

Dexamethasone in Herpes Simplex Virus Encephalitis Randomised Controlled Trial and Non- HSV Cohort Study



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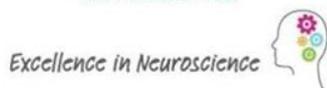
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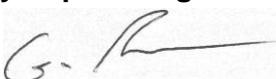
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General Information

This document describes the **DexEnceph** trial and provides information about procedures for recruiting patients. Corrections or amendments may be necessary and will be circulated to the registered investigators in the trial. Centres entering patients for the first time are advised to contact the coordinating centre Clinical Trial Research Centre to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via the CTU.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted. Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

Statement of Compliance

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, CTU Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

This study is a Clinical Trial of an Investigational Medicinal Product (CTIMP) and requires a risk assessment and a Clinical Trial Authorisation (CTA) from the MHRA. CTIMPs are regulated by the Medicines for Human Use (Clinical Trials) Regulations 2004 Statutory Instruments (SI 2004/1031) and subsequent amendments that implement EU Directives 2001/20/EC (The European Clinical Trials Directive) and 2005/28/EC (The Good Clinical Practice Directive) into UK law. CTIMPs are also regulated by subsequent regulatory amendments included in the table below and those occurring during the period of the trial.

Relationship Statements

The UK Clinical Research Collaboration (UKCRC; www.ukcrc.org) is a partnership organisation working to establish the UK as a world leader in clinical research. Following a review by an international panel, the Clinical Trials Research Centre (CTRC) at the University of Liverpool has been assessed as reaching the highest quality standard required by the UKCRC and achieved full UKCRC registration.

The CTRC encompasses clinical trials activity in areas including medicines for children (The Medicines for Children Research Network Clinical Trials Unit; MCRN CTU), neurology, personalised medicine, infection, oral health and obstetrics and gynaecology (<http://www.ctrc.org.uk/>). All CTRC activities are underpinned by methodological rigour, a modern data management system, similar technical requirements and a common set of standard operating procedures.

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Glossary

A&E	Accident and Emergency Department
ACE III	Addenbrooke's Cognitive Examination revised
AE	Adverse Event
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
AR	Adverse Reaction
CI	Chief Investigator
CNS	Central Nervous System
CPT	Cell Preparation Tube
CRF	Case Report Form
CRN	Clinical Research Network
CSF	Cerebrospinal fluid
CTRC	Clinical Trials Research Centre
CTU	Clinical Trials Unit
DNA	Deoxyribonucleic Acid
eGFR	Estimated glomerular filtration rate
GABABR	γ -aminobutyric acid receptor
GBCA	Gadolinium-Based Contrast Agent
GCS	Glasgow Coma Score
GOS	Glasgow Outcome Score
GOSE	Glasgow Outcome Score Extended
GP	General Practitioner
HDU	High Dependency Unit
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
HSVE	Herpes Simplex Virus Encephalitis
IB	Investigator's Brochure
IBW	Ideal Body Weight
ICH	International Conference of Harmonisation
IDSMC	Independent Data and Safety and Monitoring Committee
IEC	Independent Ethical Committee
IL	Interleukin
IMP	Investigational Medicinal Product
IMP	Investigational Medicinal Product
INF γ	Interferon gamma
INR	International Normalised Ratio
ITU	Intensive Care Unit
IVIG	Intravenous Immunoglobulin
LOS	Liverpool Outcome Score
LP	Lumbar Puncture
MAU	Medical Assessment Unit
MCRN	
CTU	Medicines for Children Research Network Clinical Trials Unit
MREC	Main Research Ethics Committee
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Score
NAB	Neuropsychology Assessment Battery
NIHR CRN	National Institute for Health Research Clinical Research Network

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NIMP	Non-Investigational Medicinal Product
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PIL	Patient Information Leaflet
PISC	Patient Information Sheet and Consent Form
PPI	Proton Pump Inhibitor
QA	Quality Assurance
QC	Quality Control
QDS	Four times a day
QOL	Quality of Life
R&D	Research & Development
RCT	Randomised Control Trial
REC	Research Ethics Committee
RN	Research Nurse
	When RN is referred to in this protocol it means either the research nurse or someone who has been delegated that duty
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDS	Three times a day
TMG	Trial Management Group
TNF α	Tumour Necrosis Factor alpha
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
VGKC	Voltage-Gated Potassium Channel Complex
WAIS	Wechsler Adult Intelligence Scale
WMS	Wechsler Memory Scale

1 PROTOCOL SUMMARY

Title: DexEnceph: A pragmatic, randomised, controlled, observer-blind trial comparing clinical outcomes in adults who receive dexamethasone alongside standard treatment versus standard treatment alone for Herpes Simplex Virus Encephalitis.

Phase: III

Study Centres NHS Hospitals across the United Kingdom.
Patients recruited whilst inpatients.

A. DexEnceph Randomised Controlled Trial

B. Non-HSV Cohort Study.

A. DexEnceph Randomised Controlled Trial (RCT)

Target Population: 90 patients

Duration of Patient Participation: 18 Months

Recruitment Period: 4 years and 3 months

Inclusion criteria: Enrolled patients must fulfil ALL the following criteria (1-5):

1. Suspected encephalitis criteria: New onset seizure or alteration in consciousness, cognition, personality, or behaviour*.
2. A positive HSV PCR result from CSF, reported not more than 7 days prior to randomisation.
3. Receiving intravenous aciclovir dosed at 10mg/kg TDS or at a reduced dose if clinically indicated.
4. Age \geq 16 years.
5. Written informed consent has been given by the patient or their legal representative.

* Personality / behaviour change includes: agitation, psychosis, somnolence, insomnia, catatonia, mood lability, altered sleep pattern.

Exclusion Criteria Patients are excluded if ANY criteria are present:

1. Having received oral or injectable corticosteroid therapy in the 30 days prior to the day of admission to hospital**.
2. History of hypersensitivity to corticosteroids.
3. Immunosuppression secondary to:
 - a. Known HIV infection AND CD4 count under 200cell/mm³;
 - b. Currently taking biologic therapy or other immunosuppressive agents [azathioprine, methotrexate, ciclosporin];
 - c. Previous solid organ transplant and currently on immunosuppression;
 - d. Previous bone marrow transplant;
 - e. Currently undergoing a course of chemotherapy or radiotherapy;
 - f. Known primary immunodeficiency syndrome;
 - g. Known current haematological malignancy.
4. Pre-existing indwelling ventricular devices.
5. Peptic ulcer disease in the last 6 months: defined as a peptic ulcer seen at endoscopy or an upper gastrointestinal bleed causing ≥ 2 unit haemoglobin drop in the last 6 months.
6. Antiretroviral regime containing rilpivirine as current treatment.

**Participants are not excluded if steroids are administered after admission prior to randomisation.

Intervention: Randomisation to receive dexamethasone 10mg intravenously 6 hourly for 4 days, or no dexamethasone. Dexamethasone should be administered as soon as possible after randomisation.

Aciclovir antiviral treatment will be administered as part of standard care: 10mg/kg aciclovir 8 hourly (or at a reduced dose if clinically indicated) for at least 14 days. Continuation of aciclovir is guided by follow-up CSF examination as per national guidelines on the management of HSV encephalitis.

Follow up of all Participants: Neuropsychology testing, MRI scanning, functional and disability outcome scoring, blood testing and health status and quality of life assessments (see individual time points below).

Primary Outcome: Verbal memory score, as determined by the Wechsler Memory Scale (WMS-IV) Auditory Memory Index at 26 weeks after randomisation.

Secondary Outcomes: (Time points given are from randomisation)	Neuropsychological Outcome Measures [26 weeks and 78 weeks] Visual, immediate and delayed memory (WMS-IV), Processing speed and working memory(WAIS-IV), Language (NAB) & Higher executive function (Trail Making Tests Parts A and B) Anxiety and Depression (BDI & BAI) Subjective cognitive complaints (Perceived Deficits Questionnaire) Cognitive Outcome Measures [at 30 days/discharge, 26 weeks and 78 weeks] Addenbrooke's Cognitive Assessment revised (ACE-III) Clinical Outcomes Incidence of epilepsy Time to hospital discharge Requirement of HDU/ITU admission Time to cessation of ventilatory support [if any] Time to maximum recorded GCS [up to 30days/hospital discharge, whichever is sooner] Survival Disability & Functional Outcomes [at 30 days/discharge, 26 weeks and 78 weeks] Modified Rankin Score, Barthel Index, Liverpool Outcome Score and Glasgow Outcome Score Extended Imaging Outcomes [Baseline, 2 weeks, 26 weeks and 78 weeks] Temporal lobe volume (as % of intra-cranial volume). Whole brain volume (as % of intra-cranial volume). Volume of affected region as seen on FLAIR image (as % of intra-cranial volume). Volume of affected region as seen on diffusion-weighted image (as % of intra-cranial volume). Biomarker outcomes Transcriptomic and proteomic profiling on blood at baseline, 2 weeks and 26 weeks & CSF at baseline and 2 weeks Anti NMDA receptor antibody testing at 26 weeks Safety Outcomes Proportion of patients with detectable HSV in CSF by PCR at 2 weeks White blood cell function at baseline and 26 weeks Health Status and Quality of Life [at 26 and 78 weeks] Measured by the EuroQOL-5D-5L and SF-36 self-completed questionnaires
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B. Non-HSV Cohort Study

Target population: 90 patients

Inclusion Criteria: Enrolled patients must fulfil ALL the following criteria (1-3):

1. Suspected encephalitis criteria: New onset seizure or alteration in consciousness, cognition, personality , or behaviour*
2. Age \geq 16 years
3. HSV PCR negative on CSF sample

* Personality / behaviour change includes: agitation, psychosis, somnolence, insomnia, catatonia, mood lability, altered sleep pattern.

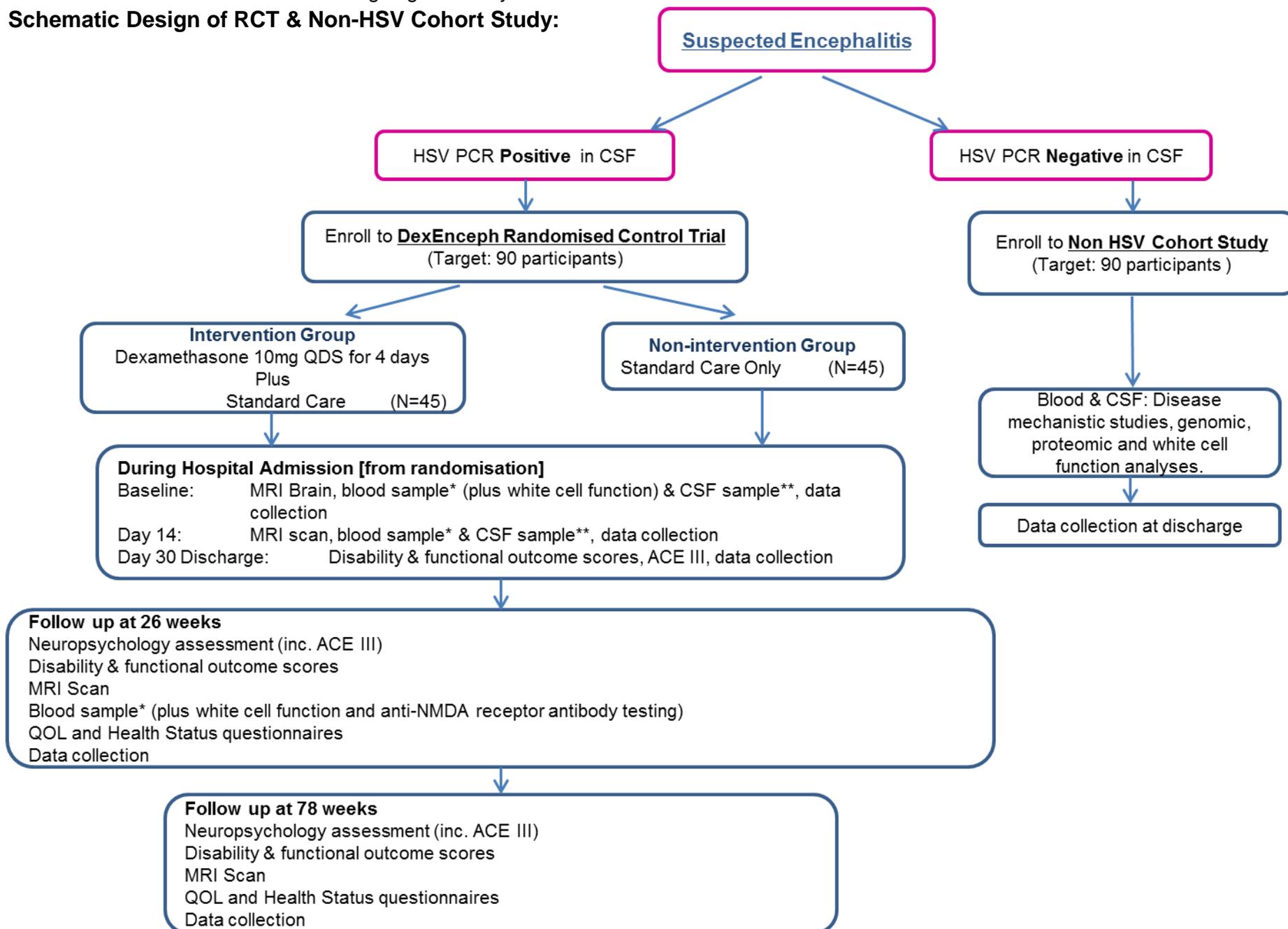
Duration of patient participation: Duration of inpatient stay.

Samples: Blood samples will be collected as per protocol. When a lumbar puncture is required as part of standard clinical care an additional CSF sample will be collected.

Outcome: To compare the disease processes and pathological mechanisms of HSV encephalitis to those who do not have HSV encephalitis.
Transcriptomic and proteomic profiling on blood & CSF and white cell function analyses on blood within 7 days of enrolment

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Schematic Design of RCT & Non-HSV Cohort Study:



*Bloods for proteomic and genomic analysis ** CSF for mechanistic studies and quantitative HSV PCR

2 BACKGROUND INFORMATION

2.1 Introduction

Encephalitis means inflammation and swelling of the brain. It is often caused by a virus, such as herpes simplex virus (HSV) or by the body's defences. HSV encephalitis has an incidence of 1 per 250-500,000(1) and meets the definition of a very rare disease (1 per 100,000). It is, however, the most commonly identified infectious cause of encephalitis in the United Kingdom(2) and accounts for 5-10% of cases of encephalitis worldwide(3).

Health Impact: The impact of HSV encephalitis is disproportionately large, with huge socioeconomic demands on patients, carers and health services(4, 5). In 2012-13, HSV encephalitis accounted for 608 finished consultant episodes, of which 542 were inpatients aged 16 and over, and which amounted to 8,828 bed days(6). Estimations of hospital stay costs in patients with encephalitis in the United States have shown a hospital admission in 2010 with HSVE cost an average of \$58,082, with total encephalitis-associated hospitalizations amounting to \$2.0 billion(7).

Clinical Outcome: Like other neurological infections, the impact of HSV encephalitis extends beyond the initial acute care needs and hospital stay because of the long-term sequelae this devastating infection has on sufferers. Prior to the use of aciclovir HSV encephalitis had a mortality rate of 70% and survivors were left with severe neurological impairments(8). With the standard use of acyclovir, mortality from HSV encephalitis dramatically reduced to about 10% at 6 months but survivors are left with lifelong neurological sequelae(9, 10). From retrospective studies using the Glasgow Outcome Score (GOS) as a measure of disability at 6 months, only 14% of sufferers of HSV encephalitis treated with aciclovir completely recovered, 23% have mild disability, 28% have moderate disability and 20% are severely disabled(11). Common sequelae in patients are memory impairment, present in 69% of survivors, personality and behavioural abnormalities, in 45% of survivors, dysphasia, in 41%, and epilepsy, in 24%(12). Neuropsychological outcomes are more severe and widespread in patients with HSV encephalitis compared to other causes of acute encephalitis(13) with anterograde memory dysfunction being the most common finding(14). Verbal memory and cognitive defects are much more common in survivors of HSV encephalitis compared to those with encephalitis due to other aetiologies (5, 15).

Long Term Outcome: After their hospital discharge survivors are usually unable to return to their previous lifestyle, thus imposing a huge impact on families and carers. In one study, 45% of survivors of HSV encephalitis that were in employment prior to their illness, were unemployed at 3 years; and of those able to return to work some returned at a part time basis or with fewer responsibilities(5). Encephalitis survivors also suffer long term adverse effects on their quality of life, with infectious encephalitis associated with the worst quality of life in adults(16). Even when patients survive apparently intact, this often proves not to be the case and families often say the person they took home with them is not the same as the one they brought to hospital with changes in personality, irritability and poor short term memory(17).

Current Management: Currently HSV encephalitis is treated with the antiviral drug aciclovir, which inhibits the herpes virus DNA polymerase enzyme and thus arrests viral replication. However, evidence indicates acute brain inflammation and swelling are major components in pathogenesis (1). Studies have proven that an acute intrathecal inflammatory response occurs in patients with HSV encephalitis and that immune-mediated pathogenicity may be related to poor outcome (18, 19). Intrathecal concentrations of several immune mediators including IL6, INF γ , TNF α , IL-2 receptor and sCD8 have been found to be increased in HSV encephalitis (18). Proinflammatory chemokines, particularly monocyte chemoattractant protein, (MCP-1), and the inflammatory cytokine production triggered by innate immunity have been linked to poor outcome(20, 21). Anecdotal case reports describe how some patients suffer such a severe inflammatory response within the limited confined space of the skull that decompressive craniectomy is required(22).

Neuroimaging: Early MRI scanning is recommended for patients with suspected HSV encephalitis to aid diagnosis due to its high specificity and sensitivity(23). The presence of radiological changes has been associated with poorer outcomes in HSV encephalitis (24-26) and bilateral temporal lobe swelling determined at MRI is associated with the severity of neuropsychological sequelae, especially memory impairment(27). In recent years our ability to detect changes and quantify cerebral oedema has improved with advancing imaging techniques and MRI allows non-invasive quantification of brain volume and oedema(28-30). We are now also able to radiologically distinguish between cytotoxic and vasogenic oedema(31), with a small number of studies suggesting both forms may be present in HSV encephalitis(32-34). Vasogenic oedema associated with intracerebral tumours responds well to corticosteroid treatment(35) however steroids have not been proved beneficial in the care of other acute neurological conditions with associated oedema such as traumatic head injury(36) and ischaemic stroke(37).

