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

Enceph-IG Trial

Protocol version 2 Date: 19/04/2021

Sponsor:	University of Liverpool Research Support Office 2nd Floor Block D Waterhouse Building 3 Brownlow Street Liverpool L69 3GL
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's SOPs.

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

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Trial Sponsor:		
Dr Neil French	Email approval	29/04/2021
Name	**Signature**	**Date**

Director: Prof Kerry Hood		
Professor Kerry Hood	Email approval	29/04/2021
Name	**Signature**	**Date**

Chief Investigator:		
Professor Tom Solomon		**19/04/2021**
Name	**Signature**	**Date**

General Information This protocol describes the ENCEPH-IG clinical trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

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Trial Co-ordination:

The ENCEPH-IG trial is being coordinated by the Centre for Trials Research (CTR), Cardiff University, a Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the ENCEPH-IG Trial Management Group (TMG).

For **all queries** please contact the ENCEPH-IG team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigators.

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Trial Administrator:	Judith Evans	Email: EvansJ62@cardiff.ac.uk	

Randomisations:

Randomisation *Detail method of accessing randomisation as appropriate* **To randomise a participant:** **(See section 9.5 for more details).**
Clinical queries **EncephIG@Cardiff.ac.uk** **All clinical queries will be directed to the most appropriate clinical person.**
SAE reporting **Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to the CTR Safety Team (CTR-Safety@Cardiff.ac.uk) within 24 hours of becoming aware of the event (See section 16 for more details).** **Contact details: CTR-Safety@Cardiff.ac.uk**

Table of Contents

Glossary of abbreviations

AE	Adverse Event
ADEM	Acute Disseminated Encephalomyelitis
AR	Adverse Reaction
CA	Competent Authority
CF	Consent Form
CI	Chief Investigator
CRF	Case Report Form
CSF	Cerebral Spinal Fluid
CT	Computer Tomography
CTA	Clinical Trials Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
DSUR	Development Safety Update Report
EBIQ	European Brain Injury Questionnaire
EME	Efficacy and Mechanism Evaluation
EMEA	European Medicines Agency
EUCTD	European Union Clinical Trials Directive
EudraCT	European Clinical Trials Database
EQ5D5L	EuroQol five-dimension scale
GAD	Glutamic Acid Decarboxylase
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GOSE	Glasgow Outcome Scale-Extended
GP	General Practitioner
HB	Health Board
HDU/ITU	High Dependence Unit/Intensive Treatment Unit
IB	Investigator Brochure
IC	Informed consent
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product

IMPD	Investigational Medicinal Product Dossier
IV	Intravenous Therapy
IVIG	Intravenous Immunglobulin
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LGI-1	Leucine-rich-glioma-1
MHRA	Medicine and Healthcare products Regulatory Agency
MOG	Myelin Oligodendrocyte Glycoprotein
MRI	Magnetic Resonance Imaging
MTA	Material Transfer Agreement
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIHR EME	National Institute for Health Research Efficacy and Mechanism Evaluation Programme
NIMP	Non-Investigational Medicinal Product
SPIS	Study Partner Information Sheet
NMDA	N-methyl-D-aspartate
NPSA	National Participant Safety Agency
PCCTU	Oxford Primary Care Health Sciences Primary Care Clinical Trials Unit
PCR	Polymerase Chain Reaction
PerLR	Personal Legal Representative
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PrLR	Professional Legal Representative
PV	Pharmacovigilance
QA	Quality Assurance
QC	Quality control
QP	Qualified Person
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGF	Research Governance Framework for Health and Social Care
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction

SmPC	Summary Product Characteristics
SOP	Standard Operating Procedure
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
USM	Urgent Safety Measures
VTE	Venous Thromboembolism
WAIS	Wechsler Adult Intelligence Scale

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
1	2	19/04/2021	Clarified that all screening procedures are part of standard of care and study specific procedures will only be done after consent is obtained Clarification that participants will be monitored for 1 hour post dose for the first infusion Removed references to albumin Clarified who had responsibility for unblinding and added that local pharmacy can unblind if the online system is down Clarified that follow through NHS digital will a separate study Clarified the role of the IDMC and clarified that there will be an analysis of retention, adherence, and contamination for the pilot data but there will be no other interim analysis

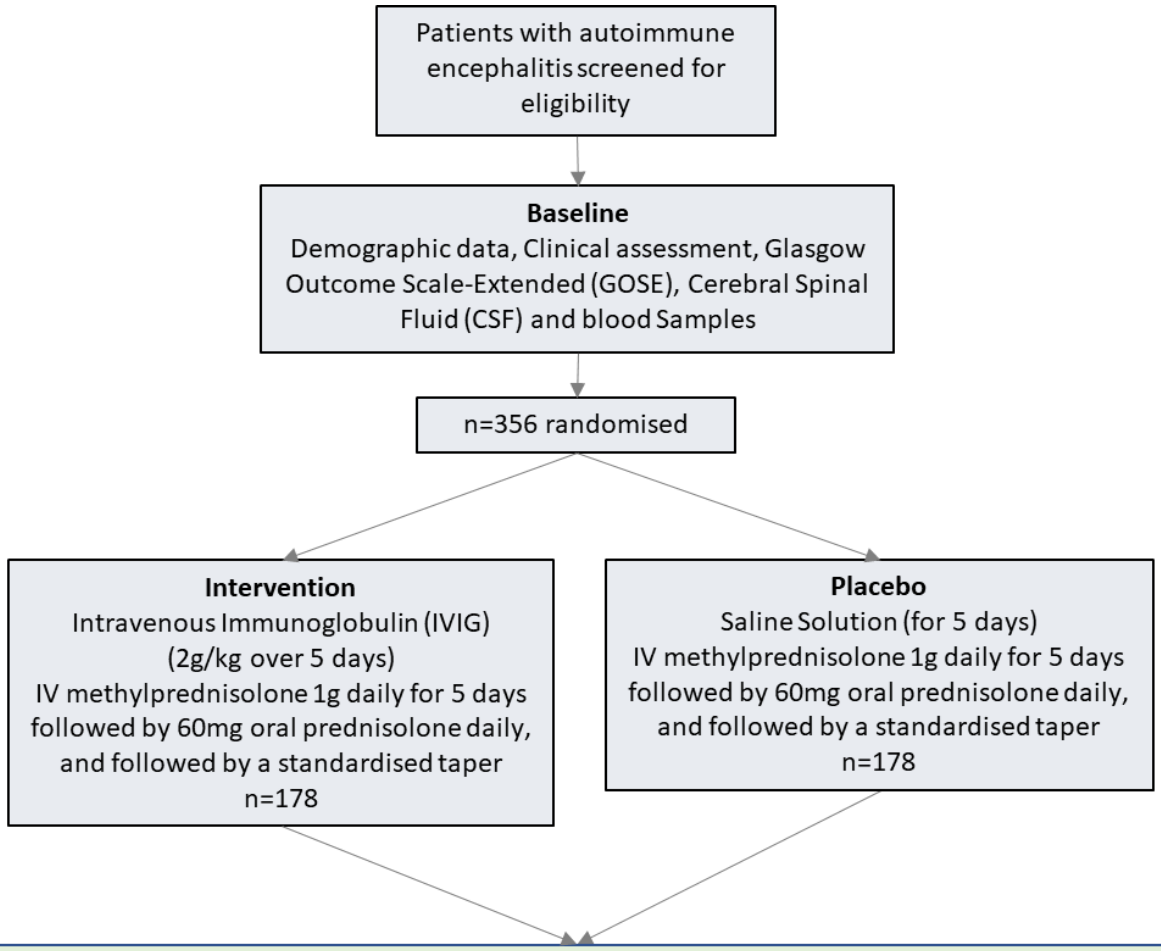
2 Synopsis

Short title	Intravenous Immunoglobulin in Autoimmune Encephalitis in Adults – A Randomised Double-Blind Placebo-Controlled Trial
Acronym	ENCEPH-IG
Internal ref. no.	
Clinical phase	Phase III
Funder and ref.	National Institute for Health Research Efficacy and Mechanism Evaluation Programme (NIHR EME) 17/60/67
Trial design	A multicentre randomised double-blind placebo-controlled trial
Trial participants	Adults (≥16 years) with autoimmune encephalitis
Planned sample size	356
Planned number of sites	50
Inclusion criteria	Adults (≥16 years) with altered consciousness level AND/OR behavioural change AND/OR working memory deficit AND/OR psychiatric symptoms, persisting for >24 hours and <3 months, in whom the clinician thinks autoimmune encephalitis is the most likely diagnosis. **AND all of:** • CSF polymerase chain reaction (PCR) negative for HSV 1 and 2, and varicella zoster virus • CSF microscopy and culture negative at 48 hours for organisms **Plus 2 or more of:** • Seizures (not explained by previously known seizure disorder) OR new movement disorder • Cerebrospinal fluid (CSF) white blood cell count 6-1000/mm3 • Electroencephalogram consistent with encephalitis • Brain magnetic resonance imaging (MRI) or computer tomography (CT) changes consistent with encephalitis
Exclusion criteria	• No other likely diagnosis • Current or recent treatment (within the last 6 months) with IVIG • Contraindication to IVIG • Intolerance of corticosteroids • Recent history of gastric ulcers • CSF analysis not performed • CSF polymerase chain reaction (PCR) positive for any virus • Brain imaging not performed • Alternative diagnosis on brain imaging (CT or MRI) • Known HIV infection • On steroids or other disease modifying anti-inflammatory therapies • Not able to live independently prior to onset of condition
Treatment duration	5 Days
Follow-up duration	3 months post randomisation for all patients, and 12 months post randomisation and annually for a subgroup of patients.
Planned trial period	73 months
Primary objective	To determine if early treatment with IVIG changes the time to recovery as measured on the Glasgow Outcome Scale - Extended (GOSE).

Secondary objectives	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. To determine the effect of IVIG on the modified Rankin Scale, Liverpool outcome score, and neuropsychological outcomes at 12 months. 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.
Tertiary/Exploratory objectives	Exploration of the mechanistic action of IVIG To better understand the development of later consequences such as epilepsy and psychiatric illness (to be funded and reported separately)
Primary outcomes	Time from randomisation to achievement of a GOSE score of 5 or more, maintained for two sequential assessments (assessed fortnightly for 3 months, and then monthly for up to 12 months or until GOSE 5 reached for two consecutive assessments. Maximum number of assessments: 15)
Secondary outcomes	1. GOSE at 3 and 12 months post-randomisation 2. Clinical outcomes: a. Adverse events, b. Time to hospital Discharge, c. Use of further immunotherapy (IVIG, steroids, plasma exchange, other), d. Clinically defined relapse, e. HDU/ITU admission, f. Seizures g. Use of ventilator support h. Mortality 3. Neuropsychological outcomes 4. Health utility and self-rated health
Tertiary/Exploratory outcomes	Exploration of the mechanistic action of IVIG
Investigational medicinal products	IVIG (2g/kg over 5 days) or placebo (0.9% Saline).
Non-Investigational Medicinal Products	All patients will also receive methylprednisolone 1g daily intravenously for 5 days, followed by 1mg/kg (up to 60mg daily maximum) oral prednisolone daily for two weeks, and then followed by a taper regime (reduction in 10mg decrements per week until 10mg, then reducing in 1mg every week until stop).
Form	Intravenous Infusion
Dose	2 g/ kg over 5 days
Route	IV

3 Trial summary & schema

3.1 Trial schema: *Enceph-IG- Intravenous Immunoglobulin in Autoimmune Encephalitis in Adults A Randomised Double-Blind Placebo-Controlled Trial*

