not otherwise involved in the trial. The internal pilot would have looked at retention, adherence, and contamination (see table 1).

3.6 TIMING OF FINAL ANALYSIS

Final analysis was planned to take place once the final recruited patient reached the primary endpoint (scored 5 or above on the GOSE scale in 2 consecutive assessments) or reached the final assessment, whichever occurred first.

However, in August 2024 the funder directed closure to recruitment, after recruitment of 22 participants and before the internal pilot analysis took place.

3.7 TIMING OF OUTCOME ASSESSMENTS

Timing of planned outcome assessments are shown in the following table (figure 3 of the protocol).

Figure 3 Schedule of Enrolment, Intervention, and Assessments

Procedures	Visits (insert visit numbers as appropriate)									
	Screening (as part of standard of care)	Baseline	Treatment Phase	2 week follow up	Week 4-10	3 month follow up	Month 4-11	12 month Follow Up	Months 24-48	As required
Eligibility assessment	X									
Brain Imagining Scan (CT or MRI scan)	X									
CSF Samples	X			X						
Informed consent		X								
Demographics		X								
Medical history		X								
Physical examination		X								
Vital signs		X	X	X		X		X		
Concomitant medications		X								X
Randomisation		X								
Dispensing of trial drugs		X	X							
Blood Samples		X		X		X				
Laboratory tests	X	X		X		X				
Compliance			X							
Use of further immunotherapy			X	X		X		X		
Adverse event assessments			X	X		X				
Clinical assessment		X		X		X		X		

Figure 3 (Continued) Schedule of Enrolment, Intervention, and Assessments

Procedures	Visits (insert visit numbers as appropriate)									
	Screening (as part of standard of care)	Baseline	Treatment Phase	2 week follow up	Week 4-10	3 month follow up	Month 4-11	12 month Follow Up	Months 24-48	As required
Glasgow Outcome Scale Extended		X		X	X	X	X	X	X	X
EQ5D5L						X		X	X	
EBIQ						X		X	X	
Modified Rankin Scale								X		
Liverpool Outcome Score								X		
Barthel Index								X		
Addenbrooke's Cognitive Examination III								X		
Wechsler Memory Scale Version IV								X		
WAIS Version IV: Processing Speed Index								X		
WAIS Version IV: Working Memory Index								X		
Confrontational Naming task (from Neuropsychology Assessment Battery)								X		
Trial Making Test Part A and B								X		
Premorbid Cognitive Ability (TOPF)								X		
Beck Depression Inventory								X		
Beck Anxiety Inventory								X		
Perceived Deficits Questionnaire								X		

4. STATISTICAL PRINCIPLES

4.1 LEVELS OF CONFIDENCE AND P-VALUES

Data will be analysed descriptively only; no confidence intervals or p-values will be calculated.

4.1.1 ADJUSTMENT FOR MULTIPLICITY

Not applicable.

4.2 ADHERENCE AND PROTOCOL DEVIATIONS

4.2.1 DEFINITION AND ASSESSMENT OF ADHERENCE

Adherence was defined as the percentage of patients that started their allocated trial treatment in the first 5 days post randomisation.

In addition, the proportion of patients that initiated treatment at any time point, the implementation of the treatment (% of doses received), the patients' persistence to it (number of days on treatment before stopping, from initiation to discontinuation), and contamination (any instance of IVIg access in the placebo arm within the first 14 days post randomisation) will also be calculated and reported.

See Section 6.1.5 for more information on this.

4.2.2 PRESENTATION OF ADHERENCE

Descriptive statistics on adherence will be presented in a table, overall and by trial arm. The proportion of non-adherence and reason for non-adherence will be reported overall and as group-wise relative frequencies and percentages.

4.2.3 DEFINITION OF PROTOCOL DEVIATION

A protocol deviation occurred when the participant, study coordinator or investigator failed to adhere to significant protocol requirements, including eligibility violations, deviation from intervention or other non-adherence to the protocol. Any deviations from dosing schedule outlined in the trial protocol were recorded on the appropriate CRF and included at minimum new dose given, and reason for dose adjustment.

4.2.4 PRESENTATION OF PROTOCOL DEVIATIONS

The number and percentage of patients with major and minor protocol deviations will be summarised overall and by trial arm. The types of deviations will be reported, grouped together where recurring deviations are present, and the potential impact on data integrity and trial interpretation will be considered (if the original target sample size had been recruited).

4.3 ANALYSIS POPULATION

At the time of study closure, 22 participants had been recruited. We will therefore describe outcomes by arm for all randomised participants with outcome data.

