Protocol for DexEnceph: a randomised controlled trial of dexamethasone therapy in adults with herpes simplex virus encephalitis


ABSTRACT

Introduction Herpes simplex virus (HSV) encephalitis is a rare severe form of brain inflammation that commonly leaves survivors and their families with devastating long-term consequences. The virus particularly targets the temporal lobe of the brain causing debilitating problems in memory, especially verbal memory. It is postulated that immunomodulation with the corticosteroid, dexamethasone, could improve outcomes by reducing brain swelling. However, there are concerns (so far not observed) that such immunosuppression might facilitate increased viral replication with resultant worsening of disease. A previous trial closed early because of slow recruitment.

Method DexEnceph is a pragmatic multicentre, randomised, controlled, open-label, observer-blind trial to determine whether adults with HSV encephalitis who receive dexamethasone alongside standard antiviral treatment with aciclovir for have improved clinical outcomes compared with those who receive standard treatment alone. Overall, 90 patients with HSV encephalitis are being recruited from a target of 45 recruiting sites; patients are randomised 1:1 to the dexamethasone or control arms of the study. The primary outcome measured is verbal memory as assessed by the Weschler Memory Scale fourth edition Auditory Memory Index at 26 weeks after randomisation. Secondary outcomes are measured up to 72 weeks include additional neuropsychological, clinical and functional outcomes as well as comparison of neuroimaging findings. Patient safety monitoring occurs throughout and includes the detection of HSV DNA in cerebrospinal fluid 2 weeks after randomisation, which is indicative of ongoing viral replication. Innovative methods are being used to ensure recruitment targets are met for this rare disease.

Discussion DexEnceph aims to be the first completed randomised controlled trial of corticosteroid therapy in HSV encephalitis. The results will provide evidence for future practice in managing adults with the condition and has the potential to improve outcomes.

Ethics and dissemination The trial has ethical approval from the UK National Research Ethics Committee.

Strengths and limitations of this study

- DexEnceph will be the first completed randomised controlled trial of corticosteroids in herpes simplex virus encephalitis, examining the utility and safety.
- DexEnceph’s primary end point is verbal memory score recorded at 26 weeks after randomisation, this represents the most important neuropsychological damage.
- The recruitment target is informed by the recent Enceph-UK programme grant of encephalitis in the UK; the trial is currently open and has recruited 82 patients of a target 90.
- Innovative methods for engaging with recruitment sites have been key to ensuring the success of the study.

INTRODUCTION

Herpes simplex virus infection (HSV) is the most commonly identified viral cause of encephalitis, inflammation and swelling of the brain caused by a virus or the body’s immune system, in the UK as in most western industrialised nations. The incidence has been estimated at 1 in 250000–500 000, with evidence it may be higher. Although a rare disease, HSV encephalitis has a disproportionately large impact due to its devastating long term neuro-psychological sequelae. These can have a marked impact on the quality of life of the patient and their family and high health economic and social costs.
Since the introduction of the antiviral drug aciclovir in the 1970s, the mortality of HSV encephalitis has reduced from around 70% to 5.5%–12%. However, survivors are commonly left with neurological impairment; less than 20% of patients are able to return to work and 48% are classed as moderate to severely disabled. Even when obvious disabilities have not occurred, families often report personality changes—the person they take home from hospital is simply not the same as the one before the illness.

HSV encephalitis can cause a broad range of cognitive impairments, but impaired memory, especially verbal memory, is the most common and likely relates to the viral predilection for the temporal lobe of the brain. The verbal memory deficits manifest as difficulties remembering names of objects and people, as well as listening to and recalling spoken information for example in conversations. In addition to memory problems, difficulties in processing speed, concentration, language and executive function are also common among survivors of HSV encephalitis, along with fatigue, poor concentration, anxiety and depression. The pathogenic mechanisms in HSV encephalitis are not fully understood. The evidence suggests that in addition to direct viral pathogenesis, inflammation of the brain in response to the virus is a key component of the disease process. This is supported by the observation that in the cerebrospinal fluid (CSF), higher levels of proinflammatory chemokines, especially monocyte chemotactic protein-1, interferon γ and interleukin 6 (IL-6) are associated with a worse prognosis. Poor prognosis is also associated with the extent of inflammation seen on neuroimaging, and the degree of temporal lobe swelling is correlated with the severity of verbal memory impairment. Relapse occurs in about approximately 10% of HSV encephalitis patients, and is sometimes associated with the development of anti-N-Methyl-D-Aspartic acid (NMDA) antibodies.

Control of the inflammation in HSV encephalitis may improve outcome, as shown in mouse models of the disease. Before the availability of aciclovir, corticosteroids were sometimes used as a treatment in humans with HSV encephalitis, and more recently both cerebral oedema on imaging and CSF IL-6 levels were shown to be reduced in patients given corticosteroids. However, because corticosteroids cause immunosuppression, which in theory facilitates increased viral replication, their role is uncertain.

In other brain infections, including bacterial meningitis and tuberculous meningitis the benefit of corticosteroids has been demonstrated in large clinical trials. For HSV encephalitis the potential benefit of using corticosteroid as an adjunct to aciclovir therapy has been suggested from small case series and retrospective comparisons, but there has been no prospective randomised study reported. One study, the German trial of Aciclovir and Corticosteroids in Herpes simplex virus Encephalitis (the GACHE trial) was stopped early because of poor recruitment rates. However, there is clearly a need for a study to answer this question. The DexEnceph Study, a randomised controlled trial of dexamethasone in HSV encephalitis, aims to achieve this.

