



A phase III multi-centre randomised, double blind, placebo controlled trial to assess the role of intravenous immunoglobulin in the management of children with encephalitis (The IgNiTE study)

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Investigator Agreement

"I have read this protocol and agree to abide by all provisions set forth therein. I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice."

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust(s), regulatory authorities, and members of the Research Ethics Committee, unless authorised to do so. The Chief Investigator and all co-investigators involved in the study declare no conflicts of interest.

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1 KEY TRIAL CONTACTS

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2 SYNOPSIS

Study Title	A phase III multi-centre randomised, double blind, placebo controlled trial to assess the role of intravenous immunoglobulin in the management of children with encephalitis	
Short Title	ImmunoglobuliN in the Treatment of Encephalitis (The IgNiTE study)	
Internal ref. no. / short title	OVG 2014/05	
Study Design	Multicentre randomised double blind, placebo controlled, parallel arm clinical trial.	
Study Participants	Children between 6 weeks and 16 years (before 17th birthday) with encephalitis.	
Planned Sample Size	308	
Planned Study Period	60 months (42 month recruitment + 12 months follow up + 6 months for data analysis)	
	Objectives	Endpoints
Primary	To compare neurological outcomes between children with encephalitis who have been treated with IVIG and those who have received matching placebo	"Good recovery", defined by GOS-E-Peds score 2 or lower at 12 months post randomisation
Secondary	(a)To compare the following between children with encephalitis who have been treated with IVIG with those who have received matching placebo: (i) **Clinical and neurological outcomes**	**During hospital inpatient stay:** (i) Glasgow coma score (ii) Neurological examination findings as documented by the clinical team (iii) Duration of invasive ventilation (if ventilated) (iv) Length of intensive care unit (ICU) stay in a subset of children admitted to ICU. (v) Length of hospitalisation

		Around 4-6 weeks after discharge from acute care (i) Strength and Difficulties Questionnaire (SDQ) ii) Adaptive Behaviours Assessment System-Second Edition (ABAS-II) (iii) Peds Quality of Life scoring algorithm (iv) Liverpool Outcome Score (v) Gross Motor Function Classification System (GMFCS) **Around 6 months (+/- 4 weeks) post randomisation** GOSE-Peds **Around 12 months (+/- 4 weeks) post randomisation)** (i) New diagnosis of epilepsy since discharge from hospital (ii) Use of anti-epileptic treatment since discharge from hospital. (iii) GOSE-Peds (iv) Strength and Difficulties Questionnaire (SDQ) (v) Adaptive Behaviours Assessment System-Second Edition (ABAS-II) (vi) Peds Quality of Life scoring algorithm (vii) Liverpool Outcome Score (viii) Gross Motor Function Classification System (GMFCS) (ix) Blinded neuropsychologist assessment of cognitive functioning depending on age using : Bayley Scales for Infant Development (BSID-III) or

		Wechsler preschool and Primary Scale of Intelligence III or Wechsler Intelligence Scale for Children IV **At any point during the study** (x) Collect information on deaths occurring up to 12 months post randomisation
	(ii) Radiological outcomes	(i) Brain MRI at around 6 months post randomisation to assess the following: (i) lesion resolution (ii) presence of new lesions (iii) distribution of persisting disease
	(b)To confirm the safety of IVIG treatment for children with encephalitis	(i) Collection of adverse events of special interest in the first five days from each dose of study drug (ii) Collection of serious adverse events from receipt of first dose of study drug up to 6 months post randomisation (iii) Full blood count check 24-48 hours after the second IMP dose to monitor for possible haemolysis with IVIG treatment
	(c)To identify a proportion of children with immune mediated encephalitis	Presence and levels of specific auto-antibodies in serum and/or CSF samples obtained before and after study treatment
	(d)To determine the effect of IVIG treatment on auto-antibody levels in children with immune mediated	Comparison of auto-antibody levels in blood and/or CSF (where lumbar puncture is performed as part of routine care) before and after administration of

	encephalitis	study treatment.
Exploratory Objectives	(a)To explore clinically relevant neuroimaging predictors. (b)To explore predictors of neurological outcomes in children with encephalitis (c) To explore radiological patterns associated with different types of encephalitis (d) To understand the host inflammatory pathways in encephalitis and the relationship with clinical parameters and the effect of IVIG treatment on these pathways	Correlate MRI findings with the primary and secondary outcomes Correlate clinical and laboratory parameters with neurological outcomes Compare brain MRI findings with aetiological diagnosis (i) Comparison of inflammatory cytokines in both groups before and after study treatment (ii) Assessment of regulatory T cell frequency and function in blood and/or CSF before and after study treatment (iii) Measurement of inflammatory markers in blood and/or CSF between participants before and after study treatment (iv)Analysis of gene expression in whole blood before and after study treatment (v) Identification of specific DNA sequence and structural genetic variants in patients with encephalitis (vi)Comparison of the host inflammatory pathways between both study groups before and after study treatment (vii)Correlation of host inflammatory responses with clinical parameters

3 ABBREVIATIONS

ABAS-II	Adaptive Behaviours Assessment System-Second Edition
ADEM	Acute Demyelinating Encephalomyelitis
AE	Adverse event
AESI	Adverse event of special interest
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPU	Aseptic Manufacturing Pharmacy Unit
ANCOVA	Analysis of Covariance
AR	Adverse reaction
BSID-III	Bayley Scales of Infant Development
cGMP	Current Good Manufacturing Practice
CI	Chief Investigator
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CRA	Clinical Research Associate (Monitor)
CRP	C-Reactive Protein
CRF	Case Report Form
CRO	Contract Research Organisation
CSF	Cerebrospinal fluid
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
CVID	Common Variable Immunodeficiency
DSMC	Data and Safety Monitoring Committee
DSUR	Development Safety Update Report
EBV	Epstein Barr Virus
EMA	European Medicines Agency
ESR	Erythrocyte Sedimentation Rate
GABA	Gamma-Aminobutyric acid
GCS	Glasgow coma score
GCP	Good Clinical Practice

GFR	Glomerular filtration rate
GlyR	Glycine receptor
GMFCS	Gross Motor Function Classification System
GOS-E	Glasgow Outcome Scale-Extended
GP	General Practitioner
HHV	Human Herpes Virus
HSV	Herpes Simplex Virus
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ICU	Intensive Care Unit
ID	Identification
IMP	Investigational Medicinal Product
IRB	Independent Review Board
ITP	Idiopathic thrombocytopaenia
ITT	Intention-to-treat
IVIG	Intravenous immunoglobulin
LOS	Liverpool Outcome Score
LP	Lumbar puncture
MCRN	Medicines for Children Research network
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MIA	Manufacturer's Importer's Authorisation
MRI	Magnetic Resonance Imaging
MOG	Myelin Oligodendrocyte Glycoprotein
NHS	National Health Service
NIHR	National Institute for Health Research
NMDAR	N-methyl-D-aspartate receptor
NRES	National Research Ethics Service
OXTREC	Oxford Tropical Research Ethics Committee
PCR	Polymerase Chain Reaction
PCV-CTU	Primary Care and Vaccines Collaborative Clinical trials Unit
PedsQL	Paediatric Quality of Life Inventory
PI	Principal Investigator

PICU	Paediatric intensive care unit
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
RCT	Randomised controlled trial
REC	Research Ethics Committee
RLBHT	Royal Liverpool and Broadgreen Hospital Trust
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SDQ	Strengths and Difficulties Questionnaire
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSC	Trial Steering Committee
TSG	Oxford University Hospitals Trust / University of Oxford Trials Safety Group
UCL	University College London
VZV	Varicella Zoster Virus
WBC	White Blood Count
VGKC	Voltage gated potassium channel

4 BACKGROUND AND RATIONALE

Encephalitis is a syndrome of neurological dysfunction caused by inflammation of the brain parenchyma, resulting in altered mental status, seizures, and/or focal neurologic deficits, usually accompanied by signs of inflammation in the cerebrospinal fluid and magnetic resonance imaging (MRI) findings. The worldwide annual incidence ranges from 3.5 to 7.4 per 100,000, rising to 16 per 100,000 in children (1). In the United Kingdom, Public Health England (formerly the Health Protection Agency) reports an annual rate of 1.5 cases per 100,000 in the general population and 2.8 per 100,000 in children, with the highest incidence in infants under 1 year of age of 8.7 per 100,000 (2).

Encephalitis is broadly either infectious or immune mediated. Infections have been considered to be the major cause of encephalitis and more than 100 different causative pathogens have been recognised. In the UK, herpes simplex virus (HSV) is the most commonly implicated virus (19%) with varicella zoster virus (VZV; 5%), enteroviruses (1%), Epstein Barr virus (EBV; 0.5%), measles (0.5%) and human herpesvirus 6 (HHV 6; 0.5%) being the other most commonly

identified (3). A host of other viruses, bacteria, and protozoa have been implicated, with reported epidemiological differences. However, despite exhaustive investigations, no identifiable viral aetiology is found in 60% of encephalitis cases in the UK (3).

Immune mediated encephalitis occurs when the body generates antibodies that interact with the brain cells. These antibodies can be generated as part of the host's immune response to infection (acute or past) suggesting a para-infectious or post-infectious phenomenon; or precipitated by certain tumours such as ovarian tumours (4) and neuroblastomas. Examples in this category include acute disseminated encephalomyelitis (ADEM) and N-methyl-D aspartate receptor (NMDAR) encephalitis. The immune mediated encephalitides are now recognised to contribute to a significant proportion of cases where no infective cause is identified (1). For example, auto-antibodies against central nervous system (CNS) surface proteins, particularly the (NMDAR) and the voltage-gated potassium channel (VGKC) complex and its associated proteins, were also found in 4% and 7% of encephalitis cases without an identified cause (3) and in 44% of children with probable autoimmune encephalitis (5). As a result, the proportion of children with immune mediated encephalitis may overall surpass that of individual viral aetiologies (6). In a significant proportion of children with encephalitis however, no aetiology is identified (3, 7)

4.1 Burden of encephalitis

Infectious and immune-mediated encephalitis are an important but under-recognised cause of neurological morbidity and mortality in childhood, with 7% mortality and up to 50% of survivors reporting deficits after prolonged follow up (3, 8). Long term complications such as severe physical impairment, behavioural, psychosocial and educational difficulties have been reported (9). Health, social and economic costs are also extended where families are left bereaved or with a child who has sustained disability. Examples include mental health among family members and familial breakdown.

Encephalitis imposes a substantial economic and resource burden on healthcare service. A 3 year review of encephalitis admissions to Paediatric Intensive Care Units (PICUs) in England and Wales showed a total of 353 admissions due to encephalitis, with an average length of stay of 4.3 days. 75% of admitted children required ventilation, and some additionally required cardiovascular support (17%) and renal dialysis (6.5%) (10). An American study reports approximately 19,000 hospitalisations (7.3 hospitalisations per 100,000 population) and 230,000 hospital days from encephalitis in a 10 year period, with an estimated cost from encephalitis associated hospitalisations of $28,000 leading to an annual national cost of $650 million (11).