5. STUDY POPULATION

5.1 SCREENING DATA

A screening log of all eligible and randomised patients was recorded at each site so that any biases from differential recruitment were detected. Tables will present the following summaries (overall and by study site): the number of days recruiting, number of patients screened, number of patients recruited, number of patients recruited per day, number of screened patients not recruited, and the reason for non-recruitment.

5.2 ELIGIBILITY

The number and proportion failing each inclusion criterion or falling into each exclusion criterion will be tabulated overall and by site.

5.3 RECRUITMENT

The number of recruited participants will be tabulated overall and by site and we will present graphs with recruitment by site over time.

5.4 WITHDRAWAL/FOLLOW UP

5.4.1 LEVEL OF WITHDRAWAL

The following levels of withdrawal were defined (but not limited to):

- Withdrawal from regular GOSE assessments (fortnightly or monthly) but still attend 3-month, 12-month or annual follow up assessments
- Withdrawal from completing questionnaires or attending clinical assessments
- Partial withdrawal from sample collection
- Complete withdrawal from further data collection
- Withdrawal of permission to use data already collected

and will be reported overall and by site.

5.4.2 TIMING OF WITHDRAWAL

The numbers (with reasons) of losses to follow-up (dropouts and withdrawals) over the course of the trial (baseline, randomisation, treatment phase, 48 months follow-up) will be presented in a CONSORT flow diagram.

5.4.3 REASONS FOR WITHDRAWAL

The following reasons for withdrawal were collected:

- Clinician's decision
- Participant's/Legal representative's decision
- Withdrawal due to SAE
- Withdrawal due to disease progression
- Other

5.4.4 PRESENTATION OF WITHDRAWAL/LOSS TO FOLLOW-UP

We will report frequencies and percentages of participant withdrawal, overall and by trial arm, broken down by level, timing, and (where available) reason for withdrawal.

5.5 BASELINE PARTICPANT CHARACTERISTICS

5.5.1 LIST OF BASELINE DATA

We will report on the following baseline data overall and by trial arm:

- Age
- Sex
- Weight (kg)
- Ethnicity
- Pregnant (weeks)
- Patient journey up to randomisation
  - ITU/HDU admission and reason
- Ventilatory support at randomisation
- Medical history
  - Previous episode of encephalitis, date, aetiology
  - Previous diagnosis of dementia and/or cognitive impairment
  - Previous diagnosis of epilepsy
  - Hospital admissions due to epilepsy in past 12 months
  - Concomitant medication
- Social history
  - Employment
  - Education
  - First language
  - Drugs/alcohol intake
- Symptoms during this illness and up to time of randomisation
  - Fever, headache, seizures, olfactory hallucinations, behavioural/personality change, alteration in cognition, alteration in consciousness
- Neurological exam
  - Abbreviated Mental Test Score, photophobia, neck stiffness/signs of meningism, dysphasia
- Lumbar puncture
- CSF and blood samples
- Glasgow coma scale
- Glasgow outcome scale extended

5.5.2 DESCRIPTIVE STATISTICS

Categorical data will be summarised by frequencies and percentages. Continuous data will be summarised by mean and SD, if data are normal, or median and IQR, if data are skewed. Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted. These will be summarised by treatment arm and in total.

6. ANALYSIS

6.1 OUTCOME DEFINITIONS

6.1.1 PRIMARY CLINICAL OUTCOME

The primary clinical outcome for the original study was time to recovery defined as achieving a score of 5 or greater on the GOSE for two assessments in a row.

6.1.2 TIMING, UNITS AND DERIVATION OF PRIMARY

The Extended Glasgow Outcome Scale (GOSE) is a measure of functional outcome and is validated for the assessment of brain injured patients via telephone or postal questionnaire. The GOSE is an extension of the original GOS, which limitations included the five broad categories and unstructured interview format. The GOSE instead uses a structured interview to grade participants on an 8-point extended scale: Death (1), Vegetative State (2), Lower Severe Disability (3), Upper Severe Disability (4), Lower Moderate Disability (5), Upper Moderate Disability (6), Lower Good Recovery (7), and Upper Good Recovery (8), with (5) meaning able to live independently.

