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BMJ Open

Protocol for DexEnceph; a randomised controlled trial of dexamethasone therapy in adults with Herpes Simplex Virus Encephalitis

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1 **Protocol for DexEnceph; a randomised controlled trial of dexamethasone therapy in adults**
2 **with Herpes Simplex Virus Encephalitis**

3 The study is funded by the National Institute for Health Research’s Efficacy and Mechanism
4 Evaluation (EME) programme.

5
6 The trial sponsor is the University of Liverpool, who are responsible for all aspects of study
7 design, implementation, analysis and write up (sponsor@liverpool.ac.uk).

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For peer review only

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Dr Tom Whitfield
Brain Infections Group
Institute of Global Health
Ronald Ross Building
University of Liverpool
Liverpool
L7 3EA
July 17, 2019

18 Dear Mr Adrian Aldcroft,

19 We wish to submit the 'Protocol for the DexEnceph; a randomised controlled trial of
20 dexamethasone therapy in adults with herpes simplex virus encephalitis' for consideration by
21 BMJ open. We confirm that this work is original and has not been published elsewhere, nor is
22 it currently under consideration for publication elsewhere.

24 In this paper, we outline our design of the DexEnceph trial, which will be the first completed
25 randomised controlled trial of corticosteroids in herpes simplex encephalitis. DexEnceph is
26 designed to answer the longstanding question of whether using steroids as
27 immunomodulation in herpes simplex encephalitis is effective and has the potential to change
28 global practice. We hope it will give insight into treatment options for managing a condition
29 that still has a high mortality rate and commonly leaves sufferers with devastating long-term
30 sequelae.

32 We believe that this manuscript is appropriate for publication by BMJ open because in
33 addition to its relevance to clinical practice, the protocol also outlines how the trial is uniquely
34 and pragmatically designed to counter logistic difficulties of recruiting participants who
35 present acutely with a very rare disease sporadic disease. This is of use and interest to other
36 researchers in less common acute conditions. The manuscript is 5000 words in length, in order
37 to cover both the SPIRIT checklist and the additional unique features of the trial. The trial is
38 currently in progress and has recruited over 75% of trial participants, this adds legitimacy to
39 the approach taken where previous trials have been unsuccessful.

41 Please address all correspondence concerning this manuscript to me at tw1@liverpool.ac.uk.

42 Thank you for your consideration of this manuscript.

43 Sincerely,

44 Tom Whitfield

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3 48 **Article Summary**
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5 49
6
7 50 **Strengths and weaknesses**
8

9 51 **'Strengths and limitations of this study'**, and containing up to five short bullet points, no
10 52 longer than one sentence each, that relate specifically to the methods.
11
12 53

- 13 54 ▪ DexEnceph will be the first completed randomised controlled trial of steroid in herpes
14 55 simplex virus encephalitis, examining the utility and safety of steroid use.
16 56
17 57 ▪ The trial will provide important information to improve outcomes in a devastating
18 58 disease with a high rates of mortality and severe sequelae.
20 59
21 60 ▪ Herpes simplex virus encephalitis is a rare sporadic disease which presents acutely,
22 61 with low numbers of expected patients (approximately 1-2 per year) at each recruiting
23 62 hospital. Screening and site engagement are key to ensuring trial success.
24 63
25 64 ▪ The pragmatic open label, observer blind design of the trial is ensuring successful
26 65 recruitment to date.
27 66
28 67 ▪ The recruitment target is informed by the recent Enceph-UK programme grant of
29 68 encephalitis in the UK; the trial is currently open and has recruited 71 patients of a
30 69 target 90.
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3 **72 Abstract**
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6 **73 Introduction**
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8
9 74 Herpes simplex virus (HSV) encephalitis is a severe form of brain inflammation that
10
11 75 commonly leaves survivors and their families with devastating long-term consequences. The
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14 76 virus particularly targets the temporal lobe of the brain causing debilitating memory
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16 77 problems, especially in verbal memory. It is postulated that immunomodulation with
17
18 78 steroids could improve outcomes by reducing brain swelling. However, there are concerns
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20 79 (so far not observed) that such immunosuppression might facilitate increased viral
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23 80 replication with resultant worsening of disease. A previous trial closed early because of slow
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26 81 recruitment.
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28