4.2 Current treatment

In the 1980s, the antiviral drug aciclovir was shown to improve outcomes of HSV encephalitis. Intravenous aciclovir has since remained the standard treatment for the HSV and VZV encephalitis. It is also used empirically for the treatment of suspected encephalitis, while awaiting results of investigations. The use of aciclovir in the treatment of viral encephalitis has resulted in reduction in mortality from HSV encephalitis (12). However this has been associated with an increased proportion of patients with sequelae, which may range from severe neuropsychiatric illness to subtle cognitive changes.

For post infectious encephalitis corticosteroid treatment may be used whereas in patients with immune mediated encephalitis, early immunomodulatory therapy in the form of plasma exchange, IVIG and/or corticosteroids are useful in reducing auto-antibody levels and thus clinical improvement. However, given the delay in the diagnosis of immune mediated encephalitis in children, institution of the appropriate treatment is usually delayed.

4.3 Rationale for the study

Despite the current standard treatment, there is still significant mortality and morbidity from encephalitis. Strategies to reduce the disability in patients with encephalitis are therefore urgently required.

Irrespective of the underlying cause, the final common pathway in the pathophysiology of this disease is brain inflammation. The common paradigm for intervention in encephalitis with the greatest presumptive benefit centres on the early attenuation of the extensive inflammation, which is the primary cause of fatality and neurological sequelae and underpins the pathogenesis of most forms of encephalitis, especially that due to HSV (13) and enterovirus71. It is expected that the attenuation of such inflammation will eventually minimise neural injury.

Intravenous immunoglobulin (IVIG) has both anti-inflammatory and immunomodulatory properties and there is theoretical and empirical evidence of a beneficial response to IVIG for both viral and auto-immune aetiologies of childhood encephalitis. Direct evidence of efficacy of IVIG in infective encephalitides is suggested by the very successful outcomes from both its therapeutic and prophylactic use in enteroviral encephalitis in the immunocompromised and in outbreaks in the Far East (14). In these cases, IVIG therapy has been shown to reduce viral replication, attachment and binding of the virus to host cells, in addition to having an anti-inflammatory effect. There is also emerging evidence from case reports to support the use of IVIG in other infectious causes of encephalitis including infections with Japanese encephalitis virus (15), West Nile virus, Coxsackie viruses and *Mycoplasma pneumoniae*, where its use has been associated with rapid improvement and reduced morbidity. Similarly, in patients with autoimmune encephalitis, the other major cause of encephalitis, first line immunotherapy often in the form of IVIG also appears to benefit both adults and children, resulting in improved outcomes (4, 5, 16). Further evidence exists to support the benefit from IVIG in various autoimmune neurological conditions that share similar underlying inflammatory mechanisms to encephalitis (17).

In clinical practice however, the use of IVIG in encephalitis varies. In the immune mediated forms of encephalitis, IVIG is typically used after inevitable delay (by weeks in some cases) while alternative diagnoses are being excluded, or a definitive diagnosis is obtained. In other cases, IVIG is used usually as a last treatment option where clinical improvement is slow. Again, this is usually after several days from hospital admission.

This variation in practice is in most part due to a lack of class 1 evidence to support the use of IVIG in encephalitis and it is currently unknown whether wider use of IVIG in infectious encephalitis and earlier use in immune-mediated encephalitis could alter the outcome of this group of conditions. There is therefore the need to fill this evidence gap.

The delay in diagnosis and institution of appropriate treatment in encephalitis may contribute to the high rate of morbidity and mortality, prolonged hospitalisation and associated costs from encephalitis.

Given the available evidence of possible beneficial role of IVIG there is a strong case for the prospective assessment of the potential role of early intervention with IVIG for all children presenting with evidence of inflammatory encephalitis, or indeed rationalise the use of this expensive and limited resource.

This study will be the first study designed to be conducted to a high standard to evaluate the effect of IVIG in childhood encephalitis and will fill in the evidence gap on the potential benefit of IVIG in reducing disease burden in children with encephalitis. The trial also aims to generate evidence to inform clinical decision making in the National Health Service (NHS) and provide added value to the NHS by addressing healthcare, quality of life and productivity costs of this expensive and resource limited product.

4.4 Research aim

The aim of this study is to identify the role of early use of IVIG in the treatment of childhood encephalitis by comparing neurological outcomes in children with encephalitis who have been treated with IVIG with those who have received matching placebo.

4.5 Potential benefits and risks

There are no robust controlled trials for the treatment of encephalitis to inform its optimal treatment. Therefore, the beneficial effect of IVIG when applied to a large group of children with encephalitis has not previously been evaluated and is unknown. However, given the available evidence to suggest a beneficial role of IVIG in encephalitis, there is the possibility that children in the treatment arm may recover quicker and/or have better clinical outcomes than those in the placebo group or children with encephalitis that are not enrolled in this study.

If early treatment with IVIG is shown to be effective in improving the outcome at 6 and/or 12 months from randomisation, then it will be an important adjunctive treatment which may substantially reduce the burden of long hospital stays, expensive treatment, neurological morbidity and even death. The research findings are expected to impact on care pathways and individual patient decisions within the health services community, both nationally and internationally and the involvement of specialists in paediatric neurology who oversee care will ensure translation into clinical practice. Future recommendations for research will also be drawn.

Due to the interventional nature of the study, there is a potential risk from administering the study treatment. Known reactions are outlined in (Table 2; expected AEs) and section 9.1 below. Given the potential risk of anaphylaxis, all participants will be monitored very closely during and 20 minutes after the administration of the intervention. Safety data will be collected during the study and regular reviews by the Data and Safety Monitoring Committee (DSMC) will occur at specified intervals.

Overall, the generation of class 1 evidence to inform the use of IVIG in encephalitis and the potential impact of detecting a positive benefit in the treatment group both at an individual level and in the wider context, as outlined above, outweigh these potential risks.

5 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Primary	To compare neurological outcomes between children with encephalitis who have been treated with IVIG and those who have received matching placebo	'Good recovery' defined by GOS-E-Peds score 2 or lower at 12 months post randomisation
Secondary	(a)To compare the following between children with encephalitis who have been treated with IVIG with those who have received matching placebo: (i) Clinical and neurological outcomes	During hospital inpatient stay: (i)Glasgow coma score (ii)Neurological examination findings as documented by the clinical team (iii)Duration of invasive ventilation (if ventilated) (iv)Length of ICU stay in a subset of children admitted to ICU. (v)Length of hospitalization **Around 4-6 weeks after discharge from acute care** (i) Strength and Difficulties Questionnaire (SDQ) (ii) Adaptive Behaviours Assessment System-Second Edition (ABAS-II) (ii) Peds Quality of Life scoring algorithm (iv) Liverpool Outcome Score (v) Gross Motor Function Classification System (GMFCS) **Around 6 months (+/- 4 weeks) post randomisation** GOSE-Peds **Around 12 months (+/- 4 weeks) post randomisation)** (i) New diagnosis of epilepsy since

		discharge from hospital (ii) Use of anti-epileptic treatment since discharge from hospital. (iii) GOSE-Peds (iv) Strength and Difficulties Questionnaire (SDQ) (v) Adaptive Behaviours Assessment System-Second Edition (ABAS-II) (vi) Peds Quality of Life scoring algorithm (vii) Liverpool Outcome Score (viii) Gross Motor Function Classification System (GMFCS) (ix) Blinded neuropsychologist assessment of cognitive functioning depending on age using : Bayley Scales for Infant Development (BSID-III) or Wechsler preschool and Primary Scale of Intelligence III or Wechsler Intelligence Scale for Children IV **At any point during the study** (x) Collect information on deaths occurring up to 12 months post randomisation
	(ii) Radiological outcomes	Brain MRI at around 6 months post randomisation scan to assess the following (i) lesion resolution (ii) presence of new lesions (iii) distribution of persisting disease
	(b) To confirm the safety of IVIG treatment for children with encephalitis	(i) Collection of adverse events of special interest in the first five days from each dose of study drug (ii) Serious adverse events from receipt of

		first dose of study drug up to 6 months post randomisation (iii) Full blood count check 24-48 hours after the second IMP dose to monitor for possible haemolysis with IVIG treatment
	(c) To identify a proportion of children with immune mediated encephalitis	Presence and levels of specific auto-antibodies in serum and/or CSF samples obtained before and after study treatment
	(f) To determine the effect of IVIG treatment on auto-antibody levels in children with immune mediated encephalitis	Comparison of auto-antibody levels in blood and/or CSF (where lumbar puncture is performed as part of routine care) before and after administration of study treatment.
Exploratory Objectives	(a)To explore clinically relevant neuroimaging predictors.	Correlate MRI findings with the primary and secondary outcomes
	(b)To explore predictors of neurological outcomes in children with encephalitis	Correlate clinical and laboratory parameters with neurological outcomes
	(c) To explore radiological patterns associated with different types of encephalitis	Compare brain MRI findings with aetiological diagnosis
	(d) To understand the host inflammatory pathways in encephalitis and the relationship with clinical parameters and the effect of IVIG treatment on these pathways	(i) Comparison of inflammatory cytokines in both groups before and after study treatment (ii) Assessment of regulatory T cell frequency and function in blood and/or CSF before and after study treatment (iii) Measurement of inflammatory markers

		in blood and/or CSF between participants before and after study treatment (iv)Analysis of gene expression in whole blood before and after study treatment (v) Identification of specific DNA sequence and structural genetic variants in patients with encephalitis (vi)Comparison of the host inflammatory pathways between both study groups before and after study treatment (vii)Correlation of host inflammatory responses with clinical parameters

6 STUDY DESIGN

This is a multicentre, randomised, double-blind placebo controlled, parallel arm clinical trial to evaluate the early use of IVIG in addition to standard medical care versus placebo with standard medical care in children with encephalitis. Early treatment is defined as within 120 hours from presentation to any hospital OR, for transferred patients, 72 hours from admission to a study hospital even if this is >120 hours from presentation to initial hospital. Approximately 308 children will be recruited from approximately 30 UK centres. The study duration is 5 years which includes up to 42 months of recruitment, 12 months of follow up and a further 6 months for data analysis.