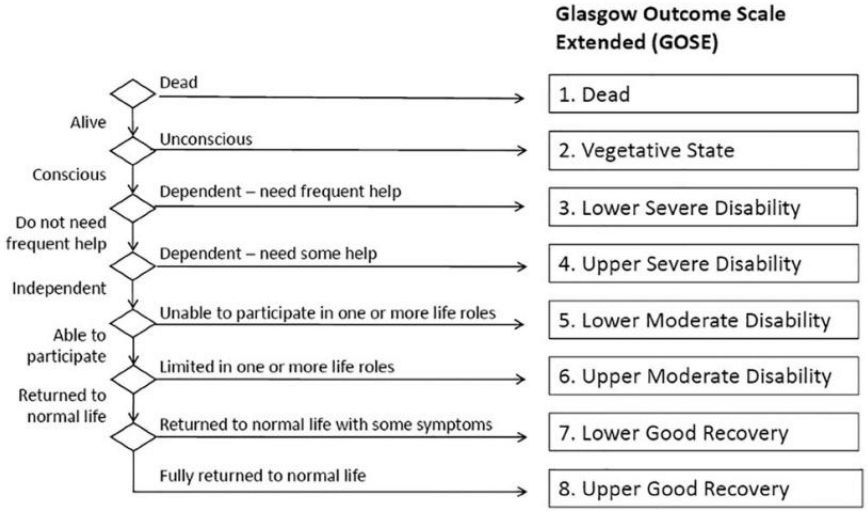

FIG. 1. GOSE hierarchy of outcomes - Glasgow Outcome Scale-Extended (Wilson et al., 2021).

The interview includes a set of multiple-choice questions, to aid assessment of the GOSE categories and areas of functioning. The questions relate to the ability to do a range of activities, and include areas such as consciousness, independence in the home, independence outside the home, work, social and leisure activities, family and friendships, and return to normal life. The GOSE outcome categories are indicated by specific responses to certain questions (deaths are recorded using participants' records) and the overall outcome is determined by the lowest GOSE category indicated by the responses. Responses where there has been no change compared to pre-injury status are not included in the assessment. The interviewer may need to make a judgement when deciding the overall score, if any of the responses are incomplete or inconsistent (Wilson et al., 2021).

The GOSE has been found to have good interrater reliability and is more sensitive to change in mild to moderate Traumatic Brain Injury (TBI). The GOSE has been widely adopted in TBI research studies, including autoimmune encephalitis (Ramanuj et al., 2014), and has been used in studies such as

Enceph-UK and DexEnceph. GOSE has also been validated for assessment in brain injured patients using telephone and postal questionnaires.

The primary outcome in this study was time to recovery, defined as achieving a score of 5 or greater on the GOSE for two assessments in a row. The study used a combination of telephone administered and patient reported outcome via a web-based format. The GOSE scale was planned to be administered every two weeks for 3 months and then monthly up to 12 months post randomisation, or until the participant reaches the primary endpoint. All participants were planned to complete the GOSE at 3 months and a subset of participants to complete it at 12-, 24-, 36- and 48-months post randomisation, even if they achieved the primary endpoint.

6.1.3 LIST OF SECONDARY CLINCAL OUTCOMES

1. The GOSE measured at 3 months (all participants), then at 12 months and annually for the duration of the trial for participants who reached those time points.
2. Neuropsychological outcomes were planned to be assessed at 12-months post randomisation for participants recruited up to month 44, measured using a standard battery of tests as well as the Modified Rankin Scale, and The Liverpool Outcome Score. The results from the standard battery will be compared with the results from previous encephalitis research.
3. EuroQoL five-dimension scale (EQ5D5L) and European Brain Injury Questionnaire (EBIQ) were planned to be assessed at 3 months, 12 months and annually for participants who reached those time points.
4. Clinical outcomes (adverse events, time to hospital discharge, further immunotherapy, relapse, HDU/ITU admission, seizures, ventilator support and mortality) were planned to be assessed at 2 weeks, 3 months and 12 months.
5. The levels of adherence, contamination, and retention were planned to be assessed at 5-days post randomisation, 14-days post randomisation, and at the end of trial, respectively.

6.1.4 ORDER OF TESTING

N/A

6.1.5 TIMING, UNITS AND DERIVATION OF SECONDARIES

1. The GOSE scale (as described in section 6.1.2) was planned to be measured at 3 months for all patients, then at 12 months and annually for the duration of the trial for patients who reached those time points.

2. Neuropsychological outcomes were planned to be assessed at 12-months post randomisation for participants recruited up to month 44, measured using a standard battery of tests as well as the Modified Rankin Scale, and The Liverpool Outcome Score. The results from the standard battery will be compared with the results from previous encephalitis research.