**Trial design**

DexEnceph is a pragmatic, multicentre, randomised, controlled, observer-blind trial to determine whether the addition of dexamethasone to standard aciclovir treatment improves clinical outcomes (in particular verbal memory score) for adults with HSV encephalitis. Additionally, neuroimaging and biomarkers are assessed along with detection of HSV in the CSF at 2 weeks after randomisation to monitor for difference in viral replication between the two groups.

**Primary objective**

To determine whether a short course of intravenous dexamethasone, in addition to standard care, improves verbal memory score in adults with HSV encephalitis at 26 weeks after treatment compared with standard care alone.

**Secondary objectives**

Secondary objectives include the following:
- To determine whether dexamethasone therapy has an effect on other neuropsychological, cognitive, clinical, disability and functional outcomes in HSV encephalitis.
- To assess the effect of dexamethasone therapy on brain swelling examined by neuroimaging.
- To determine whether dexamethasone therapy affects clearance of HSV from the CSF, the emergence of NMDA receptor antibody or causes any changes in transcriptomic and proteomic profiling in the CSF and blood.

A more comprehensive list of measures is detailed in the outcomes section.

**METHODS AND ANALYSIS**

DexEnceph is an observer-blind, open-label, prospective, randomised, controlled trial of dexamethasone at 10 mg four times daily for 4 days, versus no dexamethasone, in adults with HSV encephalitis.

**Research setting**

The trial is being conducted in up to 45 National Health Service (NHS) trusts, with a recruitment target of 0–2 patients per site per year. A full list of sites involved in DexEnceph can be obtained from [www.dexenceph.org.uk](http://www.dexenceph.org.uk). The trial uses Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines (online supplemental file 1).

**Eligibility criteria**

**Inclusion criteria**

Enrolled patients fulfil all of the following criteria:
1. Suspected encephalitis defined as: new-onset seizure or new focal neurological signs or alteration in consciousness, cognition, personality or behaviour. Personality/behavioural change includes agitation, psychosis,
somnolence, insomnia, catatonia, mood lability, and altered sleep pattern.
2. A positive HSV DNA PCR result from CSF, reported not more than 7 days prior to randomisation.
3. Receiving intravenous aciclovir administered as 10 mg/kg three times daily or at a reduced dose if clinically indicated.
4. Age ≥ 16 years.
5. Written informed consent given by the patient or their legal representative.

Exclusion criteria
Patients are excluded if they have any of the following:
1. Have received oral or injectable corticosteroid therapy in the 30 days prior to the day of entry to the study. This does not apply to topical/inhaled corticosteroids. (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 trial participation).
2. History of hypersensitivity to corticosteroids.
3. Immunosuppression secondary to:
   a. Known HIV infection and CD4 white cell count under 200/mm³.
   b. Currently taking biological therapy or other immunosuppressive agents (e.g., 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 a ≥2 unit haemoglobin drop, in the last 6 months.
6. Antiretroviral regimen containing rilpivirine as current treatment (levels of rilpivirine are known to significantly decrease in coadministration with dexamethasone, a switch to a suitable alternative can facilitate trial entry).

Intervention
Participants are randomised in a 1:1 ratio to dexamethasone four times daily for 4 days alongside standard care, or standard care alone (figure 1). Standard care includes intravenous aciclovir for a minimum of 14 days based on an ideal body weight at 10 mg/kg every 8 hours, unless dose adjustment to account for renal impairment is necessary. Participating clinicians remain free to modify or discontinue the dexamethasone administration or to give alternative treatments at any stage, if this is judged to be in the best interest of the patient.

Participants assigned dexamethasone receive 10 mg equivalent of ordinary ward stock, prescribed by an authorised member of the local study team, given intravenously four times daily for 4 days (16 doses in total) starting within 24 hours of randomisation.

The University of Liverpool employs a clinical trials unit to be responsible for screening, and monitoring data collection, quality and completeness. As there is a low number of participants to be recruited, the trials unit are able to liaise regularly with each site following randomisation to ensure all follow-up data are collected. Primary outcome is recorded by a centrally employed roving neuropsychologist, who collects the neuropsychological outcomes at 26 and 72 weeks.

Outcome measures
Primary outcome
Verbal memory score, determined by the Wechsler Memory Scale fourth edition (WMS-IV) Auditory Memory Index, at 26 weeks after randomisation. Patients that die will be allocated the lowest possible WMS-IV score.

Secondary outcomes
Other neuropsychological outcome measures (at 26 weeks and 78 weeks after randomisation):
- Verbal memory score, determined by the WMS-IV, Auditory Memory Index, at 78 weeks after randomisation.
- Visual, Immediate and Delayed Memory by Indexes of the WMS-IV, processing speed and working memory...
subscales from the Wechsler Adult Intelligence Scale Fourth Edition.

- Higher executive function using the Trail Making Test.
- Anxiety and Depression symptom levels by the Beck Depression Inventory and Beck Anxiety Inventory.
- Subjective cognitive complaints using the Perceived Deficits Questionnaire.

Cognitive Outcome Measures (at discharge or 30 days if still in hospital, 26 weeks and 78 weeks):
- Addenbrooke’s Cognitive Assessment III.

Clinical Outcomes
- Incidence of epilepsy.
- Time to hospital discharge.
- Requirement of high-dependency unit or intensive care unit admission up to 30 days after randomisation.
- Time taken to be free of ventilatory support for 14 days (if any).
- Time to reach maximum recorded Glasgow Coma Scale score.
- Survival.

Disability and functional outcomes (at discharge or 30 days if still in hospital, 26 weeks and 78 weeks):
- Modified Rankin Score, Barthel Index, Liverpool Outcome Score and Glasgow Outcome Scale Extended.