7 PARTICIPANT IDENTIFICATION

7.1 Study Participants

Children with acute or sub-acute encephalitis

7.2 Inclusion Criteria

The inclusion criteria is adapted from the Consensus Statement of the International Encephalitis Consortium case definition (18)

1) 6 weeks to 16 years of age (day before 17th birthday)

AND

2) Acute (within 24 hours) or sub-acute (between 24 hours and 4 weeks) onset of altered mental state (reduced or altered conscious level, irritability, altered personality or behaviour, lethargy) not attributable to a metabolic cause

AND

3) At least two of:

(a) fever >38^{o}C within 72 hours before or after presentation to hospital

(b) brain imaging evidence consistent with encephalitis or immune-mediated encephalopathy that is either new from prior studies or appears acute in onset

(c) CSF pleocytosis >4 white blood cells (WBCs)/microlitre

(d) generalised or partial seizures not fully attributable to a pre-existing seizure disorder

(e) new onset focal neurological signs (including movement disorders) for >6 hours

(f) abnormality on EEG that is consistent with encephalitis and not clearly attributable to another cause

AND

4) Parent/guardian/legal representative able to give informed consent

7.3 Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- high clinical suspicion of bacterial meningitis or TB meningitis (for example: presence of frankly purulent CSF; CSF WBCs >1000/microlitre; bacteria on Gram stain and/or culture)
- receipt of any IVIg product during the index admission where this was administered prior to obtaining written informed consent for the IgNiTE study
- Traumatic brain injury
- Known metabolic encephalopathy
- toxic encephalopathy (i.e. encephalopathy secondary to exposure to intoxicants, including alcohol, prescription or recreational drugs)
- hypertensive encephalopathy/posterior reversible encephalopathy syndrome
- pre-existing demyelinating disorder; pre-existing antibody mediated CNS disorder; pre-existing CSF diversion
- ischaemic or haemorrhagic stroke
- children with a contra-indication to IVIG or albumin (i.e. history of anaphylactic reaction to IVIG or albumin, known total IgA deficiency and history of hypersensitisation)
- Known hypercoagulable state

- significant renal impairment defined as GFR of 29mls/min/1.73m^2 and below (Chronic Kidney Disease Stage 4)
- Known hyperprolinaemia
- Known to be pregnant
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial
- participants who are being actively followed up in another research trial involving an investigational medicinal product
- Administration of study drug not feasible within 120 hours from presentation to any hospital OR, for transferred patients, 72 hours from admission to a study hospital even if this is >120 hours from presentation to initial hospital as determined by the study team
- Any other condition which, in the opinion of the investigator, may interfere with the ability to fulfil study requirements, especially relating to the primary objective of the study (this includes plans to be outside the UK for more than 12 months after enrolment)

8 STUDY PROCEDURES

8.1 Selection of Centres and Clinicians

Study centres will be initiated once all global (e.g. local R&D approval) and study-specific conditions (e.g. training requirements) have been met, and all necessary documents have been returned to the coordinating centre Department of Paediatrics, University of Oxford, UK. Initiation meetings will cover the requirements, which is outlined in the study specific site initiation visit plan.

The study staff participating in this multicentre trial will be trained in a uniform fashion and sites will be monitored by the clinical trials monitor or an appropriate designated study team member to ensure consistency in study execution across all centres.

8.2 Participant identification and Eligibility Assessment

Potential participants for the study will be identified by any of the following routes:

- Clinicians reviewing medical handover lists and clinical records of new admissions
- Site study team contacting relevant wards in the hospital where potential participants could be admitted (e.g. paediatric intensive care unit or high dependency unit) to enquire about any new admissions.
- Microbiologists and/or virologists identifying children who have had a lumbar puncture performed for

Suspected CNS infection

- Radiologist identifies a brain MRI scan suggestive of encephalitis
- Neurophysiologist identifies an electroencephalogram (EEG) suggestive of encephalitis

8.3 Approach and initial eligibility assessment

If a potential participant has been identified by any of the above methods, the relevant clinical team will first be informed. A member of the clinical team would then approach the parent/ guardian/legally authorised representative to seek their interest in knowing more about the study. Verbal consent will be sought from the parent/ guardian/legally authorised representative for a member of the clinical team to pass their details on to the study team. Where such consent is obtained, this will be documented in the child's medical notes. Only then would the study team contact the family and subsequently give them the participant information sheet (PIS). A member of the study team will check the patient's eligibility by asking the parent/ guardian/legally authorised representative questions, in line with the inclusion and exclusion criteria (**see section 7, patient identification**) before obtaining consent, if the parent/guardian/legally authorised representative agrees for their child to participate. If the delegated party is unsure if the patient can participate in the study they should first speak with the PI at site or contact the Department of Paediatrics, University of Oxford coordinating centre to clarify eligibility.

8.4 Informed Consent

Parents, Guardians or Legally authorised representatives

The conduct of the trial will be in accordance with the Principles of Good Clinical Practice. Every effort will be made to include non- English speakers in accordance with the National Research Ethics Service (NRES) guideline. However, we do not intend to recruit anyone whose poor command of English has the potential to compromise their understanding of the study and the study requirements such as the completion of questionnaires since this is crucial to achieving the primary objective of the study.

A Participant Information Sheet (PIS) explaining the trial (including the rationale, aims and objectives, treatment assignation), potential risks and benefits, and all the study procedures will be provided. Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part.

The parent/guardian/legally authorised representative will be allowed sufficient time to consider the information in the PIS and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. They would also be given sufficient time to consider participation in the study. It will be clearly stated that the parent/guardian/legally authorised representative is free to withdraw from the study at any time for any reason without prejudice to the participant's future care, and with no obligation to give the reason for withdrawal.

If the parent/guardian/legally authorised representative still wishes for their child/themselves to participate in the study, written Informed Consent will then be obtained by means of an appropriately signed and dated Informed Consent form before any study specific procedures are performed. It is the responsibility of the Investigator (or suitably qualified and experienced member of staff delegated by the Principal Investigator) to obtain written informed consent. The Investigator or designate should also sign and date the Informed Consent form.

A copy of the Informed Consent Form should be given to the parent/ guardian/legally authorised representative, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF).

Patients who are 16 years old at the time of enrolment

Where appropriate (i.e. where the patient has capacity), consent should be obtained from all patients who are 16 years Given that children with encephalitis will be unwell and may be confused during the acute illness, it is likely that eligible patients in the age group would be unable to provide consent prior to enrolment. Enrolment in such a case would therefore be only after consent has been obtained from the patient's parent/guardian/legally authorised representative. However, when clinically appropriate (this will be guided by an appropriate member of the clinical or study team), appropriate consent should be obtained as soon as possible. An appropriate version of the participant information leaflet should be provided to the participant who will be given ample time to read the leaflet and to ask questions. If consent is not granted then that participant should be withdrawn from the study.

Patients under 16 years

An appropriate approved Patient Information Sheet describing (in simplified terms) the details of the study procedures and risks will be provided to participants under 16 years. Assent should be obtained whenever it is judged appropriate to do so. The minor should personally write their name and date the assent form, which is then signed by the parent/guardian/legal representative and the member of the study team obtaining the assent.

An assent form is not a substitute for a consent form signed by the patient's parent/guardian/legally acceptable representative. Consent must be obtained from the patient's parent/guardian/legally acceptable representative prior to enrolment. Also, the lack of assent at the time of enrolment (either because the child is too young or lacks capacity to provide assent) does not exclude them from participating in the trial provided consent has been obtained from the parent/guardian/legal representative. If a child is capable of giving assent and this is not granted, they will not be enrolled to the study, even if appropriate consent has been obtained from their parent/guardian/legally authorised representative.

The latest version of an age appropriate information leaflet, consent and assent form must be used at all times during the study.

Participants who turn 16 years during the study

Participants who previously provided assent but turn 16 years while still in the study need to consent for themselves. Appropriate consent must be obtained from the participant and as soon as this is possible i.e. at the next study visit after their 16th birthday and if not granted then that participant will be withdrawn from the study.

8.5 Screening Log

A 'Screening log' of all screened patients will be kept and will include patients with a diagnosis of encephalitis but are not eligible, eligible patients who refuse to be approached or may not be suitable to be approached, as well as those for whom consent was declined. The reason(s) why a patient is not enrolled should be clearly documented in the screening log, including reasons for declined consent, where this is provided. To maintain confidentiality, no identifiable personal information will be recorded in the screening log.

8.6 Enrolment

Enrolment should be undertaken by an experienced delegated team member and as soon as possible after consent has been obtained to allow administration of the first dose of study drug within the stipulated timelines.

An enrolment form will then be completed into a password protected electronic database (OpenClinica™ database, stored on a secure University of Oxford server) following which a participant identification (ID) number will be automatically generated. If for some reason the server is down at the recruiting site, the Department of Paediatrics, University of Oxford coordinating centre should be contacted by phone providing details of the potential participant. The coordinating site will then enrol the participant on behalf of the recruiting site and forward a copy of confirmation of enrolment to the site via e-mail or fax to the person enrolling the patient and the PI at site. The confirmation of enrolment e-mail will have the screening number, participant ID and participant initials stated.

Once the participant is entered into the study the participant ID should be entered on the Contact details form and will be used on all documentation (e.g. CRF's) from this point.

Contact details of the study team will be provided to the participant's during the study period, for issues relating to the study.

Co-enrolment guidelines

Participants may be recruited to another study where this is considered to be appropriate. This will include where such a study does not involve the use of an investigational medicinal product (IMP) thought to have a potential immunomodulatory or neuroprotective effect as detailed in the Clinical Study Plan, and would not have any detrimental effect on the IVIG study. Where there is uncertainty, this should be discussed with the study team at the Department of Paediatrics, University of Oxford coordinating centre to ensure that co-enrolment is appropriate.

8.7 Randomisation, blinding and code-breaking

Randomisation

After enrolment, eligible participants will be randomised as soon as possible, to allow administration of the first IMP dose within five days of hospital admission. Randomisation will be at an allocation ratio of 1:1 to IVIG plus standard treatment (IVIG+S) or placebo plus standard treatment (P+S) groups using a fully validated online randomisation system developed by the Primary Care and Vaccines Collaborative Clinical Trials Unit (PCV-CTU). Allocation will be stratified by age group and steroid use, using stratified block randomisation with randomly varying block sizes. Based on the most recently published epidemiological data from a multicentre mixed (adult and children) UK study (3) and an unpublished observation of admissions to PICU with encephalitis (10), we would envisage that up to 10-30% of children in the study will have an immune mediated form of encephalitis and as such, receive steroid treatment prior to randomisation. Thus, steroid use before randomisation will be used as a stratification factor in the randomisation algorithm to ensure a balance between the groups.

A randomisation code will be generated by the randomisation system. With this, the unblinded pharmacist at each recruiting site will then supply active treatment or visually identical placebo to the research nurse for each patient. Researchers will not have access to the randomisation code.

A master list matching laboratory code, and allocation group will be held by independent delegated individuals not involved in data collection, entry or analysis (this will include an independent study statistician, and the unblinded site pharmacist) and kept with password protection in a secure location. Neither participants nor the clinical investigators will be aware of the treatment allocation.

Blinding

A rigid blinding process will be in place all through the study to ensure the validity of the data collected. Participants, their parents/guardians/authorised legal representative, in addition to study staff and clinical staff who are actively involved in the conduct of the study (including recruitment, administration of study treatment, data collection and entry) will be blind to the treatment arm allocation through the entire study period. Performance and ascertainment bias will be minimised by measures designed to maintain the blinding (e.g. identical packaging of IVIG and matched placebo). Also, all individuals involved in the assessment of study outcomes (i.e. all psychometric, neuropsychology and neuroimaging assessments) including laboratory staff who will be performing the sample analyses, will have no access to the medical records of participants and will remain blind to treatment allocation throughout the study, including during analysis of results. The site pharmacist and study monitors, who are independent of the study will be unblinded.

Unblinding procedure

Unblinding will be done by individuals who are granted appropriate access for this. Under no circumstance should either the participant/parents/guardians or study staff be unblinded unless such a circumstance affects the participant's safety and /or data integrity. In such a circumstance, treatment allocation for a particular participant will be made available, without compromising the blind for the other participants. In emergency situations, the investigator

will have the final decision and unilateral right for unblinding. A detailed procedure for both emergency and non-urgent unblinding will be provided in a Clinical Study Plan which will be made available to all study sites. An audit trail of all unblinding will be maintained. The DSMC must be informed of any case of unblinding.

8.8 Assessments

Information on participant's medical history, neurological examination, laboratory and radiological investigations and clinical progress will be collected throughout the study and entered onto the clinical trials database (OpenClinica™).