Functional outcome assessments include:

- The Modified Rankin Score: developed for the assessment of disability and dependence following stroke and widely used as an outcome measure within neurological infections and non-infectious encephalitis (Broderick, Adeoye, & Elm, 2017).
- The Barthel Index: an ordinal scale used to measure activities of daily living and assesses the ability of an individual to care for him/herself. It has been used in patients with neurological disorders and brain injury (Quinn, Langhorne, & Stott, 2011).
- The Liverpool Outcome Score: developed for the assessment of outcome following Japanese Encephalitis. It was designed for use in adolescents and adults as well as having been used in the ENCEPH UK study (Lewthwaite et al., 2010).

Neuropsychology and cognitive tests include:

- The Addenbrooke's Cognitive Examination III measures cognitive impairment, focusing on the following five cognitive domains: attention, memory, verbal fluency, language, and visuospatial abilities (Noone, 2015).
- The Wechsler Memory Scale (version IV) measures different aspects of memory functions in adults. Assessments include auditory memory index, Visual memory index, immediate memory index, and delayed memory index (Holdnack & Drozdick, 2010).
- The Wechsler Adult Intelligence (WAIS) test (version IV) measures intelligence and cognitive ability in adults. The sub-scales administered will be the Processing Speed Index and the working memory index (Holdnack & Drozdick, 2010).
- The Confrontational Naming Task from the language module of the Neuropsychology Assessment Battery will be used to assess partipants' wording finding ability (Zgaljardic & Temple, 2010).
- The Trail Making Test (Parts A and B) will be used to assess higher executive function by providing a measure of visual scanning, graphomotor speed, and mental flexibility (Lezak, 2004).
- The Test of Premorbid Functioning will assess participants' cognitive and memory functioning prior to onset of condition, providing a baseline against which their current performance is compared (Wechsler, 2009).
- The Beck Depression Inventory is a 21-item self-reported questionnaire used to assess the severity of a participant's depression (Jackson-Koku, 2016).
- The Beck Anxiety Inventory is a self-reported measure of the severity of a participant's anxiety (Beck et al., 1993).
- The Perceived Deficits Questionnaire is a self-reported questionnaire measuring the participant's perception of cognitive dysfunction. (Sullivan, Edgley, & Dehoux, 1990).

3. EuroQoL five-dimension Scale (EQ5D5L) and European Brain Injury Questionnaire (EBIQ) were planned to be assessed at 3 months, 12 months and annually for participants who reached those time points.

The EQ5D5L is a questionnaire consisting of two sections: the descriptive system and the visual analogue scale (VAS), that measures quality of life across 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each category has 5 response options, ranging from no problems to extreme problems (labelled 1-5). There should be only one response for each

dimension. Missing values can be coded as '-9'. Ambiguous values (e.g., two boxes are ticked for a single dimension) should be treated as missing values. This part of the questionnaire provides a descriptive profile that can be used to generate a 5-digit health state profile that represents the level of reported problems on each of the five dimensions. The EQ-5D-5L describes 3,125 possible unique health profiles. Health states may be converted into a summary index score by using an appropriate value set, which provides values (weights) for each health state description according to the preferences of the general population of a country. In this trial, health state index scores will be calculated using the EQ5D-3L value set derived for the UK using a standardised valuation exercise, in which a representative sample of the general population is asked to place a value on EQ5D-3L health states using the time trade-off valuation technique. Scores generally range from less than 0 (where 0 is a health state equivalent to dead; negative values are valued as worse than dead) to 1 (perfect health). The second part of the questionnaire consists of a horizontal VAS on which the participant (or relative, friend, or carer) rates their perceived health from 0 (worst imaginable health) to 100 (best imaginable health) (Dolan, 1997).

The EBIQ was designed to assess everyday difficulties, including social, emotional, and cognitive problems, in people who have experienced a brain injury. The questionnaire includes 63 questions which can be grouped into the following 9 categories: somatic (e.g., headaches, lack of energy); cognitive (e.g., trouble concentrating, forgetting appointments); motivation (e.g., lack of interest in hobbies); irritability/impulsivity (e.g., mood swings, shouting at people); depression (e.g., feeling sad, crying easily); isolation (e.g., hiding feelings, mistrusting people); consequences (e.g., neglecting appearance, uncomfortable in crowds); communication (e.g., losing contact with friends, difficulty participating in conversation); and core (having problems in general). Each question has 3 response options: "not at all"; "a little"; and "a lot". There is also a EBIQ questionnaire that can be completed by a relative, who can provide their perception of the participant's problems (Björkdahl, Nilsson, & Sunnerhagen, 2004).