29 **82 Method**
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31
32 83 DexEnceph is a pragmatic multicentre, randomised, controlled, open label, observer-blind
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34 84 trial to determine whether adults who receive dexamethasone alongside standard
35
36 85 treatment with aciclovir for HSV encephalitis have improved clinical outcomes compared
37
38 86 with those who receive standard treatment alone. Overall, 90 patients with HSV
39
40 87 encephalitis will be recruited from a target of 90 recruiting sites; patients will be
41
42 88 randomised 1:1 to the dexamethasone or control arms of the study. The primary outcome
43
44 89 measured is verbal memory as assessed by the Weschler Memory Scale fourth edition
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46
47 90 Auditory Memory Index at 26 weeks post randomisation. Secondary outcomes are
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50 91 measured up to 72 weeks include additional neuropsychological, clinical and functional
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53 92 outcomes as well as comparison of neuroimaging findings. Patient safety monitoring occurs
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56 93 throughout and includes the detection of HSV DNA in cerebrospinal fluid 2 weeks after
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59 94 randomisation, which is indicative of ongoing viral replication.
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3 95 **Discussion**
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9 97 DexEnceph aims to be the first completed randomised controlled trial of steroid therapy in
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11 98 HSV encephalitis. The results will provide evidence for future practice in managing adults with
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14 99 the condition and has the potential to improve outcomes in a life-changing disease.
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19 101 **Ethical approval**
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21 102 The trial has ethical approval from the UK National Research Ethics committee (Liverpool
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23
24 103 Central, REF: 15/NW/0545, 10/08/2015). Protocol version 2.1 July 2019
25

26 104 **Registration numbers**
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35 108 Key words: Herpes simplex, Encephalitis, Dexamethasone, Steroid, Verbal memory
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48 136 Word Count : 4916 words
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140 **Background**

141 Herpes simplex virus infection (HSV) is the most commonly identified viral cause of
142 encephalitis, inflammation and swelling of the brain caused by a virus or the body's immune
143 system, in the UK as in most western industrialised nations.¹⁻⁴ The incidence has been
144 estimated at 1 in 250,000-500,000,² with evidence this may be higher.⁴ Although a rare
145 disease, HSV encephalitis has a disproportionately large impact due to its devastating long
146 term neuro-psychological sequelae . These can have a marked impact on the quality of life of
147 the patient and their family and high health economic and social costs.^{5,6}

148 Since the introduction of the antiviral drug aciclovir in the 1970s the mortality of HSV
149 encephalitis has reduced from around 70% to 5.5-12%.⁷⁻⁹ However, survivors are commonly
150 left with neurological impairment; less than 20% of patients are able to return to work and
151 48% are classed as moderate to severely disabled.¹⁰ Even when obvious disabilities have not
152 occurred, families often report personality changes – the person they take home from
153 hospital is simply not the same as the one before the illness. ^{6,11}

154 HSV encephalitis can cause a broad range of cognitive impairments, but impaired memory,
155 especially verbal memory, is the most common and likely relates to the viral predilection for
156 the temporal lobe of the brain. ^{12,13} The verbal memory deficits manifest as difficulties
157 remembering names of objects and people, as well as listening to and recalling spoken
158 information such as conversations. ^{14,15} In addition to memory problems, difficulties in
159 processing speed, concentration, language and executive function are also common amongst
160 survivors of HSV encephalitis, along with fatigue, poor concentration, anxiety and depression.

161 ^{7,16,17}

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3 162 The pathogenic mechanisms in HSV encephalitis are not fully understood. The evidence
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6 163 suggests that in addition to direct viral pathogenesis, inflammation of the brain in response
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8 164 to the virus is a key component of the disease process.^{18–21} This is supported by the
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11 165 observation that in the cerebrospinal fluid (CSF), higher levels of proinflammatory
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13 166 chemokines, especially monocyte chemotactic protein (MCP)-1, interferon γ and interleukin
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15 167 6 (IL-6) are associated with a worse prognosis.^{22,23} Poor prognosis is also associated with the
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18 168 extent of inflammation seen on neuroimaging,²⁴ and the degree of temporal lobe swelling is
19
20 169 correlated with the severity of verbal memory impairment.²⁵