Assessment of Outcomes

A summary of all study assessments and procedures is shown in **Appendix B**

Clinical outcomes

Clinical outcomes will be collected throughout the study period and will include (but not limited to) the following information:

During admission

- Glasgow coma score as documented in clinical records
- Neurological examination findings as documented in clinical records
- Need for, and duration of ventilation (for ventilated participants)
- Admission to ICU and length of stay on ICU
- Length of hospitalisation
- Results of laboratory tests and brain MRI scans

Around 6 months (+/- 4 weeks) post randomisation

- The frequency of seizures since hospital discharge
- New diagnosis of epilepsy since hospital discharge
- Collect relevant clinical information including details about the prescription of anti-epileptic treatment since discharge from hospital

Around 12 months (+/- 4weeks) post randomisation

- The frequency of seizures since hospital discharge
- New diagnosis of epilepsy since hospital discharge
- Collect relevant clinical information including details about the prescription of anti-epileptic treatment since discharge from hospital

Radiological outcomes

Results of brain MRI scans will be collected throughout the study where performed as part of routine care (where appropriate consent has been obtained) or at around 6 months (where performed as part of the study)

Neurological outcomes

Neurological outcomes will be assessed by two ways:

(a) Use of participant/parent completed questionnaires

(b) Blinded neuropsychological assessment

Questionnaires

These will be completed around 4-6 weeks after the participant has been discharged from acute care, and around 6 and 12 months post randomisation. Some questionnaires can be completed either by the participant (where appropriate) or their parent/guardian/authorised legal representative (see below). Members of the study team or the participant's clinician (where appropriate e.g. at routine follow up visits) who are blinded to the participant group can also assist with the completion of questionnaires.

All completed questionnaires should be returned to the Department of Paediatrics, University of Oxford co-ordinating centre ideally using provided pre-paid envelopes. Where completed questionnaires have not been returned after 2 weeks of postage, the parent/guardian/authorised legal representative/participant will be contacted either by telephone or by reminder letters and/or email. If no response is received, and where appropriate consent has been obtained, the participant's GP surgery and/or hospital consultant will be contacted to enquire about any change in participant's address and contact details.

The questionnaires listed below will be used during this trial.

- **GOS-E Peds**

This is a modified version of the Glasgow Outcome Scale-Extended (GOS-E), a gold standard for measuring traumatic brain injury outcome in adults. The GOS-E Peds provides a developmentally appropriate structured interview necessary to evaluate children across different age groups, and it provides a valid measure of outcome in infants, toddlers, children and adolescents. Its use has been validated and found to be sensitive to both severity of injury and to recovery over time, at least 6 months after brain injury and has been suggested as useful in guiding treatment in the early phases of recovery from brain injury (19). A strong correlation is also seen with parent report of functional outcomes and also with most performance based cognitive tests for both younger and older children. Performance on the GOS-E Peds will be assessed around 6 months (secondary endpoint) and at around 12 months (primary endpoint) post randomisation. A 6 month assessment has been chosen as this has the advantage of improved study retention, and earlier impact assessment.

The 6 month GOSE-Peds should be completed by either a member of the research or clinical team (over the telephone, or face-to-face) while the 12 month questionnaire will ideally be completed during a face-to-face interview by the

neuropsychologist at the 12 month visit, although can be done in the same way as the 6-month questionnaire if needed.

- **Adaptive Behaviour Assessment System, second edition (ABAS -2)**

This is an internationally accepted and validated measure of non-referenced adaptive functioning from birth to 18 years. It comprises a 45 minute questionnaire evaluating areas of adaptive behaviour, specifically: community use; school/home living; self-care; social; functional; academics; communication; leisure; health and safety; self-direction and should be completed by the parent/guardian/legal representative/participant (where appropriate)

- **Gross motor function classification system (GMFCS)**

This is a one variable classification system (I-V) based on motor functioning of the child and has been validated in children from birth-18 years and should be completed by the parent/guardian/legal representative/participant (where appropriate)

- **Strength and Difficulties Questionnaire (SDQ)**

The Strengths and Difficulties Questionnaire (SDQ) is a widely accepted brief behavioural screening tool for 3-16 year olds, which measures social, emotional and behavioural functioning. There are 25-30 items (tick box questions) and it takes 15 minutes to complete. It includes versions for parents (and educators) of 3-4 year olds, 4-16 year olds and a self-report version for 11-17 year olds. Responses for each item are grouped into one of five areas: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems and prosocial behaviour. Norms have been established for children and adolescents who require further assessment. It has been validated in several cultural contexts, in school and clinical populations. The SDQ questionnaire should be completed by the parent/guardian/legal representative/participant (where appropriate)

- **Paediatric Quality of Life Inventory (PedsQL)**

The Peds QL 4.0 Core Version is an internationally accepted 23 item validated questionnaire, which takes 5 minutes to complete and should be completed by the parent/guardian/legal representative/participant (where appropriate). It assesses health related quality of life in children in four areas: Physical, Emotional, Social, and School Functioning. It is applicable for healthy children and adolescents and those with acute and chronic health conditions. The Core Version includes questionnaires applicable for: Parent of Toddler 2-4 years, Child 5-7 years, Parent of Child 5-7 years, Child 8-12 years, Parent of Child 8-12 years, Teenager 13-18 years and Parent of Teenager 13-18 years.

- **Liverpool outcome score (LOS)**

This is a validated tool for assessing the level of disability after encephalitis in infants and children and should be completed by either a member of the research or clinical team. It was originally designed to assess disease burden following Japanese Encephalitis (20) but patients with other causes of encephalitis were also studied. It assesses levels of disability and includes an assessment of the likelihood of independent living and can be administered in 3-4 minutes by a health worker with minimal training. It has been adopted by the World Health Organisation and is being used in many resource poor settings but is equally applicable to patients in the UK.

Blinded neuropsychology assessment

This is a 90-minute assessment aimed at assessing various objective measures of neuropsychological functions and taps into domains such as verbal and non-verbal skills, working memory and processing speed. The assessment will be carried out in the participant's home and will be performed by a neuropsychologist who will be blinded to the participant's treatment group. Other age appropriate measures to be used in the assessment include:

(i) 1 to 42 months: Bayley Scales of Infant Development (BSID-III)

(ii) 2:6 – 7:7 years: Wechsler Preschool and Primary Scale of Intelligence III

(iii) 6:0 – 16:11 years: Wechsler Intelligence Scale for Children-IV

The site number, participant initials and participant ID number should be clearly labelled on all these documents.

Radiological Evaluation

To address the radiological objectives of the study, consent will be sought for a research brain MRI scan at around 6 months post randomisation. Some children may require follow up brain MRI scans after discharge as part of their routine care. Therefore, where a routine (clinical) follow up brain MRI scan was performed ≥ 3 months post randomisation, a research MRI scan may not be required. On the other hand, if the routine (clinical) follow up MRI scan was performed less than 3 months from randomisation, a research scan will be required, although this is an optional part of the study.

As part of the study, consent will be obtained to use images of any follow up brain scans that are done as part of routine care. All images, devoid of any identifiable data will be sent electronically or on a compact disc (CD) to the Department of Paediatrics, University of Oxford co-ordinating centre who would then forward these on University College London (UCL), for the relevant radiological analyses which will be performed by a team of neuroradiologists who will remain blind to the participant treatment arm during the entire period of the data analysis.

They will standardise the neuroimaging acquisition protocols across study sites; set up software and hardware required for centralised analysis of neuroimaging; and supervise the subsequent analysis and interpretation of neuroimaging data. Details of this will be included in a separate analysis plan.

The following will be described from the participant's brain MRI scans

- Presence of unilateral or bilateral lesion
- Lesion location by structural anatomy (e.g. temporal, frontal, parietal, occipital, insular, brainstem, cerebellum; cortex, white matter, deep grey matter)
- Lesion location by expected functional anatomy (e.g. somatomotor/sensory cortex, limbic system, extrapyramidal system, visual/auditory cortex)
- Appearances consistent with ADEM; viral encephalitis; and immune mediated process
- Involvement of white matter and/or grey matter or limbic structures (i.e. amygdala, hippocampus, cingulate gyrus, insula)

- The presence of mass effect, hydrocephalus and enhancement

Outcomes of interest that would be documented from the 6 month MRI scan would be:

- lesion resolution
- presence of new disease
- distribution of persisting disease

Further analysis that will include using a systematic structured study proforma designed to capture data that would then subsequently be used to aid in:

(i) identifying imaging subtypes of different encephalitides for example infectious vs. demyelinating vs. autoimmune

(ii) identifying clinically relevant neuroimaging predictors.

Due to the heterogeneous study population and paucity of published paediatric MRI outcome measures, only descriptive statistics and correlation with the primary outcome will be made.

Assessment of Laboratory Outcomes

Blood and CSF samples obtained from participants enrolled to the study will be of two categories:

Scavenged samples

It is expected that children enrolled to this study will have blood and CSF samples obtained as part of their routine medical care. Consent will be obtained to use any surplus blood and CSF residues (i.e. from samples collected prior to as well as after enrolment, as part of routine care) that are remaining after completion of all necessary investigations by the laboratory as decided by the clinical team).

Additional samples

Additional biological samples may also be obtained from participants by two means:

(i) collection of extra volume of blood and/or CSF obtained at the time of sampling for routine investigations or intravenous cannulation

(ii) performing additional venepuncture as appropriate

Consenting to collection of additional samples via any of the above means will be entirely optional and additional samples will only be obtained if specific consent is obtained. Participants will still be able to enrol in the study if they do not consent to providing additional samples.

No extra lumbar puncture will be performed solely for the purpose of the trial however, if this is being done as part of routine care, optional consent will be sought to obtain extra CSF sample at the time of lumbar puncture.

All obtained samples will be labelled only with the participant's study ID and used to meet the objectives of the study. Anonymised blood and CSF samples (not including DNA) and relevant data may be sent to other laboratories for further testing, including outside the European Union.

Biobank

Parents/guardians/legally authorised representatives/participants may be approached about a separate, ethically approved, Biobank study and asked if they would like to consent to this study using a separate consent form. Participation in the Biobank is optional and samples will only be stored where appropriate consent has been obtained.