4. The following clinical outcomes were planned to be assessed at 2 weeks, 3 months, and 12 months.

- Adverse events experienced are recorded throughout the trial (see section 6.5 for definitions).
- We will calculate the time from randomisation to hospital discharge.
- We record whether the participant receives any additional drug or treatment that differs from the protocol outline and report the use of further immunotherapy (IVIG, steroids, plasma exchange, other) and reason for treatment.
- At 2-weeks, 3-months and 12-months post-randomisation, it is recorded whether the participant has been admitted to HDU or ITU since randomisation or the most recent follow-up form, the reason for admission and the date admitted.
- At 2-weeks, 3-months and 12-months post-randomisation, it is recorded whether the participant has had any seizures since randomisation or the most recent follow-up form.
- At 2-weeks, 3-months and 12-months post-randomisation, it is recorded whether the participant received any ventilatory support since randomisation or the most recent follow-up form. We record all periods where the participant has used ventilatory support.

- At 2-weeks, 3-months and 12-months post-randomisation, it is recorded whether the participant has relapsed since randomisation or the most recent follow-up form.
- We record whether the participant has passed away, the date of death, whether the death was related to Encephalitis, and whether the cause of death is possible, probably or almost certainly related to IVIG.

5. The levels of adherence, contamination, and retention were planned to be assessed at 5-days post randomisation, 14-days post randomisation, and at the end of trial, respectively. Denominators for subsequent outcomes (retention, adherence, contamination) depend on the length of time the participant was in the study

- Retention was defined as the percentage of randomised patients remaining in the study for primary outcome
- Adherence was defined as the percentage of patients commencing treatment within 5 days of randomisation
- Contamination was defined as the percentage of patients randomised to the placebo arm who receive IVIG within the first 14 days post randomisation

6.1.6 TERTIARY/EXPLORATORY OUTCOMES

The mechanisms by which IVIG reduces brain inflammation (and potentially improves patient outcome) are incompletely understood. The impact on the body's inflammatory host response and glycosylation (sugar modification) of host immunoglobulin structure (within the IgG Fc region) are thought to play a critical role. Through targeted experiments, we planned to examine the host response in autoimmune encephalitis, and test two hypotheses to explain IVIG's therapeutic effects. The hypotheses were:

1. Patients with autoimmune encephalitis have aberrant IgC Fc glycosylation affecting function, as in other autoimmune diseases, and that IVIG modulates this.
2. IVIG reduces levels of anti-neuronal antibodies, as well as down regulating pro-inflammatory host pathways, and that these correlate with clinical outcome.

Due to the recruitment status at the time of study closure, the tertiary/exploratory outcomes will not be studied or described in the SAP in further sections.

6.2 ANALYSIS METHODS

6.2.1 LIST OF METHODS AND PRESENTATION

Baseline demographics (e.g., age, gender, ethnicity, etc.) will be summarised by trial arm using appropriate descriptive statistics (section 5.5.2) (table 2 in appendix). The normality of continuous variables will be explored using histograms and boxplots. Baseline demographics will also be summarised for those who completed follow-up compared to those lost to follow-up.

The primary analysis will include all participants with data on the primary outcome. We will report the mean (SD) (or median [IQR] if data are skewed) of the time from randomisation to recovery (defined as two consecutive GOSE scores ≥5) between the IVIG and placebo arms (table 3 in appendix).

Swimmer plots will be used to provide a visual representation of the subject-level data on the time from randomisation to recovery, presented overall and by trial arm.

We will compare instances of treatment switching and the use of further immunotherapy (IVIG, steroids plasma exchange, or other). We will also compare the reasons for initiating further immunotherapy, as we suspect that the decision to initiate further immunotherapy will be because of a perceived lack of response to treatment or because of a positive anti-neuronal antibody result.

Secondary outcomes will also be explored descriptively using the appropriate descriptive statistics (section 5.5.2), between arms for participants with relevant outcome data (table 4 in appendix).

6.2.2 COVARIATE ADJUSTMENT

N/A

6.2.3 ASSUMPTION CHECKING

The normality of continuous variables will be explored using histograms and boxplots and appropriate descriptive statistics will be reported.

6.2.4 ALTERNATIVE METHODS IF DISTRIBUTIONAL ASSUMPTIONS NOT MET

N/A

6.2.5 SENSITIVITY ANALYSES

N/A

6.2.6 SUBGROUP ANALYSES

N/A

6.3 MISSING DATA

Missing data will not be imputed.