Autoantibodies: The field of encephalitis that is caused by the body's own defences attacking the brain in error, called autoimmune encephalitis, is rapidly expanding. This cause of encephalitis is becoming increasingly recognised as a significant problem. There is a continuous rise in the number of cell surface or synaptic proteins that are targets of autoimmunity. Known targets include components of the voltage gated potassium channel complex (VGKC); the N-methyl-d-aspartate receptor (NMDAR), the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), the γ -aminobutyric acid receptor (GABABR), and the glycine receptor. There are several case reports that describe the development of NMDAR antibodies after suffering HSV encephalitis(38-45). HSV has been demonstrated to be a trigger of autoimmunity and there is evidence intracranial HSV infection triggers NMDAR antibody production (38, 46). However, the link between NMDAR antibody production post HSV encephalitis and development of classic symptoms of anti-NMDAR encephalitis is still poorly understood. Some authors suggest that treatment of HSV encephalitis with corticosteroids alongside aciclovir may be beneficial in addressing the risk of recurrence from anti-NMDAR antibodies(40).

Corticosteroids: The use of the corticosteroid dexamethasone in neurological infections has proven a mortality benefit in adults with bacterial meningitis(47) and in tuberculous meningitis(48). There has been longstanding interest in the role of corticosteroids in HSV encephalitis and they were indeed used as treatment for HSVE prior to the advent of antiviral

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therapy, though their efficacy was uncertain. Retrospective analyses and animal data suggest there is a benefit and highlight the need for a randomised controlled trial to address this question(24, 26).

2.2 Rationale

Aciclovir, was introduced in the 1980s and significantly reduced the mortality from HSV encephalitis. However, the proportion of patients surviving with sequelae has actually increased (11, 12, 49). The role of corticosteroids in dampening the immune response by decreasing activation of inflammatory pathways has been postulated as the mechanism by which it may be beneficial in HSV encephalitis.

Current Knowledge: Experimental data in different animal models of HSV encephalitis suggests that glucocorticoids improve long term MRI changes when given alongside aciclovir (50), do not impair viral clearance and may even promote a decrease in HSV viral load(50-52). In one study glucocorticoids given at day 3 after inoculation of HSV in mice conferred a survival advantage compared to mice treated with aciclovir alone or those who received corticosteroids from day 0; these mice also displayed less severe clinical signs(53). In humans few case series or retrospective trials have been carried out but they have suggested a benefit in the use of steroids in HSV encephalitis (54-58). Of these, the largest is a retrospective analysis of 45 patients in which older age, lower GCS at presentation, and no corticosteroids were the three best predictors of a poor outcome and all reached statistical significance(54). There is also a theoretical benefit of corticosteroid use in HSV encephalitis for symptom recurrence secondary to anti-NMDA receptor antibodies.

The main concern regarding the administration of immunosuppressive corticosteroids to patients with HSV in CSF is that this will lead to uncontrolled viral replication and spread. Patients receiving a short course of intravenous corticosteroids may theoretically also suffer the common complications and side effects of steroid therapy. However, previous trials regarding CNS infections and corticosteroid therapy have highlighted the safety of administering short courses of steroids in this context (47). Given acutely, combination therapy with steroids and aciclovir reduces brain HSV viral loads in animal models of HSV encephalitis to the same or even a greater extent than aciclovir monotherapy (50, 51). Human studies have also highlighted the lack of correlation between HSV viral load and severity of clinical signs, degree of cranial imaging findings or overall outcome (59-62).

The study question: This trial aims to answer the question of whether steroids are beneficial and safe in treating HSV encephalitis. It will recruit adult patients with HSV encephalitis and randomise them to either receive 10mg four times a day of intravenous dexamethasone over 4 days or not. This dose, route and regimen were successfully used in patients with bacterial meningitis and is part of standard care of adult patients with suspected meningitis in the UK. It has been extrapolated for use in encephalitis. The trial will determine whether dexamethasone improves neuropsychological outcomes in sufferers of HSV encephalitis without allowing uncontrolled viral replication. It will also address whether corticosteroids improve imaging, functional and quality of life outcomes as well as provide a better understanding of the disease mechanisms in HSV encephalitis.

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Potential impact: If corticosteroids are shown to improve outcomes of patients with HSV encephalitis whilst not impacting on safety they will become part of the standard treatment for all patients, and will be incorporated into future updates of the National Encephalitis Guidelines. A better understanding of the disease mechanisms will direct us towards new more targeted immunomodulatory therapies. This information will potentially be important, not just for HSV encephalitis, but for also other forms of encephalitis.

2.3 Objectives

To evaluate a four-day treatment regimen of intravenous dexamethasone at a dose of 10mg four times a day in participating adults with confirmed HSV encephalitis. This will be given alongside standard care, which consists of the antiviral aciclovir.

The objective of the trial is to assess patients with HSV encephalitis who may or may not have received the trial intervention alongside standard care on various outcome domains.

The trial's principal objective is to evaluate whether this corticosteroid regimen improves neuropsychological outcomes in patients with HSV encephalitis, as determined by a verbal memory score at 26 weeks.

The effect of dexamethasone in participants' clinical course, and disability will also be evaluated. The trial will examine the effect of dexamethasone on brain volume and temporal lobe volume as measured by MRI and compare structural MRI changes with neuropsychological and cognitive outcomes. DexEnceph also aims to gain a better understanding of the mechanisms of inflammation and pathogenesis in HSV encephalitis and the effect of corticosteroids on these.

It will also the impact of corticosteroids on clearance of HSV from the CSF, perform functional white cell analyses, and monitor other infection parameters.

Please refer to section 4 for a full list of outcome measures.

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

The potential risks of participation will be described during the consent process to patients and family members and will also be included in the trial patient information leaflet (PIL).

As corticosteroids are immunosuppressive, there is the theoretical risk that the body's natural control of HSV replication will be impaired in the intervention arm. Animal studies suggest that corticosteroid therapy alongside aciclovir treatment does not result in worsening virological control(50, 51) and their use is not predictive of a prolonged clinical course in humans(24). Studies suggest that baseline HSV CSF viral load in humans is not predictive of clinical outcome (59, 63, 64) and persistence of HSV has been found to be a predictor of poor outcomes in some studies (63) but not others(24, 65). Thus, the theoretical risk of uncontrolled viral replication caused by corticosteroids has not been proven in clinical studies and, even if this was the case, this has not been conclusively linked to worsening of clinical outcomes.

This theoretical risk will be mitigated by the secondary endpoint of viral detection in the CSF at 2 weeks. Although a positive HSV PCR result at 14 days after commencement of aciclovir

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is possible in routine clinical practice, in this study is a reportable adverse event and CSF will be analysed centrally to enable accurate comparison of baseline and 2 weeks HSV quantification. This parameter will be carefully monitored by the Independent Data Safety and Monitoring Committee (IDSMC).

Dexamethasone given at 10mg QDS for 4 days was found to be safe in patients with bacterial meningitis with no increased risk of adverse events compared to placebo(47). Of the 157 patients enrolled in the treatment arm in that study, only three stopped treatment due to medication-related side effects; these were 2 due to hyperglycaemia and 1 due to agitation. Dexamethasone is a widely used drug with a well-established safety profile. We will monitor closely for any adverse events whilst patients take the study drug and for 30 days after to be able to pick up any increased risk during study participation. The exclusion criteria for this trial acknowledge patients at increased risk from receiving a short high-dose corticosteroid treatment regimen and does not allow their participation (59).

2.4.2 Known Potential Benefits

Patients recruited to DexEnceph will receive standard NHS care during the conduct of the trial. Participation in this trial requires compliance to national encephalitis guidelines(23) which are embedded in the processes of this protocol. This could translate into better outcomes for all trial participants regardless of the trial arm.

In addition, the intervention group will be administered corticosteroids with the potential benefit of reduction in brain oedema and consequent better neuropsychological, functional and disability outcomes.

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3 SELECTION OF CENTRES /CLINICIANS

Criteria for the selection of centres will be determined by the Trial Management Group and will be described in the supplementary document 'DexEnceph Centre Assessment Criteria'.

Initiation of centres will be undertaken in compliance with CTRC SOPs TM017 and TM018.

Centres fulfilling the criteria will be selected to be recruitment centres for the DexEnceph RCT and Non-HSV Cohort Study and will be opened to recruitment upon successful completion of all global (e.g. MREC and MHRA) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to CTU as detailed in the trial 'greenlight' checklist.

Participating centres will be listed in the 'DexEnceph Participating Centres' log, maintained separately to the protocol.

4 STUDY DESIGN

DexEnceph consists of a RCT which will assess and compare the outcomes of patients with HSV encephalitis randomised to receive dexamethasone or not. Patients will be randomised at the time of diagnosis of HSV encephalitis but they can be identified earlier and prospectively consented prior to laboratory confirmation of HSV in the CSF (please refer to section 6).

This is an observer blind, open label, prospective, randomised controlled trial of dexamethasone fixed dosing of 10mg 6 hourly for 4 days versus no dexamethasone in adult patients with HSV encephalitis.

The project also has a Non-HSV Cohort Study that aims to compare the disease processes and pathological mechanisms of HSV encephalitis to those who do not have HSV encephalitis but present to hospital with similar symptoms.

4.1 DexEnceph RCT Primary Outcome

The primary outcome is a verbal memory score as determined by the Wechsler Memory Scale (WMS-IV) Auditory Memory Index, at 26 weeks post randomisation.

4.2 DexEnceph RCT Secondary Outcomes

Neuropsychological outcome measures at 26 weeks and 78 weeks post randomisation

1. Visual Memory Index, Immediate Memory Index, and Delayed Memory Index - assessed by the Wechsler Memory Scale version IV (WMS-IV);
2. Processing speed and Working Memory - assessed by the Wechsler Adult Intelligence Scale version IV (WAIS-IV);
3. Language -assessed by the confrontational naming task of the Language Module in the Neuropsychology Assessment Battery (NAB);
4. Higher executive function -assessed by Trail Making Test Parts A and B;
5. Anxiety and depression -assessed by self-completed Beck Depression Inventory and Beck Anxiety Inventory;
6. Participant's subjective cognitive complaints- assessed by the Perceived Deficits Questionnaire.

Cognitive Assessment at 30 days/discharge, 26 weeks and 78 weeks post randomisation

7. Addenbrooke's Cognitive Assessment (ACE-III);

Clinical Outcomes

8. Incidence of epilepsy ;
9. Time to hospital discharge;
10. Requirement of intensive care or high dependency admission;
11. Time to cessation of ventilatory support [if any];
12. Time to maximum recorded Glasgow Coma Scale [up to 30days/hospital discharge, whichever is sooner];

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13. Survival;

Disability & Functional Outcomes at 30 Days /Discharge, 26 weeks and 78 weeks post randomisation

- 14. Glasgow Outcome Score Extended (GOS-E);
- 15. Liverpool Outcome Score (LOS);
- 16. Barthel Index;
- 17. Modified Rankin Scale (mRS);

Imaging Outcomes at baseline, 2 weeks, 26 weeks and 78 weeks post randomisation

- 18. Temporal lobe volume (as % of intra-cranial volume);
- 19. Whole brain volume (as % of intra-cranial volume);
- 20. Volume of affected region as seen on FLAIR image (as % of intra-cranial volume);
- 21. Volume of affected region as seen on diffusion-weighted image (as % of intra-cranial volume);

Biomarker outcomes

- 22. Transcriptomic and proteomic profiling on CSF at baseline and 2 weeks; on blood at baseline, 2 weeks, and 26 weeks;
- 23. Anti NMDA receptor antibody testing at 26 weeks;

Safety Outcomes

- 24. Proportion of patients with detectable HSV in CSF by PCR at 2 weeks;
- 25. White blood cell function at baseline and 26 weeks;

Health Status QOL Assessments at 26 weeks and 78 weeks post randomisation

- 26. Patient-completed EuroQOL-5D-5L questionnaire;
- 27. Patient-completed SF-36 questionnaire.

4.3 Non-HSV Cohort Study Outcomes

To compare the disease processes and pathological mechanisms of HSV encephalitis to those who do not have HSV encephalitis:

Transcriptomic and proteomic profiling on blood and CSF and white cell function analyses on blood within 7 days of enrolment.

5 STUDY POPULATION

5.1 DexEnceph Randomised Controlled Trial

5.1.1 Inclusion Criteria

Enrolled patients must fulfil ALL the following criteria:

1. Suspected encephalitis criteria: New onset seizure or alteration in consciousness, cognition, personality, or behaviour*.
2. A positive HSV PCR result from CSF, reported not more than 7 days prior to randomisation.
3. Receiving intravenous aciclovir dosed at 10mg/kg TDS or at a reduced dose if clinically indicated.
4. Age \geq 16 years.
5. Written informed consent has been given by the patient or their legal representative.

* personality / behaviour change includes: agitation, psychosis, somnolence, insomnia, catatonia, mood lability, and altered sleep pattern.

5.1.2 Exclusion Criteria

Patients will be excluded if ANY criteria are present:

1. Having received oral or injectable corticosteroid therapy in the 30 days prior to the day of admission to hospital.
2. History of hypersensitivity to corticosteroids.
3. Immunosuppression secondary to:
 - a. Known HIV infection AND CD4 count under 200cell/mm³;
 - b. Currently taking biologic therapy or other immunosuppressive agents [azathioprine, methotrexate, ciclosporin];
 - c. Previous solid organ transplant and currently on immunosuppression;
 - d. Previous bone marrow transplant;
 - e. Currently undergoing a course of chemotherapy or radiotherapy;
 - f. Known primary immunodeficiency syndrome;
 - g. Known current haematological malignancy.
4. **Pre-existing** indwelling ventricular devices.
5. Peptic ulcer disease in the last 6 months: defined as a peptic ulcer seen at endoscopy or an upper gastrointestinal bleed causing \geq 2 unit haemoglobin drop in the last 6 months.
6. Antiretroviral regime containing rilpivirine as current treatment.

Note:

Patients who have received oral or injectable corticosteroid therapy **AFTER** their admission to hospital will **NOT** be excluded from the study if they consent to RCT participation.

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Patients in whom MRI scanning or a second lumbar puncture is contraindicated or who refuse either of these procedures will **NOT** be excluded from the study if they consent to RCT participation.

5.2 Non-HSV Cohort Study

5.2.1 Inclusion Criteria for Non HSV Cohort Study

Enrolled patients must fulfil ALL the following criteria:

1. Suspected encephalitis criteria: New onset seizure or alteration in consciousness, cognition, personality, or behaviour*.
2. Age \geq 16 years.
3. HSV PCR negative on CSF sample.

* personality / behaviour change includes: agitation, psychosis, somnolence, insomnia, catatonia, mood lability, and altered sleep pattern.

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6 SCREENING, RECRUITMENT AND RANDOMISATION

Patients will be recruited at participating NHS hospital sites.

6.1 Screening for DexEnceph RCT

A “Screening Log” will be maintained of all the patients who undergo screening for this RCT regardless of whether they are eligible or decide to participate. Reasons for not being eligible will be recorded. Reasons for declining to participate will be asked routinely but it will be made clear that they do not have to provide a reason unless happy to do so.

This information will be anonymised and forwarded to the coordinating centre. This will provide important information for monitoring purposes and the possible reasons for non-randomisation.

There are two screening methods required for the RCT:

<p><u>Group 1</u></p> <p>Patients that fulfil the suspected encephalitis criteria (new onset seizures or alteration in consciousness, cognition, personality or behaviour)</p> <p>AND</p> <p>Aged ≥ 16 years</p>	<p><u>Group 2</u></p> <p>All patients that have laboratory confirmed HSV by <u>positive</u> PCR on CSF sample</p>
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Potential participants may be admitted from Accident and Emergency departments (A&E) or General Practice (GP) to Medical Admissions Unit (MAU), or directly to medical wards (including general medical, infectious diseases and neurology wards), High Dependency Units (HDU) and Intensive Care Units (ICU).

Potential participants will be identified by clinicians, microbiologists, virologists, pharmacists and radiologists and then reported to the site study team. As this is a rare condition the screening aims to ensure no patients are missed and every opportunity to identify eligible patients is optimised.

HSV Hotline 07714 271 804
Email Dexenceph@liverpool.ac.uk
Click the **DexEnceph Case Reporter APP**

Central PCR Laboratory and Local Hospital Laboratory: Microbiology and virology teams (regional or local) will be asked to contact the DexEnceph coordinating centre via the HSV hotline, email or App and inform them whenever a positive HSV PCR in CSF is reported in an adult (≥ 16). They will only provide the name of the hospital where this is in. No personal or patient identifiable details will be given or leave the laboratory in this process. If possible the laboratory may set up an email alert to automatically notify the coordinating centre if a

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positive HSV PCR in CSF is reported in their hospital without transferring any patient identifiable information.

Once alerted, the coordinating centre will liaise with the research team at the site to inform them they have a proven case in their hospital.

The reporting PCR laboratory will also be asked to relay the information that there is a potential recruit to whoever they pass this information to as part of their normal work processes (i.e. the local hospital laboratory at the patient's hospital or the clinical team in charge of the patient).

For every positive HSV PCR in CSF Laboratory staff will be asked to ***“Freeze and Phone”***– freeze the spare CSF that has remained after the clinically-indicated tests have been done and phone the HSV hotline who will prompt the clinical team to contact the site research team about the potential recruit (see section 8.4.2).

Clinical Teams: will notify the DexEnceph team via the HSV hotline, email or App, or inform their local research nurse that a patient has suspected encephalitis or confirmed HSV encephalitis.

Radiology: All radiology department staff will be asked to contact the DexEnceph team via the HSV hotline, email, or App to state there is a possible case at their site if there is an MRI scan requested for suspected encephalitis. Poster reminders may be put up in non-clinical areas to remind them of this.

CRN Research Nurses: will promote awareness of the study and the eligibility criteria on each ward area including A&E, MAU, ITU, HDU, medical wards, laboratories, and pharmacy and radiology departments. They will provide posters for each area mentioned and presentations of the trial at research meetings with clinical teams. They will ensure each department (laboratory, clinical wards and radiology) are advised of the case reporter app.

Pharmacy: Pharmacists will be requested to inform the local research team when intravenous aciclovir is dispensed to any ward in the hospital. They can also inform the coordinating centre via the HSV hotline, email or App. If possible the pharmacy may set up an alert on the electronic prescribing system when aciclovir is prescribed to remind prescribing clinicians to notify the coordinating centre.

The Encephalitis Society: Patients and their relatives may contact The Encephalitis Society (www.encephalitis.info) if they or their family member is hospitalised with encephalitis (contact number of Encephalitis Society Support Team: +44 (0)1653 699599). If the affected patient is suffering with HSV encephalitis and is admitted in hospital the Encephalitis Society will signpost them to the research team.

DexEnceph HSV Research Team Co-ordinating Centre: Will contact the principal investigator, research nurse or person delegated to consent to notify them that a patient at their site may be eligible. As the incidence of HSVE is low, the research team at the coordinating centre will provide updated guidance on the recruitment process and trial procedures.

6.2 Recruitment for RCT

Patients need to be identified quickly and randomised within **seven days** of the laboratory report of positive HSV PCR in CSF.

The screening methods detailed above will allow timely identification of potential participants. The target recruitment for the RCT is 90 patients.