Amount of samples

This will be in line with the World Health Organisation Guidelines o blood sample volumes in child health research available at http://www.who.int/bulletin/volumes/89/1/10-080010/en/

Timing of sampling

Table 1: Timing of blood samples

Sample type	Time of sampling	Endpoint
Additional sample	a. At any point during the study and will be obtained by any of the following means: (i) collection of extra blood samples at the time of routine blood sampling or routine intravenous cannulation or lumbar puncture during period of hospitalisation (ii) performing a venepuncture to obtain blood sample (where specific consent is obtained, when no routine sampling is planned as part of routine care) during period of hospitalisation (ii) collection of extra samples if being performed as part of routine care OR performing a venepuncture at the 6- month post randomisation follow up. b. 24 –48 hours after the 2nd IMP dose	• Auto-antibody evaluation • Immunological evaluation • Host genetic response • Full blood count check
Scavenged blood and CSF	During the entire study period: prior to and after enrolment	• Auto-antibody evaluation

		• Host genetic response

8.9 Study time points

DURING HOSPITALISATION

T0 – Enrolment (As soon as possible, to allow administration of 1st IMP dose within the stipulated timelines)

- Provide study information
- Obtain consent
- Participant enrolment and randomisation
- Obtain baseline research sample if consent given
- Completion of research notes and CRF

T1 (As soon as possible after consent is obtained and must be within 120 hours from presentation to any hospital OR, for transferred patients, 72 hours from admission to study hospital even if this is >120 hours from presentation to initial hospital

- Ensure participant still meets the inclusion criteria and none of the exclusion criteria
- Ensure participant has no contraindications to receiving the study drug*
- Obtain baseline research blood sample where consent given and if not already done (sample may be obtained at any point after consent to just before the first dose of the study drug)
- Obtain baseline research CSF sample where consent obtained and if having a routine LP (may be obtained at any point after consent to just before the first dose of the study drug)
- Check study drug allocation number against participant study ID and randomisation number
- Administer first dose of study drug
- Document vital signs during study drug administration including heart rate, temperature and blood pressure
- Monitor vital signs for 20 minutes after study treatment
- Document administration of study drug and sign drug chart
- Document date and time of study drug administration
- Complete research notes and CRF and record any adverse events (AEs) of special interest – **see section 11.3**
- Report any serious adverse events (SAEs) within 24 hours – **see section 11.4**

T1+24 hours (24 hours after receipt of first IMP dose)

- Ensure participant still meets the inclusion criteria and none of the exclusion criteria
- Obtain research blood sample (where consent given)
- Obtain research CSF sample (where consent given and if having repeat LP as part of routine care)

T2 (24-36 hours after 1st dose of study drug)

- Ensure participant still eligible and no contraindication to administering second dose of study drug*
- Obtain T1+24 research sample (where consent given) if T2 at 24 hours post T1
- Check study drug allocation number against participant study ID and randomisation number
- Administer second dose of study drug
- Document vital signs during study drug administration including heart rate, temperature and blood pressure
- Monitor vital signs for 20 minutes after study treatment
- Document administration of study drug and sign drug chart
- Complete research notes and CRF and record any AEs of special interest – **see section 11.3**
- Report any SAEs within 24 hours – **see section 11.4**

*****All participants must be signed off as medically stable by a member of the clinical team at SpR or Consultant level prior to each dose of the study drug

T2+24-48 (24 – 48 hours after 2nd dose of study drug)

- **Obtain blood sample for post IMP FBC check (consent for this is included in the main study consent and is not optional)**

T2+7: D7 post 2nd IMP dose

- Obtain research blood sample (where consent given)
- Obtain research CSF sample (where consent given and if having repeat LP as part of routine care)

T 3: Prior to discharge** (On day of discharge and up to 48 hours prior to discharge)

- Complete research notes CRF with any outstanding clinical information and laboratory investigations
- Give age appropriate questionnaires to parents for completion at 4-6 weeks' after the participant has been discharged

**The term discharge refers to the point at which the participant is deemed medically fit to be discharged from acute care either to their home or to their local hospital (for transferred participants), or a neurorehabilitation service (for those requiring on-going rehabilitation).

AFTER DISCHARGE FROM HOSPITAL

T4: Around 4 – 6 weeks post discharge from acute care

- Complete age appropriate questionnaires

T5: Around 6 months post randomisation – Participants' home/Telephone/ in hospital

- Check consent form and confirm continued consent
- Obtain participant consent (if 16 years and capable) or assent (if capable) where not done previously
- Collect information on seizures since discharge and/or use of anti-epileptic treatment
- Collect SAEs that have occurred since discharge from hospital
- Complete GOS-E Peds
- Obtain research sample as appropriate (where consent given)***
- Screening for MRI suitability (this may occur at any other routine hospital appointments, as appropriate)
- MRI scan to be performed if required (see radiological evaluation section) and where consent obtained)
- Complete research notes and CRF

***To avoid an extra visit solely for this purpose, the '6 month research sample' can be obtained at any routine follow up clinical appointments that occur after the participant has been discharged.

T6: Around 12 months post randomisation – Participants' home / in hospital

- Check consent form and confirm continued consent
- Obtain participant consent (if 16 years and capable) or assent (if capable) where not done previously
- Collect information on seizures since discharge and/or use of anti-epileptic treatment
- Complete GOS-E Peds
- Complete age appropriate outcome questionnaires
- Neuropsychology assessment
- Collect information on deaths or pregnancy occurring since the 6 month visit and report within 24 hours **see section 11.4**
- Complete research notes and CRF including termination page.

Information on clinical outcomes for the 6 and 12 month time points may be obtained over the telephone from the parent/guardian/legal representative/participant) by the PI at the recruiting centre, the participant's GP or Consultant (or a member of the clinical team) where appropriate consent is obtained for such information to be shared with the

study team. Identification of scavenged samples (blood and CSF) and entry of clinical information into research notes and CRF should be a continuous process that occurs throughout the study. As appropriate, all required clinical information should be documented as soon as they become available.

8.10 Discontinuation/Withdrawal of Participants from Study

Consent could be withdrawn at any time without providing a reason. The participant will not contribute further data to the study and the Department of Paediatrics, University of Oxford UK coordinating centre should be informed by email/ telephone/fax by the responsible physician and the withdrawal sections of the research notes and CRF should be completed. Data up to the time of withdrawal will be included in the analyses unless the patient explicitly states that this is not their wish.

In addition, the Investigator may discontinue a participant from the trial treatment at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or trial requirements
- An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures

The reason for withdrawal will be recorded in the research notes and CRF. If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised. Although a participant can be discontinued from the trial treatment by the investigator he or she will remain in the trial for follow up and analysis (unless otherwise requested by the parent/guardian).

The PI at each recruiting site should notify the Department of Paediatrics within 24 hours of being aware of any participant death, using the notification form provided, so that the family is not contacted regarding follow up visits. A serious adverse event form must also be completed and reported within 24 hours of being aware (**see section 11, safety reporting**).

Patient transfers

It is possible that some participants could be recruited in a tertiary centre and following recovery, transferred to their local hospital, which may not be a recruiting centre. In such a case, information on clinical progress will be obtained directly from parents, or through the GP or Consultant who was in charge of the participant's clinical care during the admission, where appropriate consent is obtained.

8.11 Definition of End of Study

The end of trial is on the date when all biological samples have been processed.

9 INTERVENTIONS

9.1 IMP Description

The following drugs are Investigational Medicinal Products (IMPs) in this trial:

- Human normal IVIG (Privigen®) 100mg/ml solution for infusion
- Placebo to match Human normal IVIG (Privigen®)

IVIG will be administered at a dose of 1g/kg given 24-36 hours apart. The volume of placebo to be administered will be equivalent to that for IVIG. The first dose of study drug must be administered within 120 hours from presentation to any hospital OR, for transferred patients, 72 hours from admission to study hospital even if this is >120 hours from presentation to initial hospital. The administration of IVIG or placebo will be in line with the SmPC recommendations for IVIG (Privigen®)

IVIG

IVIG is a preparation of natural antibodies made from blood donations. It is a ready-to-use liquid formulation of human immunoglobulin (IG) for intravenous (IV) administration. Two widely studied and accepted mechanisms of IVIG action are supplementation of specific antibodies and immunomodulatory effects. Each of these mechanisms may be involved in the beneficial effects of IVIG on immune-mediated diseases. IVIG is indicated as replacement therapy for patients with primary immunodeficiency associated with defects in humoral immunity, including but not limited to common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. IVIG is also indicated to raise platelet counts in patients with chronic immune thrombocytopenic purpura (ITP). Also; IVIG has been used in various forms of infectious and immune mediated encephalitis as outlined in (**Section 4.3; rationale for the study**)

Intravenous immunoglobulin (IVIG) has both anti-inflammatory and immune modulating properties and is used increasingly in the management of a range of neurological conditions. Its efficacy has been established clearly in randomised controlled trials for a handful of these conditions (17). The most relevant actions of IVIG in the therapy of neurological diseases include: (a) inhibition of complement binding; (b) neutralization of pathogenic cytokines; (c) down-regulation of antibody production; and (d) modulation of Fc receptor mediated phagocytosis (21). In addition it contains antibodies to a range of pathogens that might be beneficial in infectious encephalitis.

The IVIG brand to be used is Privigen, which is manufactured by CSL Behring (Switzerland). This 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. Privigen comes as a ready-to-use solution in single-use vials. Each IVIG vial comes as a 10g/100ml solution

and does not need to be further diluted. The active substance in Privigen is human normal immunoglobulin (antibodies of the type IgG). Privigen contains human protein of which at least 98% is IgG.

The approximate percentage of IgG subclasses is as follows:

IgG1 ..... 67.8%

IgG2 ..... 28.7%

IgG3 ..... 2.3%

IgG4 ..... 1.2%

Privigen contains trace amounts of IgA (not more than 25 micrograms/ml) and is essentially sodium free. The other ingredients (excipients) are the amino acid proline and water for injections. Privigen® solution for infusion is for single-use only.

PLACEBO

The placebo to be used in this study will be 0.1% human albumin in 0.9% Sodium Chloride solution for intravenous infusion and will be made up by the Aseptic Manufacturing Pharmacy Unit (AMPU) at Royal Liverpool & Broadgreen Hospital Trust, Liverpool under cGMP conditions under its MIA (IMP) licence.

The placebo comes as a ready-to-use solution in single-use vials.

Similar to IVIG, standard measures to prevent infections resulting from the use of albumin such as the inclusion of effective manufacturing steps for the inactivation of viruses are observed. There are no reports of virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes but there is the theoretical risk of possible transmission of infective agents, however this risk is very low.

Packaging, labelling of IMPS

The IVIG to be used in the study will be provided by CSL Behring and shipped to RLBHT in an unlabelled form. The APMU at RLBHT will be responsible for the packaging and labelling of IVIG and placebo under its MIA (IMP) licence. Both the primary container (bottle) & the secondary packing of IVIG and placebo will be labelled in an identical manner. Label designs will incorporate a structure that allows the IMP or placebo to remain blinded to clinical staff and participants. The content of the labelling will be in accordance with Annex 13 of Volume 4 of The Rules Governing Medicinal Products in the EU: Good Manufacturing Practices. All labels will carry a tear off section that will be removed by the Pharmacy Departments at participating sites at the point of blinding and dispensing. APMU at RLBHT will be responsible for the final QP certification of IMPs for the trial.

Prescription of IMPs

Study medication should be prescribed by an appropriately delegated study physician and according to the protocol. The dose of Study Drug should be calculated based on the participant's weight for all doses and the site pharmacist will dispense the required number of vials. The calculated volume for each dose should be rounded to the nearest Xg.

Further guidance on this will be provided in a Clinical Study Plan. The pharmacist will check this calculation and record it on the accountability Log. The prescription should include at least the following information:

• Protocol number

• Participant study ID

• Participant's initials

• Date

• Dose number

• Participant's date of birth

• Participant's weight

• Total calculated amount of Study Drug to be infused (in grams)

Dispensing and Distribution of IMPs

Study medication will be distributed from the AMPU at RLBHT to all study site pharmacies. A drug receipt log must be completed and signed by the person accepting the shipment.

Following randomisation, an automated email from the randomisation system will be sent to both the unblinded pharmacist and the investigator performing the randomisation. A copy of this will serve as notification of randomisation and must be filed for audit purposes. The dispensing pharmacist who will be unblinded will refer to the randomisation email to decide whether to dispense IVIG or placebo to the research team who will be blinded. The tear off section of the IMP label (both primary and secondary packaging) must be removed by the pharmacist at the point of dispensing.