6.4 ADDITIONAL ANALYSES

N/A

6.5 HARMS

The following table provides the definitions used in safety reporting:

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product
Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to an investigational medicinal product which is related to any dose administered to that participant

Serious Adverse Event (SAE)	Any adverse event that: - Results in death - Is life-threatening* - Required hospitalisation or prolongation of existing hospitalisation** - Results in persistent or significant disability or incapacity - Consists of a congenital anomaly or birth defect - Other medically important condition***
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is related to the IMP at any dose administered.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the IMP.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event, or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

***** Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

For the purposes of this trial, opportunistic infections (all grades) and unexpected or severe neuropsychiatric events (all grades) were also considered SAEs. Death due to disease progression did not require reporting as SAEs, instead it was recorded on the appropriate CRF.

Possible SAEs recorded in the 2-week and 3-month follow-up forms included:

- New onset of severe depression or worsening depression
- New onset severe paranoia or worsening paranoia
- New onset of suicidal thoughts, visual or auditory hallucinations, psychosis, or delusions
- Gastrointestinal tract infection, an intraabdominal infection, a soft tissue infection, a Clostridium difficile infection, a Urinary tract infection, a blood stream infection of unknown origin, a secondary blood stream infection, and intravascular catheter related sepsis

The frequency (percentage) of adverse and serious adverse events will be tabulated overall and by trial arm.

6.6 STATISTICAL SOFTWARE

Statistical analysis will be carried out using the latest version of Stata (StataCorp LLC, TX USA).

7. REFERENCES

7.1 NON-STANDARD STATISTICAL METHODS

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7.2 DATA MANAGEMENT PLAN

The Data Management Plan is located thus: S:\Centre for Trials Research\Research\Mixed Studies\ENCEPH-IG\8.0 Data Management & Statistics\8.1 Data Management

7.3 TRIAL MASTER FILE AND STATISTICAL MASTER FILE

The Trial Master File Is located thus: S:\Centre for Trials Research\Research\Mixed Studies\ENCEPH-IG\9.0 Trial Management

The Statistical Master File is located thus: S:\Centre for Trials Research\Research\Mixed Studies\ENCEPH-IG\8.0 Data Management & Statistics\8.5 Statistics

7.4 OTHER SOPS OR GUIDANCE DOCUMENTS

International conference on harmonisation, editor. Harmonisation tripartite guidelines E9 - Statistical Principles for Clinical Trials, Version 4: [http://www.ich.org/LOB/media/MEDIA485.pdf] 5th Feb 1998.

International conference on harmonisation, editor. Harmonisation tripartite guidelines E6(1) – Guidelines for good clinical practice, Version 4: [http://www.ich.org/LOB/media/MEDIA482.pdf] 10th June 1996.

International conference on harmonisation, editor. Harmonisation tripartite guidelines E3 – Structure and content of clinical study reports: [http://www.ich.org/LOB/media/MEDIA479.pdf] 30th Nov 1995.

European Medicines Agency. Guideline on Missing Data in Confirmatory Clinical Trials: [https://www.ema.europa.eu/en/missing-data-confirmatory-clinical-trials] 20th Sept 2010.

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SOP/008/1 – Design and implementation of a randomisation strategy template

SOP/008/2 – Statistical Analysis Plan

SOP/008/3 – Sample Size Calculations

SOP/008/4 – Statistical Reporting

SAP/ISAP DEVIATION LOG

Document number:		**Document version:**	
Reason for deviation:			

8. APPENDICES

Table 1 – completion rate of forms

Timepoint	**Form name**	**Completion (n/N)**	**%**
Baseline	Eligibility		
	Baseline form		

	Baseline sample form		
	Concomitant		
	Baseline GOSE form		
	Contact details		
2-weeks	2-week follow up form		
	2-week sample form		
	IVIG sample form		
	2-week GOSE form		
3-months	3-month follow up form		
	3-month sample form		
	3-month GOSE form		
	3-month EQ5D-5L		
12-months	12-month follow up form		
	Patient Assessments - MRS; GCS; ACE-II; Trail Making		
	Barthel Index		
	Liverpool Outcome Score		
	Becks Anxiety Inventory		
	Perceived Deficit Questionnaire		
	Becks Depression Inventory		
	EBIQ - Self		
	EBIQ - Relative		
	12-month GOSE Form		
	12-month EQ5D-5L		
24-months	24 Month GOSE Form		
	24M.EQ-5D-5L		
36-months	36 Month GOSE Form		
	36M.EQ-5D-5L		
48-months	48 Month GOSE Form		
	48M.EQ-5D-5L		
60-months	60 Month GOSE Form		