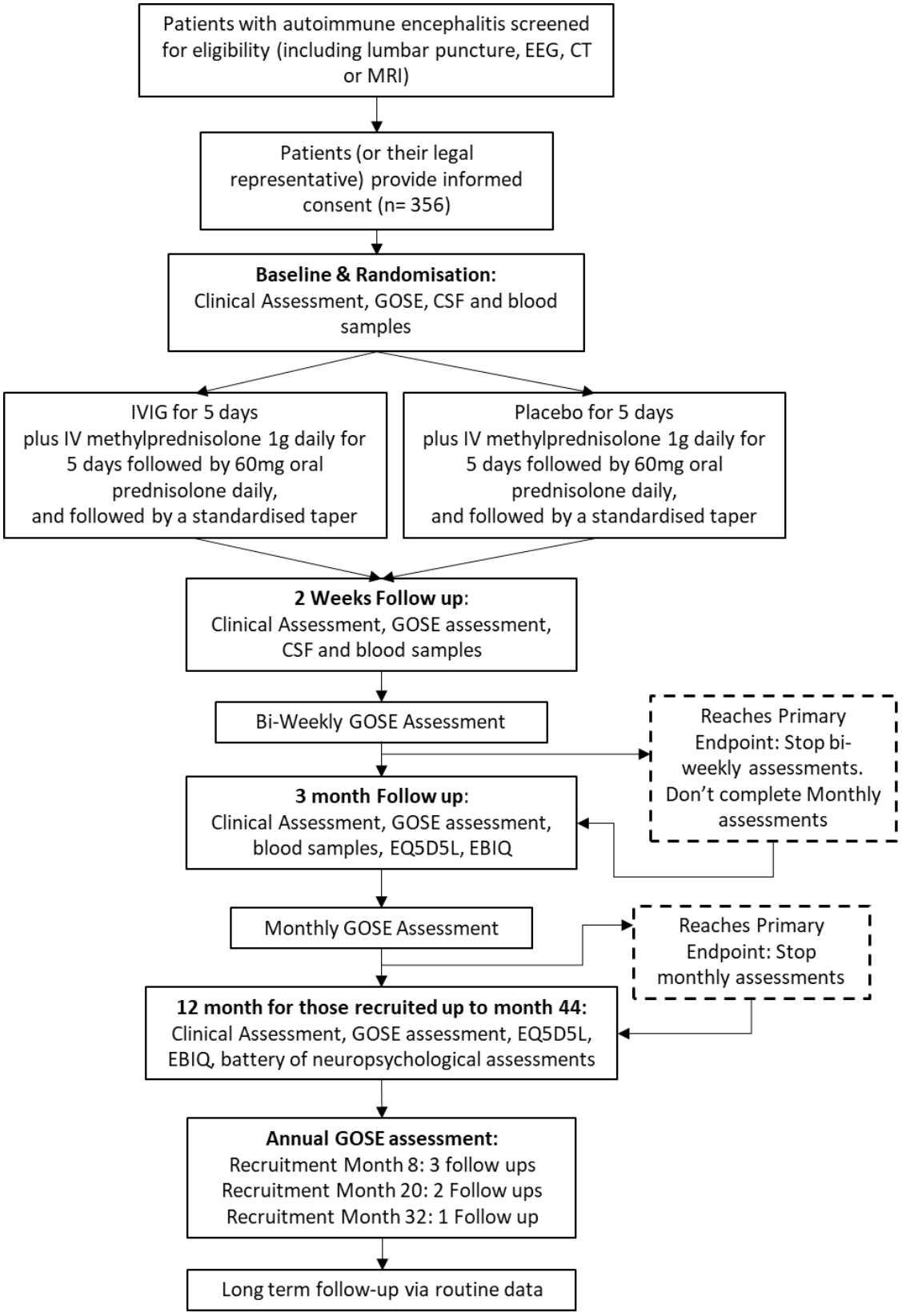


Primary outcome:
Time to recovery - GOSE of 5 or more, maintained for two sequential assessments (assessed fortnightly for 3 months, then monthly up to 12 months, until GOSE 5 reached for 2 consecutive assessments)

Secondary outcomes:
- GOSE at 3 months (all participants), 12 months and annually (subset of participants)
- Clinical condition at 3 months (all participants), 12 months and annually (subset of participants)
    - adverse events, time to hospital discharge, use of further immunotherapy (IVIG, steroids, plasma exchange, other), clinically defined relapse, High Dependence Unit/Intensive Treatment Unit (HDU/ITU) admission, Use of ventilator support, Seizures, and mortality.
- health utility and self-rated health (EuroQol five Dimension Scale (EEQ5D5L) and European Brain Injury questionnaire (EBIQ) at 3 months, and 12 months and annually (subset of participants)
- modified Rankin Scale (mRS) and Liverpool Outcome Score at 12 months
- neuropsychological outcomes, measured by standard batteries, at 12 months (subset of participants)

Longer term outcomes:
Data linkage via NHS digital (e.g subsequent epilepsy or psychiatric illness)

3.2 Participant flow diagram: Enceph-IG- Intravenous Immunoglobulin in Autoimmune Encephalitis in Adults A Randomised Double-Blind Placebo-Controlled Trial



3.3 Trial lay summary

Background

Autoimmune encephalitis is inflammation and swelling of the brain caused by the body's own immune defence system. It affects about 1 in 100,000 people per year in the UK. The symptoms can include abnormal behaviour, memory problems and seizures. Some patients recover completely, but in others it can cause death or severe disability.

Autoimmune encephalitis is treated with steroids, which reduce inflammation and swelling. If patients are not improving, intravenous immunoglobulin (IVIG) is often also given, usually after a couple of weeks. IVIG is a protein product extracted from the blood of healthy donors. It is given through a drip into a vein each day for five days and is used for other diseases that affect the nervous system.

Some doctors think that if IVIG is used from the start of treatment, patients may recover more quickly and have less side effects from the illness. While IVIG may help patients it can have side effects, including blood clots or allergic reactions, is expensive and may not help recovery. Currently it is used in about 50% of patients with autoimmune encephalitis. The ENCEPH-IG trial (Intravenous immunoglobulin in autoimmune encephalitis in adults) is a study looking at whether or not early treatment with IVIG improves recovery.

Aims

The aims of the trial are to:

1. To work out whether, in adults with autoimmune encephalitis, early treatment with IVIG leads to a different time to recovery and improves the outcome.

2. To carry out scientific studies to better understand the disease processes in autoimmune encephalitis and see how IVIG affects them.

Design and Methods

ENCEPH-IG is an individually randomised controlled trial of 356 adults: half will receive IVIG, and the other half will receive a placebo. The study will be carried out at approximately 50 hospitals in the Brain Infections UK network.

Participants who meet the entry criteria will be randomised in a ratio of 1:1. It is double blinded, meaning neither the patients nor their medical staff will know what treatment they have received. In addition, all patients will receive the standard steroid treatment.

4 Background

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. In approximately 50% of patients this is associated with an anti-neuronal antibody; the antibody may be against part of the neuronal cell surface, such as the N-methyl-D-aspartate (NMDA) receptor, or Leucine-rich-glioma-1 (LGI-1) receptor, or myelin oligodendrocyte glycoprotein (MOG), or against intracellular antigens, such as glutamic acid decarboxylase (GAD) (Dalmau, Lancaster, Martinez-Hernandez, Rosenfeld, & Balice-Gordon, 2011; Gresa-Arribas et al., 2015; Irani, Gelfand, Al-Diwani, & Vincent, 2014; Yeshokumar et al., 2017). Sometimes antibody is produced by an underlying tumour; rarely it may follow infection, for example after HSV encephalitis (Hacohen et al., 2014; Nosadini et al., 2017). However for many patients no antibody has yet been identified (Graus et al., 2018; Graus et al., 2016).

Autoimmune encephalitis responds to immunosuppressive therapy, but there is a lack of specific, targeted treatments. Currently, most patients are given corticosteroids initially, but there is disagreement about whether this should be augmented with early IVIG. Our qualitative studies, and surveys with clinicians confirm there is uncertainty: IVIG has been associated retrospectively with improved outcome (Irani et al., 2010; Titulaer et al., 2013); however it is an expensive blood product, with risks of significant adverse events, and there is no trial evidence of efficacy.

The burden on the NHS from the acute hospital care of encephalitis is estimated to be in excess of £40,000,000 per year (Granerod, Cousens, Davies, Crowcroft, & Thomas, 2013); at least 30 % of cases are autoimmune (Granerod et al., 2010). The overall cost of the disease to society is even higher because of the need for long-term outpatient multidisciplinary management, social and community care, and loss of earnings for patients and families (Granerod et al., 2017; Ramanuj et al., 2014). Improving treatment will help reduce these costs. IVIG is heavily rationed in the NHS due to its high costs, in excess of £7000 per course, and a global shortage. Our focus group discussions and survey with clinicians, who are key stakeholders, show real uncertainty about the best treatment for these patients. NHS England's Clinical Commissioning Policy Proposition (co-authored by our co-applicant Lunn) 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). This trial will establish whether

or not IVIG improves outcomes. There is a clear pathway to impact through NHS England's Clinical Commissioning Groups, and future updates of the National Encephalitis Guidelines (led from Liverpool by Chief Investigator Solomon).

Although autoimmune encephalitis is relatively rare its consequences overall are enormous because of its devastating impact on quality of life. For the 94 patients with autoimmune encephalitis in our Enceph-UK cohort, 4 (4%) had died by 3 months after discharge and 35 (37%) had a poor outcome, meaning they could not live independently. In another series, looking at longer term outcomes for 77 patients in the USA, 9 (12%) died and 26 (34%) had a poor outcome at a mean follow-up of 4.4 years; 86% patients had persistent neuropsychiatric symptoms (Yeshokumar et al., 2017). IVIG has been associated retrospectively with improved outcomes (Irani et al., 2010; Titulaer et al., 2013), but whether it is truly efficacious can only be answered using a randomised placebo-controlled trial design. There is an urgent need to conduct such a trial. 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 IVIG, but there is no clarity over whether it is needed. If we show that IVIG is effective it will become the standard care for patients with autoimmune encephalitis, and patient outcomes will improve overall; in contrast if we show it is not effective, this expensive and potentially dangerous treatment will be avoided.

4.1 Rationale for current trial/Justification of Treatment Options

The primary hypothesis for the clinical study is 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 will test two hypotheses to explain IVIG's therapeutic effects:

1. We hypothesise 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 hypothesise 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.

5 Trial objectives/endpoints and outcome measures

The aim of this trial is 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 aims to understand the mechanism by which IVIG may change recovery time.

5.1 Primary objectives

To determine if early treatment with IVIG changes the time to recovery as measured on the GOSE

5.2 Secondary objectives

The secondary objectives are to determine the effects of IVIG on the following:

1. GOSE at 3 and 12 months post-randomisation
2. Rates of clinical outcomes:
    a. Adverse events,
    b. Time to hospital Discharge,
    c. Use of further immunotherapy (IVIG, steroids, plasma exchange, other),
    d. Clinically defined relapse,
    e. HDU/ITU admission,
    f. Seizures,
    g. Use of ventilator support
    h. Mortality,
3. Neuropsychological outcomes
4. Health utility and self-rated health

5.3 Primary outcomes measure(s)

The primary outcome is time to recovery defined as achieving a score of 5 or greater on the GOSE for two assessments in a row. The current trial will use a web-based version of the GOSE, which was pilot tested with 229 encephalitis patients and families. The scale will be administered every two weeks for 3 months and then monthly up to 12 months post randomisation or until they reach the primary endpoint. All participants will complete the GOSE at 3 months and a subset of participants will complete it 12, 24, 36, and 48 months post randomisation even if they have achieved the primary end point.

The GOSE is a measure of functional outcome and is validated for the assessment of brain injured patients via telephone or postal questionnaire. GOSE ranges from 1 (death) to 8 (full recovery), with 5

meaning able to live independently. The Glasgow Outcome Scale and GOSE have been used in many brain injuries, including autoimmune encephalitis (Ramanuj et al., 2014). GOSE is used in the Enceph-UK and DexEnceph studies. It has been validated for assessment in brain injured patients previously using telephone and postal questionnaires. In this study we have converted this to a web-based format.