Imaging Outcomes: Change from Baseline at 2 weeks, 26 weeks and 78 weeks
- Temporal lobe volume (as percentage of intracranial volume).
- Whole brain volume (as percentage of intracranial volume).
- Volume of affected region as seen on fluid-attenuated inversion recovery image (as percentage of intracranial volume).
- Volume of affected region as seen on diffusion-weighted image (as percentage of intracranial volume).

Biomarker outcomes
- Transcriptomic and proteomic profiling on blood at convalescence (2 weeks and 26 weeks), compared with acute baselines, and on CSF at 2 weeks compared with acute baseline.
- Anti-NMDA receptor antibody testing at 26 weeks.

Safety outcomes
- Proportion of patients with detectable HSV in CSF by PCR at 2 weeks.
- Health Status and Quality of Life (at 26 and 78 weeks):
  - Measured by the EuroQoL-5 Dimension-5 Level quality of life scale and 36 item Short-Form Survey self-completed questionnaires.

Screening
The majority of potential patients are identified by the local research team through identifying patients with a relevant clinical presentation suspicious of HSV encephalitis and/or detection of HSV in a CSF sample. A screening log is completed for all potential patients. A strong link with the local laboratory is essential as a key factor in ensuring eligible patients are not missed by the investigative team. Investigators for the local research team include neurologists, infectious disease clinicians, acute medics, microbiologist and virologists.

Because this is a rare disease, most centres will only see 1-2 potential patients a year. Extra measures have therefore been taken to try and maximise recruitment. On identifying a suitable patient, sites are able to contact the trial management team for intensive support via a dedicated telephone hotline, email, or an app. Short videos which explain the trial to patients, families and to healthcare workers also support recruitment. Every month, the trial management team monitor the screening reports of each site for the previous 3 months, to ensure they are actively looking for patients. Lower than expected screening is followed up by the central study team making contact with the study site to review their screening methodology and offer support.

Randomisation
Participants are randomised using a 24-hour secure web-based programme, which is centrally controlled by the clinical trials research centre. Designated members of the trial team at the site (detailed on the delegation of responsibilities log) are provided with a unique username and password which is required to access the web-based randomisation system. In the event of system failure, the patient can be randomised centrally electronically or through secure envelopes. Each participant is allocated a unique study number (randomisation number), the primary identifier for all the participants in this study.

The neuropsychologist collecting the primary outcome and other outcome assessors such as radiologists and the lead investigators are blinded to randomisation during the trial. Trial participants and local site study teams, as well as the trial manager and trial data manager at the clinical trials unit are aware of what treatments have been allocated. The independent data safety and monitoring committee (IDSMC) and statisticians have access to unblinded data grouped by intervention throughout the trial and make recommendations to the trial’s steering committee who would only become unblinded in the event of a serious event.

Participant timeline
The time schedule for enrolment, interventions and assessments is given in table 1.

Statistical considerations
Sample size
The primary outcome variable is verbal memory, assessed as part of 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. In that study the mean (SD) verbal
memory score was 88.9 (18.9) compared with the population mean (SD) of 100.15 This score can only be assessed in survivors, we estimate approximately 10% of patients in the trial will die before assessment of the primary outcome.8 43 44 In instances where the death is judged to be associated with encephalitis the verbal memory score is recorded as 40, (the lowest possible value which would be obtained even where a patient recorded no recall of any of the items administered in the memory subtests). Where the cause of death is thought to be independent of having encephalitis, those patients will be recorded as lost to follow-up. Similarly, for patients who are too unwell, due to encephalitis, to undergo the assessment, the score is recorded as 40. Decisions as to whether the reasons for death or non-completion of the measures were due to encephalitis will be made by an independent committee blinded to dexamethasone allocation. Adjusting the estimate of mean and SD from survivors, to include the 10% of patients that die having the lowest possible value of 40, gives a total population mean of 84.8, with a SD of 23.1. A final sample size of 36 participants per group allows us to detect a clinically meaningful difference of 15.5 on the verbal memory 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.

### Statistical analysis

For the primary outcome, participants are included in the analysis based on the intention-to-treat principle. Verbal

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(X)—As indicated/appropriate.
*Only applicable when patients are prospectively consented for the randomised controlled trial.
†Procedures required before randomisation.
‡Baseline MRI done for clinical purposes can be done from hospital admission up to 7 days after randomisation.
§Diagnostic lumbar puncture done prior to randomisation.
¶Recorded prior to randomisation, daily for the first 14 days and then weekly until discharge/30 days (whichever sooner).
**Recording of clinical laboratory tests done for clinical purposes, not as part of trial.

Table 1 Time scale for patients randomised in the DexEnceph study
memory score will be compared between groups using linear regression. The model will be adjusted for prespecified variables which are judged to be potentially related to the outcome, including age and admission Glasgow Coma Scale Score. No interim analysis is planned, but there is regular monitoring by the IDSMC.

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.

For continuous secondary outcome variables, comparisons between groups will be analysed as per the primary outcome. The results for residual viral presence in the CSF at 2 weeks will be reported with a 95% CI for the difference in proportions between groups. Time to event outcomes will be analysed using Kaplan-Meier curves, log-rank tests and Cox proportional hazards models. Binary secondary outcomes will be analysed using logistic regression.