As required	Unblinding CRF		
	Admission & Discharge Form		
	Relapse Form		
	Additional Treatment Form		
	Lumbar Puncture Form		
	IVIG Accountability Form		
	Placebo Accountability Log		
	Placebo Destruction Form		
	Sample Transfer Form		
	Sample Disposal Form		
	ADHOC GOSE Form		
End of trial	Death Form		
	Withdrawal Form		

Table – Concomitant Medication

		Overall – n/n (%) or mean (SD) & median [IQR]	**Intervention** – n/n (%) or mean (SD) & median [IQR]	**UC** – n/n (%) or mean (SD) & median [IQR]
Medication type	Antimicrobial			
	Antiepileptic medication			
	Anticoagulant			
	Diabetic medication			
	Gastric protection			
	Immunomodulatory treatment			
	Neuropsychiatric medication			
	Steroids			
	Other type			

Medication name				
Route of administration				
Frequency				
Length of prescription				
Continuing at time of discharge				

Table 2 – descriptive summary of baseline data

		Overall – n/n (%) or mean (SD) & median [IQR]	**Intervention** – n/n (%) or mean (SD) & median [IQR]	**UC** – n/n (%) or mean (SD) & median [IQR]
Age				
Sex (%)	Male			
	Female			
Weight (Kg)				
Ethnicity (%)	White			
	Mixed/multiple ethnic groups			
	Asian or Asian British			
	Black/African/Caribbean/Black British			
	Other			
Pregnant (%)				
Admitted to ITU/HDU (%)				
Reason for admission (%)	Uncontrolled seizures/status epilepticus			
	Requirement of ventilator support			
	Decreased conscious level			
	Requirement of cardiovascular support			

	Closer monitoring required due to altered personality or behaviour			
	Other (please specify)			
Ventilatory support at randomisation (%)				
Previous episode of encephalitis (%)				
Days since most recent episode				
Aetiology (%)	HSV-1 encephalitis			
	HSV-2 encephalitis			
	NMDA encephalitis			
	VGKC encephalitis			
	Unknown aetiology			
	Other			
Previous diagnosis of dementia and/or cognitive impairment (%)				
Previous diagnosis of epilepsy (%)				
Number of hospital admissions due to epilepsy in the past 12-months				
On at least 1 antiepileptic drug before admission				
Past medical history				
In paid employment prior to admission (%)				
Type of employment (%)	Full time			
	Part time			
	No answer given			
If not in work (%)	Student			
	Retired			
	Homemaker			
	Other			
	Left school at aged 12			

Highest educational achievement (%)	Left school at aged 16			
	Finished school aged 18			
	Obtained university degree			
	Obtained postgraduate diploma			
	Obtained higher degree			
	Other			
	No answer given			
Patient is known to take recreational drugs (%)				
	By injection (%)			
Patient drinks alcohol (%)				
	Units of alcohol per week			
Experienced fever (>37.5 degrees C) (%)				
Experienced headache (%)				
Experienced seizures (%)				
Experienced olfactory hallucinations (%)				
Experienced behaviours/personality change (%)				
Experienced an alteration in cognition (%)				
Experienced an alteration in consciousness (%)				
Abbreviated Mental Test Score				
Shortened AMT				
Photophobia (%)				
Neck stiffness/signs of meningism (%)				
Dysphasia (%)				
Glasgow Coma Scale on day of randomisation total score				
White blood cell count				

Sodium (mmol/L)				
Immunoglobulin levels	IgA (g/l)			
	IgG (g/l)			
	IgM (g/l)			
GOSE (%)	Upper good recovery			
	Lower good recovery			
	Upper moderate disability			
	Lower moderate disability			
	Upper severe disability			
	Lower severe disability			
	Vegetative state			
	Death			

Table 3 – descriptive summary of primary outcome data

		Overall – n/n (%) or mean (SD) & median [IQR]	**Intervention** – n/n (%) or mean (SD) & median [IQR]	**UC** – n/n (%) or mean (SD) & median [IQR]
Time (days) to recovery				
BL GOSE (%)	Upper good recovery			
	Lower good recovery			
	Upper moderate disability			
	Lower moderate disability			
	Upper severe disability			
	Lower severe disability			
	Vegetative state			
	Death			
2W GOSE (%)	“”			