5.4 Secondary outcome measure(s)

The secondary outcome measures are as follows:

1. The GOSE measured at 3 months (all patients), then at 12 months and annually for the duration of the trial for patients who reach those time points.
2. Neuropsychological outcomes: Administered to patients recruited up to month 44. This will be measured using a standard battery of tests (see section 12.1 assessments) as well as modified Rankin Scale, and The Liverpool Outcome Score. This will be administered at 12 months post randomisation. 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): Measured at 3 months, then at 12 months and annually for patients who reach those time points.
4. Clinical outcomes assessed at 2 weeks, 3 months, and 12 months: This includes adverse events, time to hospital discharge, use of additional immunotherapy rescue treatments, relapse, HDU/ITU admission, Seizures, Use of ventilator support, and mortality.

5.5 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 will examine the host response in autoimmune encephalitis, and test two hypotheses to explain IVIG's therapeutic effects. The hypotheses are:

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.

6 Trial design and setting

The aim of the study is to test the effectiveness of early IVIG treatment on time to recovery for autoimmune encephalitis. This will be a multicentre double-blind two-arm placebo-controlled randomised superiority trial of IVIG in adults with autoimmune encephalitis, incorporating 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. A total of 356 adult participants with a diagnosis of autoimmune encephalitis, will be randomised from 50 UK based secondary and tertiary care centres in a ratio of 1:1 to receive either IVIG (2g/kg over 5 days) or placebo treatment (0.9% Saline). 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 (see section 1.4 for full dosing schedule).

The total trial duration is 73 months and the end of trial will be defined as last participant, last visit. There will be 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 will comprise of clinical data, questionnaires, and samples. GOSE assessments will occur fortnightly for the first 3 months and then monthly till 12 months post randomisation. Clinical assessment will occur at 2 weeks, 3 months and 12 months post randomisation, and annually. Participants will be followed up post study completion through the use of data linkage via NHS digital. This will constitute a separate study and will be 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 40 controls - patients who had a lumbar puncture for non-inflammatory causes such as migraine and idiopathic intracranial hypertension. Serum IgG glycosylation samples will be taken again at 3 months.

6.1 Risk Assessment

A Risk Assessment has been completed to identify the potential hazards associated with the study and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the MRC/DH/MHRA Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to participants
- How high the risk is compared to normal standard practice

- How the risk will be minimised/managed

This trial has been categorised as B risk, where the level of risk is slightly higher than the risk of standard medical care. A copy of the study risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 25.1).

7 Site and Investigator selection

This trial will be carried out at participating sites within the UK. Interested sites were identified by sending out an invitation to participate to all principle investigators within the Brain Infections UK Network as well as other interested individuals who have previously participated in the Brain Infections UK programme. 50 sites will be selected based on their ability to meet recruitment targets open to recruitment in a timely manner, and deliver the treatment as per protocol.

Before any Site can begin recruitment a Principal Investigator at each site must be identified. The following documents must be in place and copies sent to the Enceph-IG Trial email account (see contact details on page 4):

- The approval letter from the site's R&D Department, following submission of the local information pack
- Favourable opinion of host care organisation/PI from Main Ethics committee
- MHRA approval
- A signed Trial Agreement
- Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)
- Completed Site Delegation Log and Roles and Responsibilities document
- Full contact details for all host care organisation personnel involved, indicating preferred contact
- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper
- A copy of the most recent approved GP letter on host care organisation headed paper
- A set of laboratory normal ranges and laboratory certification/accreditation from the host care organisation laboratory being used for analyses
- Pharmacy confirmation that they have received the first shipment of IMP prior to opening the site. N.B. This is not a regulatory requirement more good practice.
- Executed MTA for studies that had a translational component
- Returned Source Data Agreement signed by the PI

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Principal Investigator detailing that the centre is now ready to recruit participants into the trial. This email must be filed in each site's Site File. Along with the written confirmation, the site should receive their trial drug supplies and a trial pack holding all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

Site initiation will be by conducted either in person or by tele/video conference.

8 Participant selection

Participants are eligible for the trial if they meet all the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Trial Manager before randomisation/registration.

8.1 Inclusion criteria

- Adults (≥16 years) with altered consciousness level **AND/OR** behavioural change **AND/OR** working memory deficit **AND/OR** psychiatric symptoms
- Persisting for >24 hours and <3 months
- In whom clinician thinks autoimmune encephalitis is the most likely diagnosis
- CSF polymerase chain reaction (PCR) negative for HSV 1 and 2, and varicella zoster virus
- CSF microscopy and culture negative at 48 hours for organisms

PLUS 2 or more of:

- Seizures (not explained by previously known seizure disorder) OR new movement disorder
- Cerebrospinal fluid (CSF) white blood cell count 6-1000/mm3
- Electroencephalogram consistent with encephalitis
- Brain magnetic resonance imaging (MRI) or computer tomography (CT) changes consistent with encephalitis

8.2 Exclusion criteria

The patient is not eligible for the trial if any of the following apply:

- No other likely diagnosis
- Current or recent (within last 6 months) treatment with IVIG
- Contraindication to IVIG
- Intolerance of corticosteroids
- Recent history of gastric ulcers

- CSF analysis not performed
- CSF polymerase chain reaction (PCR) positive for any viruses
- Brain imaging not performed
- Alternative diagnosis on brain imaging (CT or MRI)
- Known HIV infection
- On steroids or other disease modifying anti-inflammatory therapies
- Not able to live independently prior to onset of condition

9 Recruitment, Screening and registration

9.1 Participant identification

Potential participants for the study will be identified among hospital inpatients by clinical and laboratory staff, supported by automatic alerts for specific tests, (e.g. requests for anti-neuronal antibodies, Herpes Simplex virus PCR, or other viral CSF PCR). Recruiting hospitals will screen patients with suspected encephalitis for possible recruitment into the study. Once patients have been identified as potentially suitable, eligibility will be confirmed by a clinician listed on the delegation log and recorded in the patient notes.

9.2 Screening logs

A screening log of all potential patients who were screened but found to be ineligible, and those eligible but not consented/not approached as well as the identification pathway will be kept at each site so that any biases from differential recruitment will be detected. Screening activity at sites will be monitored regularly. When at site, logs may contain identifiable information, but this **must** be redacted prior to being sent to the CTR. The screening log should be sent to EncephIG@Cardiff.ac.uk every month (see section 25 for further detail on data monitoring/quality assurance). Screening activity will be reviewed regularly at the TMG along with the different stop/Go decision time points to ensure that recruitment is on target.

9.3 Informed consent

Due to the nature of the condition (autoimmune encephalitis) eligible patients may lack capacity to provide informed consent. Encephalitis is characterised by a progressive decrease in the level of consciousness and altered cognition, and memory, especially retention of new information, may be impaired early in the clinical course (Lancaster 2016). Consent procedures will be conducted in accordance with the Mental Capacity Act 2005 and, as it is a Clinical Trial of a Medicinal Product

(CTIMP), with the Medicines for Human Use (Clinical Trial) Regulations 2004 and the incoming Clinical Trials Regulations 536/2014.

As detailed below, consent procedures will differ according to the mental capacity of the patient. Informed consent must be obtained from the patient or a legal representative prior to any trial procedures being undertaken. It will also be necessary to collect contact details for friend or relative who will act as a study partner for the participant. This will facilitate data collection once the participant has been discharged from hospital. A participants' study partner may be asked to complete questionnaires on behalf of the patient, if the participant is unable.

The following information sheets apply:

Participant

- Participant Information Sheet
- Participant Consent Form
- Recovered Capacity Participant Information Sheet
- Recovered Capacity Participant Consent Form
- Pictorial Participant Information Sheet

Legal Representative (Personal or Professional)

- Legal Representative Information Sheet
- Legal Representative Consent Form

Study Partner

- Study Partner Information Sheet
- Study Partner Consent Form

Mental Capacity Assessment: According to the principles of the Mental Capacity Act, potential participants will be assumed to have capacity unless it is established that they lack capacity. A person who 'lacks capacity' means a person who lacks capacity to make a particular decision or take a particular action for themselves at the time the decision or action needs to be taken.

Where there is a concern that a potential participant lacks capacity to provide informed consent for themselves to participate in the trial, they will be assessed for mental capacity by delegated individuals (e.g. recruiting clinician) according to the Mental Capacity Act 2005, which provides a legal framework within which health and care professionals must act. To help determine if a person lacks capacity to make particular decisions, the Mental Capacity Act sets out a two-stage statutory test of capacity. The Mental Capacity Code of Practice provides comprehensive advice on good practice for the assessment of capacity, which is time and decision specific.

A standard template for recording of the mental capacity assessment will be provided to participating sites, together with specific training on the use of this template. This document will be reviewed by a delegated individual (e.g. recruiting clinician) to enable a decision to be made regarding the mental capacity of the potential participant, prior to seeking consent. The mental capacity assessment and outcome will be documented using the template provided.

Consent will be sought from potential participants able to provide informed consent. Where a potential participant is assessed as lacking capacity to consent to the trial, informed consent will be sought from their legal representative (see below).

Participant informed consent: Consent may be taken by the local Principal Investigator or a trained member of the study team delegated to do so. The potential participant will be provided with information about the trial via the Participant Information Sheet (PIS).

The participant will be given sufficient time after the initial invitation to participate, and the opportunity to ask questions, before being asked to sign the Consent Form. Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial. One copy of the signed Consent Form to be given to the participant, and the original copy to be kept in the investigator site file and a further copy to be kept with participant's hospital notes.

The right of the participant to refuse to participate in the trial without giving reasons must be respected. Similarly, the participant remains free to withdraw at any time from the protocol treatment or any trial activity, including use of samples, without giving reasons and without prejudicing his/her further treatment.

Participants lacking capacity: Where a potential participant lacks capacity to provide consent for themselves, in accordance with the Medicines for Human Use (Clinical Trial) Regulations 2004, a legal representative will be identified and approached to provide consent. The legal representative is someone who 'by virtue of their relationship' with the potential participant, is suitable to act as their legal representative for the purposes of the trial and is available and willing to act as a legal representative. This will usually be a friend or relative, who acts as a **Personal Legal Representative (PerLR)**. In the unusual circumstance that no friend or relative can be identified, or there is insufficient opportunity to identify and approach such a person, a doctor or other health care worker who is not connected to the study will be approached to act as a **Professional Legal Representative (PrLR)**.

Legal representative consent (PerLR and PrLR): The legal representative will be provided with information about the trial and the Legal Representative Information Sheet. They will be asked to consider what the person's views would have been regarding inclusion in the research if they had

capacity to make the decision for themselves, and will be asked to provide informed consent on their behalf that represents the person's 'presumed will'. The legal representative should be given sufficient time after the initial invitation, and an opportunity to ask questions, before being asked to sign the Legal Representative Consent Form.

Participants regaining or losing capacity during the trial: Mental capacity is subject to fluctuations, and participants who lack capacity to consent at the time of enrolment may regain capacity during the trial. Appropriate trial personnel (clinicians, Research Nurses) will conduct ongoing assessment of participants' capacity during data collection and trial assessment visits. If a participant who was initially assessed as lacking capacity, regains capacity during the trial period, the participant will be fully informed about the trial and provided with Recovered Capacity Participant Information Sheet, and informed consent to remain in the trial will be sought from the participant and documented on the Recovered Capacity Participant Consent Form.

If there are concerns about the capacity of a participant who provided consent at the time of enrolment, a capacity assessment may be required. Whilst the participant's informed consent for the trial will remain valid under the Medicines for Human Use (Clinical Trial) Regulations 2004, the involvement of a Legal Representative should be sought in order to advise regarding any future withdrawal from the trial.