**Trial promotion and engagement**

Because a previous similar study (the GACHE trial) was stopped early due to poor recruitment rates, we have put particular effort into maximising recruitment. This has included keeping the (NOTE) principal investigators, research nurses and the community engaged in the trial. The trial is being publicised regularly using the Encephalitis Society website and newsletter, social media, and patient journey articles. The Encephalitis Society are playing a key role in providing additional support to the patients and their families aside from their work for the trial. At the annual World Encephalitis Day we have engaged with clinicians, patients, families and the public to raise awareness of encephalitis and the trial, especially through social media, newspapers, radio and television. To promote site engagement, study days are arranged for research teams to attend, along with scheduled research nurse teleconferences to allow ideas on maximising recruitment and updates on trial progress to be shared. Research investigators are invited to the annual Neurological Infectious Diseases course in Liverpool. Sites are also kept updated through our website (www.dexenceph.org.uk), and newsletters. In addition, we use an innovative sticker chart, whereby a sticker is sent to every site each time a patient is recruited anywhere in the country, approximately once a month (Figure 2); this helps keep the study at the forefront of investigators minds. In addition, in case the DexEnceph study did not recruit to target a parralele study was set up by French colleagues, using the same protocol, so that data could be pooled if needed.

**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. The trial may be closed prematurely by the trial steering committee, on the recommendation of the IDSMC if there is sufficient evidence of risk to patient safety.

**Pharmacovigilance**

Oversight of the trial is provided by the trial steering committee, which meets at least annually to review trial progress, safety, and adverse events (AEs). The committee is also informed of any protocol changes by the clinical trial research unit.

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions are used for AE, adverse reaction (AR), unexpected AR, serious AE (SAE), serious AR (SAR) or suspected unexpected SAR (SUSAR). Depending on the nature of the event the reporting procedures below are followed:

1. SAEs occurring up to 30 days after randomisation are reported through an SAE Form (if serious) or in the 30 days/discharge case record forms (CRF) if they are a notable event (positive PCR in CSF at second lumbar puncture, gastrointestinal bleed, hyperglycaemia requiring change in medical management, opportunistic infections, unexpected/severe neuropsychiatric events).

2. SAEs occurring after 30 days from randomisation are monitored through reporting in the CRFs with safety data collected in the 26 weeks and 78 weeks CRFs if serious.

The research investigator at each study site (or designated other) assesses all AEs for seriousness, causality...
and severity. The chief investigator (or designated other) assesses all adverse drug reactions for expectedness from known side effects of the use of dexamethasone. All serious ARs, AEs and SUSARs occurring up to 30 days from randomisation (apart from death unless the investigator suspects causality) require reporting to the clinical trials unit, within 24 hours of the site becoming aware of the event. In the case of death of a patient causality will be assessed by the trial steering committee.

The clinical trials unit will notify the Medicines and Healthcare products Regulatory Agency and main research ethics committee of all SUSARs that occur 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 are informed of all SUSARs occurring throughout the study.

SAEs occurring after 30 days from randomisation are monitored by the clinical trials unit via the 26 weeks and 78 weeks CRFs. These CRFs need to be received at the clinical trials research unit by 4 weeks after the 26 and 6 weeks after 78 weeks time points.

Safety data are 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 ensures action is taken as needed should they become aware of trends in reported AEs that raise safety concerns.

**Trial funding and financial arrangements**

Contractual agreements are in place between the sponsor and collaborating centres that describe financial arrangements. Trial participants are not paid to participate in the trial but are paid travel expenses for the follow-up visits. Payments to sites are made per site initiation but the bulk of payments are made per patient recruitment. Sites receive payment for: clinical time oversight, research nurse time, administrative support, MRI scanning and pharmacy oversight.

**Patient and public involvement**

The Encephalitis Society was consulted and provided advice on the design of the trial and the difficulties participants and their families encounter. The chief investigator of the DexEnceph study is the President of the Encephalitis Society. The chief executive of The Encephalitis Society is a coapplicant on the grant application and a coauthor on this paper.

The Encephalitis Society has also provided patient representatives at our trial steering committee and assisted in the production and dissemination of trial promotional materials.

The Encephalitis Society will support publication and dissemination of the trial findings among lay, therapeutic and health professionals through the use of web materials, newsletters and guides as well as at conferences and seminars. All patients and their family/carers will be acknowledged in any outputs from the trial. We also work with The Encephalitis Society on a programme of teaching events and produce guides for healthcare professionals and lay people.

In instances where trial participants and their families have ongoing difficulties the central study team seek help for them through the Encephalitis Society and appropriate specialists for further assistance.

**Ethics and dissemination**

The 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 is registered with the Medicines and Healthcare products Regulatory Agency (MHRA) and granted Clinical Trial Authorisation (CTA). The EUDRACT number for CTA reference is 2015-001609-16. Ethical approval has been obtained from a multicentre research ethics committee 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 a clinical trial of investigational medicinal products (CTIMP). Clinical Research Governance approval was given through the Sponsor, The University of Liverpool. The trial protocol was approved by a National Research Ethics Service Committee reference is 2015-001609-16 (Attained 31 March 2016) and underwent independent review at the Research and Development offices at participating sites. 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 by the Medicine for Human Use (Clinical Trials) regulations 2004 (S.I.2004:1031) and all following amendments which are incorporated into UK law.

**Informed consent process**

In obtaining and documenting informed consent, the investigators adhere to National Institute for Health Research (NIHR) Good Clinical Practice guidelines and the ethical principles derived from the Declaration of Helsinki. Staff delegated by the principal investigator and appropriately trained with experience in obtaining informed consent, discuss the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted with the patient or if the patient lacks capacity with a legal or professional representative. Trial information documents and points of contact for further information are provided and the potential participants are given adequate time to consider their decision (online supplemental file 2).

As this is a CTIMP, the clinical trial regulations for incapacitated adults are followed (Medicines for Human Use Clinical Trial Regulations 2004 and amendments). When a legal representative has given consent for a patient to participate in the trial and the patient subsequently regains capacity, the research team will provide the patient information sheet and request consent from...
the participant. Patients are allowed to withdraw from the study at any point and may request withdrawal of their data collected until this point. Prospective consent can also be obtained prior to a positive PCR result so participants may have adequate time for contemplation.