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24 170 Control of the inflammation in HSV encephalitis may improve outcome, as shown in mouse
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26 171 models of the disease.^{26–28} Before the availability of aciclovir, corticosteroids were also used
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29 172 routinely as a treatment in humans with HSV encephalitis,^{29,30} and more recently both
30
31 173 cerebral oedema on imaging and cerebrospinal fluid IL-6 levels were shown to be reduced in
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33 174 patients given corticosteroids.²³ However, because corticosteroids cause
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35
36 175 immunosuppression which in theory facilitates increased viral replication, their role is
37
38 176 uncertain.³¹

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41 177 In other brain infections, including bacterial meningitis and tuberculous meningitis the benefit
42
43 178 of corticosteroids has been demonstrated in large clinical trials.³² For HSV encephalitis the
44
45 179 potential benefit of using corticosteroid as an adjunct to aciclovir therapy has been suggested
46
47 180 from small case series and retrospective comparisons, but there has been no prospective
48
49 181 randomised study reported.^{33–38} One study, the German trial of Aciclovir and Corticosteroids
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51 182 in Herpes simplex virus Encephalitis (the GACHE trial) was stopped early because of poor
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53 183 recruitment rates.³⁹ However, there is clearly a need for a study to assess this question. The
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3 184 DexEnceph Study, a randomised controlled trial of dexamethasone in HSV encephalitis, aims
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6 185 to achieve this.
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12 187 **Trial design**
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15 188 DexEnceph is a pragmatic, multicentre, randomised, controlled, observer-blind trial to
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17 189 determine whether the addition of dexamethasone to standard aciclovir treatment improves
18
19 190 clinical outcomes (in particular verbal memory score) for adults with HSV encephalitis.
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21 191 Additionally, neuroimaging and biomarkers will be assessed along with detection of HSV in
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23 192 the cerebrospinal fluid at 2 weeks post randomisation to monitor for difference in viral
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25 193 replication between the two groups.
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33 195 **Primary objective**
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36 196 To determine whether a short course of intravenous dexamethasone, in addition to standard
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38 197 care, improves verbal memory score in adults with HSV encephalitis at 26 weeks post
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40 198 treatment compared to standard care alone.
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47 200 **Secondary objectives**
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50 201 Secondary objectives include the following:
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54 202 To determine whether dexamethasone therapy has an effect on other neuropsychological,
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56 203 cognitive, clinical, disability and functional outcomes in HSV encephalitis.
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3 204 To assess the effect of dexamethasone therapy on brain swelling assessed by neuroimaging
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6 205 imaging.

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9 206 To determine whether dexamethasone therapy affects clearance of HSV from cerebrospinal
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11 207 fluid, the emergence of anti-N-Methyl-D Aspartic acid (NMDA) receptor antibody or causes
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13 208 any changes in transcriptomic and proteomic profiling in the CSF and blood.

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18 210 A more comprehensive list of measures is detailed in the outcomes section.

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22 23 24 212 **Methods**

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27 213 DexEnceph is an observer blind, open label, prospective, randomised, controlled trial of
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29 214 dexamethasone at 10mg four times daily for 4 days, versus no dexamethasone, in adults with
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32 215 HSV encephalitis.

33 34 35 216 **Research setting**

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38 217 The trial is being conducted in up to 45 NHS trusts, with a recruitment target of 0-2 patients
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40 218 per site per year. A full list of sites involved in DexEnceph can be obtained from
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42
43 219 www.dexenceph.org.uk

44 45 46 220 **Eligibility criteria**

47 48 49 221 **Inclusion Criteria**

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52 222 Enrolled patients fulfil all of the following criteria:

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57 224 1. Suspected encephalitis defined as: new onset seizure OR new focal neurological signs OR
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59 225 alteration in consciousness, cognition, personality, or behaviour. Personality / behaviour
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3 226 change includes agitation, psychosis, somnolence, insomnia, catatonia, mood lability, altered
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6 227 sleep pattern.

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10 229 2. A positive HSV DNA polymerase chain reaction (PCR) result from CSF, reported not more
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13 230 than 7 days prior to randomisation.

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18 232 3. Receiving intravenous aciclovir administered as 10mg/kg three times daily or at a reduced
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21 233 dose if clinically indicated.