6.2.1 Research team requesting consent

Consent will be requested by an appropriately trained member of the research team who is formally delegated the role by the Principal Investigator and this is recorded on the delegation log. This role may be delegated to research nurses or clinicians. The PI or delegated team member will check whether the patient is eligible by following the eligibility criteria (refer to section 5)

Determining eligibility: If consent is completed by a research nurse, a medically qualified clinician on the delegation log will confirm the patient is eligible prior to being randomised and write this in the medical notes and case report form.

Determining capacity: Patients potentially eligible for the RCT may not have capacity to provide valid informed consent. If there are concerns regarding a patient's ability to provide valid informed consent a medically qualified clinician will assess capacity, confirm if the patient lacks capacity, and write this in the medical notes. In this situation a personal or professional legal representative will be approached to consent on the patient's behalf. The regulations refer to an adult lacking capacity as 'an adult unable by virtue of physical or mental incapacity to give informed consent' (Part 1 4a of Schedule 1 to SI 2004/1031).

6.2.2 Consent

Potentially eligible patients with **suspected or confirmed** HSV encephalitis will be invited to participate in the RCT study and will be offered a participant information leaflet and consent form. They will then have the opportunity to discuss the trial with the researcher or their clinical team.

A continuous consent process will ensure that participants or their legal representative are informed at each stage and given the opportunity to reconfirm their willingness to participate or withdraw at any time.

This study includes patients that lack capacity and have a fluctuating level of consciousness particularly in the acute stage of their illness but often for considerably longer. If consent has been given by a legal representative, it will be requested from the participant if they subsequently regain capacity. Consenting participants that regain capacity will be required before trial related procedures at 6 months, after the acute stage of their illness.

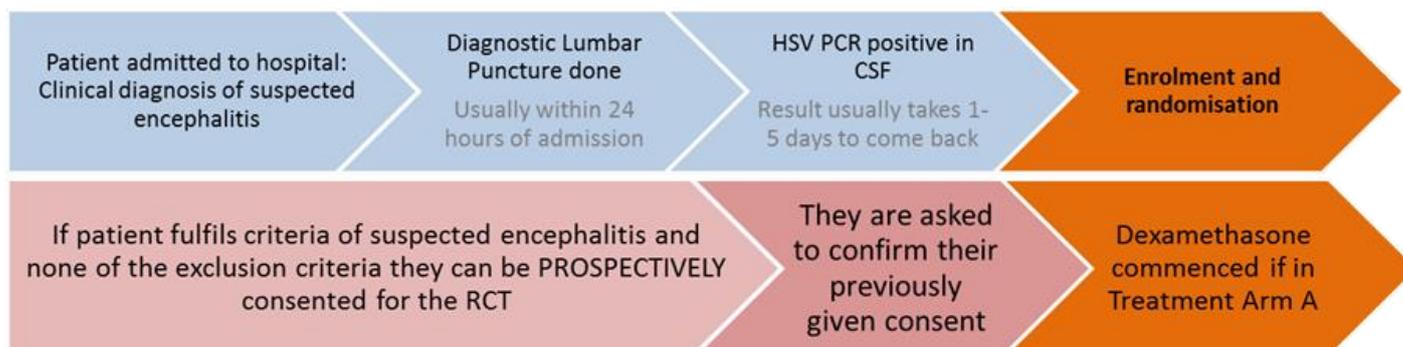
Every effort will be made to include non-English speakers. In these circumstances we will attempt to use validated versions of the neuropsychological tests in different languages.

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6.2.3 Prospective Consent

To ensure ample time to consider participation, consent may be provided prospectively for the RCT if the patient meets all other inclusion and exclusion criteria **prior** to the CSF HSV PCR result becoming available. The patients will be approached by the research team, introduced to the RCT and asked to sign a consent form. Only those with laboratory confirmed HSV encephalitis from a positive PCR in the CSF are eligible to be randomised.

Participants will therefore consent to participation in the RCT, and when their eligibility is confirmed when the HSV result is positive will be randomised.



The target recruitment for the RCT is 90 patients that meet all the inclusion /exclusion criteria, are HSV PCR positive in CSF, and are randomised. Prospective consent will be obtained from more than 90 patients as some will subsequently have a negative HSV PCR in CSF.

Those not eligible may then consent to the Non-HSV cohort study in participating sites. Their previously signed RCT consent form will be kept at the local hospital site and does not require sending to the coordinating centre.

For more information regarding the consent process please refer to section 11 and if you have any further queries please contact the DexEnceph team via telephone 07714 271 804 or alternatively email DexEnceph@liverpool.ac.uk.

6.3 Screening and Recruitment for the Non-HSV Cohort Study

Patients with suspected encephalitis who are subsequently not eligible for the RCT (as they are HSV negative) may be approached to participate in a Non-HSV Cohort.

The sample size of the Non-HSV Cohort is 90 patients and therefore not all sites will be required to recruit into this study. Sites asked to recruit into the study may be required to stop recruiting once 90 patients are enrolled.

Potential patients will be identified by clinicians, microbiologists and virologists and radiologists and reported to the site study team. They can also report eligible patients to the coordinating centre who will then liaise with the site study team through the following mechanisms:

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HSV Hotline 07714 271 804
Email DexEnceph@liverpool.ac.uk
DexEnceph Case Reporter APP

The Non-HSV Cohort enrolment form will be completed and the patient will be allocated an enrolment number. A “screening log” will be completed when screening patients for the Non-HSV Cohort

6.4 Emergency Deferred Consent for Collection of Samples

Suspected encephalitis is a medical emergency and clinically required samples of blood and CSF are collected immediately after admission. A clinical decision to perform a lumbar puncture or take a blood sample in someone with suspected encephalitis may be within the first few hours of admission.

Due to the nature of this illness participants are unlikely to have capacity to consent in the acute stage. Legal representatives may either not be available or not have ample time to consider consent prior to the clinical sampling procedure. These early samples are valuable to understand the changes in inflammatory response and pathological markers in the acute stage, and to inform the safety outcomes of the trial.

Using emergency deferred consent for samples will involve taking additional samples of blood and CSF **only** if the procedure is required for clinical care. If deferred consent has been used, written consent will be requested from either the patient or a legal representative as soon as is feasible and appropriate. At this point patients will be approached and asked to consent for RCT participation.

Deferred consent does not take the place informed consent and if the patient or their legal representative are willing and able written, informed consent is still the preferred method.

Participants or their legal representatives who decline to take part in the RCT or Non-HSV Cohort Study will be offered a participant information leaflet and consent form to request consent for these samples that have already been taken to be used for research purposes. This is the SAMPLES Collected during a Clinical Procedure PISC.

If they choose to decline to provide written consent the samples will be destroyed.

Deferred consent will only be used for the collection of blood and CSF samples and basic anonymised data including demographic data and in relation to this admission, **NOT** enrolment in the Randomised Controlled Trial or any other trial-specific interventions.

Death is anticipated in this patient population. We are sensitive to the needs of bereaved families and have worked with encephalitis survivors and their families to use acceptable consent processes in the trial.

Participants may die before consent for the use of samples that were collected by emergency deferred consent has been sought. In this case relatives will be approached early after the death by the clinical team, who will ask for their permission for these samples to be used then, rather than being contacted at a later stage. The SAMPLES Collected during a Clinical Procedure Patient Information leaflet and consent form will also be used in

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these cases. The researcher will ask clinicians to discuss this with relatives at the time of death if they judge this to be appropriate in such a sensitive situation. In the event that there is not an appropriate opportunity for the clinical team to ask relatives in the early stage the samples collected will be included in the research rather than contacting families at a later time.

This approach is based on Patient and Public Involvement feedback from The Encephalitis Society. 98% of encephalitis survivors and their relatives felt these samples should not be discarded and most preferred not to be contacted at a later stage.

If samples are used, data will be anonymised and the samples retained for research purposes. This will include samples from non-HSV patients and those subsequently confirmed as HSV positive, irrespective of whether they enrolled to either study. These samples may provide particularly important data for those with more severe encephalitis. If families decline to give consent the samples will not be used for research.

6.5 Enrolment/ Baseline

For the purpose of the RCT a patient will be considered as 'enrolled' when they have been randomised into the trial. Consent will be obtained either from the patient or legal representative where applicable

As mentioned in section 6.2.3 some patients can be prospectively consented for the RCT, in this instance the Eligibility Form will only be completed once the HSV PCR is positive in CSF. All Eligibility Forms require signing by the PI or a member of the research team who is formally delegated the role by the Principal Investigator and who is medically qualified to assess eligibility for the trial.

Enrolment into the RCT consists of completion of the Consent Form, Participants Details Form and Eligibility Form to confirm that patient is eligible to be randomised (enrolled). The Eligibility Form can be completed electronically as part of the randomisation process (see 6.6). Copies of the Participant Details Form and Consent Form documents need to be forwarded to the coordinating centre (by post, fax or encrypted email). If posting the participant details form and consent form these **should be sent separately** (separate envelope) to any CRFs in order to preserve the anonymity of the clinical data.

This process is the same for patients enrolled in the Non-HSV Cohort Study. In this instance a copy of the Non-HSV Cohort Study Consent Form and Participants Details Form needs to be forwarded to the coordinating centre in the post and the Enrolment Form can be completed electronically or on paper. If it is completed on paper, the Enrolment Form requires posting in a separate envelope to the Consent Form and Participant Details Forms as it contains anonymised data.

The research team will then complete the RCT or Non-HSV Cohort Study Baseline CRF. The Baseline CRF will only be completed once consent has been obtained for study participation (if it is not obtained or patients refuse to provide consent a Withdrawal CRF needs to be completed and all trial samples discarded).

6.6 Randomisation

<<Randomisation Tel/fax numbers, web access or postal address to be printed here>>

(Note that the CTU is open from 0900 – 1700, Monday – Friday, excluding public holidays)

Patients will not be randomised in the RCT until:

- Written informed consent has been obtained from the patient or their legal representative
- A clinician (medically qualified doctor) on the delegation log has confirmed in writing they meet the eligibility criteria
- The Eligibility Form has been completed.

Participants will be randomised using a secure (24-hour) web based randomisation programme centrally controlled by the CTRC. Designated members of the trial team at the site (detailed on the delegation of responsibilities log) will be provided with a unique login username and password which will be required to access the web-based randomisation system. Research staff will be trained to use the randomisation system by designated CTRC personnel. Following which they will be issued with usernames and passwords. Each participant will be allocated a unique study number (randomisation number), which will be the primary identifier for all the participants in this study. Treatment allocation will be displayed to the authorised randomiser on a secure webpage and an automated email confirmation will be sent to the authorised randomiser, PI, authorised research nurse, and the trial coordinator.

In the event of a randomisation system failure, the hospital site should contact immediately the coordinating centre or the CTRC (Monday to Friday between 9:00 to 17:00 excluding bank holidays) to try to resolve the problem. If the problem cannot be resolved the central coordinating centre will perform central randomisation and randomise the participant using the back-up randomisation system. The back-up randomisation system is an exact replica of the live system but is based on a stand-alone PC at the CTRC.

6.7 Patient Transfer and Withdrawal

6.7.1 Patient Transfers

6.7.1.1 Patients Moving Area

Regardless of the stage of follow up, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient.

The CTRC should be notified as soon as possible of patient transfers via a Patient Transfer CRF sent by the original site to the CTRC.

A copy of the patient case report forms (CRFs) should be provided to the new site by the original recruiting centre. Regardless of the stage of follow up within the trial, the patient (or

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legal representative) will be asked to sign a new consent form at the new site; until this occurs, the patient remains the responsibility of the original centre

6.7.1.2 Patients moving to another hospital within the same area prior to assessment at 30 days/ discharge

For patients transferring to another hospital during the time up to and including their assessments at 30 days/discharge every effort should be made for the patient to be transferred to a participating trial centre. The receiving centre will take over the responsibility for the patient.

The CTTC should be notified as soon as possible of the patient transfer via the Patient Transfer CRF sent by the original site to the CTTC.

A copy of the CRFs should be provided to the research and clinical teams at the new site. The patient will be re-consented at the centre to which they move; until this occurs they remain the responsibility of the original centre.

6.7.1.3 Patients staying in the same area after assessment at 30 days or discharge

It is highly likely that patients will be discharged from the hospital after 30 days. Destinations will include their own homes, relative's homes, rehabilitation centres and care facilities. When this occurs the patient will remain under the care of the original enrolling trial centre that will coordinate follow up data accrual.

6.7.2 Withdrawal from Trial Intervention

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

- The patient or their legal representative withdraws consent.
- Unacceptable toxicity or an adverse reaction to the study drug (i.e. dexamethasone).
- Patient not on appropriate antiviral **whilst receiving** study drug (i.e. dexamethasone).
- Any change in the patient's condition that is thought to be unrelated to the study drug but which justifies discontinuation of trial treatment in the clinician's opinion. This will be discussed with the Chief Investigator.

If a patient has an adverse reaction to the trial drug or their clinical condition changes justifying a stop in the trial drug, it will be discontinued. Patients will remain in the study, because primary analysis will be an intention to treat analysis. This will be explained to the patient at the initial consent process and on stopping the trial drug.

If a patient or their legal representative voluntarily withdraws from trial treatment, centres should request whether they would be willing to allow data already collected to be used for trial purposes and continue scheduled evaluations. They will also be provided with appropriate care under medical supervision if an adverse event has occurred until the symptoms of this have resolved and the patient's condition is stable. Generally, follow-up will continue unless the patient explicitly withdraws consent for follow-up (see section 6.7.3).

Follow up of participants will be continued through the trial Research Nurses and the lead investigator at each centre in close partnership with coordinating centre.

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6.7.3 Withdrawal from Trial Completely

Patients or their legal representatives are free to withdraw consent in further trial participation at any time without providing a reason. For patients wishing to withdraw consent, anonymised data collected up to the point of withdrawal will still be included in the analyses unless the patient /legal representative explicitly states this is not their wish. The patient will not contribute further data to the study thus the CTRC should be informed in writing and a withdrawal CRF should be completed. The withdrawal CRF can be posted, sent in an encrypted email or sent to the coordinating centre by fax [number 0151 706 5932].

7 TRIAL TREATMENT/S

7.1 Introduction

Patients with proven HSV encephalitis will be randomised to Treatment Arm A or to Treatment Arm B.

Treatment Arm A will receive dexamethasone 10mg every 6 hours for four days.

Treatment Arm B will not be administered dexamethasone.

Randomised treatment should be started as soon as possible after the positive HSV PCR result becomes available at the laboratory, and **not after 7 days**. Assessments that should be carried out prior to commencing randomised treatment are detailed in sections 6 and 8. As part of standard care all patients will be given the antiviral drug aciclovir at 10mg/kg 8 hourly (or at a decreased dose if clinically indicated) for at least 14 days as per the national encephalitis guidelines.

7.2 Arm A

7.2.1 Formulation, Packaging, Labelling, Storage and Stability

This study is classified as IMP risk category Type B with a risk somewhat higher than standard medical care. This is because, even though dexamethasone is a widely used medication in the field of neurological infections and acute care, it is being used outside of its licensed indication.

Patients in this trial will have characteristics consistent with those covered by the indications in the marketing authorisation (adults with brain oedema).

The dexamethasone used will be standard ward or NHS hospital pharmacy stock administered within the hospital. Dexamethasone will be supplied to the hospital wards as per normal clinical practice. Annex 13 labelling will not be required as the IMP will be used within normal NHS clinical practice, there will be no modification to the product or its outer packaging, and the study is not blinded.

The temperature monitoring requirements in this trial will be consistent with those required in normal clinical practice (inclusive of preparations that require refrigeration). There will be no additional requirements for drug accountability logs or temperature monitoring within the study as this drug is dispensed and administered within the NHS.

7.2.2 Preparation, Dosage and Administration of Study Treatment/s

Patients in Arm A will receive 10mg of dexamethasone (base) intravenously every 6 hours for 4 days commenced as soon as possible after randomisation. Ordinary ward or pharmacy stock will be used. This will mean patients receive a total of 16 doses of the study drug.

Dexamethasone will be given undiluted as a slow IV injection over 3-5 minutes or as an infusion diluted for administration in glucose 5% or sodium chloride 0.9% over 15-20 minutes according to standard local practice.

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Table A: Dexamethasone is most commonly available as the following brands:

Brand	Concentration	Available Preparations	Volume required for 10mg dose
Hameln	3.3mg/ml	3.3mg in 1 ml amp 6.6mg in 2ml amp	- 3mls
Hospira	3.3mg/ml	3.3mg in 1 ml amp 6.6mg in 2ml vial	- 3mls
Aspen	3.8mg/ml	3.8 in 1ml vial	2.6mls*

* some trusts consider 3.8mg of dexamethasone to be equivalent clinically to 4mg – in this case local practice would be to administer 2.5ml for a 10mg dose

Other brands can be used providing a 10mg dose of dexamethasone base is given 6 hourly for 4 days. Different combinations of the study treatment brands can be used in one participant.

7.2.3 Dose Modifications

No modifications to the dose of dexamethasone are anticipated.

Any suspected adverse events will be detailed. For further information regarding adverse event monitoring please refer to section 10.

7.2.4 Accountability Procedures for Study Treatment/s

Given the nature of this pragmatic trial there is no requirement for drug accountability to be undertaken. Hospital stocks of dexamethasone are used and will be dispensed as per local NHS hospital practice. The 4-day course of the IMP will be administered during the participant's hospital admission.

7.2.5 Assessment of Compliance with Study Treatment/s

Dexamethasone will be administered intravenously by the nursing staff at the hospital and therefore no issues regarding patient compliance with treatment are anticipated. The CRF will include details on drug administration to ensure there is a record of administered doses of the study treatment. The primary analysis will not be adjusted for adherence.

7.3 Arm B

Participants in the control arm will not be given any study drug. They will be given standard treatment for HSV encephalitis which is the antiviral drug aciclovir in accordance to national encephalitis guidelines.

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7.4 Accountability Procedures for Study Treatment/s

Despite this being an IMP risk category Type B, dexamethasone is a commonly used drug for a multitude of conditions in hospital practice, therefore, drug accountability needs will be consistent to normal NHS hospital practice. No trial-specific accountability records need to be undertaken. Site will be asked to record the name of the Dexamethasone preparation used in the CRF.

7.5 Assessment of Compliance with Study Treatment/s

The study drug is administered intravenously by hospital staff according to guidelines in section 7.2.2. The CRF will include details from the patient's drug administration chart assessing whether prescribed doses of dexamethasone were administered, as per section 7.2.5. The CRF will also include the dates of aciclovir administration, dose of aciclovir and record of any missed doses.

7.6 Non-Investigational Medicinal Products, Concomitant Medications or Treatments

Aciclovir is a concomitant medication given as part of standard care therefore classed as a non-investigational medicinal product (NIMP). This drug will be provided from NHS hospital stock and prescribed as standard clinical practice.

Both arms of the study will be treated with intravenous aciclovir for a minimum of 14 days at a dose of 10mg/kg 8 hourly, as per national guidelines. A completed dose will be rounded to the nearest 5mg of aciclovir for ease of administration. Adjustment of dosing will be required in renal impairment. This is part of standard care for HSV encephalitis.