As suspected encephalitis is a medical emergency, a deferred consent process is used for the collection and retention of some samples as part of routine clinical management. Using emergency deferred consent for samples involves taking additional samples of blood and CSF only if the procedure is being performed for clinical care. If deferred consent has been used, written consent is requested from either the patient or a legal representative as soon as is possible and appropriate, with samples discarded if this is declined. This approach is based on discussions with patients and the public through the Encephalitis Society.

**Data capture methods**

Data are stored securely in line with the Data Protection Act 1998. The randomisation system, data capture form and CRF have been designed to optimally protect participant information and to maintain confidentiality. Trial data are captured at local sites using paper CRFs. These are then sent into the clinical trials research unit for data entry into the study-specific database. Completed CRFs are returned to clinical trial research centre within 7 days of completion. A copy of the CRF sent over to the clinical trials research unit is retained at site. CRFs and consent forms are stored separately and securely at all times in dedicated areas of the clinical trials research unit.

CRFs are checked for data quality by the clinical trials research unit in Liverpool responsible for ensuring data collection and storage.

Patients’ anonymised and labelled neuroimaging data are put on to discs at site and sent to the clinical trials research unit; the images can also be transferred via the Image Exchange Portal in an encrypted manner. The final dataset will be solely accessible to the central study team at the University of Liverpool for analysis and write up.

**Dissemination**

The results of the DexEnceph trial will be published in a high impact journal in a timely manner to present the findings to front-line clinicians. They will be presented at the annual conference organised by the Encephalitis Society and at other meetings. Authorship of the final papers will be determined in accordance with the international committee of medical journal editors’ guidelines. The investigators will be involved in the preparation and drafting of the manuscripts. There is no intended use of professional writers.

**DISCUSSION**

This protocol describes the design of a randomised controlled trial to examine the role of dexamethasone in the management of patients with HSV encephalitis. HSV encephalitis is a rare sporadic acute disease, and the trial has been designed to take this challenge into account, along with the practicalities of running the trial in a UK National Health Service setting. In particular lessons were learnt from a previous similar European study, the GACHE trial, which was stopped early because of recruitment difficulties. Recruitment to the GACHE trial necessitated patients had focal neurological signs of no longer than 5 days prior to admission, while DexEnceph has less stringent criteria and reflects the diverse ways in which HSV encephalitis may present. DexEnceph has been designed to be both practical and pragmatic, in that patients must be recruited within 7 days of the PCR result becoming available. This allows for occasions where it may take longer to get the PCR performed, and also allows time for patients admitted to district general hospitals, which may not be study centres, to be transferred to larger hospitals which are. DexEnceph also has the advantage in that its recruitment projections were based on preliminary data garnered from the ENCEPH-UK NIHR programme (www.encephuk.org) and from a multicentre cohort study of encephalitis in England, run by the Health Protection Agency (fore-runner to the Health Protection Agency). These two studies provided direct information on the number of HSV encephalitis patients presenting to UK hospitals. The GACHE study was a double-blind placebo controlled study. Our choice of an open-label observer-blind study, avoided the logistic challenges of ensuring blinded study drug was available across the large number of centres, which might each see only one to two patients per year. We are confident our robust monitoring and trial promotion ensures the majority of eligible patients are recruited. NMDA receptor antibody encephalitis (which is treated with corticosteroids and other immunomodulatory therapies) is being recognised increasingly as a late complication of HSV encephalitis. DexEnceph may also be able examine whether corticosteroids reduce the incidence of this complication. If there is demonstrable efficacy of corticosteroid in improving neuropsychological, imaging and quality of life outcomes, without compromising patient safety the results will be far reaching.

**Collaboration with France**

Because we recognised from the start that there may be difficulties keeping to recruitment targets in the DexEnceph study, we worked with colleagues in France to develop a parallel French study (DexEnceph-France). This follows the UK DexEnceph protocol as closely as possible, while being pragmatic about the constraints of a different country’s healthcare system. The French trial is based in 10 hospitals with the lead centre being Grenoble Alpes University Hospital and the aim of recruiting 30 patients.

The intention is for the two trials to be analysed separately, with the option of also combining them into an
overall analysis which will give additional power to detect a treatment effect.

**Trial status**

The trial was opened in the UK in August 2016. By June 2019 it was running at 45 NHS trusts, and by February 2020 71 patients had been randomised. However, in March 2020 recruitment to the trial was paused, along with most other NIHR-funded studies, because of the Covid-19 pandemic. However ongoing assessment was completed for patients in the study, and the primary outcome was not missed for a single such patient. Conducting such assessments despite social distancing requirements required some ingenuity on the part of the neuropsychology team. Recruitment to the study reopened in June 2020 (one of the first non-Covid-19 studies to do so) and by June 2021 had recruited 82 (91%) of the target 90 patients. The progress of the trial through the pandemic is a testament to the commitment of the research teams around the country, as well as the patients and their families. The trial is currently expected to complete recruitment in January 2022, and to complete follow up for the primary outcome 6 months later. The research team have used the lessons learnt in conducting a randomised controlled acute treatment trial of this rare disease to apply successfully for funding to study the role of intravenous immunoglobulin (IVIG) in autoimmune encephalitis. If you are interested in seeing whether your hospital could become involved in the Enceph-IG study please visit www.liverpool.ac.uk/encephig, or email: encephig@liverpool.ac.uk