Monitoring of Vital Signs Study Drug infusion

All participants will be monitored closely during administration of study drug and for 20 minutes after completion of each dose of study treatment. The following should be recorded during the monitoring period: heart rate (HR), respiratory rate (RR), blood pressure (BP), and temperature (including method of measuring this i.e. oral, axillary or aural). In addition, the participant would be observed for any signs of anaphylaxis.

Reactions during IMP administration

Certain reactions could occur during IMP administration and include mild reactions such as flushing, urticaria, fever and nausea, rigors, hypertension, hypotension, feeling cold, tachycardia, tremor, or very rarely, severe reactions such as dizziness, shock, bronchospasm, dyspnoea, chest tightness, stridor, dizziness and anaphylaxis could occur. Treatment should depend on the nature and severity of the adverse reaction, and should be in line with local hospital practice. Some reactions may be related to the rate of the infusion and disappear when this is slowed. The infusion must be discontinued immediately if an anaphylactic reaction occurs. Staff administering the study drugs must be trained in the acute management of anaphylaxis reactions including the use of intra-muscular adrenaline. Adrenaline must be available at all times around the time of administration of study treatment and should be prescribed on the

participant's drug chart prior to administration of study treatment. In addition, staff must be aware of the local emergency procedures, available at their NHS trust.

9.2 Storage of IMP

Both IVIG and placebo will be stored in the pharmacy at each study site following the manufacturer's recommendations, and in accordance with site-specific SOPs. Site pharmacies are responsible for the safe and proper storage of IMPs at the site. IMPs should be stored in a secured area with limited access.

Storage requirements:

- Do not store above 25 °C.
- Do not freeze.
- Keep the vial in the outer carton, in order to protect from light.

Appropriate storage conditions must be ensured by completion of a temperature log in accordance with local requirements on a regular basis, showing minimum and maximum temperatures reached over the time interval. In case an out-of-range temperature is noted, it must be immediately communicated to the research team.

9.3 Compliance with Trial Treatment

Administration of study drugs should be performed by a qualified, experienced, and appropriately delegated member of the study team or clinical staff who has received study specific training. Administration must be legibly documented in an appropriate drug chart and research notes, including the date, time, name and signature of the study team member who administers the drug. The study drugs must be administered within 120 hours from presentation to any hospital OR, for transferred patients, 72 hours from admission to study hospital even if this is >120 hours from presentation to initial hospital after this time will constitute significant non-compliance and must be reported as a protocol deviation to the PI at the recruiting site who would in turn inform the CI of the study.

9.4 Accountability of the Trial Treatment

Accountability of both used and unused study drugs will be conducted in accordance with site-specific SOPs. Responsible site personnel must maintain accurate accountability records of the IMPs, including, but not limited to, the number of vials received, the number of vials dispensed to which subject, batch number, expiry date, returns, and date of transaction.

Used vials will be discarded at the point of administration. Unused vials will be returned to pharmacy and should only be disposed of following authorisation from the coordinating centre. In the event that an infusion is not given as scheduled, reasons must be documented in the research notes and CRF.

9.5 Concomitant Medication

In general, concomitant medications and/or other therapies for encephalitis will be permitted throughout the study in accordance with the local standard of care. It is likely that participants in the study will receive intravenous aciclovir and steroid treatment and these are not contraindicated in this study. However, since the use of either treatment potentially could confound the study results, information on their use will be recorded in the research notes and CRF. Concomitant medications or other infusions, including dextrose, should not be delivered simultaneously through the same IV lumen with the Study Drug due to lack of data on drug-drug interactions.

Interactions include:

1) Live attenuated virus vaccines: Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines.

2) Interference with serological testing: After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing. Passive transmission of antibodies to erythrocyte antigens, e.g. A, B D may interfere with some serological tests including the antiglobulin test (Coomb's test).

Details of all other agents that might interact with Privigen can be found in the British National Formulary (BNF) (http://www.bnf.org/bnf/).

9.6 Imaging Interventions

A brain MRI will be performed at around 6 months after receipt of the study treatment for a subset of all participants for whom appropriate consent has been obtained. The participant's eligibility to have a MRI scan must be checked prior to obtaining optional consent for this. Also, eligibility must be re-confirmed at the time of the scan. Some participants may require light anaesthetic for the brain MRI scan therefore, all participant's for whom consent is obtained will undergo an assessment with an anaesthetist to ensure that there are no contraindications to having an anaesthetic, in case required.

There are side effects associated with every anaesthetic. Most of these are mild and include nausea, sore throat, dizziness, fatigue. There is the rare chance of an anaphylactic reaction to the anaesthetic medicines in about 1:5000 to 1:20 000 people. For this reason, adrenaline must be available and within easy reach within the MRI department. Where an MRI has been performed under general anaesthesia, the participant must undergo a period of observation in hospital as per local hospital guidelines.

During the actual scanning procedure, there may be loud banging noises, therefore where age appropriate, participants will be given earplugs and protective headphones. Some children may find that being in the scanner is claustrophobic.

These should be discussed at the time of consent. Where appropriate, participants should be offered a chance to see the scanner to make sure that they are comfortable in it.

Once contraindications to magnetic resonance imaging are excluded, the risks of undergoing a scan are minimal. MRI uses no ionising radiation. There are, however, potential hazards to those unsuitable to enter a magnetic environment. This includes children with metallic implants, such as pacemakers, cochlear implants, or body piercing. An MR technician will go through a safety checklist and a list of possible risks with the participant before scanning. If a participant for whom consent has been obtained for a brain MRI scan becomes pregnant during the study, this should be discussed with the PI as this may make the participant unsuitable for a MRI scan.

10 LABORATORY

10.1 Blood sample collection

At each blood sampling visit, blood taken will be immediately aliquotted into collection tubes in accordance with the study specific sample collection and processing guide. Analysis of obtained samples will be in accordance with the study specific laboratory analysis plan.

10.2 Blood processing

Auto-antibody testing

Auto-antibody testing will be performed by the clinical neuroimmunology service in Oxford. It is expected that some samples will be sent for autoantibody testing as part of routine clinical care. These will be processed and results sent as normal. Testing will be done for VGKC-complex, NMDAR, MOG and others as appropriate to the clinical presentation. Similar testing will be performed for the trial samples, (serum and/or cerebral spinal fluid). Research samples for auto-antibody testing will be collected in plain (clotted) tube. Positive antibodies will be titrated at first detection, and again in parallel with samples obtained after study treatment (where available) in order to determine any change in antibody levels.

Cellular immunology studies

Blood obtained for T cell analysis (Lithium Heparin) will processed in accordance with the lab analysis plan. Peripheral blood mononuclear cells (PBMCs) will be isolated using Lymphoprep density gradient centrifugation.

Host inflammatory response

Whole blood (Paxgene), plasma (Lithium heparin) and blood (EDTA) will be analysed for transcriptome, cytokine, and DNA analysis respectively.

11 SAFETY REPORTING

11.1 Table 2: Definition of Serious Adverse Events

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse event of Special Interest (AESI)	Any adverse event of significant scientific, medical, and public interest, relating to an investigational medicinal product and for which ongoing monitoring and rapid communication by the investigator to the study sponsor could be appropriate
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • Requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected	A serious adverse reaction, the nature and severity of which is not consistent

Serious Adverse Reaction (SUSAR)	with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Exposure during Pregnancy

No formal pregnancy testing will be performed as part of the study. However, any pregnancy occurring in a female participant during the study must be reported to CSL Behring within 24 hours of the investigator becoming aware of such information.

Any pregnancy occurring during the clinical trial must be followed up by the clinical team in charge of the participant's on-going medical care and the outcome should be recorded. If a congenital abnormality or birth defect is identified this would fall within the definition of an SAE and should be reported as such.

11.2 Causality

A medically qualified member of the study team should determine the relationship of each adverse event to the trial drug. Relationship should be categorised according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

11.3 Procedures for Recording Adverse Events

Careful clinical monitoring of all patients will be undertaken during infusion of IVIG as part of the standard of care in accordance with CTIMP requirements. For the first five days following IMP administration, adverse events of special interest as specified in the research notes, or any other significant medical event as judged by the investigator will be recorded in the CRF.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. The severity of events will be assessed based on the

degree to which these affect routine care and will be on the following scale: 1 = mild, 2 = moderate, 3 = severe, 4=life threatening, 5=death. AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether or not such an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

11.4 Reporting Procedures for AEs and Serious Adverse Events

Serious adverse events (SAEs)

All SAEs occurring within the 6 month period following randomisation, and all reported pregnancy cases or deaths during the entire study period must be reported on the SAE reporting form and sent by email/fax to the Chief Investigator and CSL Behring within 24 hours of the Site Study Team becoming aware of the event. Other delegated individuals at the Oxford coordinating site will be included in group SAE email list. Receipt of the SAE will be acknowledged by the CI or delegated individual at Oxford. Additional information received for a case (follow-up or corrections to the original case) should be detailed on a new SAE form and faxed or emailed to the Chief Investigator and other relevant individuals at the coordinating site, and CSL Behring.

In the patient study population, it is expected in routine clinical care that acute illness, infections, new medical problems or deterioration of existing medical problems could lead to prolonged hospitalisation, hospital re-admission, significant or permanent disability, incapacity or death. Thus, any significant medical condition that is as a direct result of encephalitis such as (but not limited to) seizures, neurological deficit, significant or permanent disability, learning, behavioural, and speech difficulties do not require immediate reporting. However, these must be discussed with the PI at each recruiting site, and if in doubt, with the CI. An exception to this is where the magnitude of such an event is thought to be disproportionate to expected outcomes from encephalitis or is directly related to administration of the study drug.

The DSMC Chair will be informed, and review all SAEs. However, the timing of reporting to the DSMC would depend on relatedness to the study IMP. SAEs that are judged to be related to the study IMP must be reported to the DSMC Chair within 24 hours of the CI (or delegate) becoming aware. SAEs that are judged to be unrelated to the IMP do not require reporting to the DSMC within 24 hours. A summary list of all SAEs (including those unrelated to the IMP) will be provided in a safety report to the DSMC which will be submitted at regular interval as specified in the DSMC Charter.