The dose of aciclovir needs to be based according to "Ideal Body Weight" (IBW):

$\text{IBW Male} = 50\text{kg} + [(\text{height (cm)} - 154) \times 0.9]$ $\text{IBW Female} = 45.5\text{kg} + [(\text{height (cm)} - 154) \times 0.9]$

At 14 days post commencement of aciclovir (+/- 3 days) all patients will have a repeat lumbar puncture that will be tested for HSV PCR unless clinically contraindicated. If there is still HSV detected by PCR in their CSF aciclovir should continue with weekly CSF testing until this is HSV PCR negative. This treatment is in accordance with the British Infection Association Viral Encephalitis Guidelines(23).

A contrast agent will be administered for the MRI scans and is also classed as a NIMP as it is required to obtain appropriate scan images. The contrast agent will be administered as per local NHS hospital practice and patients are made aware of the risk of contrast agents prior to each scan.

Gadolinium based contrast agents (GBCA) are used every day in most MRI departments with low adverse effects for both allergic reaction (anaphylactic reaction rate of 1 in 100000) and nephrotoxicity.

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Local guidelines can vary but typically patients are screened for impaired renal function in order to prevent risk of Nephrogenic systemic fibrosis, an extremely rare but serious and potentially life threatening condition. Patients with moderate renal impairment (eGFR 30-59 ml/min/1.73m²) should only have administration of lower risk GBCA (cyclic products) after clinical review. In patients with severe renal impairment (eGFR <30 ml/min/1.73m²) use of GBCA is contraindicated.

GBCA should also be avoided in patients who may be pregnant or breastfeeding. Consent will be provided from the participant or their legal representative for the administration of this NIMP at enrolment.

Decisions regarding other concomitant medications or treatments will depend on the local medical plan and clinical management. The Baseline, 2 Week and 30 day/Discharge CRFs will collect information on new medication given during the patient's clinical stay.

Some centres may choose to prescribe patients in Treatment Arm A gastric protection with a PPI or antacid, this decision is down to the treating physician.

7.6.1 Medications Permitted

All medications will be allowed apart from rilpivirine, this is detailed in section 7.6.2. Patients randomly allocated to Treatment Arm A or B will be reassured that if their treating physician feels it is clinically indicated for them to receive a course of corticosteroids of any formulation (including inhalers, creams, eye drops) at any point during the study follow up regardless of the indication this will not be denied to them.

7.6.2 Medications Not Permitted/ Precautions Required

Corticosteroids: If the patient has received a course of oral or intravenous corticosteroids in the 30 days preceding the day of admission to hospital they will automatically be excluded from the trial and will not be randomised. Topical or inhaled corticosteroids are allowed. Oral or intravenous corticosteroids received after admission to hospital are allowed.

Rilpivirine (antiretroviral): Randomised patients will not be permitted to be on an antiretroviral regime containing rilpivirine due to interaction with dexamethasone. Rilpivirine can be found in rilpivirine-only containing tablets or in fixed dose combination as Eviplera. The PI or delegated other in the local research team should discuss with the patient's primary HIV physician whether a switch of antiretrovirals to a rilpivirine-free regime prior to randomisation is appropriate to allow enrolment.

Cautions - Treatment Arm A

Coumarin (warfarin): patients who are on coumarin treatment (e.g. warfarin) will need close monitoring of their INR while on the study drug given the risk of high-dose dexamethasone of increasing their anticoagulant effect.

Amphotericin (antifungal): patients on amphotericin need close monitoring of their electrolytes, particularly potassium, whilst on the study drug. This is due to the risk of hypokalaemia when co-administering dexamethasone and amphotericin.

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Ritonavir (antiretroviral): patients on ritonavir will require close monitoring of their clinical state after completion of dexamethasone given the increased risk of adrenal suppression. Symptoms and signs of adrenal insufficiency include anorexia, nausea, vomiting, abdominal pain, weakness, fatigue, lethargy, fever, confusion, coma and hypoglycaemia. If patients randomised to Treatment Arm A who are on ritonavir present these symptoms acutely after the corticosteroid regime is completed they should be investigated for adrenal insufficiency.

Live Vaccinations: caution should be taken in administering live vaccinations to patients whilst they are on dexamethasone and for 3 months after the completion of their 4 day course. This will not apply to patients in Treatment Arm B.

7.6.3 Data on Concomitant Medication

We will record a detailed drug history. The following will be collected: all antimicrobials (including antibiotics, antivirals and antifungals), Intravenous immunoglobulin (IVIG), plasmapheresis, antiepileptics, Proton Pump Inhibitors and antacids, diabetic medication (including insulin), and other anti-inflammatories and immunomodulatory drugs.

7.7 Dose Modifications

Aciclovir for HSV encephalitis is dosed at 10mg per kg 8 hourly. Dose reductions are necessary in the event of renal impairment. As this is standard treatment for HSVE and incorporated in clinical guidelines, dose reductions will depend on local clinical management. No other dose modifications are anticipated.

Studies of dexamethasone which used the schedule and dosing regime as in DexEnceph found no increased risk of adverse events in the treatment arm compared with placebo(47). Any suspected adverse events will be detailed as detailed in section 10.

7.8 Co-enrolment Guidelines

To avoid confounding issues patients should not be recruited to other interventional trials that may influence the neuropsychology outcome. Where recruiting into another trial is considered appropriate and to no detrimental effect to DexEnceph, those recruiting should discuss co-recruitment with the Trial Management Team who will discuss this with the CI or delegated other.

Patients may be co-recruited to the ENCEPH-UK COHORT observational study.

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8 ASSESSMENTS AND PROCEDURES

8.1 Schedule for Follow-up of DexEnceph RCT

The expected duration of each participant on the RCT is 18 months.

Procedures	Follow-up Schedule						
	Screening	Baseline	2 weeks	Discharge or Day 30 of admission (whichever is sooner)	26 weeks	78 weeks	Premature Discontinuation
Signed Consent Form	X†	X*					
Assessment of Eligibility Criteria	X	X*					
Review of Medical History		X*					
Review of Concomitant Medications		X*	X	X	X	X	X
Physical Exam		X		X			
Study Intervention		X					
Clinical Data Collection		X	X	X	X	X	
MRI scan (including bloods to for eGFR if contrast is planned and no eGFR is available in the 3 months previous)		X _μ	X		X	X	
Research Blood Testing		X	X		X		
Lumbar Puncture		X _γ	X				
Disability & Functional Outcomes				X	X	X	
Glasgow Coma Scale		X _∞	X _∞	X _∞	X	X	
Addenbrooke's Cognitive Examination revised				X	X	X	
Neuropsychology assessment					X	X	
Health Status and QOL questionnaires					X	X	
Clinical Laboratory: Haematology, Biochemistry		X _α					
Assessment of Adverse Events			(X)	(X)	(X)	(X)	(X)

† Only applicable when patients are prospectively consented for the RCT

*Procedures required before randomisation.

μ Baseline MRI done for clinical purposes can be done from hospital admission up to 7 days after randomisation

γ Diagnostic lumbar puncture for clinical purposes done prior to randomisation

α Recording of clinical laboratory tests done for clinical purposes, NOT as part of trial

∞ Recorded at baseline, daily for the first 14 days and then weekly until Discharge/30 days (whichever sooner)

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(X) – As indicated/appropriate

8.2 RCT Trial Follow Up Schedule

8.2.1 Screening [case of suspected encephalitis brought to attention of local research team]

Review eligibility criteria:

- If fulfils all inclusion and exclusion criteria for RCT consent for RCT
- If fulfils all inclusion criteria and exclusion criteria apart from the CSF HSV PCR result which is still pending consent prospectively for RCT [ensuring patient or legal representative understands this is not valid until the HSV PCR in CSF is positive]

If they do not fulfil the criteria for suspected encephalitis do **NOT** complete the Eligibility Form, the screening log will record reasons for non-eligibility.

8.2.2 At Baseline [+ive HSV PCR in CSF notified by laboratory/brought to attention of research team]

Review of eligibility criteria:

- If does not fulfil criteria for RCT - record on the screening log only.
- If fulfils criteria for RCT consent for RCT
Patients may have already consented prospectively if they were approached due to suspected encephalitis (section 8.2.1). If so, the patient or legal representative need to be made aware of the positive HSV PCR result and ensure they are agreeable for their previously given consent to still stand.

Complete enrolment paperwork (see section 6.5)

Randomisation and commence study intervention if randomised to Trial Arm A.

Glasgow Coma Score: Record GCS on the day of randomisation, daily for the next 14 days and then weekly until Discharge/Day 30 (whichever is sooner). This information is to be recorded on the study procedures checklist inserted in the patient's medical notes.

Completion of RCT Baseline CRF form: please complete this form **within 2 weeks** after randomisation. It will include details of:

- a. Demographics
- b. Past Medical History
- c. Current medications
- d. Details of current presentation, clinical state and location in hospital
- e. Information regarding (1) results from LP where HSV PCR was positive prompting entry into study and (2) clinical laboratory results taken for clinical purposes.

Collection of samples [for further details about the collection, storage and transport of samples please refer to section 8.3.5]

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- Blood:
 - a. Up to the day of randomisation please collect 5mls of blood in a BD Vacutainer Serum Separator Tube (SST) and 2.5mls in a PAXgene tube [total of 7.5mls].
 - b. From the day of randomisation and up to 7 days after please collect 20mls of blood in BD Vacutainer CPT Tubes. The samples need to be transported to the University of Liverpool within 24 hours from being taken and received Monday-Thursday.

- CSF: The CSF samples taken at baseline will be from the initial diagnostic LP. Research samples required are 2.5mls of CSF in a cryovial container/universal container and 2.5mls in a PAXgene tube. If the lumbar puncture has already been performed existing stored CSF will be used for research purposes. This process is explained in section 8.3.5.
 - If not sufficient CSF was taken from the baseline LP for all the research samples and a repeat LP is done on clinical grounds up to day 7 after randomisation, CSF from the repeat LP can be used for baseline samples.

MRI Scanning: If not already performed please arrange an MRI scan as per section 8.3.1. This MRI will be done for clinical reasons as per the national encephalitis guidelines and, ideally, include the sequences detailed in section 8.3.1 where possible. This baseline scan can be done at any point in the patient's clinical stay from hospital admission up to 7 days after randomisation.

Ensure study protocol and study procedures checklist are inserted into patient's notes and communicate this to the patient's primary clinician.

8.2.3 At 2 Weeks

Complete 2 week CRF: this requires completion between weeks 2-4 after randomisation:

- a. Survival
- b. Adverse events monitored through CRF

2nd lumbar puncture: this is usually part of routine care 14 days after the start of aciclovir [range +/- 3 days] and. CSF Samples should be sent for tests required for the patient's routine care. Testing for presence of HSV in CSF after 14 days of aciclovir is recommended in the UK treatment guidelines for HSVE. Detection of HSV in CSF at the second lumbar puncture is the **primary safety outcome** in this study. As part of the research protocol a total of 5mls of CSF should be collected, 2.5mls in a cryovial tube/universal container and 2.5mls in a PAXgene tube [please refer to section 8.3.5 for details of collection and storage].

Blood Samples: this should be done on the same day as the 2nd LP [+/- 1 day]. 5mls of blood in a BD Vacutainer Serum Separator Tube and 2.5mls in a PAXgene tube [total of 7.5mls] is required.

2nd MRI scan: this should be done 14 days after randomisation [range +/- 5 days]. This scan should follow the recommendations specified in section 8.3.1. Please ensure the

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participant's last eGFR is $\geq 30\text{ml/min/1.73m}^2$ and this result is from, at most, 3 months prior to the scan.

Review notes for other adverse events, these should be notified if indicated [please refer to section 10 for more information on reporting of adverse events].

8.2.4 At 30 days post randomisation OR hospital discharge [whichever is sooner]

Completion of 30 day CRF: This needs to be completed within 2 weeks of the 30 days/discharge time point.

- a. Requirement of intensive care or high dependency admission
- b. Time to cessation of ventilator support [if any]
- c. Time to hospital discharge
- d. Daily GCS from randomisation until day 14 and then weekly GCS from day 14 up to 30 days or discharge (whichever sooner)
- e. Survival
- f. HSV PCR in CSF at 2 weeks as measured in local hospital laboratory
- g. Seizure incidence
- h. Medication details
- i. Aciclovir administration details
- j. Adverse events monitored through CRFs

Disability & Functional Outcome Scoring [performed by the local team on reviewing hospital notes and discussion with patient, relatives and health professionals involved in patients care]

- mRS
- Barthel Index
- LOS
- GOS-E

Cognitive Outcome Scoring: Addenbrooke's Cognitive Examination III [performed by clinical or research team]. This can be done in a range of +/- 3 days from discharge day/ 30 day.

Review notes for adverse events, these should be notified if indicated [please refer to section 10 for more information on reporting of adverse events].

8.2.5 At 26 weeks post randomisation (6 months)

Neuropsychology & Cognitive testing: **Verbal Memory Testing in the Neuropsychology assessments done at this time point is the study's PRIMARY OUTCOME.** This can be done in a time range of +/- 4 weeks from the 26 weeks post randomisation time point. Patients, family members or carers will be contacted, usually by telephone, by the coordinating centre to book a convenient time for the tests. This testing will include the battery of neuropsychology tests included in section 8.3.2 and the ACE-III.

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Completion of 26 week CRF: This will be done by reviewing patient's clinical notes at a range of +/- 4 weeks from the 26 weeks post randomisation time point. It may also require contacting the patient or their legal representative. It will include details on:

- a. Requirement of intensive care or high dependency admission [if previous CRF done whilst patient still at inpatient]
- b. Time to cessation of ventilator support [if any] [if previous CRF done whilst patient still at inpatient]
- c. Time to hospital discharge [if previous CRF done whilst patient still at inpatient]
- d. Survival
- e. Seizure incidence
- f. Adverse events monitored through CRFs

MRI Scanning: This is required at a time range of +/-4 weeks from the 26 weeks post randomisation time point. To have the scan with contrast the participant's last eGFR has to be $\geq 30\text{ml/min/1.73m}^2$ and this result needs to be, at most, 3 months prior to the scan. If there is no eGFR available in the last 3 months the Principal Investigator will arrange for the patient to have a renal function check prior to the scan. Scans will be booked by the local research team who will also liaise with the patient or their legal representative as per section 8.3.1 and also send them a copy of the patient information leaflet.

Blood Samples: Research blood samples are required at a time range of +/-4 weeks from the 26 weeks post randomisation time point. This will preferably be done when a patient attends for their MRI scan to minimise research burden. This will require 8.5-27.5mls of blood and will include:

- 5ml in a BD Vacutainer Serum Separator Tube
- 2.5mls in a PAXgene tube
- 20mls in BD Vacutainer CPT tubes. This test needs to be sent to the University of Liverpool within 24 hours of being taken and arrive Monday-Thursday.

In this time period it may also be necessary to take blood test for an eGFR test prior to the MRI scan.

Disability & Functional Outcome Scoring: Performed by the local clinical team on reviewing hospital notes and discussion with patient, relatives and health professionals involved in patients care either by telephone or face-to-face. This requires completion in a time range of +/- 4 weeks from the 26 weeks post-randomisation time point (to be able to discuss with patients when they attend for their MRI scan):

- mRS
- Barthel Index
- LOS
- GOS-E

Health Economics & QOL: Patients will be asked to complete the EuroQOL 5D-5L and SF-36 at 26 weeks post randomisation [+/- 4 weeks]. These will be posted to their residence or handed to them during a hospital visit as detailed in section 8.3.4.

Review notes for adverse events, these should be notified if indicated [please refer to section 10 for more information on reporting of adverse events].

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8.2.6 At 78 weeks post randomisation (18 months)

Completion of 78 weeks CRF: This will be done by reviewing patient's clinical notes at a range of +/- 6 weeks from the 78 weeks post randomisation time point. It may also include contacting the patient or their legal representative.

- a. Survival
- b. Seizure incidence
- c. Adverse events monitored through the CRF

MRI Scanning: This is required at a time range of +/- 6 weeks from the 78 weeks post randomisation time point. To have the scan with contrast the participant's last eGFR has to be $\geq 30\text{ml/min/1.73m}^2$ and this result needs to be, at most, 3 months prior to the scan. If there is no eGFR available in the last 3 months the Principal Investigator will arrange for the patient to have a renal function check prior to the scan. Scans will be booked by the local research team who will also liaise with the patient or their legal representative as per section 8.3.1 and also send them a copy of the patient information leaflet.

Disability & Functional Outcome Scoring performed by local clinical team on reviewing hospital notes and discussion with patient, relatives and health professionals involved in patients care either by telephone or face-to-face. This will be completed in a time range of +/- 6 weeks from the 78 weeks post-randomisation time point (to be able to discuss with patients when they attend for their MRI scan):

- mRS
- Barthel Index
- LOS
- GOS-E

Neuropsychology & Cognitive testing: This can be done in a time range of +/- 6 weeks from the 78 weeks post-randomisation time point. Patients, family members or carers will be contacted, usually by telephone, by the coordinating centre to book the tests for a convenient time. This testing will include the neuropsychology tests included in section 8.3.2 and the ACE-III.

Health Economics & QOL: Patients will be asked to complete the EuroQOL 5D-5L and SF-36 at 78 weeks post-randomisation [+/- 6 weeks]. These will be posted to their residence or handed to them during a hospital visit as detailed in section 8.3.4.

Review notes for adverse events, these should be notified if indicated [please refer to section 10 for more information on reporting of adverse events].

8.3 Assessments

Assessments performed will be exactly the same in patients in both treatment arms.

8.3.1 Neuroimaging

Patients will have MRI performed as part of their standard medical care when they are diagnosed with encephalitis as per the national encephalitis guidelines. This represents the

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baseline MRI scan and, ideally, will include the sequences detailed below. This baseline MRI scan will occur from the time of hospital admission to 7 days post randomisation, and ideally as close to the point of randomisation as possible.

Research MRI scans will occur at 2 weeks after randomisation, and then again at 26 weeks (+/- 4weeks) and 78 weeks (+/- 6 weeks).

For all 4 scans the standard brain protocol at each hospital will be used, with the inclusion/addition of the following sequences where possible (in order of importance):

1. 3D T1-weighted sequence with 1mm isotropic resolution.
2. 2D coronal T2-weighted FLAIR sequence (with maximum 1.0 mm in-plane resolution and 5 mm slice thickness).
3. 2D axial Diffusion weighted imaging sequence (with maximum 2.0 mm in-plane resolution and 5 mm slice thickness, high b-value 1000 s/mm²).
4. 3D T1-weighted sequence with 1mm isotropic resolution (sequence 1), post-contrast.
5. 2D axial Diffusion tensor imaging sequence (with maximum 2.0 mm in-plane resolution and 5 mm slice thickness, at least 6 gradient directions, high b-value 1000 s/mm²).
6. 3D T2-weighted FLAIR sequence with 1mm isotropic resolution

All sequences should have whole brain coverage. Note that sequences 1, 2 and 3 above may be very similar to those in the standard brain protocol. If this is the case, the standard protocol should be altered accordingly (e.g. there is no need to collect 2 sets of 2D coronal T2-weighted FLAIR images with slightly different resolution).