Study Partner: Due to the nature of the condition it may be necessary to ask the patient's friend or a family member to complete some of the questionnaires on their behalf. The friend or family member will be approached at the same time that the participant will be approached. The friend or family member will be provided with information about the trial and their role in the trial (i.e. Study Partner Information Sheet (SPIS). The detailed SPIS will include: the exact nature of the trial; what it will involve for the participant and the patient's friend or relative, the implications and constraints of the protocol; and any risks involved in taking part. They will be given sufficient time to review the information sheet and ask any necessary questions. Participants with capacity will also be asked to confirm they are happy for the friend or a family member to answer any necessary trial questionnaires on their behalf if they are unable to do so. If the family member or friend is also the legal representative we will ask them to sign the study partner consent form as well.

9.4 Registration and Randomisation

9.4.1 Registration

Once patients are identified and deemed eligible via the screening procedure, informed consent is taken either from the participant themselves or a legal representative (see section 9.3 for details), and participant's study partner will provide consent for their contact details to be stored. Consent and eligibility will then be confirmed on the trial database for participant registration. On registration, all participants will be assigned a unique identification number. All screening procedures are part of standard of care, and no protocol-required evaluations will be conducted until after informed consent is obtained.

9.4.2 Randomisation

Following confirmation of consent, sites will complete of the baseline assessments. Participants will then be individually randomised to either receive IVIG or placebo. Patients will be randomised 1:1 to IVIG or placebo using random permuted blocks stratified by site, and time from symptom onset. The final randomisation lists, which will contain investigational medicinal product identifications and corresponding allocations (IVIG / placebo), will be generated by a statistician otherwise not involved in the trial and will be supplied to the manufacturing and site pharmacy for appropriate labelling, as well as the CTR safety team. Randomisation will take place online using Vanilla, a system created by the Cardiff University Centre for Trials Research. It will be available 24 hours a day. On randomisation, a participant will be 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.

In the instance that the online randomisation system is not working, sites will contact the trial team by emailing the trial inbox (EncephIG@Cardiff.ac.uk). The trial team will then let sites know when the system is functioning again. Sites will be informed in advanced of any scheduled downtime in the servers that would prevent them from using the system. If necessary, randomisation may be performed by CTR staff using hardcopy lists.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Although the IMP in this trial is used in the patient population for this indication, its use is in addition to current standard practice but poses minimal risk to the participant. The treating clinician will retain

oversight on whether or not to adhere to the protocol treatment plan. Participants have the right to withdraw consent for use of clinical data collected in any aspect of the trial at any time. The participants' care will not be affected at any time by declining to participate or withdrawing from the trial. Some participants may wish to withdraw the use of the data upon first approach for deferred consent, following treatment with the IMP. For both participants who provides deferred consent and those who provide consent from the outset but then subsequently request to withdraw from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

i. Withdrawal from regular GOSE assessments (fortnightly or monthly) but still attend 3 month, 12 month or annual follow up assessments.

ii. Withdrawal from completing questionnaires or attending clinical assessments

iii. Partial withdrawal from Sample collection

iv. Complete withdrawal from further data collection

v. Withdrawal of permission to use data already collected

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal, unless participants withdraw consent to use data that has already been collected.

Participants who consent and subsequently withdraw are invited to complete a withdrawal form (see Withdrawal Form in trial pack). If they decline, the withdrawal form should be completed by the researcher/clinician based on information provided by the participant. The information from the withdrawal form should also be recorded in the patient's medical notes. This withdrawal form should be sent to the trial inbox (EncephIG@cardiff.ac.uk). Any queries relating to potential withdrawal of a participant should be forwarded to the trial inbox (EncephIG@cardiff.ac.uk).

It is important to collect safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event. If a participant wishes to stop taking part in the trial completely, they will need to be seen one last time for an assessment and tests. If the participant is suffering a serious reaction to the trial treatment when they decide to stop, you will need to continue to collect information about them for as long as the reaction lasts. At time of registration, consent for collecting data relating to a serious reaction after a participant withdraws from the trial will be collected. This information is contained in the participant information sheet.

10.2 Lost to Follow Up

Sites will contact patients for each visit in accordance with the procedure outlined in section 13.2. If patients are not able to be contacted after three missed regular (fortnightly or monthly) GOSE assessment, a letter will be sent out to the participant asking them to get in contact with the trial team. Participants will not be contacted again until the 3 month, 12 month, or annual follow up occurs. Sites will record all details regarding attempts to contact the participant on the appropriate CRF. To minimise missing data, participants will be able to complete the primary outcome online or over the phone. In addition, contact details for participant's study partner will be collected and they will be able to complete the primary outcome on behalf of the participant. All data from participants will be collected regardless of their adherence to the protocol.

11 Trial Intervention

Patients will receive IVIG (2g/kg over 5 days) or placebo (Saline solution).

IVIG is a preparation of antibodies made from blood donations. It is licensed for use in patients with primary and secondary immunodeficiencies and for certain neurological conditions, such as Guillain-Barré syndrome. IVIG is given to many patients with autoimmune encephalitis. However, its efficacy is not known, and being a blood product, it carries risk of side effects.

We choose 2g/kg IVIG over 5 days (0.4g/kg/day for 5 days) because it is the dosing regimen most commonly used in neuro-inflammatory conditions, including in Guillain-Barré syndrome, and is the dose used in the pilot study of IVIG in encephalitis (Rayamajhi et al., 2015).

All patients will also receive methylprednisolone 1g daily intravenously for 5 days, followed by 1mg/kg (up to 60mg daily maximum) oral prednisolone daily for two weeks, followed by a taper regime (see section 11.4 for full dosing schedule).

11.1 Treatment(s)

The trial is being carried out under a CTA. The drug is therefore only to be used by the named investigators, for the participants specified in this protocol, and within the trial. Sites may use any brands in accordance with local hospital policy. IVIG comes as a sterile clear, or slightly opalescent and colourless to pale yellow solution, which is isotonic, with an approximate osmolality of 320 mOsmol/kg. IVIG is licensed for use in the UK. Despite being commonly used to treat autoimmune encephalitis, it is not currently licensed for this use. IVIG comes in ready to use single use vials, containing 10g/100ml

solution which does not need to be diluted and contains human protein of which at least 98% IgG, trace amounts IgA (no more than 25 micrograms/ml), and is essentially sodium free. Other ingredients are amino acid proline and water. The responsibility for the safety profile, including screening for COVID-19, of the IVIg will lie solely with the manufacturers of the product.

The placebo is saline solution. The solution will contain 0.9% sodium chloride. The placebo will be bottled in matched 100ml single use vials. Placebo bottles should be stored below 30°C in all original packaging.

The current trial will use a Summary of Product Characteristics. Sites should ensure to consult the appropriate SmPC for clinical management decisions.

Patients will receive an infusion via IV of IVIG (2g/kg over 5 days) or placebo (saline solution). All patients will also receive methylprednisolone 1g daily intravenously for 5 days, followed by 1mg/kg of body weight, with a maximum dose of 60mg, oral prednisolone daily for two weeks. This will be followed by a taper regime (see section 11.4 for full dosing schedule).

For the first 14 days post randomisation, all other immunomodulatory treatment should be avoided. Once the 14-day period has elapsed, anti-neuronal antibody results will be reviewed and assessment on whether the patient has improved, stabilised or deteriorated will be made. If deemed necessary further non-IVIG treatment such as steroids, or plasma exchange will be considered. IVIG may be an option only after these alternatives have been considered. This procedure will be used in the event of subsequent deterioration or in the event the treating clinician determines additional treatment is necessary.

Figure 1 Treatment Schedule

Treatment Day	IVIG or Placebo	Methylprednisolone	oral prednisolone	Recovery Assessment	Further Treatment
1	0.4g/kg	1g			
2	0.4g/kg	1g			
3	0.4g/kg	1g			
4	0.4g/kg	1g			
5	0.4g/kg	1g			
6			1mg/kg (max 60mg)		
7			1mg/kg (max 60mg)		
8			1mg/kg (max 60mg)		
9			1mg/kg (max 60mg)		
10			1mg/kg (max 60mg)		

11			1mg/kg (max 60mg)		
12			1mg/kg (max 60mg)		
13			1mg/kg (max 60mg)		
14			1mg/kg (max 60mg)		
15			1mg/kg (max 60mg)		If participant hasn't improved
16			1mg/kg (max 60mg)		If participant hasn't improved
17			1mg/kg (max 60mg)		If participant hasn't improved
18			1mg/kg (max 60mg)		If participant hasn't improved
19			1mg/kg (max 60mg)		If participant hasn't improved
20			1mg/kg (max 60mg)		If participant hasn't improved
21			Start Taper Regime		If participant hasn't improved

If, for reasons relating to patient safety, a clinicians deems it is necessary to provide additional rescue treatment within the 14 day window post randomisation or to administer IVIG at any point they must alert the central trial team by emailing EncephIG@Cardiff.ac.uk within a week and record the information on the appropriate CRF. This, by itself, will not constitute a reason to withdraw the patient from the trial.

11.2 Treatment supply and storage

IVIG and Placebo:

Sites will use their standard hospital stock of IVIG. To maintain the blind both IMP and placebo will be packaged and labelled identically and in sequentially numbered packages. The labelling will be in accordance with Annex 13 of the Rules Governing Medicinal Products in the EU: Manufacturing Practices. The sequential numbering will remain on the packaging to allow for emergency unblinding. The manufacturing pharmacy unit will also be responsible for the final QP certifications for placebo. The manufacturing pharmacy unit will be responsible supplying the individual sites with the placebo.

Storage for IVIG will be in accordance with its SmPC. Once opened, IVIG should be infused immediately as it contains no preservatives. It is able to be stored in its original packaging for up to 3 years. Sites should follow standard local practices for monitoring temperature.

Steroids:

Steroids will be provided as part of standard care. Therefore, standard hospital stock will be used and stored according to local practices and relevant summary product characteristics. Annex 13 labelling and accountability is not required.

11.3 Treatment prescribing and dispensing

IVIG

Sites will use their hospital stock of IVIG. The placebo will be distributed to each site pharmacy by the manufacturing pharmacy unit. A drug receipt log must be maintained and will log at minimum date of delivery and person accepting shipment. The logs will be returned to the CTR for monitoring. An IMP inventory log will also be provided. Sites can use their own logs as well as all necessary information is captured.

Once a patient is randomised, a randomisation email will be sent to the unblinded pharmacist who will prepare the correct vial for dispensing. They will ensure the tear off section of the label, that labels bottle as IMP or placebo, is removed and that the packaging is adequately sealed to maintain the blind. The bottles will be labelled with a number that will allow for emergency unblinding. The trial prescription should contain at minimum the following information:

- Participant study ID
- Participant Initials
- Date
- Dose Number
- Participant DOB
- Participant's weight
- Total Calculated amount of IMP to be infused (in grams)

Steroids:

Steroids will be dispensed using standard local hospital procedure and prescriptions.

11.4 Dosing schedule

IVIG/Placebo:

2g/kg IVIG/placebo over 5 days. This is approximately 0.4g/kg body weight per day but the daily dose should be rounded down to the nearest complete vial, with any remaining prescribed dose being

infused on the final day. IVIG/placebo dose is capped at 200g over the 5 days and sites should not infuse more than 1g/kg per day. Treatment should be started within 5 days of randomisation.

Sites should make sure to consult their local policy for IVIG infusions rates. Prior to infusing IVIG, sites should ensure patients are adequately hydrated, especially those with a risk factor for thrombosis, renal complications, and diabetes mellitus. All patients, particularly those who are considered high risk (previous Venous Thromboembolism (VTE), family history, or known pregnancy), should have a VTE risk assessment performed. During administration of the first infusion of trial treatment participants' vital signs must be monitored during and for 60 mins after infusion. For infusions 2-5, vital signs must be monitored during and for 20 minutes after infusion and relevant information recorded on the appropriate CRF. Participants must also be observed for any signs of anaphylaxis.