11.5 Expectedness

Expectedness of an adverse event will be determined according to the Summary of Product Characteristics for IVIG as listed in Table 3. Expected reactions from the albumin component of the placebo are listed in **Section 9.1.**

Table: 3: List of expected reactions from IVIG

MedDRA System Organ Class (SOC)	**Adverse Reaction**	**Frequency**
Blood and lymphatic system disorders	Haemolysis, anaemia, leukopenia, anisocytosis	Uncommon
Nervous system disorders	Headache	Very common
	Dizziness, head discomfort, somnolence, tremor, sinus headache, migraine, dysaesthesia	Uncommon
Ear and labyrinth disorders	Vertigo	Uncommon
Cardiac disorders	Palpitations	Uncommon
Vascular disorders	Hypertension	Common
	Hypotension, flushing, peripheral vascular disorder	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea, oropharyngeal blistering, painful respiration, throat tightness	Uncommon
Gastrointestinal disorders	Nausea, vomiting	Common
	Diarrhoea, abdominal pain upper	Uncommon
Hepatobiliary disorders	Hyperbilirubinaemia	Uncommon
Skin and subcutaneous tissue disorders	Urticaria, rash	Common
	Pruritus, skin disorder, night sweats	Uncommon

Musculoskeletal and connective tissue disorders	Back pain	Common
	Neck pain, pain in extremity, musculoskeletal stiffness, muscle spasms, musculoskeletal pain, myalgia, muscular weakness	Uncommon
Renal and urinary disorders	Proteinuria	Uncommon
General disorders and administration site conditions	Pyrexia, chills, fatigue, asthenia, influenza-like illness	Common
	Chest pain, general symptom, hyperthermia, pain, injection site pain	Uncommon
Investigations	Bilirubin conjugated increased, blood bilirubin unconjugated increased, Coombs' direct test positive, Coombs' test positive, blood lactate dehydrogenase increased, haematocrit decreased, blood pressure increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood pressure decreased, blood creatinine increased, body temperature increased, haemoglobin decreased	Uncommon

Frequencies have been evaluated using the following convention: Very common (≥1/10 infusions), Common (≥1/100 to <1/10 infusions), Uncommon (≥1/1 000 to <1/100 infusions), Rare (≥1/10, 000 to <1/1,000 infusions), Very rare <1/10,000 infusions).

Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally. Rarely human normal immunoglobulin may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin. Reversible haemolytic reactions have been observed in patients, especially those with non-0 blood groups in immunomodulatory treatment. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment. Increase in serum creatinine level and/or acute renal failure have been observed. Very rarely: Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses. Overdose may lead to fluid overload, particularly in patients with renal impairment.

Transmissible agents

Standard measures to prevent infections resulting from the use of IVIG include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing

steps for the inactivation/removal of viruses. The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), and for the non-enveloped viruses such as hepatitis A virus (HAV) and parvovirus B19. There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins. However, these measures undertaken do not apply to unknown or emerging viruses and other pathogens. As such, the possibility of transmitting infective agents cannot be totally excluded.

A strict data sheet will be kept by CSL Behring which would include the randomisation code aligned to the batch number of assigned IVIG product and in order to maintain a link between the participant and the batch of the product.

11.6 SUSAR Reporting

The CI or delegate will report all SUSARs to the relevant Research Ethics Committee (REC), CSL Behring, the MHRA, and the Sponsor. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days. The CI or delegate will also inform all principal investigators concerned of relevant information about SARs that could adversely affect the safety of participants.

11.7 Safety Monitoring Committee

For the total duration of the study, a DSMC will also be convened to provide independent real-time assessment throughout the study. The chair of the DSMC will be contacted for advice where an investigator feels independent advice or review is important. The DSMC will review safety data (in person or by communication) throughout the study with stopping guidance as specified in the DSMC Charter, or at unscheduled reviews determined by the nature and severity of reported AEs or SAEs. Reports for the DSMC will be prepared by the unblinded trial statistician and will be kept confidential in a restrictive access computer drive and the documents will be password protected. The DSMC Chair will be notified immediately of all SAEs that the CI considers to be of significant safety concern. The DSMC will advise the Chair of the Trial Steering Committee (TSC) if, in their view, the randomised comparison in this study has provided both (a) “proof beyond reasonable doubt” that for all, or for some types of patient, treatment with IVIG is clearly indicated or clearly contraindicated in terms of a net difference in the main outcome measures, and (b) evidence that might reasonably be expected to influence the patient management by many clinicians. Individual participants will be withdrawn from the study treatment if it appears that to continue would be deleterious for their health or safety. This can be determined by the patient or parent/legal guardian, the treating clinician and/or the research team.

The DSMC will be responsible for:

- Review of data quality including completeness of data collected on enrolled participants
- Monitoring recruitment and compliance with protocol by participants and study cites

- Monitoring evidence for treatment differences in the main efficacy outcome measures and any evidence of treatment harm
- The recommendation of the trial to continue or terminate recruitment either for everyone or for some treatment groups and/or some participant subgroups
- Monitoring planned sample size assumptions
- Assessment of impact and relevance of external evidence.

11.8 Development Safety Update Reports

In addition to the expedited reporting above, the Department of Paediatrics, University of Oxford shall submit once a year throughout the clinical trial or on request, a Development Safety Update Report (DSUR) to the REC, Sponsor, Medicines for Healthcare Regulatory Authority (MHRA), and CSL Behring.

12 STATISTICS AND ANALYSIS

12.1 Description of Statistical Methods

Statistical Analysis

The primary statistical analysis will be carried out on the basis of intention-to-treat (ITT). Our primary intention-to-treat analysis will account for steroid use before randomisation as a covariate. We will actively collect information on the use of steroid treatment during the trial and will compare the use of steroid after randomisation between the treatment and placebo group. As required, we will use appropriate methods to investigate the treatment effect accounting for the use of steroid after randomisation as an exploratory analysis. After randomisation, participants will be analysed according to their allocated treatment group irrespective of what treatment they actually receive. We will endeavour to obtain full follow-up data on every participant to allow full ITT analysis, but we will inevitably experience the problem of missing data due to withdrawal, loss to follow up, or non-response questionnaire items. Data analysis will be performed using a mixed effect model for repeated measures, i.e. to incorporate all outcome data collected during the 12 months follow-up, in order to apply the intention-to-treat principle as far as possible and to account for potential biases arising from loss to follow-up. The model will include treatment group, time, treatment-by-time interaction, and baseline covariates. An unstructured correlation matrix will be used to model the within-participant error correlation structure. An appropriate contrast will be specified to test for treatment efficacy between randomised groups at 12 months. We will, also perform various sensitivity analyses using other imputation methods, as well as analysis of 12 month data cross-sectionally, to test whether the results are robust to different assumptions about the missing data. The results from the trial will be prepared as comparative summary statistics (difference in response rate or means) with 95% confidence intervals. All the tests will be done at a 5% two-sided significance level. The study results will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) 2010 statements. A full detailed analysis plan (including plans for any interim analysis, subgroup analysis, and sensitivity analysis) will be prepared and finalised before the first interim analysis.

12.2 The Number of Participants

There is a paucity of RCT data from previous studies to estimate sample size for this study. However, to detect at least 20% clinically significant treatment difference from 43% in the "good recovery" rate (i.e. GOS-E-Peds score 2 or lower) by 12 months after randomisation would be deemed clinically significant. This is similar to a large observational study on autoimmune encephalitis by Titulaer et al (4). Therefore, with 90% power and 5% level of significance (2-sided), a sample size of 308 (154 per group) is required including approximately 10% attrition rate.

12.3 Analysis of Outcome Measures/Endpoints

Primary outcome

The primary efficacy end point in this study is "good recovery", defined by GOS-E-Peds score 2 or lower, at 12 months from randomisation. This will be analysed using a Generalised Linear Mixed Effect model, utilising data collected at discharge, 6 and 12 months from randomisation. An interaction between time and randomised group will be fitted to allow estimation of treatment effect at each time point. The model will adjust for baseline value and other stratification factors (e.g. age and steroid treatment at the time of randomisation).

Secondary and other outcomes

As far as possible, we will use similar method for secondary continuous outcomes collected at multiple time points or analysis of covariance (ANCOVA) for those collected at 12 months only, adjusting for baseline measures (if collected) and any stratification variables. Otherwise, an equivalent nonparametric method will be used for outcomes that violate the normal distribution assumption. A log-binomial regression will be performed on binary outcomes with similar adjustment of baseline covariates. Chi-squared or Fisher's exact test will be used to analyse adverse events and non-adherence.

12.4 Criteria for the Termination of the Trial

This study may be suspended or prematurely terminated if there is sufficient reason to think that that the safety of participants is affected by the study procedures. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the REC, MHRA, and CSL Behring and will provide the reason(s) for the termination or suspension.

Interim analysis

Analysis for the Data and Safety Monitoring Committee will be performed in accordance with the DSMC Charter. Interim reports containing safety and outcome data, along with any other analyses that the committee may request, will be sent to the DSMC in strict confidence. Close monitoring to assess practical aspects of delivering the study interventions and recruitment will also be undertaken. Measures to maximise recruitment will be put in place, as necessary.

12.5 Procedure for Accounting for Missing, Unused, and Spurious Data

Missing data will be reported with reasons given where available and the missing data pattern explored. We will explore the mechanism of missing data, though the mixed effects model does implicitly account for data missing at random.

12.6 Procedure for Reporting any Deviation (s) from the Original Statistical Plan

Any deviation from the analysis plan will be documented in both the latest version of the analysis plan and the final statistical report.

13 DATA MANAGEMENT

13.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained (except where CRF is the source). These include, but are not limited to, patient medical notes (from which medical history, investigation results, previous and concurrent medication may be summarised into OpenClinica), research notes, clinical charts, laboratory results, pharmacy records and drug charts, brain imaging pictures, questionnaires, and any correspondences relating to the participants involvement in the trial.

All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent form and participant identification log, the participant will be referred to by the trial participant number/code, not by name.

13.2 Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

13.3 Data Recording and Record Keeping

OpenClinica is the primary data collection instrument for the study and will be a password protected, central web based database OpenClinica, based at Oxford. This database is stored on a secure sever within the UK with accountability records and will include validation processes to encourage high quality data entry. All data requested in OpenClinica must be recorded. All missing data must be explained.

All entries made to the research notes should be printed legibly. If any entry error has been made, to correct such an error, a single straight line should be drawn through the incorrect entry and the correct data entered above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, the clarification should be printed above the item, and this should also be initialled and dated. Information entered into the research notes must be subsequently transferred onto OpenClinica.

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data file.

The study admission record should be completed within 2 weeks of the patient's admission and once discharged the all other required data should be entered onto OpenClinica within 4 weeks.

If any relevant information has not been recorded in the hospital notes or for situations where a participant is transferred to a non-participating hospital, this will be obtained from either the participant's parent or carer, GP or the clinician involved in the participant's ongoing care.

The University of Oxford UK coordinating centre will retain a sponsor file of all non-patient identifiable information relating to the trial from all participating sites.

Study Records Retention

The investigator at each investigational site must make arrangements to store the essential study documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (International Conference on Harmonisation (ICH) E6, Guideline for Good Clinical Practice) including the Investigator Site File. All study documents will be retained after the completion or discontinuation of the trial for 3 years after the youngest participant turns 18 years.

In addition, the investigator is responsible for archiving of all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The University of Oxford UK coordinating centre undertakes to store any of the above documents including returned questionnaires for the same period. The University of Oxford UK coordinating centre will archive the documents in compliance with GCP utilising the Records Management Service of the University of Oxford. All electronic CRFs and study data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

14 QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations, site-specific and study-specific SOPs (as detailed in the relevant sections of the protocol). Regular monitoring will be performed according to GCP and the study monitoring plan. This will comprise both site visits and remote monitoring. The investigator sites will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the Sponsor's representative and inspection by local and regulatory authorities. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Data Safety Monitoring

A DSMC will be convened to provide independent real-time assessment throughout the study. At the minimum, the committee will comprise a chairman and two other appropriately qualified members. The DSMC will review safety data throughout the study according to the DSMC Charter.