**Author affiliations**

1. Department of Clinical Infection, Medical Microbiology and Immunology, University of Liverpool, Liverpool, UK
2. Clinical Trials Research Centre, University of Liverpool, Liverpool, UK
3. PLEASE REMOVE THIS ADDRESS ENTRY X, X, X
4. Tropical and Infectious Diseases Unit, Liverpool University Hospitals Foundation Trust, Liverpool, UK
5. Neurology Department, Alder Hey Children’s NHS Foundation Trust, Liverpool, UK
6. Pharmacy Department, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK
7. Department of Biostatistics, Faculty of Health and Life Sciences, University of Liverpool, Liverpool, UK
8. Department of Clinical Neuropsychology, The Walton Centre NHS Foundation Trust, Liverpool, UK
9. Neuroradiology Department, The Walton Centre NHS Foundation Trust, Liverpool, UK
10. South London Specialist Virology Centre, King’s College Hospital NHS Foundation Trust, London, UK
11. Division of Neuroscience & Experimental Psychology, University of Manchester, Manchester, UK
12. The Queen’s Medical Research Institute, The University of Edinburgh, Edinburgh, UK
13. The Encephalitis Society, Malton, North Yorkshire, UK
14. Service des Maladies Infectieuses et Tropicales, CHU Grenoble Alpes, Grenoble, Rhône-Alpes, France
15. Department of Neurology, Alder Hey Children’s NHS Foundation Trust, Liverpool, UK
16. REMOVE THIS ADDRESS X, X, X, XXX
17. Infectious Diseases Department, University of Grenoble, Grenoble, UK
18. Department of Neurology, Walton Centre NHS Foundation Trust, Liverpool, UK
19. National Institute for Health Research Health Protection Research Unit in Emerging and Zoonotic Infections, Institute of Infection Ecology and Veterinary Sciences, University of Liverpool, Liverpool, UK

**Contributors** All authors were consulted and inputted into the article, below lists the particular role within Dexepong: TW: clinical research fellow, CF: clinical research fellow, KD: trials manager, SD: contributor to trial design and running, MG: Clinical and laboratory biomarkers lead, CH: neuropsychology researcher, RT: trial pharmacist, GB: trial statistician, AR-H: trial statistician, PM: neuropsychology lead, KDAs: neuroimaging lead, MZ: virology, LP: neuroimaging, SK: neuroimaging, NR: neuroimaging, AE: encephalitis society chief executive advisor, ST: study coordinator France, AK: clinical lead brain infections UK, JPS: principal investigator France, TS: chief investigator responsible for the trial.

**Funding** This trial is funded by the NIHR Efficacy and Mechanism Evaluation Programme for the Department of Health reference 12/205/28.

**Competing interests** TS is supported by the National Institute for Health Research (NIHR) Health Protection Research Unit in Emerging and Zoonotic Infections (Grant No. IS-HPU-1112-10117), NIHR Global Health Research Group on Brain Infections (No. 17/63/110), and the European Union’s Horizon 2020 research and innovation program ZikaPLAN (Preparedness Latin America Network), grant agreement No. 734384.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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**ORCID iD**
Thomas Whitfield http://orcid.org/0000-0002-4016-2712

**REFERENCES**


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47 Gilbert GJ, Levyfolt F, Dalmu J. Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. *Neurology* 2014;82:2041

### SPIRIT checklist for protocol of the DexEnceph clinical trial.

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random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism

Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Allocation: implementation

Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions

Blinding (masking)

Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how

Blinding (masking): emergency unblinding

If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection plan

Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

Data collection plan: retention

Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

Data management

Plans for data entry, coding, security, and storage,
including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

Statistics: outcomes

**#20a** Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

Statistics: additional analyses

**#20b** Methods for any additional analyses (eg, subgroup and adjusted analyses)

Statistics: analysis population and missing data

**#20c** Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

### Methods: Monitoring

Data monitoring: formal committee

**#21a** Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

Data monitoring: interim analysis

**#21b** Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms

**#22** Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing

**#23** Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
### Ethics and dissemination

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<td><strong>Data access</strong> #29</td>
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<td><strong>Dissemination policy: trial results</strong> #31a</td>
<td>Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions</td>
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<tr>
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authorship professional writers

Dissemination policy: #31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials #32 Model consent form and other related documentation given to participants and authorized surrogates Appendix 1

Biological specimens #33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable NA
RCT Adult with Capacity Information Sheet
Version 5.0, 25 May 2018

DexEnceph: A study of dexamethasone in adults with Herpes Simplex Virus (HSV) encephalitis
Brain Infections Group, University of Liverpool

We understand this is a difficult and stressful time for you, so we firstly want to thank you for taking the time to read this leaflet.

You are being invited to take part in a research study on HSV encephalitis. This condition is extremely rare and is probably something you had never heard about before. This is why a team member will go through this leaflet with you, explaining what taking part in the study would involve and answering any questions.

**Important things you need to know**

- This is a study for patients with encephalitis (swelling of the brain) caused by a virus called herpes simplex virus (HSV).
- Encephalitis can make you confused, drowsy, behave out of character, affect your sleep and memory, change your mood or may cause you to have fits.
- We want to find out if reducing the swelling with a drug called dexamethasone is of benefit to patient’s memory in the longer term.
- In the study there will be two groups of patients, one that receives dexamethasone and one that does not.
- If you are in the group that receives dexamethasone this will be for 4 days in hospital.
- Both groups will have the same investigations to see if dexamethasone has been of benefit.
- Dexamethasone is a commonly used drug in brain swelling and many other conditions. Like all medicines, dexamethasone has side-effects. We will explain what these can be later.