Non-IMP: Steroids

All patients will also receive methylprednisolone 1g daily intravenously for 5 days, followed by 1mg/kg of body (maximum dose 60mg) oral prednisolone daily for two weeks. This is followed by a reduction in 10mg per week until patient is taking 10mg daily, and then a further reduction in 1mg per week until stop. Minor variations in steroid dosing to due to participant's tolerance are allowed. All patients should have their blood sugar monitored while on steroids but those who are considered high risk (known diabetics, know pregnancy etc.) may require additional monitoring checks. In addition all patients will get a protein pump inhibitor (or similar alternative) to protect against gastric ulcers, and a calcium supplement and bisphosphate to protect against bone loss for the duration of steroid treatment. If adrenal deficiency is suspected, sites should follow standard local practice to manage the condition. It is recommended that all sites follow the NICE guidelines for steroids use during pregnancy. If sites have concerns regarding steroid regime or dose adjustments they should discuss with the site PI, and if necessary, they should contact the central trial team for guidance.

11.5 Dose modification for toxicity

The list of expected reactions for IVIG can be found in the appropriate SmPC and treatment for them will depend on the nature of the reaction as well as local hospital practice. IMP/Placebo dose can be modified in the event of a toxicity but must be reported on the appropriate CRF. Any toxicities that meets the definition of an SAE (see section 15.2 and 15.3) must be reported within 24 hours of knowledge of the event according to the procedure outlined in section 15.6.

11.6 Management of toxicity and hypersensitivity reactions

If anaphylaxis should occur, IMP treatment must be stopped immediately. Staff administering the IMP must be trained in acute management of anaphylaxis reactions and this must include the administration of intra-muscular adrenaline and be specified on the delegation log. Adrenaline must be available during administration and should be prescribed on the participant's drug chart prior to administration of IMP.

11.7 Management of overdose

If an overdose is suspected, site staff should monitor for fluid overload, renal impairment and hyperviscosity. Sites should notify the trial manager by emailing EncephIG@Cardiff.ac.uk in all cases of suspected overdoses. If the overdose causes an event that meets the criteria of an SAE (see section 15.2) it must be reported as an SAE according to the procedures outline in section 15.6.

11.8 Pre-medication

There are no pre-medication requirements

11.9 Prohibited medications and interaction with other drugs

During the first 14 days post randomisation, the use of additional immunomodulatory treatment will not be allowed. Once this period has elapsed, and it is determined the patient requires further treatment, non-IVIG treatment such as steroids or plasma exchange must be first considered. If after other treatment options have been considered, clinicians may administer IVIG if appropriate.

Clinician should avoid administering loop diuretics. If immunomodulatory treatment is administered within the initial 14 day window, the central trial team must be notified immediately and the appropriate CRF completed as soon as possible.

IVIG:

IVIG can impair the effectiveness of live attenuated virus vaccinations for up to 3 months. In the case of the measles vaccination, it can reduce the effectiveness for up to a year. It is recommended to wait for at least 3 months after IVIG treatment prior to having a live attenuated virus vaccination. In the case of patients receiving the measles vaccination, it is recommended they have their antibody status checked. Full details can be found in the SmPC.

Steroids:

For information relating to contraindications, trial staff should consult their specific SmPC.

11.10 Permitted concomitant medications and additional clinical procedures

All other medications are permitted except those listed in 11.10.1 trial restriction of the protocol and any medication listed in the appropriate SmPC.

Sites should monitor for complications arising from any lumbar punctures and manage them according to standard local practice.

11.10.1 Trial restrictions

Patients on Dinutuximab should not be prescribed immunoglobulins.

11.11 Accountability procedures

All accountability procedures will be outlined in the trial specific pharmacy manual and IMP management plan. Local pharmacies will be asked to log vial numbers, batch number, expiry date, date drug was dispensed, initials of trial member who requested drug, and returns. All bottles, even if empty, must be returned to the pharmacy. Upon return of any IMP/Placebo bottles, the pharmacy will confirm receipt of bottle and confirm that the packaging was not tampered with. To dispose of the drug, the pharmacy will contact the central trial team who will then issue a letter confirming permission to destroy trial stock. Destruction date will be recorded on the accountability log. In the event that the IMP was not administered according the outlined schedule (see section 10.4), the reason must be documented in the appropriate CRF.

11.12 Compliance

Any deviations from dosing schedule outlined in the trial protocol will be recorded on the appropriate CRF and will include at minimum new dose given, and reason for dose adjustment.

12 Sample Management

Participants will be asked if they are willing to consent to provide blood and/or CSF samples for the exploratory sub-studies. These samples will be used to explore the mechanisms by which IVIG produces benefit in patients. No samples collected for research (i.e. the exploratory sub-studies) will be used to inform primary or secondary trial outcome measures. The research samples (extra volumes of blood and/or CSF) will be collected at baseline (prior to IVIG treatment), 2 weeks and 3 months.

Samples will aim to be collected when the patient undergoes venepuncture / lumbar puncture as part of their clinical care at these time-points in their illness (to minimise unnecessary extra procedures).

As part of the consent process participants will be also be asked if any left-over CSF / blood remaining in the hospital laboratory after their initial clinical investigations (to determine if the patient had encephalitis) can be 'salvaged' and used to support the exploratory studies. These samples will particularly inform exploratory measurements for the 'acute' time-point of hospital admission. Local hospital laboratories will be informed of all participants who have consented for salvaged samples to be stored for the exploratory sub-studies.

Research samples (collected and salvaged) will initially be stored at hospital site in accordance with local policy. They will then be transported in batches to the University College London (UCL) Neuroimmunology and CSF Laboratory for central storage. Once received and logged by the lab at the University College London, samples will undergo exploratory measurements of inflammatory/host response markers (including glycosylation studies), and host biomarkers of brain damage at UCL. Some samples may also be transferred to the lab in University of Oxford to undertake detection / measurement for novel auto-antibodies. At the end of the trial, if consent is received samples will be sent to the University of Liverpool Ronald Ross building for storage in their biobank.

Figure 2 Sample Schedule and Quantities

Time	Acute	Baseline	2 weeks	3 months
CSF	5ml split into 4x1000µl and 2x500µl aliquots 1.proteome 100µl 2.cytokines 1000µl 3. Brain Damage Markers (e.g. neuro-filaments (NFL), Tau, S100B, 14-3-3) 1000µl 4.OCB,IgG,IgM,Albumin 1000µl 5. Host (+/-virus) Seq 500µl		4ml split into 3x1000µl and 2x500µl aliquots 1.proteome 100µl 2.cytokines 1000µl 3. Damage Markers (e.g. NFL, Tau, S100B, 14-3-3) 1000µl 4.OCB,IgG,IgM,Albumin 1000µl 5. Host (+/-virus) Seq 500µl	
CSF	ONLY local sites to Oxford: 6. CSF Cell separation: 1000µl			
Blood		1. Serum – BD Vacutainer SST 8.5ml [red/grey marble top] tube. [This tube will collect 3.5ml of serum. Following venepuncture invert 5 times to mix. Rest for at least 30 mins (ideally 2 hrs) for clot activation. Centrifuge 2000g 10min (or 3000g 5min) within 48hrs. Then aliquot serum into 7x500ul aliquots and freeze -80°C] a.IgG glycosylation 100µl b. brain damage markers 1000µl	1. Serum – BD Vacutainer SST 8.5ml [red/grey marble top] tube. a.IgG glycosylation 100µl b. damage markers 1000µl c. cytokines - 1000µl d. proteome 400µl e. Albumin, OCB, IgG,IgM 1000µl	1. Serum – BD Vacutainer SST 8.5ml [red/grey marble top] tube. a.IgG glycosylation 100µl b. damage markers 1000µl c. cytokines - 1000µl d. proteome 400µl e. Albumin, OCB, IgG,IgM 1000µl

Time	Acute	Baseline	2 weeks	3 months
		c. cytokines - 1000µl d. proteome 400µl e. Albumin, Oligo-Clonal Bands (OCB), IgG,IgM 1000µl		
		2. RNA stabilized – 2.5ml Host transcripts	2. RNA stabilized – 2.5ml Host transcripts	2. RNA stabilized – 2.5ml Host transcripts
		3. BD Vacutainer EDTA [lilac top] – 3ml Host DNA/ HLA sequencing		
		4. BD Vacutainer Sodium Heparin 10ml [green-top] tube: - Whole blood-PBMC Separation Plasma-AutoAb (ONLY local sites to Oxford)		

Any baseline samples should be taken prior to starting treatment. Given that some samples will be obtained from samples taken as part of routine care and that it may not be possible to obtain the necessary volume of blood or CSF, the samples should be collected in the order of importance and prepared in the manner specified below and:

For CSF Samples:

CSF must be taken in polypropylene tubes (can then be decanted / aliquoted into cryovial tubes at the local laboratory for ease of storage): draw 5mls

Laboratory Processes: Labs will be asked to "Freeze and Phone" any CSF from screened participants that is sent for analysis and is not used for clinical reasons (spare CSF). Any spare CSF will be ring fenced until consent is confirmed. Once consent for use of the sample is confirmed that lab will process and aliquot the sample. If consent is not confirmed, the sample will be destroyed.

If there is no spare CSF available following lumbar puncture (LP) at screening this will not preclude entry to the RCT. Sites are asked to phone in all instances. Where patients undertake a follow-up LP we request an additional volume of CSF is collected during the LP for research purposes.

For Blood Samples:

a. Blood in PAXgene tubes: 2.5mls

   Filled Blood collection tubes should initially be gently mixed by inverting five times, then rested at ambient temperature for 2 hours. Tubes should then be frozen at -80°C (an initial period (up to 1 month) at -20°C is acceptable)

b. Blood in BD Vacutainer Serum Separator Tubes (SST): 8.5mls

   Filled Blood collection tubes should initially be gently mixed by inverting five times, then rested at ambient temperature for 2 hours. Next, they should be centrifuged at 2000g 10min (or 3000g 5min) within 48hrs. The resulting serum should then be aliquoted into 7x500ul aliquots and frozen at -80°C

c. Blood in BD Vacutainer EDTA tube: 3mls

   Filled Blood collection tubes should initially be gently mixed by inverting five times, then rested at ambient temperature for 2 hours. Tubes should then be frozen (-80°C).

d. Blood in BD Vacutainer Sodium Heparin tube: 10mls (ONLY at sites local to Oxford/Liverpool)

   Sodium Heparin tubes should only be collected at hospital sites local to Liverpool or Oxford. The tubes need to be transported within 24 hours of collection and arrive at the University (Liverpool or Oxford) on a Monday-Thursday 9-5pm. During

collection/transportation the tubes should be kept at ambient temperature. Tubes can be sent via NHS courier systems (e.g. DX) established at the participating sites. The tubes will be processed at the relevant University

The coordinating centre will provide sample packs for sites to use. The location of these packs will be in the site file. Locally sourced tubes can also be used. If additional sample packs are required, sites should email EncephIG@Cardiff.ac.uk.

12.1 Cytogenetics and Molecular Genetics

DNA will be extracted from participant's blood samples. See Figure 2 for amounts and vials required. DNA (EDTA sample) will be stored on patients for future genetic disease association studies. These future studies will look whether genetic polymorphism within patients, particularly within a region of the DNA called the Human Leukocyte Antigen (HLA) system, are linked to different clinical outcomes.

13 Trial procedures

Follow up assessments will place take place at weeks 2, 4, 6, 8, and 10, and then at months 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12, 24, 36, and 48 post randomisation. All patients will complete the 2 weeks and 3 months follow up. The number of fortnightly assessments completed will depend on when they reach the primary endpoint and the number of monthly follow ups completed when they are recruited (see section 13.2 for time point cut-offs for assessments). Data collection be completed 3 months after the last patient is recruited.

Along with the main trial, there will be a mechanistic study looking at the role of glycosylation of the IgG Fc region. Samples will be taken at baseline and 2 weeks and then compared to samples from healthy volunteers who have undergone a lumbar puncture for non-inflammatory conditions. The CSF samples from healthy volunteers will be requested from the Walton Research CSF biobank. The biobank is managed by the Walton Centre NHS Foundation Trust, has full ethical approval from Wales REC4 and all samples are kept under the Human Tissue Authority License. The biobank request will be made independent of this trial and protocol. Full details of the mechanistic study can be found in section 19.