It is planned that Sequences 1-4 will be administered at all sites, and sequences 5-6 at all sites where these more advanced MR imaging protocols are feasible. Sequences 1-4 take about 20 minutes, and the whole set of procedures takes about 60 minutes. If a patient cannot tolerate the full investigation, perhaps because of agitation, the focus will be on obtaining 3D T1-weighted image (sequence 1). The sequences will be standardised so that MR images are obtained with the same resolution and will be matched as far as possible (with obvious alterations at different field strengths to ensure similar contrast) with regard to other acquisition parameters. The key secondary outcome measure will be derived from the coronal FLAIR and T1-weighted images with matched resolution and similar contrast at all sites, thus ensuring comparable estimates of volume. Because this outcome is based around within-subject comparisons of volume, any remaining inter-site differences in volume accuracy will be immaterial.

Some patients may have already had a baseline MRI scan when enrolled and randomised into the study. All 2 week, 26 week and 78 week scans should use the same protocol as the baseline scan with additional sequences as detailed above where possible. Individual participants should ideally have all scans in the same scanning department.

Scans will be organised by the local research team who will liaise with the patient and radiology department to arrange a convenient appointment. Patients will be contacted by a telephone call to arrange scans at 26 and 78 weeks. In the case of patients that lack capacity their legal representative will be called. Patients and their legal representatives will

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be sent the study information leaflet reminding them of the implications of having an MRI scan. All participants will be encouraged to attend for MRI scans with a close family member (this may be their legal representative if they lack capacity). These arrangements will allow a continuous consent process.

Scans can require the administration of contrast (sequence 4, administered in all sites). Participants will need to have their renal function checked at any point in the 3 months prior to each scan. The scan will only go ahead if the last eGFR is $\geq 30\text{ml/min/1.73m}^2$. If patients have not had an eGFR checked at any point in the 3 months before the scan the Principal Investigator will arrange for them to have their eGFR tested a few days/weeks prior to the scan.

If there is no available eGFR prior to the scan, the patient does not consent for administration of contrast or the eGFR is $<30\text{ml/min/1.73m}^2$ the scan can go ahead but WITHOUT the administration of contrast.

Scan images will be reviewed by a local radiologist at site for incidental findings, and communicate these to the patient's clinical team.

Scan images will be anonymised at site and downloaded on discs. These will then be sent to the coordinating centre via the post. They will be stored in locked filing cabinets.

8.3.2 Neuropsychology & Cognitive Testing

There will be a roving assistant psychologist from the coordinating centre who will perform neuropsychology and cognitive tests at 26 and 78 weeks post randomisation. The patients, family members or carers will be contacted by the coordinating centre to organise a date, time and location convenient for the patient to be assessed. They will be contacted, usually by phone, to arrange the 26-week and 78-week assessment.

In some recruiting sites neuropsychology and cognitive testing may be able to be provided by clinical neuropsychology teams.

Neuropsychology testing will include:

- Wechsler Memory Scale version IV (WMS-IV), which takes 70 minutes to complete. This includes assessment of Verbal Memory assessed by the Auditory Memory Index, **the primary outcome for the study**, Visual Memory Index, Immediate Memory Index, and Delayed Memory Index. There are well established population norms for each aspect of the Wechsler Memory Scale. For the Auditory Memory Index the mean is 100 with a standard deviation of 15; the minimum score possible is 40, and maximum 160.
- Wechsler Adult Intelligence Scale version IV (WAIS-IV), Processing Speed and Working Memory (15 minutes)
- Confrontational naming task from the language module of the Neuropsychology Assessment Battery (NAB) to assess language (5 minutes)
- Trail Making Test Parts A and B to assess higher executive function (5 minutes)
- Premorbid cognitive ability (TOPF) (5 minutes)

In addition the patient will be asked to complete:

- Beck Depression Inventory and Beck Anxiety Inventory (5 minutes)

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- Perceived Deficits Questionnaire (5 minutes)

The Cognitive Test used will be the Addenbrooke's Cognitive Examination revised (ACE-III) that lasts 15 minutes.

Some data will also be collected by the assistant psychologist regarding the participant's demographics, education and previous and current employment that will help assess their premorbid function and impact of their illness on their level of functioning. These questions will not take more than 10 minutes

The complete assessment thus takes approximately two hours. The verbal memory component of the WMS-IV will be the **first test to be completed** to ensure the study's primary outcome is addressed at the beginning of the assessment and not influenced by patient fatigue. This test takes about 30 minutes.

If patients are tiring, the self-assessment components can be done by the patients at a later date and the assessment can be spaced out over a number of sessions.

For patients who find it difficult to come to a clinical centre to be assessed, because of disability or inconvenience, we will arrange to assess them at a place convenient to them. This may include their place of residence, rehabilitation centre, hospital, or other convenient locations.

Some patients will have had neuropsychology assessments as part of their routine medical care during the timeframes stipulated for the study's neuropsychology assessments (i.e. +/- 4 weeks for the 26-week test and +/- 6 weeks for the 78-week test). If this is the case, results of assessments including those in the research battery above will be used for research purposes to avoid duplication of testing. The roving assistant psychologist will therefore only complete the tests not included in the participant's clinical assessment.

Conversely, at the end of each research assessment we will ask patients whether they wish to have the results of their neuropsychology tests added to their clinical notes for future reference.

Patients unable to complete the verbal memory test will have a GOS and an ACE-III assessment by the roving assistant neuropsychologist.

At the time of the neuropsychology visits, completion of the Disability Scoring, Health Status and QoL Questionnaires will be checked; and if they have not been completed, the neuropsychology visit will be used to assist with completion of these outcomes.

The roving assistant neuropsychologist will need to be blinded and patients and their carers will be reminded of this prior to their assessment.

8.3.3 Disability & Functional Outcome Assessments

Glasgow Outcome Score Extended	Modified Rankin Scale	Barthel Index	Liverpool Outcome Score
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Ability to perform <u>activities of daily living.</u>	Ability to perform <u>usual activities & mobility.</u>	Ability <u>to self-care.</u>	<u>Motor skills, dexterity and behaviour</u>
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These four assessments will be included in the 30 days/discharge, 26 week and 78 week CRFs. They will be completed by the local clinical team. Data used for completion can be obtained from the patient's clinical notes, discussions with the patient's healthcare providers (including physicians, rehabilitation specialists & nurses), and discussions with the patient and their relatives and carers. The results of clinically-performed tests can be used for research purposes if completed in the required timeframe.

1. Modified Rankin Score [mRS]

Developed for the assessment of disability and dependence following a stroke and widely used as an outcome measure within stroke cohorts, neurological infections and non-infectious encephalitis (e.g. para-neoplastic, auto-immune).

2. Glasgow Outcome Score Extended [GOS-E]

The GOS was developed to categorise outcome following traumatic brain injury. The GOS-E was developed to address the limitations of the original GOS, and compared to the GOS it has been shown to be more sensitive to change in mild to moderate traumatic brain injury.

3. Barthel Index

The Barthel Index is an ordinal scale used to measure activities of daily living and assesses the ability of an individual to care for him/herself. It has been used in patients with stroke, neurological disorders and brain injury. This test is commonly used in hospitals by nursing staff.

4. Liverpool Outcome Score [LOS]

The LOS was developed for the assessment of outcome following Japanese Encephalitis. Despite the fact that its use to date has been in paediatric cohorts, it was designed for use in adolescents and adults as well and has been successfully used in the ENCEPH UK study which enrolls both adults and children.

8.3.4 QOL and Health Economics Questionnaire

Quality of Life and health status will be assessed at 26 and 78 weeks post randomisation. These questionnaires have been extensively used in previous studies.

SF-36 Questionnaire: Assesses health status across several domains (physical and social function, roles physical and emotional, mental health, energy/vitality, pain and general health); including a question that attempts to assess the perceived changes in health status over time.

EuroQOL 5D-5L Questionnaire: A validated instrument to assess health status using a short questionnaire and visual-analogue-scale.

Both questionnaires will be given to patients when they attend clinic visits or study-specific procedures by their local clinical team. They can hand the completed questionnaires over to

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their local team when completed or send them directly back to the coordinating centre in a prepaid envelope supplied with the questionnaires after photocopying them. If the coordinating centre has not received the completed questionnaires back by 28 weeks and 80 weeks post randomisation they will contact the patients and enquire whether they would like another pack sending to them which may be followed up by a further telephone call and/or letter to offer assistance.

The follow-up administration of the questionnaires will be coordinated centrally by the coordinating centre

8.3.5 Sample Collection

Blood and CSF will be collected from both treatment arms to allow a better understanding of the disease mechanisms and host responses. It will also allow monitoring of safety outcomes.

Full details of the processing and analysis of the samples will be contained in the samples processing and study analytical plan. Samples will be stored at site in accordance with local hospital policy in the first instance and then transported to the University of Liverpool Ronald Ross building for storage prior to being processed.

8.3.5.1 Collection:

Table B: RCT Research samples Collection Timeline

RCT Research Samples Required	Time of Sample and Sampling Window				Volume required	After collection
	Baseline	Baseline	14 Days after starting aciclovir.	26 weeks after randomisation		
	Anytime up to and including the day of randomisation	From randomisation and up to 7 days after. To arrive at University of Liverpool Monday-Thursday.	LP: +/- 3 days after starting aciclovir Bloods: +/- 1 day of this 2nd LP	+/- 4 weeks		
CSF: Cryovial / Universal container	✓		✓		2.5mls	Freeze at site
CSF: PAXgene Tube	✓		✓		2.5mls	Freeze at site
Blood: BD Vacutainer Serum Separator Tubes (SST)	✓		✓	✓	5mls	Centrifuge then freeze at site
Blood: PAXgene Tube	✓		✓	✓	2.5mls	Freeze at site

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Blood: BD Vacutainer CPT tubes					20mls (may need 3-5 tubes)	Keep at ambient temperature. Transport to the University of Liverpool within 24 hours.
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In order of importance, the research CSF samples to be taken are:

1. CSF in cryovial/universal containers (can be taken in universal containers then decanted into cryovial tubes at the laboratory for ease of storage): 2.5mls
2. CSF in PAXgene tubes: 2.5mls

If the patient is very difficult to bleed, the blood samples to be taken in order of importance are: [Please note not all samples will be required at every time point or at every site]

1. Blood in PAXgene tubes: 2.5mls
2. Blood in BD Vacutainer Serum Separator Tubes: 5mls
3. Blood in BD Vacutainer CPT tubes: 20mls (may need 3-5 tubes to collect total volume)

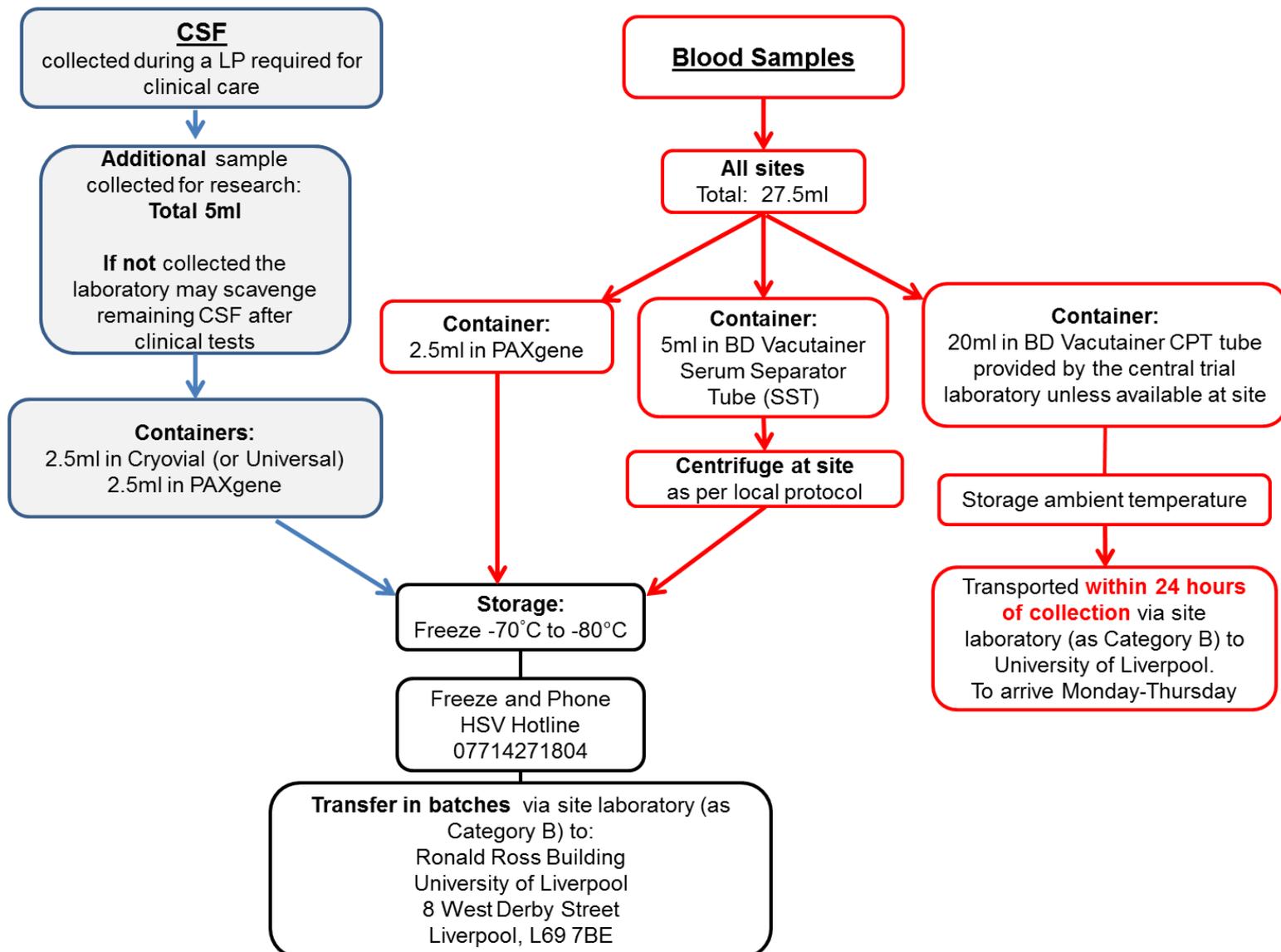
The coordinating centre will provide samples packs for sites to use in enrolled patients. The location of these packs will be in the site file and on the trial webpage. Locally sourced tubes can also be used.

Note on Samples to be kept at ambient temperature after collection: Blood in BD Vacutainer CPT Tubes needs to be processed in the laboratory at the University of Liverpool. They need to be transported within 24 hours of collection and arrive from Monday-Thursday.

8.3.5.2 Storage:

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Samples Flow Chart



Samples to be stored immediately in the freezer after collection (-70 to -80°C):

- CSF in Universal/Cryovial Container (preferentially store in cryovial containers)
- CSF in PAXgene tubes
- Blood in PAXgene tubes

Samples stored in the freezer should ideally be stored at -70 to -80°C but can be stored at -20°C for 1 month and then transported to a -70 to -80°C freezer.

Samples to be centrifuged at local hospital site and then frozen

- Blood: Serum Separator Bottles containing 5mls of blood

Samples stored in the freezer should ideally be stored at -70 to -80°C but can be stored at -20°C for 1 month and then transported to a -70 to -80°C freezer.

Samples to be kept at ambient temperature after collection

- Blood: 20mls of blood in BD Vacutainer CPT tubes

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These samples **need to be processed in the University of Liverpool laboratory within 24 hours of collection**. They need to be transported from the local hospital laboratory to the University Laboratory within 24 hours of collection.

8.3.5.3 Transport:

BD Vacutainer CPT Tubes cannot be frozen or refrigerated before processing as this degrades the samples. They need to be kept in ambient temperature and processed within 24 hours after collection. These samples need to be transported to the University of Liverpool within 24 hours of the samples being taken to arrive Monday-Thursday.

Frozen samples will be couriered in batches back to the coordinating centre

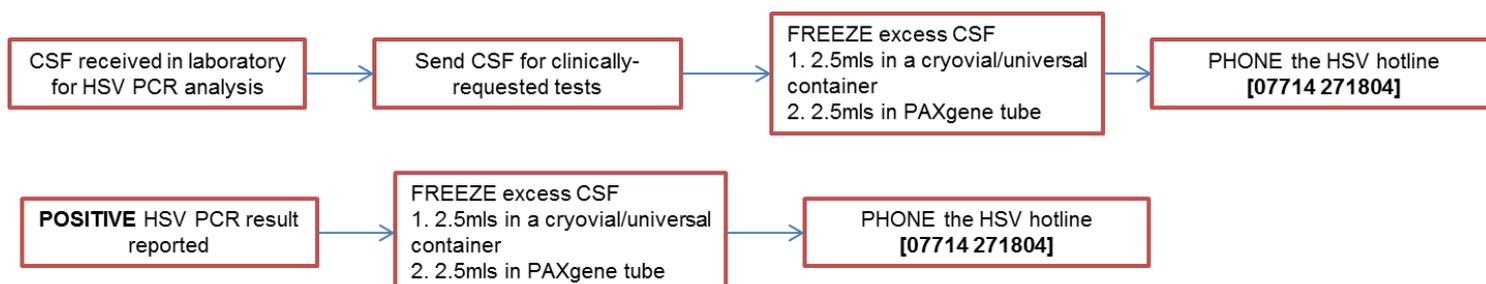
For any queries regarding transport of samples contact the HSV Hotline: 07714 271 804.

8.3.5.4 Laboratory Processes:

Labs will be asked to **“Freeze and Phone” any CSF that is sent for HSV PCR analysis or is HSV PCR positive that is not used for clinical reasons.**

The patient will then be consented to be enrolled in the RCT if they are eligible. If there is no extra CSF available this will not preclude entry to the RCT and labs are asked to phone the HSV hotline in all instances.

If this patient is then enrolled in the trial the baseline blood tests should be done as soon as possible, and certainly only up to the first day of the trial intervention.



8.4 Non-HSV Cohort Study

Table C: Schedule for Follow Up for Non-HSV Cohort Study

Procedures	Follow-Up Schedule		
	Screening	Baseline	Hospital Discharge
Signed Consent Form	X†	X†	
Assessment of Eligibility Criteria	X	X	
Sample Collection		X	
Review of Medical History		X	X
Review of Concomitant Medications		X	X

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			Follow-Up Schedule
	Screening	Baseline	Hospital Discharge
Procedures			
Clinical Data Collection		X	X

†May be done prior to samples collection or after sample collection if deferred consent has been used

The Non-HSV Cohort study aims to determine the difference in host immunologic responses, and pathological mechanisms between patients that have encephalopathy secondary to HSV and those that present to hospital with a clinical syndrome resembling HSV encephalitis but who have alternative diagnoses.