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26 235 4. Age \geq 16 years.

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30 237 5. Written informed consent given by the patient or their legal representative⁴⁰

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36 239 **Exclusion Criteria**

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39 240 Patients are excluded if they have any of the following:

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42 241 1. Have received oral or injectable corticosteroid therapy in the 30 days prior to the day of
43
44 242 admission to hospital. This does not apply to topical/ inhaled corticosteroids. [Patients who
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46 243 have received oral or injectable corticosteroid therapy AFTER their admission to hospital will
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48
49 244 not be excluded from the study if they consent to trial participation].

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54 246 2. History of hypersensitivity to corticosteroids.

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59 248 3. Immunosuppression secondary to:

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3 249 a. Known HIV infection and CD4 white cell count under 200/mm³
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6 250 b. Currently taking biologic therapy or other immunosuppressive agents [e.g.
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8 251 azathioprine, methotrexate, ciclosporin]
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10 252 c. Previous solid organ transplant and currently on immunosuppression
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13 253 d. Previous bone marrow transplant
14
15 254 e. Currently undergoing a course of chemotherapy or radiotherapy
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18 255 f. Known primary immunodeficiency syndrome
19
20 256 g. Known current haematological malignancy
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25 258 4. Pre-existing indwelling ventricular devices.
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30 260 5. Peptic ulcer disease in the last 6 months, defined as a peptic ulcer seen at endoscopy or
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32 261 an upper gastrointestinal bleed causing a ≥ 2 unit haemoglobin drop, in the last 6 months.
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36
37 263 6. Antiretroviral regime containing rilpivirine as current treatment [Levels of rilpivirine are
38
39 264 known to significantly decrease in co-administration with dexamethasone, a switch to a
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41 265 suitable alternative can facilitate trial entry].
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267 **Intervention**

268 Participants are randomised in a 1:1 ratio to dexamethasone four times daily for four days
269 alongside standard care, or standard care alone (Figure 1). Standard care includes intravenous
270 aciclovir for a minimum of 14 days based on an ideal body weight at 10mg/kg every 8 hours,
271 unless dose adjustment to account for renal impairment is necessary. Participating clinicians

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3 272 remain free to modify or discontinue the dexamethasone administration or to give alternative
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6 273 treatments at any stage, if this is judged to be in the best interest of the patient.
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10 275 Participants assigned dexamethasone receive 10 mg equivalent of ordinary ward stock,
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13 276 prescribed by an authorised member of the local study team, given intravenously four times
14
15 277 daily for four days (16 doses in total) starting within 24 hours of randomisation.
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20 279 The University of Liverpool employs a clinical trials unit to be responsible for screening, and
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22
23 280 monitoring data collection, quality and completeness. As there is a low number of
24
25 281 participants to be recruited, the trials unit are able to liaise regularly with each site following
26
27 282 randomisation to ensure all follow up data are collected. Primary outcome is recorded by a
28
29 283 centrally employed roving neuropsychologist, who collects the neuropsychological outcomes
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31
32 284 at 26 and 72 weeks.
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3 296 **Outcome measures**
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6 297 **Primary Outcome**
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9 298 Verbal memory score, determined by the Wechsler Memory Scale 4th edition (WMS-IV)

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12 299 Auditory Memory Index, at 26 weeks after randomisation.
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14

15 300 **Secondary Outcomes**
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17

18 301 Other neuropsychological outcome measures [at 26 weeks and 78 weeks after
19
20 302 randomisation]:
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22

23 303 • Verbal memory score, determined by the WMS-IV, Auditory Memory Index, at 78
24
25 304 weeks after randomisation.
26
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28 305 • Visual, Immediate and Delayed Memory by Indexes of the WMS-IV, processing speed
29
30 and working memory subscales from the Wechsler Adult Intelligence Scale Fourth
31 306 Edition.
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36 308 • Higher executive function using the Trail Making Test.
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38 309 • Anxiety and Depression symptom levels by the Beck Depression Inventory and Beck
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40 Anxiety Inventory.
41 310
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43 311 • Subjective cognitive complaints using the Perceived Deficits Questionnaire.
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45