13.1 Assessments

Screening:

During the screening, participants will undergo a clinical assessment, MRI or CT scan using local site standard scanning protocols, lumbar puncture, and blood samples as part of the standard diagnostic procedures to determine if the patient has suspected autoimmune encephalitis and if they meet all the inclusion criteria and none of the exclusion criteria. If patients are eligible they are consented, randomised and treatment will be started within 5 days.

2 week follow up:

Clinical assessment will be repeated at 2 weeks (±2 days), post randomisation. Blood samples will be repeated at 2 weeks. Section 12 for details on blood samples.

Clinical assessment:

- Adverse events
- HDU/ITU admission
- Seizure incidences
- Use of ventilator support
- Time to hospital discharge
- Use of further treatment
- Clinically defined relapse
- Mortality

GOSE assessments will occur fortnightly (± 2 days) for the first 3 months post randomisation, and then monthly (± 7 days) up to 12 months post randomisation. Once a participant has scored a 5 or greater on the GOSE for two assessments in a row participants will be considered as having reached the primary end point and the regular GOSE assessments will stop. All participants will still complete the GOSE at 3 months post randomisation even if they have achieved recovery. The GOSE will be completed at 12, 24, 36, and 48 months post randomisation for those participants who reach those time points.

Patients will have the option of completing the GOSE online, or via the telephone. Telephone help can be provided to those completing it online if necessary. Automated alerts will be set up to help patients complete the GOSE in the right time window, and to inform the study team if this appears not to be happening. If patients are still in hospital during GOSE assessments the study team and/or study partner will assist the patient to complete the assessment at the bedside, taking into account the assessments of allied health professionals such as occupational therapy and physiotherapy where necessary. Once patients are discharged from hospital, they and their study partner will receive a reminder on the day before the GOSE follow up window starts and a reminder on the first day of the

follow up window, that the GOSE should be completed. If the GOSE is not completed on the correct day, the trial team will receive a notification and they will attempt to contact the participant by phone for 4 days (for fortnightly assessments) or 6 days (for monthly assessments), or until the assessment is completed.

3 Months:

Clinical assessment, the GOSE, and blood samples will all be repeated at 3 months (±7 days). Participants will also be asked to complete the EQ5D5L and the EBIQ.

12 Months:

Clinical assessment, the GOSE, EQ5D5L, and the EBIQ will all be repeated at 12 months (±7 days). Patients will also complete a battery of functional assessments, and neuropsychological and cognitive tests. The Neuropsychological and cognitive tests will be administered by an appropriately trained and supervised psychologist. In some sites this will be by the local clinical neuropsychology team but the central trial team will have a roving assistant psychologist who will be able to administer the relevant tests at sites where it is not possible for the local team to administer them.

Functional Outcome Assessments:

- **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.
- **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.
- **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.

Neuropsychology and Cognitive Testing:

- **Addenbrooke's Cognitive Examination III**: measures cognitive impairment
- **Wechsler Memory Scale version IV**: measures different aspects of memory functions in adults. Assessment will include auditory memory index, Visual memory index, immediate memory index, and delayed memory index.
- **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.

- **Confrontational Naming Task**: task taken from the language module of the Neuropsychology Assessment Battery. Assesses wording finding ability.
- **Trail Making Test Parts A and B**: Used to assess higher executive function
- **Test of Premorbid Functioning**: Assesses an individual's cognitive and memory functioning prior to onset of condition.
- **Beck Depression Inventory**: Self report measure of the severity of a patient's depression
- **Beck Anxiety Inventory:** Self report measure of the severity of a patient's anxiety
- **Perceived Deficits Questionnaire:** a self-report questionnaire measuring the perception of cognitive dysfunction.

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		

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	
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		

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**
Beck Depression Inventory								X		
Beck Anxiety Inventory								X		
Perceived Deficits Questionnaire								X		

13.2 Follow-up

Data collection will continue for all patients until 3 months after the last patient is recruited. The primary outcome measure will be collected fortnightly for the first 3 months for all participants, and then monthly until 12 months post-randomisation for a subset of participants, unless participant reaches primary endpoint. A subset of participants will also complete the GOSE annually until the end of the trial. Clinical follow up assessments and assessments of self-rated health will be completed at 3 month for all participants, and then at 12 months and annually for a subset of participants. Participants recruited after month 45 of recruitment, will complete all assessments up to and including the 3 month assessment. Patients recruited up until month 44 of recruitment will complete all assessments up to and including the 12 month assessment, patients recruited up until month 32 of recruitment will complete all assessments up to and including the 24 month assessment. Patients recruited up until month 20 of recruitment will complete all assessments up to and including the 36 month assessment. Those patients recruited up to month 8 of recruitment will complete all assessments up to and including the 48 month assessment. A detailed schedule of the assessments can be found in figure 3 in section 13.1.

For the fortnightly assessments, the follow up window is ±2 days. Participants will be notified 1 day before the follow up window starts and then again on the first day of the follow up window. If the participant does not complete the assessment on the first day, they will be contacted every day until they complete the assessment or the follow up window closes. For the monthly assessment, the follow up window is ±7 days. The same procedure will be used, except if participant doesn't complete the assessment on day 1 of the follow up window, they will be contacted every other day until the window closes. Any assessments that require in person attendance must be scheduled within the appropriate follow up window. Participants will be contacted at each assessment time point regardless of whether they completed the previous assessment point unless they withdraw their consent to take part in that section of the trial or the trial as a whole.

14 Internal pilot and recruitment rates

We have included Stop/Go decision points based on initiating the study at 10 months, and recruitment progress. Recruitment progress will be 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 takes to recruit the first 50 patients for the internal pilot. We will use 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 are RED then this would indicate that the project would automatically stop.

14.1 Internal Pilot

Figure 4 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%

The statistical analysis of the internal pilot data from the placebo arm will be conducted and reported during the closed session of the IDMC by a statistician not otherwise involved in the trial. The internal pilot will look at retention, adherence, and contamination (see figure 4 for definition). Internal pilot findings which do not present outcomes by trial arm will be presented to the TMG and TSC but otherwise communication regarding other internal pilot outcomes will be provided via recommendations from the IDMC to the TSC.

14.2 Recruitment rates

A total of 356 participants will be recruited at an expected rate of 2.5 participants per site per year. Recruitment rates will be monitored via several stop/go decision time points outlined in section 14.1 and review by the TMG, IDMC, and TSC at each meeting. The internal pilot will comprise of the first 50 patients recruited.

15 Pharmacovigilance

The Principal Investigator is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR PV and Safety Specialist unless the SAE is specified as not requiring immediate reporting (see section 15.3). This includes SAEs related to IMPs and non-Investigational Medicinal Products (nIMPs).

15.2 Definitions

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.

15.3 Trial Specific SAE Reporting requirements

In addition to the SAE reporting requirements above, for the purposes of this trial the following events will also be considered SAEs and must be captured on the SAE form and reported to the CTR with 24 hours of knowledge of the event:

- Opportunistic Infections (all grades)
- Unexpected or severe neuropsychiatric events (all grades)

For the purposes of this trial the following events will not require reporting as SAEs because they are anticipated events. They must be recorded on the appropriate CRF. If causality is suspected, they must be reported in the usual SAE time frames:

- Death due to disease progression

These should be completed in the participant's notes and on the relevant toxicities CRF page and forwarded to the CTR in the normal timeframes for CRFs.

15.4 Causality

Causal relationship will be assessed for IMPs, other trial treatments (nIMPs) and procedures:

IMPs: IVIG **nIMPs:** methylprednisolone, Oral prednisolone

The Principal Investigator (or another delegated medically qualified doctor from the trial team) and Chief Investigator (or another medically qualified doctor from the Trial Management Group) will assess each SAE to determine the causal relationship based on the assumption that the participant received the IMP:

Relationship	Description	Reasonable possibility that the SAE may have been caused by the IMP?
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

15.5 Expectedness

The Chief Investigator (or another delegated appropriately qualified individual) will assess each SAR to perform the assessment of expectedness.

The expectedness assessment should be made with reference to the current Reference Safety Information (RSI) for each IMP. Expectedness decisions must be based purely on the content of the

RSI; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease.

SARs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. For example, an event more specific or more severe than that described in the RSI is considered unexpected.

The table below lists the RSIs that should be referenced.

IMP	RSI to be used for expectedness assessment	Relevant section to be used for expectedness assessment
Gamunex	Summary of Product Characteristics 10g/100ml vials	Section 4.8

Reference Safety Information (RSI) on any CTR trial will be reviewed regularly according to CTR procedures.

15.6 Reporting procedures

15.6.1 Participating Site Responsibilities

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, date of birth and initials. The participant's name should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, CTR may request additional information relating to any SAEs/SARs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

CTR-Safety@Cardiff.ac.uk

SAE Fax number:

0203 0432 376

Serious adverse events should be reported from time of signature of informed consent, throughout the treatment period up to, and including 3 months post randomisation. Serious adverse reactions (such as long term side effects of trial treatment under investigation) should continue to be reported until the end of follow up.

Adverse events (AE) should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The toxicity grades should be recorded on the toxicity part of the CRF.

An SAE form is not considered as complete unless the following details are provided:

- Full participant trial number, and either Initials or DOB
- An Adverse Event / Adverse Reaction
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log).

If any of these details are missing, the site will be contacted and the information must be provided by the site to the CTR within 24 hours.

All other AEs should be reported on the CRF following the CRF procedure described in Section 18.1

15.6.2 The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow-up information must be provided on a new SAE form.

The CTR should continue reporting SAEs until 3 months post randomisation. Serious adverse reactions should continue to be reported until the end of follow-up.

Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator (or their delegate) for an assessment of expectedness.

Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs are reported to the MHRA, and Main Ethics Committee.

15.7 SUSAR reporting

University of Liverpool is undertaking the duties of trial Sponsor and has delegated to the CTR the responsibility for reporting SUSARs and other SARs to the regulatory authorities (MHRA and relevant ethics committees):

SUSARs which are fatal or life-threatening must be reported to the MHRA and REC within 7 calendar days of receipt at the CTR. If report is incomplete then additional follow-up information should be reported within a further 8 calendar days of submitting the initial report.

SUSARs that are not fatal or life-threatening must be reported to the MHRA and REC within 15 days of receipt at the CTR. Any additional, relevant information must be reported within a further 15 days.

N.B. There is no requirement for the CTR to report SUSARs to nIMPs to the MHRA except in the following instances:

- If the adverse reaction is suspected to be linked to an interaction between a nIMP and IMP, and is serious and unexpected, CTR should report as a SUSAR due to the interaction with the IMP.
- If a SUSAR is suspected and might be linked to either a nIMP or an IMP and cannot be attributed to only one of these.
- If the adverse reaction due to the nIMP is likely to affect the safety of trial subjects then CTR should report it to the MHRA and REC in accordance with the relevant Standard Operating Procedure for reporting Urgent Safety Measures.

15.8 Unblinding for the purposes of SUSAR reporting

To enable processing of a SAR in this blinded trial, expectedness should be assessed initially using the assumption that the IMP has been given to the trial participant.

If it is assessed as unexpected as per the RSI of the IMP, the SUSAR will be unblinded by the CTR safety group prior to reporting to the MHRA and REC.

If after unblinding, it is evident that the trial participant received the placebo, this event will not require expedited reporting to the MHRA and REC, unless in the opinion of the Principal Investigator or Chief Investigator the event was related to the placebo (for example an allergic reaction to an excipient).

15.9 Safety Reports

A list of all SARs (expected and unexpected) will be reported annually to the MHRA, REC, and trial sponsor in the form of a Development Safety Update Report (DSUR). This report must be submitted within 60 days of the anniversary of the MHRA CTA approval date.

The CTR will report a list of all SARs (expected and unexpected) and any other safety recommendations to all PIs once a year throughout the course of the trial. This frequency may be reviewed and amended as necessary. The reporting frequency and changes will be fully document in the Enceph-IG risk assessment. This reporting will be done via the Investigator safety report (ISR).