14.1 **Audit & Inspection**

The Quality Assurance manager maintains an internal audit program to ensure that systems relating to trial conduct, data recording, analysis and reporting are functional to meet the requirements of the protocol, GCP and regulators. The audit program also includes laboratory activities taking into consideration the MHRA and EMA guidelines for GCP in the laboratory. The internal audits will supplement the external monitoring process and will review processes not covered by the external monitor.

The Sponsor may carry out audit to ensure compliance with the protocol, GCP and appropriate regulations. GCP inspections may also be undertaken by the MHRA to ensure compliance with protocol and the Medicines for Human Use (Clinical Trials) Regulations 2004.

14.2 Trial Progress

The CI will oversee the progress of the trial

15 SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

16 ETHICAL AND REGULATORY CONIDERATIONS

16.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate REC, regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4 Reporting

The CI or delegate shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation, the Sponsor and CSL Behring. In addition, an End of Study notification and final report will be submitted to the same parties.

16.5 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the research notes and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

16.6 Reimbursement

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

16.7 Other Ethical Considerations

The testing of samples and examination of the MRI scans are intended solely for research and may not diagnostic purposes and therefore are not a substitute for a clinical appointment. Analysis of samples and MRI scans may not be done in a timely fashion to be useful clinically. In the case of an incidental finding of a possible abnormality, the results will be discussed with the clinical team at the site where the participant was recruited. Where the participant's ongoing care is in a local hospital not participating in the study the PI will inform the appropriate clinical team. The clinical team will discuss implications with the parent/guardian/legally authorised representative/participant and further investigations will be arranged as necessary.

17 FINANCE AND INSURANCE

17.1 Funding

This study is funded though by the National Institute for Health Research (Efficacy and Mechanism Evaluation theme). The study drugs will be provided by CSL Behring via the Interlaken Award.

17.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment which is provided.

18 PUBLICATION POLICY

The Investigators will be involved in preparing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the National Institute for Health Research and CSL Behring. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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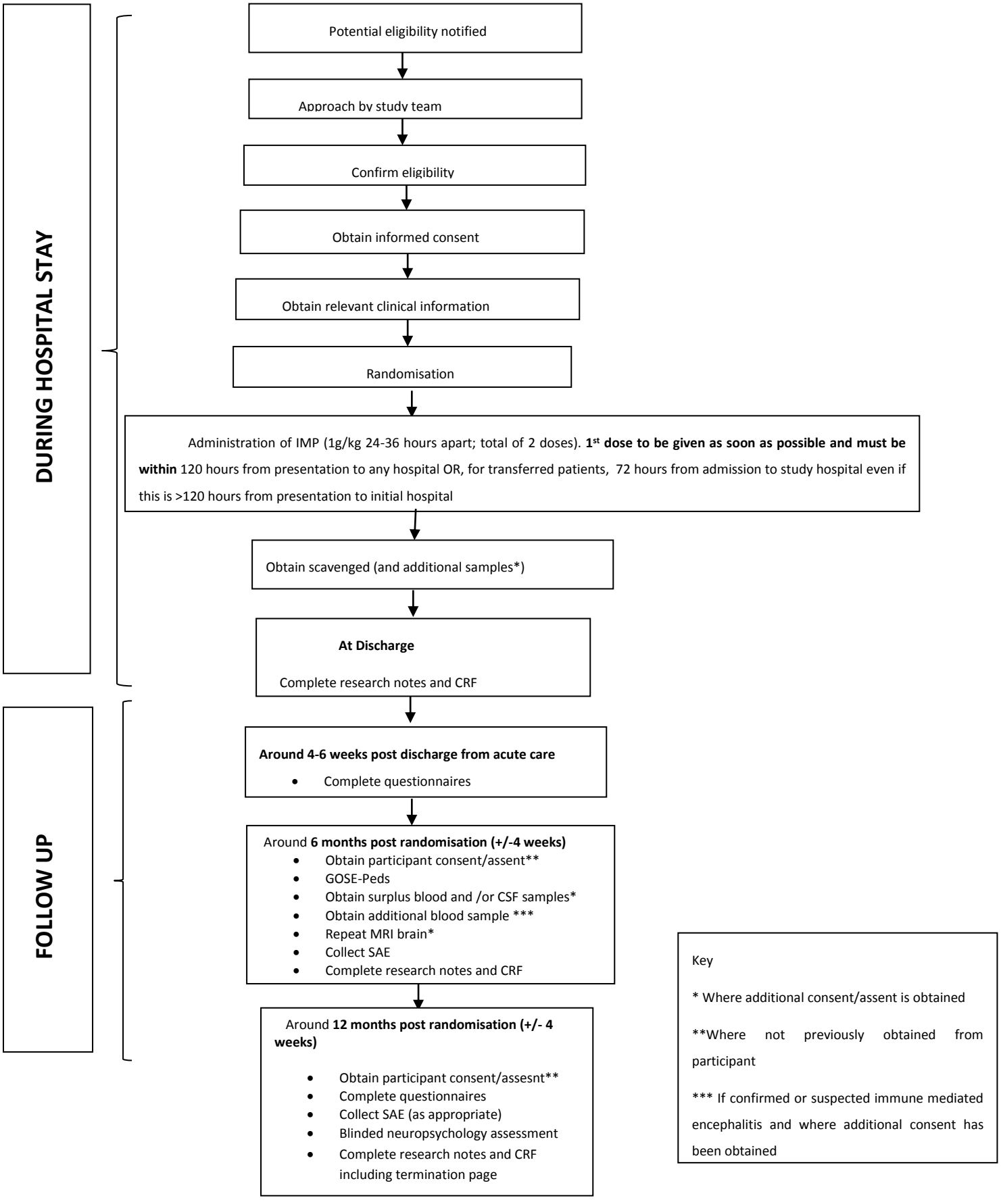
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20 APPENDIX A: STUDY FLOW CHART



21 APPENDIX B: SCHEDULE OF STUDY PROCEDURES

	T0 (as soon as possible, to allow administration of 1st IMP dose within the stipulated timelines)	T1 (As soon as possible and must be within 120 hours from presentation to any hospital OR, for transferred patients, 72 hours from admission to study hospital even if this is >120 hours from presentation to initial hospital	T1+24 (24 hours following receipt of 1st IMP dose)	T2 (24-36 hours after 1st dose of study drug)	T2+24-48 (24-48 hours after the 2nd dose of study drug)	T2+7 (7 days following 2nd IMP dose)	T3 (On day of discharge and up to 48 hours prior to discharge)	T4 (Around 4-6 weeks post discharge from acute care	T5 (Around 6 months +/-4 weeks post randomisation)	T6 (Around 12 mont weeks post randomis
Eligibility assessment	X									
Informed consent ^	X						X@		X@	X@
Confirm consent		X							X	X
Demographics	X									
Medical history	X	X		x			x		X	X
Obtain relevant clinical information	X	X	X	X		X	X		X	X
Enrolment	X	X**								
Randomisation	X	X**								
Scavenged samples#	X	X	X	X		X	X	X	X	X

additional (research) sample if consent obtained)	X	X**	X	X**		X			X[b]	
Mandatory FBC					X					
IMP administration and monitoring		X		X						
SAE assessment		X	X	X		X	X	X	X	X*
Completion of research notes and CRF[#]		X	X	X		X	X	X	X	X
Questionnaire completions								X	X	X
Research MRI scan (if consent obtained)~									X	
Neuropsychologist assessment										X

Key:

^ Consent and assent must be obtained from all participants when clinically appropriate during the study

*Only deaths or where a serious adverse event is judged to be directly related to the IMP

Identification of scavenged samples and entry of clinical information into the research notes and CRF should be an ongoing process that occurs throughout the study. As appropriate, any required information should be entered as soon as they become available

**where not previously done

[@]participant consent (if 16 years and where if not previously obtained)

~May not be required if routine follow up MRI scan is planned, depending on timing of this. See Section 8.8 (radiological evaluation)

[b] To avoid an extra visit solely for this purpose, the '6 month research sample' can be obtained at any routine follow up clinical appointments that occur after the participant has been discharged.

Note: Baseline research sample can be obtained at either T0 or T1 while T1+24 can be obtained just before the 2nd IMP dose if this is being given at 24 hours after the 1st IMP dose.

22 APPENDIX D: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.1	18.12.2014	Mildred Iro	1. SUSAR reporting section was modified to permit delegation of SUSAR reporting responsibilities by the CI 2. Clinicaltrial identifier was added 3.Study short title was added
2	1.2	21.01.2015	Mildred Iro	1. Changes to study design (i) Addition of mortality as a study endpoint (ii) Amendment to time window for administration of the 1st dose of the study IMP (iii) Clarification of text relating to the neuroimaging aspects of the protocol (iv) Amendment to text relating to where the neuropsychology assessment should

				be performed (v) Removal of gene expression and Biobank as study endpoints (vi) Addition of a further exclusion criterion relating to prior receipt of IVIg treatment 2. Addition of text relating to the recruitment of non-English speakers 3. Amendment to text relating to the unblinding process 4. Changes relating to the cellular immunology aspects of the protocol: (i) Amendment to blood volume to be obtained for the cellular immunology analyses (iii) Amendment to the window for processing the cellular immunology blood samples 5. Clarification of level of training required for administration of the study IMP 6. Clarification of text relating to the treatment of reaction occurring during

				IMP administration 7. Clarification of text relating to IMP exposure during pregnancy 8. Correction made to SAE definition 9. Clarification of time points for obtaining research blood samples 10. Several minor administrative changes made to text for clarity
3	2.0	05/08/15	Mildred Iro	1. Change to the timing of completion of discharge questionnaires 2. Removal of GOSEPeds at discharge 3. Amendment to text relating to one of the exploratory objectives and clarification of outcome measures to achieve this objective 4. Change to and addition of new study time point for research blood sampling 5. Removal of 'region' as a stratification factor for randomisation 6. Amendment of information relating to documentation of

				participant Study ID 7. Clarification on the process of questionnaire completion 8. Amendment to text relating to blood processing for clarity 9. Amendment to the Study Flow Chart and Schedule of Study Procedures 10. Several minor amendments made to text for clarity.
4	2.1	17.09.15	Mildred Iro	1. Clarification of time window for administration of first IMP dose 2.Clarification of exclusion criterion relating to IgA deficiency 3.Clarification to text relating to research sample type being collected 4.Clarification of text relating to withdrawal of participant from study treatment 5.Clarification of the role of DSMC relating to review of data quality 6.Amendment to the risk of anaphylaxis following general anaesthesia 7.Minor amendment made to schedule of study

				procedures to clarify timing of research blood sampling.
5	3.0	04.11.2015	Mildred Iro	1. Addition of mandatory full blood count check 24-48 hours following the 2nd IMP dose as a risk mitigation measure to monitor for signs of haemolysis with IVIG treatment 2. Amendment to age ranges that define which of the neuropsychology assessments will be done
6	4.0	10.03.2016	Amanda Wilkins	1. Page 36: Time point '***T6*** Around 12 months post randomisation' was incorrectly documented as '***T5*** Around 12 months post randomisation'. This has been corrected to read T6. 2. Page 42: Section 9.5 Concomitant Medications - The sentence '*Participants*

				should not be enrolled if they are still being actively followed up in another study that involves an IMP' has been removed, consistent with similar changes in version 3.0 of the protocol, as per the decision at the previous DSMC meeting.