It will recruit patients in a limited number of sites. The information about which sites recruit patients to the Non-HSV Cohort Study will be in the local site file and trial webpage.

Patients cannot be recruited to both the RCT and Non-HSV Cohort.

8.4.1 Screening and Baseline [case of suspected encephalitis brought to attention of local research team]

As per section 6.3 those patients with suspected encephalitis that are not HSV positive will be approached for participation in the Non-HSV Cohort

When the research team becomes aware of a patient with suspected encephalitis that does not fulfil the criteria for the RCT:

- Review eligibility criteria: If fulfils criteria of Non-HSV Cohort Study consent for this
- If consent to participate in Non-HSV Cohort Study complete the Eligibility Form
- If do not fulfil the criteria or do not consent to participate record in the screening log.

8.4.2 Collection of Samples and Data Collection

The extra research CSF will be taken when a lumbar puncture is done as part of routine care. Samples taken will be the same as those taken at baseline in the RCT, thus if these were collected by the process of emergency deferred consent for the RCT they can still be used for the Non-HSV Cohort.

CSF will be taken from the diagnostic LP and any other LPs done during their hospital stay. Blood will be taken as close to admission as possible and **within 7 days of enrolment**. A baseline CRF will be completed and further data collection will be done at discharge. No procedures will be undertaken that are not part of routine medical care

1. Blood: 5ml of blood a BD Vacutainer Serum Separator Tube, 2.5mls in a PAXgene tube, and 20mls in BD Vacutainer CPT tubes is required as close to admission as possible and within 7 days of enrolment. BD Vacutainer CPT Tubes require sending to the University of Liverpool within 24 hours of collection.

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2. CSF: The CSF taken will be from the diagnostic LP or any further LPs done for clinical reasons during the patient's hospital stay. Research samples required are 2.5mls of CSF in universal containers/cryovial tubes (preferably cryovial) and 2.5mls in a PAXgene tube.

If the patient has already had a lumbar puncture prior to enrolment, there should be frozen CSF in the hospital laboratory through the “**Freeze and Phone**” method.

We will scavenge left over CSF from the lab with the patients consent if there is no stored frozen CSF.

If the patient has any further LPs during their hospital stay and there was insufficient CSF for research purposes on the initial LP, we will ask for extra volume to be taken to complete the required research tests.

Table D: Non-HSV Cohort Study Sample Collection Timeline

Research Samples Required	Time of Sample	Volume	After Collection
	Up to 7 days after enrolment		
CSF: Cryovial / Universal container	✓	2.5mls	Freeze at site
CSF: PAXgene Tube	✓	2.5mls	Freeze at site
Blood: BD Vacutainer Serum Separator Tubes (SST)	✓	5mls	Centrifuge then freeze at site
Blood: PAXgene Tube	✓	2.5mls	Freeze at site
Blood: BD Vacutainer CPT tubes	✓	20mls (may need 3-5 tubes)	Keep at ambient temperature. Transport to University of Liverpool within 24 hours, to arrive Monday-Thursday.

For information on storage and transport of samples **please refer to section 8.3.5.2 and 8.3.5.3.**

3. Data Collection: Complete the Non-HSV Cohort CRF at patient discharge. This data will be taken from the patients notes and will include information on:
 - a. Demographics
 - b. Past Medical History
 - c. Details of presentation and clinical state
 - d. Information regarding results from LP where samples were taken from
 - e. Diagnosis at discharge

8.5 Loss to Follow-up

When a patient is discharged the research nurse will check and record what address they have been discharged to, their contact details and their legal representative if they lacked capacity on discharge.

Different methods of contact, giving consideration to the individual's needs, will be offered when arranging follow up research-specific procedures, such as mobile phone number, home phone number, email address and writing to their home address. If they cannot be contacted by any of these methods, the hospital patient information system will be checked for any change of address or to ascertain whether the participant has had any further illnesses.

The patient's legal representative may also be contacted through any of the above methods. This information will be included on the patient information sheet.

Finally, the participant's GP will be contacted to seek further contact with the participant.

Wherever possible, information on the reason for loss to follow-up will be recorded

8.6 Trial Closure

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database.

However, the trial may be closed prematurely by the Trial Steering Committee, on the recommendation of the Independent Data and Safety Monitoring Committee. The IDSMC will review the data regularly (as detailed in section 16.3). Any stopping decision will take account of the fact that, whilst virus clearance might theoretically be inferior in Treatment Arm A, we would not want the study to stop early if the efficacy data (neuropsychology, functional, imaging clinical outcomes) suggested the treatment was efficacious. These issues will be carefully discussed with the IDSMC and allow them to make decisions based on the data monitoring that they will do).

DexEnceph has no planned interim analysis point, but will rely on the monitoring of the IDSMC.

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

A separate and full Statistical Analysis Plan will be developed prior to the final analysis of the trial. The Statistical Analysis Plan will be agreed with the Trial Steering Committee before being sent to the IDSMC for comment and approval.

9.2 Method of Randomisation

Treatment allocation will use a minimisation program, which will utilise a set of factors likely to be associated with outcome. These factors are not specified in the protocol, and will not be made known to individuals in charge of recruitment, to minimise any potential for predicting allocation.

9.3 Outcome Measures

See Section 4 for primary and secondary outcome measures.

9.4 Sample Size

The primary outcome variable is the Auditory (verbal) Memory Index, assessed as part of the Wechsler Memory Scale version IV (WMS-IV).

In one published series of adults who survived HSV encephalitis, 19 of 22 had memory impairment evident at follow up, with verbal memory being most severely affected(14). In that study the mean (standard deviation, SD) verbal memory score was 88.9 (18.9) the population mean (SD) for the scale is 100 (15).

This estimate is based only on survivors, and we estimate that approximately 10% of patients in the trial will die before assessment of the primary outcome. In these cases, the Auditory Memory Index score will be recorded as 40, which is the lowest possible value on the scale. Adjusting the estimate of mean and standard deviation from survivors, to include 10% of patients with the lowest possible value of 40, gives a mean of 84.8, with a standard deviation of 23.1.

A final sample size of 36 participants per group will allow us to detect a clinically meaningful difference of 15.5 on the Auditory Memory Index score with 80% power, at a two sided significance level of 0.05. Allowing for up to 20% dropout gives an initial target sample size of 45 participants per group, for a total of 90.

9.5 Interim Monitoring and Analyses

No formal interim analysis is planned, but there will be regular monitoring by the Independent Data and Safety Monitoring Committee (IDMSC), who will meet at least annually, and will have the option of unblinding if there are concerns about safety, especially

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to virus clearance versus efficacy measures. After each meeting, the IDSMC will provide a recommendation to the TSC on the continuation of the trial.

9.6 Analysis Plan

A full and detailed statistical analysis plan will be developed prior to the final analysis of the project and before any unblinded analysis is carried out. The main features of the statistical analysis plan are included here.

For the primary outcome of verbal memory, participants will be included in the analysis set based on the intention-to-treat principle. Any participants who have died prior to outcome assessment will have cause of death assessed by the chief investigator. If the cause of death is considered possibly related to encephalitis, the primary outcome will be imputed as the lowest possible scale score. If the cause of death is judged to be unrelated to encephalitis, the outcome will be considered lost to follow-up.

Verbal memory score will be compared between groups using linear regression. The model will be adjusted for pre-specified variables which are judged to be potentially related to the outcome, including the factors used in the minimisation program. Consideration will be given to using mixed models to allow for random variation between centres. A detailed statistical analysis plan will be developed before any unblinded analysis is carried out. No interim analysis is planned, but there will be regular monitoring by the IDMSC, who will have the option of unblinding if there are concerns about safety, especially to virus clearance versus efficacy measures.

As there may be some missing primary outcome data due to death, inability to complete the assessment, or loss to follow up, a sensitivity analysis will be carried out. All randomised patients will be included in this analysis. Patients lost to follow-up with no primary outcome data will have reason for dropout this assessed by the chief investigator as to whether this could be informative of likely outcome. If the reason for missing primary outcome is due to encephalitis (death or inability to complete the assessment), this will be used to impute appropriate estimates of the primary outcome. For those who died for reasons unrelated to encephalitis, or were lost to follow-up for non-informative reasons, multiple imputation will be used to complete the data set. The imputed data set will be analysed in the same way as in the primary analysis, and the results compared to assess their robustness to the missing outcome data.

For continuous secondary outcome variables comparisons of between groups will be analysed in the same way as the primary outcome. The results for residual viral presence in the CSF at 2 weeks will be reported with a 95% confidence interval for the difference in proportions between groups.

10 . PHARMACOVIGILANCE

10.1 Terms and Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

Adverse Event (AE)

Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)

Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR)

An adverse reaction the nature and severity of which is not consistent with the information set out in the summary of product characteristics in the case of a product with a marketing authorization, such as dexamethasone.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- other important medical events***

*'life-threatening' in the definition of 'serious' refers to an event in which the patient 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.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

10.2 Reporting Time Period and Procedures

Adverse Events or Reactions should be reported from randomisation and continue for 30 calendar days after randomisation. This includes reporting all Serious Adverse Events or

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Reactions in this time frame and the non-serious adverse events specified in the protocol as critical to the evaluations of the safety of the trial (section 10.7.1) . Following this period, further safety data will be collected in the case report form for the length of the 18 month follow up.

It is not expected that adverse reactions would occur after 30 calendar days but the investigator should continue to report any serious adverse reactions they feel are related to the study medication regardless of the timing.

Depending on the nature of the event the reporting procedures below should be followed:

1. Adverse events occurring up to 30 days after randomisation will be reported through an Adverse Event Form or in the 30 day/discharge CRFs. See section 10.7 for further information.
2. Adverse events occurring after 30 days from randomisation will be monitored through reporting in the CRFs with safety data collected in the 30 days / discharge, 26 week and 78 week CRFs

Please refer to section 10.8 for guidance regarding reporting inclusions and exclusions. Any questions concerning adverse event reporting should be directed to the CTU in the first instance. A flowchart is given below to aid in determining reporting requirements.

10.3 Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.

Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities

Moderate: interferes with routine activities

Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event (SAE).

10.4 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in Table F.

If any doubt about the causality exists, the local investigator should inform the study coordination centre who will notify the Chief Investigators. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Table F: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.5 Reference Safety Information

The Summary of Product Characteristics (SPC) for Dexamethasone will provide the reference safety information and will be the document against which expectedness assessments will be made.

10.6 Expectedness

It is not a regulatory requirement for a reporting physician at the research site to provide their opinion of expectedness and therefore, they will not be asked to make the assessment of expectedness. The assessment of expectedness will be made by the CI (or designated other) using the reference SmPCs for dexamethasone following receipt of the SAE form at CTU.

An AE whose causal relationship to dexamethasone is assessed by the investigator as “possible”, “probable”, or “almost certainly” is an Adverse Drug Reaction and is reportable. Expectedness should be assessed for all adverse drug reactions; a list of expected adverse reactions is defined by the product's SPC.

The research investigator at each study site (or designated other) will assess all adverse events for seriousness, causality and severity. The CI (or designated other specified in the protocol) will assess all adverse drug reactions for expectedness. All events judged by the designated investigator to be possibly, probably, or almost certainly related to the IMP and graded as **serious unexpected** (i.e. defined in section 10.1 and not listed in the product's SPC) should be reported as a SUSAR.

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10.7 Reporting Procedures

Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the CTU in the first instance. A flowchart is given below to aid in determining reporting requirements.

10.7.1 Non serious ARs/AEs

Non serious adverse events that require monitoring are:

1. Notable events: reported through the 30day/discharge CRFs
2. Suspected adverse reactions: reported through the AR CRF

Notable events are non-serious adverse events specified by the sponsor as requiring monitoring as an evaluation of safety of the trial. These are:

- Positive HSV PCR in CSF at 2nd lumbar puncture (i.e. after at least 14 days of intravenous aciclovir)
- Gastrointestinal bleed
- Hyperglycaemia requiring a change in medical management
- Opportunistic infections
- Neuropsychiatric events the PI believes to be secondary to dexamethasone administration.

These notable events will be reported in the 30 days /discharge CRF and reported as part of safety data monitoring at intervals advised by the IDSDMC. These adverse events should be reported from the point of randomisation until 30 days after randomisation.

Suspected adverse reactions are non-serious adverse events considered to be possibly/probably/almost certainly related to the intervention and will also be monitored. These should be reported through the Adverse Reaction CRF and sent to CTRC as per normal reporting procedures. They will be assessed for expectedness at the coordinating centre.

These non-serious events will be submitted in a DSUR to the MREC and regulatory authorities (including IDSMC).

10.7.2 Serious ARs/AEs/SUSARs

Serious ARs, serious AEs and SUSARs should be reported from the point of randomisation and up to 30 days. Thereafter they will be systematically collected in the case report forms at 26 weeks and 78 weeks. The investigator should continue to report any serious adverse reactions including death if they feel it is related to the study medication regardless of the timing.

10.7.2.1 SAE Exempt from Expedited Reporting

Anticipated serious adverse events in patients with HSV encephalitis includes:

- Death: Death is anticipated in patients with HSV encephalitis and therefore will be exempt from expedited reporting.

Current studies suggest that the mortality rate in patients with HSVE treated with aciclovir is around 10%(1, 11, 25). Timely reporting is required therefore a Death Report Form will be

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completed and sent to the CTRC **within 7 days** of the PI being aware. However, if the investigator suspects causality this should be reported in an expedited manner.

Information on **ALL** SAE's that occur **AFTER** 30 days from randomisation will be systematically collected on the 30 days / discharge, 26 weeks and 78 week CRFs. It is not expected that dexamethasone will cause adverse events after 30 days but the systematic collection of information will allow the identification of unexpected causality of adverse events associated with it. The CRFs will include information otherwise collected on an SAE form, including information on the nature of the event, data of onset, severity, corrective therapies given, outcome and causality. This data will be provided to the IDSMC, responsible for safeguarding the interests of trial participants and included in annual safety reports.

10.7.2.2 Serious ARs/AEs/SUSARs Reporting

All serious ARs, AEs and SUSARs occurring **up to 30 days** from randomisation (apart from death unless the investigator suspects causality) require reporting within 24 hours of the site becoming aware of the event. They should be reported through an SAE form.

The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

The CTU will notify the MHRA and main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required locally

Safety data will be provided to the IDSMC, who are responsible for safeguarding the interests of trial participants and assessing the safety of the interventions during the trial; the IDSMC will ensure action is taken as needed should they become aware of trends in reported AEs that raise safety concerns.

SAE occurring **after 30 days** from randomisation will be monitored by the CTU via the 30 days/discharge, 26 week and 78 week CRFs. These CRFs will need to be received at the coordinating centre by 2 weeks after the 30 days/discharge time point, 4 weeks after the 26 and 6 weeks +/- 78 week time points.

10.8 Adverse Event Inclusions and Exclusions

The following inclusion and exclusion criteria are relevant to all Serious Adverse Events or Reactions and the Non-Serious specified in the protocol

10.8.1 .Include

- An exacerbation of a pre-existing illness

NOTE: Further minor amendments undergoing review by ethics committee

- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents

10.8.2 Do NOT Include

- Medical or surgical procedures - the condition which leads to the procedure is the adverse event;
- Pre-existing disease or conditions present before treatment that do not worsen;
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery;
- Overdose of medication without signs or symptoms;
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition;
- Prolongation of hospital stays due to social factors, for example, geographical location of the trial participant's home.

10.9 Reporting in Pregnancy

Pregnant women are eligible to participate in the trial as a short course of steroid therapy is not contraindicated in pregnancy. Only long term steroids or repeated courses have led to intrauterine growth restriction and there is no evidence they cause congenital abnormalities (66). The information in the Baseline CRF will inform the coordinating centre whether a trial participant is pregnant.

The pregnant participant will not have any MRI brain scanning as part of the trial although she may have these as part of her normal clinical care if decided by her physician. Otherwise, trial participation will continue as scheduled. Appropriate obstetric care should be arranged. When the baby is born, an assessment of the pregnancy and information regarding birth defects, congenital abnormalities or growth restriction in the new-born will be included in the 30 Day/Discharge, 26 week or 78 week CRF (whichever follows the birth outcome).

Pregnancy during the follow up period is not considered to be an AE or SAE. However, pregnancy in a trial participant requires follow-up because a congenital abnormality or birth defect is considered an SAE and must be included in the safety evaluation of the intervention studied. Any pregnancy that occurs during the study will be reported to the coordinating centre using a Pregnancy CRF within 7 days of the site becoming aware of its occurrence. Follow up in the trial will continue but the patient will have no further MRI scans within the trial. When the baby is born, an assessment of the pregnancy and information

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regarding birth defects, congenital abnormalities or growth restriction in the new-born will be included in the 30 Day/Discharge, 26 week or 78 week CRF (whichever is straight after the birth of the child).

The coordinating centre will report all pregnancies to the trial sponsors, MHRA and MREC.

10.10 Reporting of Overdose

Study drug overdose (i.e. dexamethasone) is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects. Any study drug overdose or incorrect administration of study drug should be noted on the CRF. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the AE CRF. If the associated AE fulfils the serious criteria, the event should be reported to the CTU immediately (i.e. no more than 24 hours after learning of the event).

10.11 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.12 Responsibilities – Investigator

An Investigator is responsible for reporting adverse events that are observed or reported during the study regardless of their relationship to the study product according to the reporting procedures in section 10.7.

These include:

- All adverse events considered to be possibly/probably/almost certainly related to the intervention by the Investigator (i.e. adverse reactions) occurring up to 30 days after randomisation as per routine schedule in an Adverse Event Form.
- Notable events specified in the protocol via the 2 weeks and 30 day/discharge CRF
- All SAEs occurring up to 30 days after randomisation (as per reporting schedules detailed in section 10.7.2)
- All pregnancies within 7 days of the site becoming aware of its occurrence

All SAE occurring up to 30 days after randomisation require reporting in writing to CTRC by completion of and SAE report (in exceptional circumstances this may be an oral report followed by a detailed written report) within 24 hours of the site becoming aware of the event. SAEs occurring after 30 days will be reported via the appropriate CRFs. SAE's that occur 30 days after randomisation will be systematically collected on the 30days / discharge, 26 weeks and 78 week CRFs.