15.10 Pregnancy

15.10.1 Pregnancy reporting whilst participating in the trial

Pregnancy, or the pregnancy of a partner occurring whilst participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in a trial, either in a female participant or the female partner of a male participant, this should be followed up until at least the end of pregnancy, whether that is a live birth, abortion etc. Without follow-up of the pregnancy, it would not be possible for the CTR to know if a congenital anomaly or birth defect occurred, and therefore if there was an SAE that must be included in the safety evaluation of the IMP. Information on a pregnancy in a trial participant will be captured on the CTR Pregnancy Report Form supplied to sites by the CTR.

Sites should report pregnancy occurring within SAE reporting periods stipulated in the trial protocol (for example, some trial protocols may state that SAEs should be reported during the trial treatment period and up to 30 days after the last date of treatment, this timeline would also apply to the reporting of pregnancies). Congenital anomalies or birth defects are considered an SAE and so these events must also be reported to the CTR on a trial-specific SAE form. Congenital anomalies or birth defects related to the IMP and unexpected with respect to the IMP Reference Safety Information (RSI) must be submitted by the CTR within expedited SUSAR time frames (7 or 15 days) to the MHRA, relevant REC and the drug manufacturer of the IMP (to comply with any contractual agreement).

15.11 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator or Principal Investigator may carry out in order to protect the subjects of a study against any immediate hazard to their health or safety. Any urgent safety measure relating to this study must be notified to the Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

16 Statistical considerations

16.1 Randomisation

Patients will be randomised 1:1 to IVIG or placebo using random permuted blocks stratified by site, and time from symptom onset. The final randomisation lists, which will contain investigational medicinal product identifications and corresponding allocations (IVIG / placebo), will be generated by a statistician otherwise not involved in the trial and will be supplied to the manufacturing and site pharmacy for appropriate labelling, as well as the CTR safety team. Randomisation will take place online using Vanilla, a system created by the CTR. It will be available 24 hours a day. On randomisation, a participant will be 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.

16.2 Blinding

This will be a multicentre double-blind two-arm placebo-controlled randomised trial of IVIG in adults with autoimmune encephalitis. Patients, family, health care workers and study team will be blinded to protect against performance and ascertainment bias. There will be no planned unblinding while the trial is ongoing.

Blinding information (i.e. codes corresponding to IVIG/placebo allocations) will be held by:

- Manufacturing Pharmacy Unit
- The Pharmacovigilance team at the Centre for Trials Research, Cardiff University;
- A study-independent statistician at the Centre for Trials Research, Cardiff University.

Final unblinding prior to statistical analysis

The statistician responsible for conducting the final statistical analysis will be unblinded following database lock, data cleaning, and derivation of variables required to perform analysis has taken place.

Unblinding for analysis to be reported at IDMC meetings

Statistical analyses for IDMCs which require reporting of data by trial arm or for one arm only (e.g. as proposed for the internal pilot) will be prepared by a study-independent statistician.

Emergency unblinding

Unblinding will only occur in situations in which it is critical for the clinical management of the patient. In the cases of an SAE, the reporting clinician should treat the participant as if they had received the IMP. In the event of a SUSAR, the CTR safety team will be able to break the blind.

Site PI or appropriately delegated individual (listed in delegation log) is responsible for making decisions regarding emergency unblinding.

The following procedure should be followed in all instances of unblinding:

1. A web-based unblinding system will be made available to the local investigational team. Access will be controlled using a unique username and password.
2. An authorised member of the investigational team will log on to the unblinding system. On entering the required information, including the Pack ID of the participant, the treatment allocation will be revealed. The allocation will be transmitted to the person primarily responsible for their care.
3. A delegated member of the research team will complete the Enceph-IG Unblinding CRF, to be returned to the CTR within 24 hours of the event.
4. The trial treatment allocation should not be included on the CRF and the allocation should not routinely be revealed to CTR staff.

In the event sites are not able to access the randomisation system, sites can contact their local pharmacy or, the CTR safety team (during office hours), who will arrange for unblinding to be performed by accessing the online system or using the hardcopy master randomisation list.

16.3 Sample size

We will require 356 participants in total (178 per arm). This is 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 is inflated to account for 5% drop-out. As our outcome is time-to-event based, and participation in the trial following the initial five-day treatment period revolves around providing follow-up data, we expect drop-out and missing data to be low.

As a secondary outcome, our study will be 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 is 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 will be 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 is 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 will have 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).

16.4 Missing, unused & spurious data

Our primary outcome will be analysed as a time-to-event variable, with missing observations censored at the final time at which data were available.

Further detail is provided in the ENCEPH-IG Statistical Analysis Plan (SAP).

16.5 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

16.6 Termination of the trial

Progression criteria for the internal pilot phase are described in section 14. There is potential for the study to terminate early if our funder assesses the trial as not being feasible following an assessment of progress against our targets at the end of the internal pilot with input from our TSC and IDMC.

16.7 Inclusion in analysis

This is a trial of a rare disease and is likely to be the definitive trial of IVIG in autoimmune encephalitis. While this trial was funded to determine the efficacy of early IVIG on recovery in patients with autoimmune encephalitis, there are several factors which may limit the ability to do so:

- A pragmatic definition of autoimmune encephalitis upon trial entry;
- The ability of treating clinicians to provide therapeutics to participants which may confer similar benefits as IVIG, and treatment decisions likely to be based on evidence of clinical improvement following randomisation (i.e. the primary outcome);
- Theoretical access to therapeutic IVIG in both arms, which may be given under similar conditions to the above.

For these reasons, it is necessary to consider several analysis populations, reflecting both the explanatory and pragmatic aspects of our study design:

- Intention to treat (Effectiveness) analysis population – all randomised participants, regardless of treatments received. This is a typical definition of an intention to treat population and will be used to assess the effectiveness of the treatment strategy of early IVIG.
- Efficacy analysis population – participants who receive the treatment to which they were allocated. This reflects a typical definition of a per-protocol population. This will be used to assess the efficacy of early IVIG.

17 Analysis

17.1 Main analysis

The primary analysis will be based on the intention to treat analysis population and will use Cox regression to estimate the difference in time from randomisation to recovery (defined as two consecutive GOSE scores ≥5 according to the assessment schedule defined in Section 5.3) between the IVIG and placebo arms. A two-level frailty model will be used to account for any clustering of participants within sites. Results will be reported as hazard ratios, with associated 95% confidence intervals and p-values. Considering the efficacy analysis population, we will estimate the efficacy of early IVIG on time

to recovery using inverse probability-of-censoring weighting methods (Dodd, Williamson, & White, 2017). This will account for instances of treatment switching and the use of further immunotherapy (IVIG, steroids plasma exchange, or other), while importantly maintaining a comparison of groups as randomised. Our weights will consider both baseline and time-varying covariates that predict treatment changes. 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. We will therefore ensure that sufficient data are collected to capture these decisions.

Secondary outcomes will be analysed by fitting a two-level regression model accounting for participants within sites (linear, logistic, Poisson, or Cox proportional hazards model), as appropriate. For both our effectiveness and efficacy populations, we will consider the impact of missing data on the conclusions drawn on our analyses. Plausible missing data mechanisms will be considered, and approaches allowing us to arrive at treatment effect estimates which are valid under Missing At Random (e.g. multiple imputation) and Missing Not At Random (e.g. selection or pattern mixture models) will be considered as sensitivity analyses.

A fully detailed statistical analysis plan will be written and signed-off prior to database lock. All data manipulation prior to analysis will be undertaken by the main trial statistician, who will remain blind to treatment arm until the point of analysis. The study results will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement.

17.1.1 Sub-group analysis

Subgroup analyses will explore differential intervention effects on the primary outcome by age, disease severity on admission, and antibody status. The statistical model used for the primary analysis will be extended to include the subgroup and a trial arm x subgroup interaction term.

18 Data Management

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents."* There is only one set of source data at any time for any data element, as defined in site source data agreement.

The source data for ENCEPH-IG trial will be from a variety of sources (see figure 5). Data will be collected using an electronic system (eCRF system) with paper CRF back up. There will also be data collected from participants' medical notes and patient reported questionnaires. Training for completion of study CRFs will be provided to the appropriate trial staff prior to trial commencement at site initiation.

Figure 5 Source Data

Trial data	*Source Data*					
	CRF	*Participant medical notes*	*Electronic System*	*Pharmacy File*	*Questionnaire*	*SAE form*
Medical History		X				
Concomitant Medications		X				
Adverse events			X			x
Demographics			X			
Physical examination		X				
Vital signs		X				
Eligibility assessment			X			
MRI/ CT Scan		X				
Compliance			X			
Glasgow Outcome Scale Extended			X			
Use of further immunotherapy		X				
Clinical assessment		X				
EuroQoL Five Dimension Scale			X			
European Brain Injury Questionnaire			X			
Modified Rankin Scale			X			
Liverpool Outcome Score			X			
Barthel Index			X			
Addenbrooke's Cognitive Examination III					X	

Trial data	*Source Data*					
	CRF	*Participant medical notes*	*Electronic System*	*Pharmacy File*	*Questionnaire*	*SAE form*
Verbal Memory Test					*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						
Physician's Withdrawal Checklist			*X*			

18.1 Completion of CRFs

All assessments and data collection will be completed using web-based CRFs, except for the SAE from and several of the neuropsychological assessments. This is a secure encrypted system accessed by username and password and complies with General Data Protection Regulation 2016. In the event that the web-based system is not accessible, paper CRFs will be used to record data. The data will then be inputted by local site staff into the web-based system once it is accessible. A full Data Management Plan will accompany this protocol and will be stored in the TMF.

18.1.1 Electronic CRFs

It is intended to develop data recording for this trial as a web-based system. This is a secure encrypted system and complies with the General Data Protection Regulation 2016 standards. The system can accessed by an institutional password supplied to investigators upon completion of all processes

required prior to opening. Participants and study partners will be sent a unique link to be able to complete the GOSE safely and securely online. All electronic CRFs will be developed and tested in accordance with the relevant Centre for Trials Research SOPs. Electronic CRFs will contain validations and checks to maintain data quality.

18.1.2 Paper CRFs

A select number of forms, including the SAE form and those administered as part of battery of the neuropsychology and cognitive tests, will be completed on paper first and the finalised scores entered into the electronic database.

For all other forms, if the electronic database is not available, paper CRFs will be used and data will be entered on to the database at a later point (within a week) by local site staff. In accordance with the principles of GCP, the PI is responsible for ensuring accuracy, completeness, legibility and timeliness of the data reported to the CTR in the CRFs.

If missing or questionable data are identified, a data query will be raised on a data clarification form. The data clarification form will be sent to the relevant site. The site shall be requested to respond to the data query on the data clarification form. The CRF pages should not be altered. All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant site. The completed data clarification form should be returned to the CTR and a copy retained at the site along with the participant's CRFs.

The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner. Further details of data management procedures will be specified in the Data Management Plan.

19 Exploratory sub-studies

The mechanisms of action of IVIG are incompletely understood.

Glycosylation of host immunoglobulin (IgG Fc region) is thought to play a critical role. Through targeted experiments, we will examine the host response in autoimmune encephalitis, and test two hypotheses to explain IVIG's therapeutic effects.

1. We hypothesise that patients with autoimmune encephalitis have aberrant IgG Fc glycosylation, and that IVIG modulates this (Czajkowsky et al., 2015).

2. As a result of the above, we hypothesise that IVIG will reduce levels of anti-neuronal antibodies, as well as down-regulating pro-inflammatory host pathways, and that this will correlate with clinical improvement.

IgG Fc glycosylation (serum and CSF) will be measured at baseline and 3 months among participants. We will examine whether glycosylation differs among participants treated with IVIG compared to placebo (adjusted for baseline glycosylation). We will also examine whether glycosylation titres relate to the presence of anti-neuronal antibodies , host inflammatory markers (measured at baseline) or clinical outcome.