**We would like to invite you to take part in a research study**

- Before you decide to take part it is important you know why the research is being done and what it will involve.
- You can discuss with family, friends and clinical staff before making a decision.
- You are free to decide whether you would like to take part.
- If you choose to take part and then decide you no longer want to be involved you can stop taking part without giving a reason. Your care will not be affected.
- Please let us know if there is anything in this leaflet that is not clear or if you would like more information. A member of our team will answer your questions.
- If you decide to take part we will offer you a copy of this form and ask you to sign a consent form.
# HSV encephalitis

1. **What is HSV encephalitis?**
   Encephalitis means swelling of the brain and has many different causes. It is often caused by a virus. Herpes Simplex Virus (HSV) is the most common virus that causes encephalitis in the UK.

   HSV encephalitis is very rare. It is diagnosed by finding the virus in fluid around the brain and spinal cord. This fluid is called CSF (cerebrospinal fluid). The CSF is obtained by the doctor who performs a lumbar puncture (LP).

   HSV encephalitis is treated with the drug aciclovir. Despite treatment, some people are left with significant loss of memory. About 2 out of every 3 people will have memory difficulties long term.

## The study

2. **Why are we doing this study?**
   We know dexamethasone can reduce swelling. Reduction in swelling of the brain may improve the recovery of patients with HSV encephalitis.

   This study, called DexEnceph, will allow us to compare the recovery of patients that received dexamethasone and those that did not.

3. **Why have I been invited to take part?**
   There are two reasons why you may have been invited to take part:

   **A.** Your doctors have diagnosed you with having HSV encephalitis.

   **OR**

   **B.** You may have been invited to take part before the diagnosis is made. This is because your doctors think there is a chance you may have HSV encephalitis. This will mean you have more time to think about taking part.

4. **What will happen to me during the study?**

   All patients in the study will receive aciclovir. This is standard treatment for HSV encephalitis.

   In addition, if you decide to take part in the study, you may be offered a short course of dexamethasone. This will be decided at random by a computer. This is to be fair, so neither you, your doctor, nor the research team, can choose whether you receive dexamethasone or not. Half of the people in the study will receive dexamethasone and half will not.

   If you receive dexamethasone this will be 4 times a day for 4 days. It is given in a line you already have for clinical care.

## What taking part involves

5. **What tests are done if I take part?**

   ![Diagram showing the stages of the study](image.png)

   All the tests done when you sign up to the study and the CSF tests after 2 weeks will be...
be done as part of your care whether you take part in the study or not.

6. What do the memory tests involve?
These tests are the most important in the study as they will help us find out if dexamethasone improves memory problems from HSV encephalitis. These tests are sometimes called Neuropsychology tests. They are completed 6 and 18 months after the illness.

The key part of this test takes about 35 minutes. If you are not too tired we can continue with further tests that will provide useful information. These can take up to 2 hours.

They are not pass or fail tests. They provide information about your memory and thinking processes.

They can be done in one day or divided over a few short visits. If you have left hospital we can travel to see you in a convenient place for you. The test will be arranged on a day(s) which suits you.

The results can be added to your hospital notes for future reference if you wish or kept confidential within the trial.

7. What does the MRI scan involve?
As part of your care your doctor will organise an MRI scan when you are in hospital. If you take part in the study we will ask you to have another 3 scans later on.

MRI scans allow us to assess if the brain has been affected by the infection and, if so, which parts.

Each scan takes about 20 minutes. The scan can be noisy but you will be offered headphones.

The extra 3 scans are planned for:
- 2 weeks after the first one (when you are still in hospital)
- After 6 months
- After 18 months

The scans will be done at a hospital near you. We will reimburse mileage or public transport costs for any research visits.

We will check with you that you are still happy to have the scan each time. Sometimes scans may find something not related to this illness. If this happens the doctors looking at the scans will tell your own hospital doctors who will look into this further.

None of the research scans are compulsory so if you do not wish to have them you can still be part of the study.

8. Are there risks to having an MRI scan?
There are no known risks from an MRI scan. They do not use radiation. MRI scans are done routinely in patients with HSV encephalitis.

Because MRI scans use strong magnets you will not have the scan if you have any metal implants or fragments in your body.

Where you lie is quite enclosed and some people may find this unsettling. If you have a fear of confined spaces you should discuss this with your doctor before you go for the scan.

If you think you may be pregnant let your local research team know. We will not ask pregnant women to have MRI scans due to possible risks to the foetus.

9. What samples are collected? What does this involve?
We will collect blood and CSF samples during the study.

All patients with HSV encephalitis need a lumbar puncture (LP) when they come to hospital to find out why they are unwell. The doctor uses a small needle to take a sample from the lower part of the back. This is repeated after 2 weeks of treatment to see if all the virus has gone. Both lumbar punctures are part of the standard care in all patients with this condition.
We will take a little extra fluid at this time for the research tests. The amount of fluid we ask for each time is about 1 teaspoon, 5.5mls.

If you have already had a lumbar puncture before being told about the study, we will take stored CSF that is leftover for research tests.

Blood tests are requested at 3 different times spread over 6 months. We take between 1 to 4 teaspoons of blood, this is 5 to 23mls.

With these blood and CSF tests we will be able to better understand how the infection affects your body and how the body tries to defend itself against it.

10. What will happen to the samples that are collected? Will any genetic tests be done?

All samples will be taken at your hospital and then transported to the University of Liverpool or other laboratories supporting the study. The samples will not have any of your personal information written on them. In the University they will be stored in a secure building.

There is an option for the blood and CSF collected to have tests looking at DNA. DNA is found in all cells of the body and contains the genetic information for the working of all human beings. This study collects DNA samples to find out why some people get HSV encephalitis and others do not, and why some people have severe problems due to HSV and others do not. The information we learn from DNA may benefit others with this condition in the future but will not influence your treatment or your future health.