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Minimum information required for reporting:

1. Study identifier
 2. Study centre (& number)
 3. Patient's randomisation number
 4. A description of the event
 5. Date of onset
 6. Current status
 7. Whether study treatment was discontinued
 8. The reason why the event is classified as serious
 9. Investigator assessment of the association between the event and study treatment
- i. The SAE form should be completed by a designated investigator, a physician named on the 'signature list and delegation of responsibilities log' as responsible for reporting SAEs and making trial related medical decisions.
The investigator should assess the SAE for the likelihood that it is a response to the investigational medicinal product. In the absence of the designated investigator the form should be completed and signed by an alternative member of the research site trial team and submitted to the coordinating centre. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the coordinating centre.
The initial report shall be followed by detailed reports as appropriate.
- ii. When submitting an SAE to the coordinating centre research sites should also telephone the appropriate trial co-ordinator/data manager on telephone number **0151 706 5932** to advise that an SAE report has been submitted. Send the SAE form by fax (within 24 hours or next working day) to the CTU:
Fax Number: 0151 706 5932
- iii. The responsible investigator must **notify** their R&D department of the event (as per standard local governance procedures).
- iv. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary. If the SAE is resolved on the initial report the initial report will be accepted as the final report.
- v. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.
- vi. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

10.13 Responsibilities - CTU

The CTU is undertaking duties delegated by the trial sponsor, The University of Liverpool, and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities as follows:

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- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the CTU is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the CTU first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial or the development of the IMP and likely to affect the safety of the subjects, such as:
 - a. A SAE which could be associated with the trial procedures and which could modify the conduct of the trial;
 - b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
 - c. A major safety finding from a newly completed animal study (such as carcinogenicity).
 - d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;
- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at CTU will liaise with the Chief Investigator (or designated other specified in the protocol) who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs will be reported to regulatory authorities and MREC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The PIs at all institutions participating in the trial will be notified of any SUSARs.

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

10.13.1 Safety reports

Safety reports will be generated during the course of the trial which allows for monitoring of SAE and ADR reporting rates across sites. The CTU will send developmental safety update reports containing a list of all SARs to regulatory authorities and MREC.

Periodic updates of any SUSARs will be supplied to participating investigators in accordance with the DexEnceph data monitoring plan. If a significant safety issue is identified, either upon receipt of an individual case report or upon review of aggregate data, e.g. by the IDSMC, this will be communicated to participating investigators as soon as possible.

10.14 Maintenance of Observer Blinding

This trial requires observer blinding and this involves blinding of those performing neuropsychological assessments and statisticians who will be involved in the study's primary outcome. Where possible those performing laboratory work and imaging analyses will also be blinded. The site investigator caring for the patient and completing SAE reports, coordinating centre staff and sponsor (and their respective delegated staff) do not require to be blinded.

DSUR reports will be in a blinded fashion as a method of concealing unblinded data from staff working on the trial. However, cases that are reported to the regulator (i.e. SUSARs) will be in an unblinded format and thus the DSUR may contain unblinded data. The front title page of the DSUR will include a cautionary note warning of potential exposure to unblinded data.

10.15 Serious Breaches

A breach of the protocol or GCP is "serious" if it is likely to affect the safety or physical or mental integrity of the trial subjects or the scientific value of the trial to a significant degree. All serious breaches of GCP or the trial protocol should be reported to the MHRA by the trial sponsor.

If the CTU become aware of a potential serious breach during the trial, a potential serious breach report should be produced by the TMG and sent to the sponsor, TSC and IDSMC for a decision.

The TSC and IDSMC will communicate their opinion to the TMG. Where all parties consider that a serious breach of the protocol or GCP has occurred, the TMG will liaise with the sponsor and other involved parties to establish:

1. The extent of the breach
2. The initiation of a substantial amendment or urgent safety measures
3. Other corrective actions/training that are identified

It is the overall responsibility of the Sponsor to assess the impact of the breach on the scientific value of the trial. However, the Trial Statistician should be consulted to help to determine the impact of the breach on the scientific value of the trial.

The trial sponsor will inform the TMG of its decision regarding the potential serious breach and confirm that onward reporting to the REC and the relevant Regulators has occurred where appropriate. Any requests for additional information from the sponsor or MHRA will be actioned promptly and open communication will be maintained with sponsor and oversight committees to ensure appropriate corrective actions are taken and documented.

10.16 Urgent Safety Measures

An urgent safety measure is a procedure not defined by the protocol that is put in place prior to authorisation by the regulatory authority and REC in order to protect clinical trial participants from any immediate hazard to their health and safety.

NOTE: Further minor amendments undergoing review by ethics committee

If the study is temporarily halted for any reason the CTU, in liaison the trial sponsor, as detailed in the study Pharmacovigilance Reporting Guidelines, will notify the MHRA and REC as soon as possible and not later than 3 days as a substantial amendment, clearly explaining the reason for halting the trial. In this case the trial may not recommence until authorised to do so by the regulatory authority and REC.

If the study is terminated before the date specified for its conclusion (in the application), the sponsor should notify the MHRA and REC within 15 days of the date of termination by submitting a declaration of the end of a clinical trial form.

10.17 Contact Details and Medical Cover

DexEnceph participants will be inpatients during the intervention period. Clinicians responsible for their care will be aware of randomisation and the treatment administered, enabling them to make appropriate and informed decisions about their care in the event of an emergency. As such, emergency clinical care out of hours will be provided as local standard of care.

All patients will be issued with a copy of the signed information sheet and consent form. This document will include information about the patient's participation in DexEnceph and contacts in the research team locally who may be contacted if needed.

During office hours Professor Solomon, Dr Griffiths and Dr Fernandez will provide medical advice and can be contacted via the coordinator at the CTU or the HSV hotline.

The CI and designated others will be contactable for trial-related medical queries from the 09:00 until 17:00 Monday to Friday. Methods of contact for the DexEnceph team for any trial related queries are:

Telephone:	0151 706 5932
Mobile:	07714 271 804
Email:	DexEnceph@liverpool.ac.uk

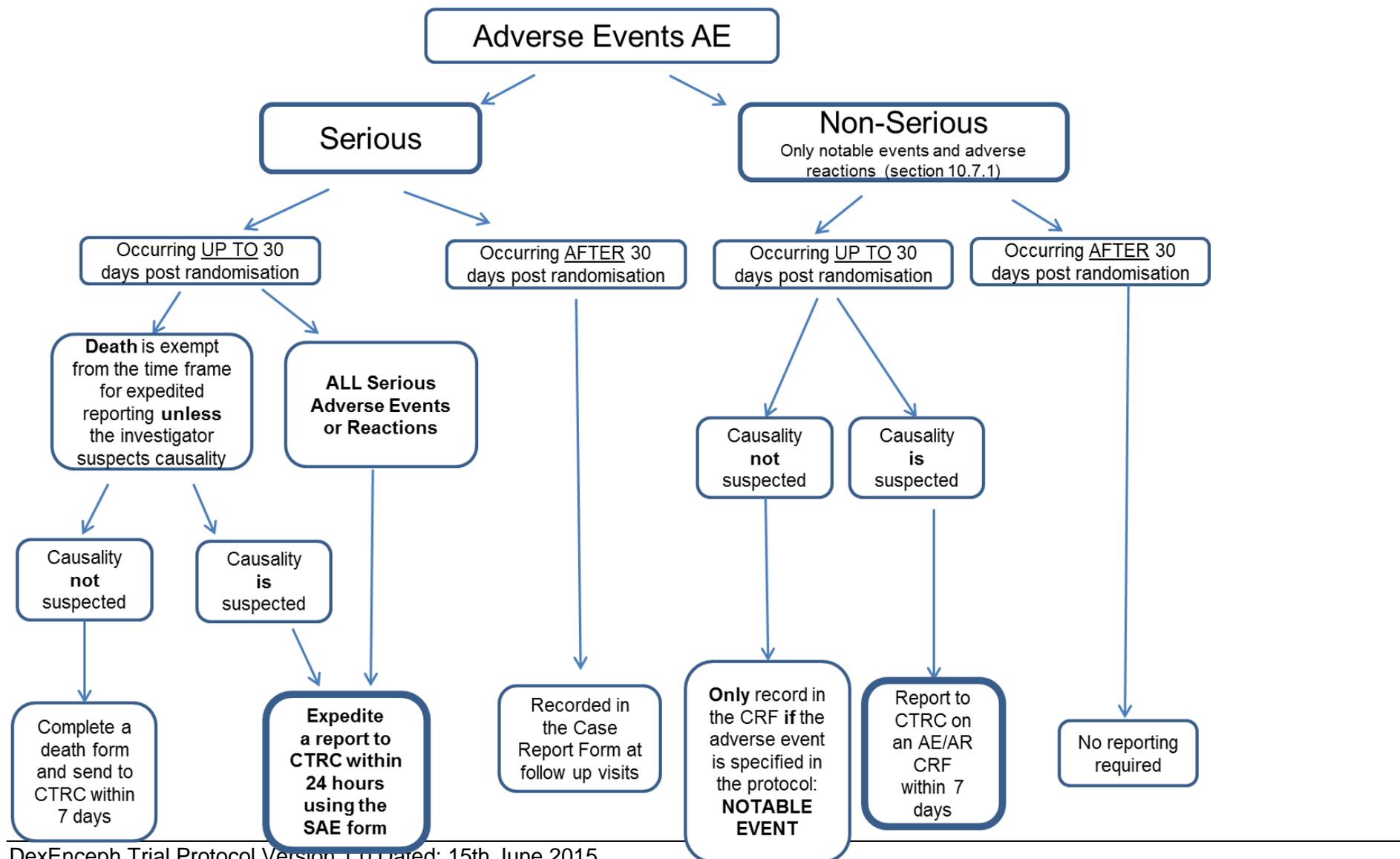
Out-of-hours cover by the CI is deemed not to be necessary as the IMP, dexamethasone, is a widely used drug in general medicine, neurology and brain infections with a well-established safety profile. Patients will be discharged home having not been taking the IMP for several days or weeks.

The Local Investigator and local research team at each site will be contactable in-hours to address trial-related medical queries from other members of staff. A copy of the trial protocol will be filed in every participant's notes for reference.

The care of hospitalised participants in the trial will be the responsibility of their primary physician and the on-call team when out of hours. Once discharged, the patient will be provided with appropriate contact details for the local research team to contact in-hours if necessary. If the participant or their relative feels that they need prompt medical care once they have been discharged they will be advised to contact their local A&E department.

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Schematic Design of Adverse Event Reporting Requirements:



DexEnceph Trial Protocol Version 1.0 Dated: 15th June 2015

NOTE: Further minor amendments undergoing review by ethics committee

11 ETHICAL CONSIDERATIONS

This study abides by the principles of the World Medical Association Declaration of Helsinki (1964) and Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996). Due to the nature of this trial it also abides but the Medicine for Human Use (Clinical Trials) regulations 2004 (S.I.2004:1031) and it's following amendments which are incorporated into UK law.

The specific ethical issues relating to participation in this study are detailed here:

11.1 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Staff delegated by the PI and appropriately trained with experience in obtaining informed consent will discuss the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted.

The patient information leaflet and consent discussion will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. All participants will be given opportunity to ask any questions that may arise, should have the opportunity to discuss the study with their surrogates and time to consider the information prior to agreeing to participate. A contact point where further information about the trial may be obtained will be provided.

Due to the low incidence of eligible patients, consenting patients for the trial will be a rare occurrence. Therefore the coordinating centre will be available to provide further guidance to the investigator through the consent process.

The patient or legal representative will then sign and date the informed consent document. Both the person taking consent and the participant or their legal representative must personally sign and date the form. The original copy will be filed in the site files. A copy of the informed consent document will be given to the patient or their legal representative for their records, another copy of the consent form should be sent to the CTU and a final copy will be kept in the patient notes.

Participant information sheets, consent forms and their subsequent amendments will require approval by the study's ethics committee. The current approved version for each recruiting site will be listed on the trial web site. The trial logo will be used as a header for the information sheets. The UK Study Wide Governance Criteria for R&D Review (HRA) and Standard Operating Procedures for National Research Ethics Service version 6.1 do not require the site's letter head to be included on the Participant Information Sheet or Consent Form. Participants or their legal representatives will be offered the information sheet whilst

NOTE: Further minor amendments undergoing review by ethics committee

inpatients therefore it will be clear that the information is being provided by their clinical team. Local contact details will be added on the dedicated contact section at the site .

The patient or their legal representative may, without being subject to any resulting detriment, withdraw from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

A continuous consent process will ensure the participant or their legal representative are informed at each stage and given the opportunity to reconfirm their willingness to participate or withdraw at any time.

11.1.1 Prospective Consent

For participation in the RCT patients can be consented when:

1. **Confirmed HSV Encephalitis:** the eligibility criteria is met including a positive HSV PCR in CSF.
2. **Suspected HSV Encephalitis:** prospective consent may be requested prior to the HSV PCR result being available if the patient meets all other inclusion and exclusion criteria. The patient will not be randomised until there is a confirmed positive laboratory result of HSV in CSF. This will require revisiting the eligibility criteria once the HSV PCR result in CSF is reported. If the HSV PCR in CSF is positive the patient or legal representative will be asked to confirm whether they continue to be willing to participate in the trial. This is part of a continuous consent process. If the CSF is HSV negative they will be requested to consent to the Non-HSV Cohort study (if they are in a site recruiting into this study).

For optimal respect of a patient's autonomy, written informed consent from the participant or their legal representative will be sought before study participation.

The patient benefit in allowing prospective consent is to allow more time for patients and relatives to consider participation. It will also allow more timely recruitment of patients allocated to the intervention arm.

11.1.1 Research team requesting consent

Consent from patients will be requested by an appropriately trained member of the research team who is formally delegated the role by the Principal Investigator. Their training will include GCP, training in the protocol and the consent processes in it. They will be recorded on the delegation log. This role may be delegated to research nurses or clinicians.

11.1.2 Determining eligibility

The PI or delegated team member will check whether the patient is eligible by following the eligibility criteria (refer to section 5).

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In the situation that a nurse has consented a patient, prior to being randomised a medically qualified clinician on the trial delegation log will confirm the patient is eligible and write this in the medical notes and case report form.

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Informed Consent Flow Chart

Suspected HSV Encephalitis*

Eligibility criteria met **except for** a confirmed HSV PCR in the CSF (**pending** the laboratory result)



Standard care determined by the clinical team at this point often includes:

- MRI Scan
- Lumbar Puncture
- Clinical Bloods
- IV Aciclovir (antiviral)



Additional CSF and blood can be taken for research at the same time the clinical blood and CSF samples are taken

RCT Consent Agreed
Prospective / on confirmation of HSV in CSF.
By patient or legal representative

RCT Consent Declined

CSF HSV positive:

Confirm eligibility



Randomise **if** within 7 days of a confirmed HSV report



If consented by a legal representative re-consent the patient when they **regain capacity**



Follow up at 6 and 18 months:

Resend the participant information sheet to the patient (and legal representative) prior to MRI scan.

CSF HSV negative:

Consent for the Non-HSV Cohort Study (**Only** if the patient is at a cohort recruiting site- listed on study website)

Deferred Consent requested for early samples

If a legal representative declines to these samples will not be used for research. In the event of death consent will be requested (see section 10.2.10)

* New seizure or personality / behaviour change includes: agitation, psychosis, somnolence, insomnia, catatonia, mood lability and altered sleep pattern.

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11.2 Recruitment of Patients Lacking Capacity

As this is a CTIMP the clinical trial regulations for incapacitated adults is relevant (Medicines for Human Use Clinical Trial Regulations 2004 and amendments).

England and Wales:

The MHRA GCP Guide recommends that, although the provisions for approving research under sections 30-33 of the Mental Capacity Act 2005 for England and Wales do not apply to trials, the remainder of the Act does apply(67). The Mental Capacity Act defines capacity and details the process in ascertaining whether a person has capacity in the following terms:

- A person must be assumed to have capacity unless it is established that he lacks capacity.
- A person is not to be treated as unable to make a decision unless all practicable steps to help him to do so have been taken without success.
- A person is unable to make a decision for himself if he is unable:
 - To understand the information relevant to the decision;
 - To retain that information;
 - To use or weigh that information as part of the process of making the decision, or;
 - To communicate his decision (whether by talking, using sign language or any other means).
- A person is not to be regarded as unable to understand the information relevant to a decision if he is able to understand an explanation of it given to him in a way that is appropriate to his circumstances (using simple language, visual aids or any other means).

Scotland: Adults with Incapacity (Scotland) Act 2000, under section 1 (6) of the act, states a person is incapable if due to mental disorder or inability to communicate because of physical disability he is incapable of:

- (a) acting; or
- (b) making decisions; or
- (c) communicating decisions; or
- (d) understanding decisions; or
- (e) retaining the memory of decisions.

But people should not be treated as unable to communicate if they can be assisted to do so by any means.

Northern Ireland: there is no equivalent legislation, and matters relating to capacity would be determined by the common law.

11.2.1 Informed consent for patient's lacking capacity

A significant proportion of patients may be unable to give legal consent to being involved in this trial; this inability to give consent may be a direct consequence from HSV encephalitis. To provide a true representation of the population of people with HSV encephalitis it is necessary to enrol participants who lack capacity. These patients are those who will be most

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severely affected by HSV encephalitis and participation in this trial may be of direct benefit to them by attempting to reduce the severity of brain damage and sequelae. Participants may also have general cognitive impairment affecting their understanding.

Reasonable steps will be taken to identify a personal legal representative. This will be a person not included in the conduct of the trial, suitable to act as the legal representative by virtue of their relationship with the adult, and be available and willing to do so.

11.2.2 Informed Consent by a Legal representative

Hierarchy of informed consent for an incapacitated adult	
<i>England, Wales and Northern Ireland</i>	<i>Scotland</i>
<p><u>1. Personal legal representative</u> A person not connected with the conduct of the trial who is: (a) suitable to act as the legal representative by virtue of their relationship with the adult, <u>and</u> (b) available and willing to do so.</p>	<p><u>1. Personal legal representative</u> 1A. Any guardian or welfare attorney who has power to consent to the adult's participation in research. 1B. If there is no such person, the adult's nearest relative as defined in section 87(1) of the Adults with Incapacity (Scotland) Act 2000.</p>
<p><u>2. Professional legal representative</u> A person not connected with the conduct of the trial who is: (a) the doctor primarily responsible for the adult's medical treatment, or (b) a person nominated by the relevant health care provider (e.g. an acute NHS Trust or Health Board). A professional legal representative may be approached if no suitable personal legal representative is available.</p>	<p><u>2. Professional legal representative</u> A person not connected with the conduct of the trial who is: (a) the doctor primarily responsible for the adult's medical treatment, or (b) a person nominated by the relevant health care provider. A professional legal representative may be approached if it is not reasonably practicable to contact either 1A or 1B before the decision to enter the adult into the trial is made. Informed consent must be given before the subject is entered into the trial.</p>

Table G: Hierarchy of informed consent for an incapacitated adult (Part 1 4a of Schedule 1 to SI 2004/1031).

The legal representative will be provided with a participant information leaflet by the research team, given the opportunity to discuss the trial with them and given a contact point. They will meet a member of the research team who will explain the objectives, risks and inconveniences of the trial and the conditions under which it is conducted. They will be informed of the right to withdraw the participant from the trial at any time.

If there is no available personal legal representative, a professional legal representative will be approached. This will be the doctor primarily responsible for the patient's medical treatment who is not connected to the conduct of the trial or a person nominated by the relevant healthcare provider.