19.1 Laboratory methods

IgG Fc glycosylation (sialylation and agalactosylation) will be measured with an immunoassay technique using lectins (a class of proteins, mostly from plants, which bind to specific sugars) (Wong et al., 2016). In order to investigate glycosylation patterns in more detail we will a subset of IVIG treated patients with the greatest change in glycosylation profile (n=10) and analyse samples by ultra-high performance liquid chromatography-mass spectrometry, as we have done previously, to give a more detailed picture of IgG Fc structure and shed light on potential interactions with the Fc gamma receptor (Pleass will lead these studies) (Blundell, Le, Allen, Watanabe, & Pleass, 2017).

Inflammatory responses will be measured across a range of host mediators, including cytokines, transcripts and proteins. Cytokine analysis (via bead array) is already established in Liverpool (Michael, Griffiths, Granerod, Brown, Davies, et al., 2016; Michael, Griffiths, Granerod, Brown, Keir, et al., 2016). In addition, by measuring blood mRNA (via sequencing or targeted PCR) we will look for other host mediators that distinguish IVIG responders from non-responders, which will allow us to stratify treatment in the future, building on our earlier host transcriptomic studies (Griffiths et al., 2005; Hemingway et al., 2017). We have recently shown for another inflammatory brain condition (meningitis) that as few as four host genes may be used to distinguish those who respond to treatment (antibiotics) from those who do not (patent No. GB1606537.7 filed 14th April 2016; lead, Griffiths). Biomarkers of brain damage (such as neuro-filaments (NFL), Tau protein and S100B) will be measured in CSF (and serum) via ELISA in Liverpool and/or UCL. Novel auto-immune antibodies will be searched for using techniques established in the Irani group at Oxford. CSF will also be saved for exploratory proteomic studies, to be funded separately (Irani et al., 2010; Irani, Fukushima, Yazaki, & Vincent, 2007; Michael, Griffiths, Granerod, Brown, Davies, et al., 2016).

19.2 Mechanistic studies sample size

In a recent study of the effect of IVIG on sialylation of IgG Fc in chronic inflammatory demyelinating polyneuropathy (Wong et al., 2016), IVIG treatment resulted in a 68% increase in IgG Fc sialylation. Including samples from 228 randomised patients will provide 90% power with a two-sided 5% alpha to detect an absolute mean difference of approximately 5.7 x10^3 mm^2 Optic Density on western blot (assuming a mean glycosylation of 22 x10^3 mm^2 Optic Density Units in the placebo arm, a common standard deviation of 13.3, and 20% of participants not providing samples at 3-months). This translates into a 26% relative difference. Assuming 30% of these participants will be antibody positive (i.e. n = 68), we will have 90% power with a two-sided 5% alpha to detect an absolute mean difference of approximately 10.6 units within this sub-group, which translates into a 48% relative difference. We would look to further increase power by including baseline glycosylation as a covariate in the analyses. These sample sizes and analytical approaches would also allow further exploration within sub-groups (e.g. anti-neuronal antibody titres and inflammatory markers).

19.3 Statistical analysis of mechanistic studies

We will use independent samples t-tests to compare mean glycosylation at study entry between patients with autoimmune encephalitis and controls. We will repeat this analysis comparing patients that are antibody positive against controls.

Our main statistical analysis will compare mean glycosylation levels at 3-months between trial arms using analysis of covariance, with baseline glycosylation levels included as a covariate. Extending this analysis, we will consider subgroup analyses by antibody status, antibody titres, and inflammatory markers to understand the moderating effects of these variables.

We will explore the extent to which the effect of IVIG on clinical outcome at 12 months is mediated through glycosylation at 3 months. We will pre-specify in full our hypothesised pathways following discussion among the research team (including clinicians, basic scientists, statisticians, and patient-representatives). These pathways will be illustrated using a Directed Acyclic Graph. Using the g-computation formula, we will estimate causal effects with mediation (including the controlled direct effect, natural direct/indirect effects, and total effect)(Daniel, De Stavola, & Cousens, 2011).

20 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice (GCP) to the CTR in writing as soon as they become aware of it.

The CTR will assess the nature and severity of any issues of non-compliance in accordance with their SOPs.

Minor changes in steroid dosing schedule due to patients' tolerance will not constitute a protocol non-compliance but should be recorded on the appropriate CRF.

21 End of Trial definition

The end of the trial is defined as the date of final data capture to meet the trial endpoints. Sponsor must notify the main REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

22 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 15 years. The CTR will send the TMF and TSFs to Sponsor for archiving. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

23 Regulatory Considerations

23.1 CTA

This trial has Clinical Trials Authorisation (CTA) from the UK Competent Authority: MHRA.

Classification of whether any changes to the protocol is defined as a substantial amendment or not will be based on HRA guidance and sponsor assessment. All amendments will be reviewed by the TMG, and if necessary sponsor rep, for approval prior to being submitted, via IRAS and email, to REC, HRA, and if necessary the MHRA. The central trial team will alert all site trial teams and R&D departments once approval has been received for the amendment. The amendment history will be listed in the protocol and in the amendment log which is filed in the TMF.

23.2 Ethical and governance approval

This protocol will be submitted to a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval. A favourable ethical opinion will be obtained from the REC before commencement of any study procedures (including recruitment of participants).

This trial protocol will be submitted through the relevant permission system for global governance review via the Health Research Authority (HRA).

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

All substantial protocol amendments must be approved by the REC responsible for the study, in addition to approval by NHS Research and Development (R&D). Minor amendments will not require prior approval by the REC.

If the study is stopped due to adverse events or an urgent safety measure it will not be recommenced without reference to the REC responsible for the study.

The outcome of the study (e.g. completed) will be reported to the REC responsible for the study within 90 calendar days of study closure. In the event of the study being prematurely terminated a report will be submitted to the REC responsible for the study within 15 calendar days.

A summary of the results will be submitted to the REC responsible for the study within one year of completion of study closure.

23.3 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2016/679. The data custodian for this trial is the Chief Investigator at Liverpool University (sponsor). There will be a joint data controller responsibility shared between Liverpool University (sponsor) and the CTR. The translational sample custodian for this trial is the University of Liverpool.

Participants will always be identified using their unique study identification number and any additional identifiers. This includes collection of NHS number (or equivalent – e.g. CHI number in Scotland), name and postcode to register and trace participants with NHS Digital. Any identifiable details will be stored separately to the clinical data. All data will be stored in the trial specific database detailed in section 18. The database will be held and maintained on secure servers hosted by Cardiff University. Access to the database is password protected and only granted to those relevant trial personal listed on the delegation log and appropriately trained. All paper CRFs will be held securely at site in locked cabinets and separately from any study documentation containing identifiable information.

23.4 Indemnity

ENCEPH-IG is sponsored by The University of Liverpool and will be co-ordinated by the CTR at Cardiff University. The Sponsor does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability: NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven. The Sponsor does not accept liability for any breach in any other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not.

> **Clinical negligence is defined as:**
> "*A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process*".

The Sponsor has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of a clinical trial, including but not limited to the authorship of the Clinical Trial Protocol. The University of Liverpool has appropriate insurance in place to cover this liability.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

23.5 Trial sponsorship

University of Liverpool will act as Sponsor for the study. Delegated responsibilities will be assigned to the sites taking part in this study.

The Sponsor shall be responsible for ensuring that the study is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments.
- Conditions and principles of GCP.
- Declaration of Helsinki (1996)
- Research Governance Framework for Health and Social Care (Welsh Assembly Government 2009 and Department of Health 2nd July 2005).
- The General Data Protection Regulation (EU2016/679).
- The Human Tissue Act 2004.
- Other regulatory requirements as appropriate.

The Sponsor has delegated certain responsibilities to CTR, the CI, PIs, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and study type.

23.6 Funding

This project was funded by the NIHR EME Programme (project number 17/60/67) and will be published in full by the NIHR. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the EME programme, NIHR, NHS or the Department of Health. The study will be adopted on the NIHR portfolio.

24 Trial management

24.1 Project Team

The Project Team (PT) will meet fortnightly and will include the Chief Investigators, Trial Manager, Data Manager, Statistician, Administrator and other research staff directly employed to the trial. The project team will discuss all day-to-day management issues and will refer any key management decisions to the Trial Management Group (TMG).

24.2 TMG (Trial Management Group)

The TMG will typically meet monthly by teleconference and if possible will meet face-to-face quarterly, during the initial phases of set and recruitment. As the trial progresses this may be adjusted based on recruitment success and the stop/go decision criteria. It will include the Chief Investigators (CIs), all other co-applicants, and the central project team. The TMG will provide specialist advice, develop study procedures/documents and advise on the conduct of the study. The Trial Manager will be responsible for trial conduct and will be accountable to the CI. Regional research staff supervised

by the site Principal Investigator (PI) will be responsible for recruitment, assessments and data collection. Data will be securely stored locally and entered on a secure electronic recording system compliant with data management procedures. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

24.3 TSC (Trial Steering Committee)

A TSC will be established with an independent chair and at least two other independent members including PPI representatives and an independent statistician. The TSC will meet prior to trial commencement to review the protocol, roles, responsibilities, and timelines for meetings and agree the remit and conditions set out in the TSC Charter.

TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

24.4 IDMC (Independent Data Monitoring Committee)

An IDMC will be established with an independent chair and at least two other independent members. The main role of the IDMC is to review the data relating to trial progress (recruitment and retention, GOSE completion rates, additional treatment within 14-day window, rate of treatment starting within 5 days of randomisation), and trial safety (SAE rates, and unblinding log) at each meeting, and make recommendations to the TSC. The IDMC will also review the results of the pilot analysis (see section 14). Timelines for meetings will be outlined in the IDMC Charter. IDMC members will be required to sign up to the remit and conditions as set out in the IDMC Charter which will be filed in the TMF.

25 Quality Control and Assurance

25.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the ENCEPH-IG trial. Medium monitoring levels will be employed and are fully documented in the trial monitoring plan. Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

25.2 Audits & inspections

The trial is participant to inspection by the MHRA as the regulatory body for CTIMP trials and the HTA as the regulatory body for the use of human tissue.

The trial is participant to inspection by the NIHR EME programme as the funding organisation. The study may also be participant to inspection and audit by University of Liverpool under their remit as Sponsor.

The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC/ IRB review, and regulatory inspection(s), providing direct access to source data / documents.

The site must inform the CTR of any MHRA inspections.
The study may be audited by NHS Digital Audit Team.

26 Publication policy

All publications and presentations relating to the study will be authorised by the TMG and will be in accordance with the trial's publication policy. In addition to the required final report and monograph for the NIHR EME Programme, we will publish the main study results in international peer-reviewed journals and present at national and international scientific meetings. With the assistance of our collaborators and lay representatives we will disseminate the trial findings to a wide NHS and general audience and vigorously promote uptake of the trial results into clinical care. Any outputs that include data collected through NHS digital or equivalent data provider will include an acknowledgement of the role of the data provider.

The aim will be for the results to be revealed initially at the annual Encephalitis Conference, organised by the Encephalitis Society. The results of the study will then be used to inform national and international guidelines on the management of encephalitis. The Liverpool team led the development of the UK national encephalitis guidelines (Solomon et al., 2012), and is currently leading the production of European Guidelines, on behalf of the European Academy of Neurology and the European Society of Clinical Microbiology and Infectious Diseases to be published in 2020. We expect the results of the Enceph-IG study to be available towards the end of 2025 in time for the revision of these guidelines.

The mechanistic work will give us a better understanding of the postulated abnormalities in IgG Fc glycosylation, and how IVIG modulates this. In combination with the host response work, this might not only allow us to predict who will have the best response to IVIG treatment, it may also point the way to new more specific treatments in the future.

27 Milestones

The trial will have 5 stop/Go decision time points. The first will be after 10 months and the subsequent stop/Go time points are at 6, 12, 18, and 24 months of recruitment. All criteria for stop/go decisions are outline in section 14.

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