3M GOSE (%)	“”			
12M GOSE (%)	“”			
24M GOSE (%)	“”			
36M GOSE (%)	“”			
48M GOSE (%)	“”			
60M GOSE (%)	“”			

Table 4 – descriptive summary of secondary outcome data

		Overall – n/n (%) or mean (SD) & median [IQR]	**Intervention** – n/n (%) or mean (SD) & median [IQR]	**UC** – n/n (%) or mean (SD) & median [IQR]
3M GOSE (%)				
12M GOSE (%)				
48M GOSE (%)				
60M GOSE (%)				
Modified Rankin Score (%)	0: No symptoms at all			
	1: No significant disability despite symptoms; able to carry out all usual duties and activities			
	2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance			
	3: Moderate disability; requiring some help, but able to walk without assistance			
	4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance			
	5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention			
	6: Dead			
Barthel Index				

Liverpool Outcome Score (%)	1 = Death			
	2 = Severe sequelae, impairing function sufficient to make patient dependent			
	3 = Moderate sequelae mildly affecting function, probably compatible with independent living			
	4 = Minor sequelae with mild effects on function or personality change or on medication.			
	5 = Full recovery & normal neurological examination			
Addenbrooke's Cognitive Examination III				
Wechsler Memory Scale (IV)				
Wechsler Adult Intelligence test (IV)				
Trail Making Test - Part A (seconds)				
Trail Making Test - Part B (seconds)				
Test of Premorbid Functioning				
Beck Depression Inventory				
Beck Anxiety Inventory				
Perceived Deficits Questionnaire				
EQ5D5L	Summery index score			

	Visual analogue scale			
EBIQ	Somatic score			
	Cognitive			
	Motivation			
	Impulsivity			
	Depression			
	Isolation			
	Physical			
	Communication			
	Core Symptoms			
Experienced an adverse event (%)				
Time (days) to hospital discharge				
Use of further immunotherapy	Steroids (%)			
	Plasma exchange (%)			
	Other (%)			
Clinically defined relapse (%)				
Admitted to HDU/ITU (%)				
Experienced seizures (%)				
Use of ventilator support (%)				
Mortality (%)				
	Days until death			
Adherence (%)				
Contamination (%)				

Retention (%)				

Table 5 – descriptive summary of level of withdrawal

		Total - n/N (%)	Prior to starting treatment - n/N (%)	Intervention - n/N (%)	UC - n/N (%)
Withdrawal from treatment					
Withdrawal from regular GOSE assessments (fortnightly and/or monthly assessments)	Only complete GOSE assessment monthly				
	Withdrawal from all regular GOSE assessments				
	Only complete GOSE every other month				
Complete withdrawal from further data collection					
Withdrawal from sample collection					
Withdrawal from blood sample collection					
Withdrawal from CSF sample collection					
Withdrawal of consent to any future storage of tissue samples					
Complete withdrawal from all treatment and further data collection					
Withdrawal of permission to use data/samples already collected					

Table 6 – descriptive summary of reasons for withdrawal

	Total - n/N (%)	Prior to starting treatment - n/N (%)	Intervention - n/N (%)	UC - n/N (%)
Clinicians' decision				
Participants'/legal representatives' choice				
Withdrawal due to SAE				
Withdrawal due to disease progression				
Other				

Table 7 – descriptive summary of AEs

	Total - n/N (%)	Intervention - n/N (%)	UC - n/N (%)
Experienced an AE			

Table 8 – descriptive summary of SAEs

		Total - n/N (%)	Intervention - n/N (%)	UC - n/N (%)
Experienced an SAE				
Resulted in death				
Life-threatening				
Required inpatient hospitalisation or prolongation of existing hospitalisation				
Persistent or significant disability / incapacity				
Consists of a congenital anomaly or birth defect				
Other medically important condition				
Unexpected or severe neuropsychiatric events (all grades)	**New onset of severe depression or worsening depression**			
	New onset severe paranoia or worsening paranoia			

	New onset of suicidal thoughts			
	New onset of visual or auditory hallucinations			
	New onset of psychosis			
	New onset of delusions			
Opportunistic infections (all grades)	**Gastrointestinal tract infection**			
	Intraabdominal infection			
	Soft tissue infection			
	Clostridium difficile infection			
	Urinary tract infection			
	Blood stream infection of unknown origin			
	Secondary blood stream infection			
	Intravascular catheter related sepsis			