NOTE: Further minor amendments undergoing review by ethics committee

If consent is withheld by the legal representative the patient will not be included in the trial; and samples collected will be destroyed. Informed consent given by a legal representative shall represent the presumed will of an incapacitated adult.

Even though the patient is not able to give informed consent they will receive information about the trials risks and benefits according to their capacity of understanding. If the patient is capable of assessing this information and forming an opinion about it, and consequently expresses an explicit wish to refuse participation or to withdraw from the clinical trial at any time, this will be given serious consideration by the investigator.

11.2.3 Regaining capacity to consent

When a patient's participation in the RCT has been consented for by a legal representative and the patient then regains capacity, the research team will provide the patient information sheet and request consent from the participant. Patients will be advised that consent is voluntary and they may withdraw without any detriment to their care. If a patient regains capacity once discharged from hospital they will be approached to ask whether they would like to continue participating at their next scheduled research-assessment. If they choose to continue to participate in the trial they will be requested to sign the consent form.

11.2.4 Informed Consent from patients who then proceed to lose capacity

If the patient that has consented then becomes unable to give informed consent, the previously obtained consent remains valid. They will be monitored for any signs of objection or distress during trial specific procedures that would prompt a reconsideration of their continued participation. This would also be the case if their nominated relative raised concerns regarding their continued participation.

11.2.5 Emergency Deferred Consent for Collection of Research Samples

In order to achieve the aims of this study it is important that research samples are taken at the time the admission blood and CSF samples are collected for clinical care. These clinical samples are routinely required within the first few hours of the admission. An extra amount of CSF will be taken at the time the admission lumbar puncture is required for their clinical care. Consent for this may be deferred until a more appropriate time to discuss with patients or their legal representatives.

If research samples have been collected, deferred consent to use these can be taken:

- As part of consent for the RCT participation (preferable method).
- Using the SAMPLES Collected During a Clinical Procedure consent form pending the HSV PCR result.

If written informed consent for use of these samples is declined by the patient or their legal representative after these have been taken, the samples will not be used for research purposes.

Emergency deferred consent does not take the place informed consent. For optimal respect of a patient's autonomy written informed consent before study participation is preferable. However, in the emergency setting (as suspected encephalitis is a medical emergency) this is not always possible for the early samples.

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If the additional samples are taken for research and the patient is then diagnosed as NOT having HSV encephalitis, in a centre that is NOT recruiting into the Non-HSV Cohort, they will be informed that samples were taken and that these not be used for research as the centres recruiting to the cohort study are limited.

11.2.1 Deferred Consent for Samples following the death of a participant

Death is anticipated in this patient population. When research samples are taken in the acute stage and consent is deferred, the patient may die before consent has been provided. In this event consent may be requested from the relatives to use these samples for research.

In this case relatives will be approached early after the death by the clinical team, who will ask for their permission for these samples to be used then, rather than being contacted at a later stage. The SAMPLES Collected During a Clinical Procedure Information leaflet and consent form will be used. The researcher will ask clinicians to discuss this with relatives at the time of death if they judge this to be appropriate as this is such a sensitive situation. In the event that there is not an appropriate opportunity for the clinical team to ask relatives in the early stage the samples collected will be included in the research rather than contacting families at a later time. This is based on information following patient public involvement conducted by the Encephalitis Society.

11.2.2 Consent for Further Assessments

As part of a continuous consent process a patient's willingness to continue to participate will be discussed at each visit. Consent for procedures at 26 (6 months) and 78 weeks (18 months) will be included in the initial written consent form. Participants will be contacted to organise assessments at these two time points at which point they can withdraw consent if they so wish.

Patients will be contacted by a telephone call to arrange the MRI scans at 26 and 78 weeks. In the case of patients that lack capacity the local team will call their legal representative. Patients and their legal representatives will be sent the study information leaflet reminding them of the implications of having an MRI scan. The legal representative will be required to attend with their relative if they lack capacity.

11.2.3 Consent for Non-HSV Cohort

If a patient is not eligible for the RCT they may be considered for participation in the Non-HSV Cohort if they are in a site that recruits into this study. Information about whether a site is participating in the Non-HSV Cohort Study will be in the study website and in local study site file.

If CSF samples have already been collected for research they can be used with the participants consent. If no samples have been collected for research patients can participate in the Non-HSV Cohort as long as CSF samples can be scavenged from the laboratory.

11.3 Randomisation

Participants and/or their legal representatives need to fully understand that they are randomly allocated to a treatment arm and therefore may be allocated to the control arm (Arm B).

The trial design will be explained in the consent process prior to signing the consent form. Patients that are eventually randomly allocated to the control arm (Arm B) will be reassured that if their clinician feels it is necessary for them to receive corticosteroids of any formulation at any point during the study follow up regardless of the indication this will not be denied to them.

11.4 Additional Assessments

Neuropsychology testing is occasionally done in routine practice in patients with encephalitis as patients frequently suffer neuropsychological sequelae. In this trial neuropsychological sequelae has been chosen as a primary outcome as it provides a measure directly relevant to patient's clinical outcome.

Patients will be offered visits by an assistant neuropsychologist at a location of their choice this may be their own home, care home where they reside, rehabilitation setting where they are temporarily residing or other convenient locations. They may also arrange patients to attend a hospital for these assessments as long as this is convenient.

Refusal to continue with a neuropsychology test once commenced will not automatically exclude patients from other trial procedures unless they withdraw from the trial completely. If a neuropsychology assessment including the tests performed in the trial has already been completed by the patient as part of their routine clinical care this may be used for research purposes to avoid duplication and reduce research burden. In this instance the roving research assistant will only complete the tests not included in their clinical assessment. Some sites may also have the ability to perform the research neuropsychology assessments.

As part of the trial patients will have an MRI scan at 2 weeks, 26 weeks and 78 weeks; this is considered to not be part of routine care. Despite this, some patients will have MRI scans as part of their routine care and, if done in the time frame of the study imaging, these images can be used and should be done following the parameters in section 8.3.1. The MRI scans at 26 and 78 weeks will involve a visit to a clinical facility, and thus these will be attempted to be at times convenient for the study participant. The MRI will require a cannula inserting and therefore, the study blood tests will be attempted to be done at the same time to avoid repeated venepuncture. If the patients or their legal representative consent, contrast media will be used with all research scans. To allow for this, a participant's renal function will have to be checked within 3 months prior to the scan if there is not one already available in this time frame. If there is no available eGFR prior to the scan, the patient does not consent for administration of contrast or their eGFR is $<30\text{ml}/\text{min}/1.73\text{m}^2$ the scan can go ahead but WITHOUT the administration of contrast.

If patients refuse to have either their blood test or MRI scan they will not be withdrawn from the study unless they specifically request this [please refer to section 6.7.3].

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11.5 Ethical and Governance Approval

The trial protocol has been submitted to a NRES Committee and must undergo independent review at the R&D offices at participating sites. The local R&D office should be sent the appropriate site specific information form complete with the necessary authorisation signatures, plus any other documentation requested for review. A copy of local Research & Development (R&D) approval should be forwarded to CTU before the site is initiated and patients recruited.

The clinician will remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient remains free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing the further treatment.

11.6 Study Discontinuation

In the event that the study is discontinued, participants will be treated according to usual standard clinical care. Information regarding the processes in voluntary withdrawal from trial specific procedures or from the trial completely are detailed in section 6.7.

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12 REGULATORY APPROVAL

This trial falls within the remit of the EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended. This trial will be registered with the MHRA and granted a Clinical Trial Authorisation (CTA). [The EUDRACT number for CTA reference is 2015-001609-16].

Ethical approval will be sought from an appropriate Multi-centre Research Ethics Committee (MREC) familiar with the principals of the Mental Capacity Act 2005 guidance for sites in England and Wales and the Adults with Incapacity Act 2008 for sites in Scotland as the principals are relevant to CTIMP.

Clinical Research Governance approval is given through the Sponsor, The University of Liverpool

13 TRIAL MONITORING

Trial monitoring is carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial. A risk assessment is performed for each trial coordinated by the CTU to determine the level and type of monitoring required for specific hazards. The nature and extent of monitoring will be specific to the individual trial and can take the form of on-site visits or central monitoring. This monitoring plan will be described in a separate, detailed trial monitoring plan.

Trial Oversight Committees related to the monitoring of the trial are detailed in section 16.

13.1 Risk Assessment

In accordance with the CTRC SOP TM005 a risk assessment will be completed in partnership between:

- Representative/s of the Trial Sponsor
- Chief Investigator
- Trial Coordinator and supervising Trial Manager
- Trial Statistician and supervising Statistician
- Information Systems team
- CTRC Director

In conducting this risk assessment, the contributors consider potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur. The outcome of the risk assessment is expressed as a percentage, assigned according to the following categories:

1. Score $\leq 33\%$ = Low risk
2. Score ≥ 34 to $\leq 67\%$ = Moderate risk
3. Score ≥ 68 to $\leq 100\%$ = High risk

Monitoring of DexEnceph will be informed by the DexEnceph risk assessment. The detailed monitoring plan will describe who will conduct the monitoring, at what frequency this will be done, and what level of detail monitoring will be conducted.

Guidance issued by the MRC, Department of Health and the MHRA on risk-adapted approaches to the management of CTIMPs(68) propose a three level categorisation for the potential risk associated with the IMP, assigned according to the following categories:

Type A 'no higher than that of standard medical care';

Type B 'somewhat higher than that of standard medical care';

Type C 'markedly higher than that of standard medical care'.

This level of risk informs the risk assessment, regulatory requirements, nature and extent of the monitoring, and the management processes used in the trial. DexEnceph is a trial of dexamethasone, a commonly used and licensed medication with a well-established safety profile.

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DexEnceph is a pragmatic trial that uses market authorised drugs for an off label indication. Based on this marketing authorisation status of the medicines being investigated the trial is expected to be categorised as Type B. This level of risk informs the risk assessment, regulatory requirements, nature and extent of the monitoring, and the management processes used in the trial.

13.2 Source Documents

Source data: includes all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).

Source documents: includes original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).

In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF. The following data recorded in the CRF should be consistent and verifiable with source data in source documents *other* than the CRF (e.g. medical record, laboratory reports and nurses' notes). Identified source documents other than the CRF for this trial are:

1. Hospital patient records
2. Hard copy questionnaires
3. Neuroimaging on discs
4. Study procedures checklist document
5. Laboratory reports
6. Neuropsychology assessment forms

Therefore, for data where no prior record exists and which is recorded directly in the CRF, the CRF will be considered the **source document**, unless otherwise indicated by the investigator. All such exemptions should be identified prior to the clinical phase of the trial. In addition to the above, date(s) of conducting informed consent process including date of provision of patient information, registration number, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically, i.e. when treatment is allocated to the patient.

13.3 Data Capture Methods

Trial data will be captured using paper CRFs. CRFs will be sent into coordinating centre for data entry into the study specific database. Completed CRFs should be returned to CTC

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within 7 days of completion. A copy of the CRF sent over to the coordinating centre should be retained at site.

13.3.1 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "ND". If the item is not applicable to the individual case, write "N/A". Or if the data item is un-known, write "NK". If a data item has not been recorded on source data then write 'NR'.

All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

The Case Report Forms will be completed by the local research team. Once each CRF has been fully completed and signed off, a copy should be taken to be kept in the local CRF folder. The originals should then be photocopied and sent to the CTRC within 7 days (photocopies of completed CRFs should be kept in the site file). If data queries are raised after the originals have been sent to the CTRC, these queries should be responded to via the data query form, with the copies left unaltered. Once the CRFs have been received at the coordinating centre they will be stored in locked filing cabinets.

13.3.2 Patient Completed Data

Patients will be asked to complete two questionnaires: the EuroQoL 5D-5L and SF-36, and three self-assessments: the Beck Depression Index, Beck Anxiety Index and the Perceived Deficits Questionnaire. The site number, participant's initials and randomisation number will be clearly labelled on all documents. These will be sent back to the coordinating centre via a prepaid envelope, collected by the research nurse at clinic visits or collected via the roving assistant neuropsychologist.

13.3.3 Electronic Data

Patient's neuroimaging data will be put on to discs at site and sent over to the coordinating centre. These discs will need to be labelled with the site number, participant's initials and randomisation number. At the coordinating centre they will be stored in locked filing cabinets.

13.4 Central Data Monitoring at the Co-ordinating Centre

Data stored at CTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the CTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to CTRC. The

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forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database.

Central checks of consent and eligibility for the RCT will be completed for each participant to ensure validity of enrolment, completeness of consent, and that the timing of consent is in line with the protocol.

There are a number of monitoring features in place at the CTRC to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan.

13.5 Clinical Site Monitoring

In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient records, laboratory reports, appointment books, etc. The investigator will permit trial-related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data/documents. Since this affects the patient's confidentiality, this fact is included on the Parent Information Sheet and Informed Consent Form.

13.5.1 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. For patients eligible for the DexEnceph RCT study, case report forms will be labelled with the patient's initials and unique trial randomisation number. Patients enrolled only to the Non-HSV Cohort will have case reports labelled with the patient's initials and unique trial enrolment number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

CRFs and consent forms will be stored securely in a dedicated area of the coordinating centre.

The CTU will be undertaking activities requiring the transfer of identifiable data:

1. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the coordinating centre by recruiting centres, which requires that named data will be transferred to the CTU. This will be archived securely. **Consent forms should not be posted with other trial data this includes CRF.**
2. The coordinating centre will be responsible on occasions to send questionnaires to trial participants following discharge from hospital and will therefore be required to receive contact details including name, address and telephone details. This information is collected in the Participants Information Form and this **should not be posted with other trial data this includes CRF**
3. The neuropsychology team from the coordinating centre will be responsible in contacting the participants following discharge from hospital to arrange neuropsychology testing. They will also be required to receive contact details including name, address and telephone details. This information is collected in the Participants Information Form and this **should not be posted with other trial data this includes CRF**

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This transfer of identifiable data is disclosed in the PISC. The CTU will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

13.5.2 Quality Assurance and Control

Quality Assurance (QA) includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. Quality Control (QC) includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled.

- The PI and designated staff from each centre will attend the site initiation meeting, arranged by the coordinating centre, in conjunction with co-lead investigators, which will incorporate elements of trial-specific training to fulfil requirements of the protocol;
- The Trial Co-ordinator will verify appropriate approvals are in place prior to the initiation of a site, and that the relevant personnel have attended study specific training;
- The Trial Co-ordinator will check safety reporting rates between centres;
- The Trial Co-ordinator is to monitor screening, recruitment and drop-out rates between centres;
- The Trial Co-ordinator will oversee data entry consistency checks and follow-up of data queries;
- Data will be evaluated for compliance with protocol and data accuracy and consistency in relation to source documents;
- Independent oversight of the trial will be provided by the Independent Data and Safety Monitoring Committee and independent members of the Trial Steering Committee.

13.6 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File and Pharmacy Site File, until the Clinical Trials Unit informs the investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest).

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (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 coordinating centre undertakes to store originally completed CRFs for the same period, except for source documents pertaining to the individual investigational site, which are kept

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by the investigator only. The coordinating centre will archive the documents in compliance with ICH GCP utilising the Records Management Service of the University of Liverpool. All trial 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 INDEMNITY

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

Clinical negligence is defined as:

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

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15 FINANCIAL ARRANGEMENTS

This trial is funded by the NIHR Efficacy and Mechanism Evaluation Programme for the Department of Health. Contractual agreements will be in place between the Sponsor and collaborating centres that will describe financial arrangements.

Trial participants will not be paid to participate in the trial. Participants will be paid travel expenses for the follow up visits. In DexEnceph the patient will be required to travel to a hospital for the MRI scan assessment at 26 weeks and 78 weeks. This will be estimated as £50 per visit.

15.1 NHS Research Costs

15.1.1 Per site

To reflect site personnel time to fulfil the needs of the research e.g. preparing for an attending initiation/ monitoring meetings, a per site payment is included in the budget and detailed in contracts.

15.1.2 Per patient recruited payment

Research related activity, including data collection, will be supported by a *per patient* payment. This is to support robust recruitment and follow-up of participants a per patient payment is budgeted and detailed in contracts.

This will be part of the contract between recruiting sites and the Sponsor but may include:
Clinical Time for Medical Oversight 4 hours per participant @ £72.14 per hour total
£289.76

Research Nurse to follow up patients 13 hours @ £30.10 = £903 per patient

Administrative support @ £14 x 2 hours = £28 per patient

MRI scan £443.73 up to 3 per patient

Pharmacy oversight 1 hour @ £30.10 per patient randomised to dexamethasone.

Patient travel if claimed by the site for longer term follow up up to £50 .

15.1.3 NHS Support Costs:

This trial will be adopted by the NIHR CRN portfolio and infrastructure support will be available through the CRN network. This will allow Trusts to apply for service support costs provided by the CRN.

15.2 Treatment Costs:

Supplies for the trial will be secured through the usual NHS commissioning arrangements and treatment costs are covered via usual NHS arrangements.

16 TRIAL COMMITTEES

16.1 Trial Management Group (TMG)

A TMG will be responsible for the day-to-day running of the study. It will consist of the Chief Investigator, key co-investigators and members of the CTRC team. The TMG will meet every month in the pre-award period and for the first year of the study and then every other month subsequently. The TMG can meet more frequently as needed. Meetings will be held in Liverpool, with members from other locations joining by teleconference and will report to the Trial Steering Committee.

16.2 Trial Steering Committee (TSC)

The TSC will comprise three independent members, including an independent statistician, an independent chairperson and a lay member and representatives of the Trial Management Group. It will also have up to seven Principal Investigators.

The responsibility of the TSC is to provide overall supervision for the trial and advice through its independent chairperson. The TSC will meet twice a year. The ultimate decision for the continuation of the trial will lie with the TSC. (Refer to the TSC terms of reference and trial oversight committee membership document for further details).

16.3 Independent Data and Safety Monitoring Committee (IDSMC)

The IDSMC consists of an independent chairperson, plus 2 independent members, a statistician and a clinical trialist.

The IDSMC will be responsible for reviewing and assessing recruitment, monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will meet at least annually, and will provide a recommendation to the Trial Steering Committee concerning the continuation of the trial. The first meeting will occur prior to the start of recruitment. (Refer to the IDSMC charter and trial oversight committee membership document for further details).

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17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (<http://www.icmje.org/>) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

Regular updates regarding the study will be published on the DexEnceph website. Regular e-mails will be sent to participating sites to inform them when the website has been updated.

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18 PROTOCOL AMENDMENTS

18.1 Version 1 (15/06/2015)

Original Approved version.

NOTE: Further minor amendments undergoing review by ethics committee

19 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

- Patient and legal representative's information sheets
- Consent form for patients and legal representatives
- SF-36 Questionnaire
- EuroQoL 5D-5L Questionnaire
- List of Participating sites
- List of Central laboratories
- GP Contact Letter
- Study Procedures Checklist

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NOTE: Further minor amendments undergoing review by ethics committee

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