Some of your samples may be left over. We will ask you if they can be used for this and future studies run by the University of Liverpool.

11. How do you review activities of daily living?

We will find out how the illness has affected your day-to-day life.

The research team will look at your hospital notes. They may also talk to you and, if you choose, your relatives. This will happen when you are in hospital and when you have gone home.

We will compare patients who received dexamethasone to those that did not and see if it made a difference.

12. What are the health questionnaires?

Two questionnaires will be sent through the post. They will ask you your views about your health and quality of life. Please send them back in a pre-paid envelope.

Dexamethasone

13. What are the side effects of dexamethasone?

Dexamethasone is used widely in patients and the side-effects are well known as this medicine has been prescribed for a long time. A short course of dexamethasone will be prescribed in this study. Side effects are less common when dexamethasone is given for shorter periods.

It is important you know about the possible side-effects before you decide to take part. These are:

- Stomach pain, indigestion, having more appetite than usual, feeling or being sick.
- Feeling tired or fatigued
- Mood and behaviour changes, especially at the beginning.
- Higher blood sugars.

Other possible risks can include:

- Stomach ulcers and bleeding of ulcers.
- Decreased response to infections.
You will be in hospital when you take dexamethasone so you can tell your doctors immediately if you have any problem.

If you suffer side effects you or your doctor can decide to stop the dexamethasone at any point.

Dexamethasone is prescribed to women who are pregnant or breast feeding as there are no known risks to the foetus.

16. Who will know I have taken part in this study?
Only people in your clinical care team and people involved in the study will have access to personal data. With your consent we will tell your GP that you are taking part.

All information collected about you during this study will be confidential and anonymised. It will be handled, stored and destroyed in accordance with the General Data Protection Regulation.

University of Liverpool is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. University of Liverpool will keep identifiable information about you for 15 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information http://www.dexenceph.org.uk/. Our Data Protection Officer is Victoria Heath and you can contact them at V.Heath@liverpool.ac.uk.

17. What are the benefits of taking part?
You may benefit from receiving dexamethasone, however we will not know this until the end of the study. You...
may also benefit from the increased monitoring of having extra scans and memory tests.

The information we get from this study may benefit patients in the future.

18. What are the possible disadvantages and risks of taking part?
The disadvantage in taking part in this study may be the risk of having the side-effects of dexamethasone listed in question 13 (this will not be the case if you are in the group that does not have dexamethasone).

There is the inconvenience of having the dexamethasone through the drip when you are in hospital. Once you leave hospital there is the inconvenience of travelling to hospital for 2 scans, having the memory tests and completing questionnaires.

Contact details

If you have any questions about this study, then please contact the study team members:

Principal Investigator (Doctor leading this study in your hospital):
Name: __________________________

Telephone: ______________________

Research Nurse:
Name: __________________________

Telephone: ______________________

Name of your Hospital: ____________

Further information

This study is being run at your hospital and many other NHS hospitals throughout the UK. It aims to recruit 90 patients over 4 years.

It is organised by the University of Liverpool and is funded by the National Institute for Health Research (NIHR), the public body in charge of research in the UK.

Our study team includes The Encephalitis Society, a charity that supports patients and families (www.encephalitis.info).

The study has been reviewed for scientific content by expert members of NIHR. The National Research Ethics Service Committee Liverpool Central has reviewed the study and given approval for it to take place.
RCT Adult with Capacity Consent Form
Version 5.0, Dated: 25/May/2018
EudraCT Number: 2015-001609-16

Centre Name: ____________________________
Name of Principal Investigator: ________________
Study Number: ______________________________

Centre Code: ________________________________

Please complete this form. When completed give one copy to the participant to keep, send one copy to CTU [fax/encrypted email/post], and keep one in the participant’s medical notes. Please put the original in the site file.

For patient: once you have understood each statement please initial the YES OR NO box

<table>
<thead>
<tr>
<th>Statement</th>
<th>YES</th>
<th>NO</th>
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<tr>
<td>1. I confirm I have read and understand the Information Leaflet (dated DD/MM/YYYY) for the above study, and have had the opportunity to ask questions and have these answered satisfactorily.</td>
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<td>2. I agree to take part in this study.</td>
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<td>3. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason and without my care or legal rights being affected.</td>
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<td>4. I agree for my consent form and contact details to be passed to the University of Liverpool for the administration of the study.</td>
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<td>5. I understand that relevant sections of my medical notes and any data collected during the study may be looked at by authorised individuals from the research and clinical team and Regulatory Authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.</td>
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<tr>
<td>6. I agree for genetic tests to be done on blood and CSF collected. I understand these genetic tests will not be of any individual significance to me.</td>
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</table>
7. I agree to have MRI scans as part of the trial.

8. I agree for my GP and hospital doctors to be informed if the scan picks up something unexpected.

9. I agree to gift the remainder of any blood or CSF sample to the University of Liverpool where it will be stored for use in future research. This may include genetic tests.

10. I agree to any images or scans that are taken to be used for teaching, education and publication (in scientific journals, books or internet).

11. I agree for my GP to be informed I am taking part in this study.

<table>
<thead>
<tr>
<th>Name of Participant (Please print)</th>
<th>Signature</th>
<th>Date (DD/MM/YYYY)</th>
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<tr>
<th>Researcher*</th>
<th>Signature</th>
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*Important: Prior to signing please ensure local research contact details are complete on page 6.

Information to Research Team:
Once a Consent Form has been signed, please copy three times: One for the participant, one to file in the medical notes and fax/post/encrypted email one to CTU. Please place original in the site file.

Please fax/encrypt email/post this consent form to CTU separately to other anonymised trial documents (e.g. CRF).