46 312 Cognitive Outcome Measures [at discharge or 30 days if still in hospital, 26 weeks and 78
47
48 313 weeks]
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50 314 • Addenbrooke's Cognitive Assessment III.
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53 315 **Clinical Outcomes**
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55 316 • Incidence of epilepsy.
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58 317 • Time to hospital discharge.
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3 318 • Requirement of high dependency unit or Intensive care unit admission up to 30 days
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6 319 post randomisation.
7
8 320 • Time taken to be free of ventilatory support for 14 days [if any].
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11 321 • Time to reach maximum recorded Glasgow coma scale score.
12
13 322 • Survival.
- 15 323 Disability & Functional Outcomes [at discharge or 30 days if still in hospital, 26 weeks and 78
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17 weeks]:
18 324
19
20 325 • Modified Rankin Score, Barthel Index, Liverpool Outcome Score and Glasgow
21
22 Outcome Scale Extended.
23 326
- 25 327 Imaging Outcomes: Change from Baseline at 2 weeks, 26 weeks and 78 weeks
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27
28 328 • Temporal lobe volume (as % of intra-cranial volume).
29
30 329 • Whole brain volume (as % of intra-cranial volume).
31
32
33 330 • Volume of affected region as seen on fluid-attenuated inversion recovery (FLAIR)
34
35 331 image (as % of intra-cranial volume).
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37
38 332 • Volume of affected region as seen on diffusion-weighted image (as % of intra-cranial
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40 333 volume).
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- 43 334 Biomarker Outcomes:
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45 335 • Transcriptomic and proteomic profiling on blood at convalescence (2 weeks and 26
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47 336 weeks), compared to acute baselines, and on CSF at 2 weeks compared to acute
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49 baseline.
50 337
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52 338 • Anti-NMDA receptor antibody testing at 26 weeks.
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- 55 339 Safety Outcomes:
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57 340 • Proportion of patients with detectable HSV in CSF by PCR at 2 weeks.
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- 60 341 Health Status and Quality of Life [at 26 and 78 weeks]:

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3 342 • Measured by the EuroQoL-5 Dimension-5 Level quality of life scale (EQ-5D-5L) and 36
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6 343 item short form survey (SF-36) self-completed questionnaires.
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11 345 **Screening**
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13
14 346 The majority of potential patients are identified by the local research team through
15
16 347 identifying patients with a relevant clinical presentation suspicious of HSV encephalitis and/or
17
18 348 detection of HSV in a CSF sample. A screening log is completed for all potential patients. A
19
20 349 strong link with the local laboratory is essential as a key factor in ensuring eligible patients are
21
22 350 not missed by the investigative team. Investigators for the local research team include
23
24 351 neurologists, infectious disease clinicians, microbiologist and virologists.
25
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29
30 353 Because this is an uncommon disease, extra measures have been taken to try and maximise
31
32 354 recruitment. On identifying a suitable patient, sites are able to contact the trial management
33
34 355 team for intensive support via a dedicated telephone hotline, email, or an app. Short videos
35
36 356 which explain the trial to patients, families and to health care workers also support
37
38 357 recruitment. Every month, the trial management group monitor the screening reports of each
39
40 358 site for the previous 3 months, to ensure they are actively looking for patients. Lower than
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42 359 expected screening is followed up by the central study team making contact with the study
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44 360 site to review their screening methodology and offer support.
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55 363 **Randomisation**
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58 364 Participants are randomised using a 24-hour secure web-based programme, which is centrally
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60 365 controlled by the clinical trials research centre. Designated members of the trial team at the

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2
3 366 site (detailed on the delegation of responsibilities log) are provided with a unique username
4
5
6 367 and password which is required to access the web-based randomisation system. In the event
7
8 368 of system failure, the patient can be randomised centrally electronically or through secure
9
10 369 envelopes. Each participant is allocated a unique study number (randomisation number), the
11
12
13 370 primary identifier for all the participants in this study.

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18 372 The neuropsychologist collecting the primary outcome and other outcome assessors such as
19
20 373 radiologists and those responsible for paper authorship are blinded to randomisation during
21
22
23 374 the trial. Trial participants and local site study teams, as well as the trial manager and trial
24
25 375 data manager at the clinical trials unit are aware of what treatments have been allocated. The
26
27
28 376 independent data safety and monitoring committee (IDSMC) and statisticians have access to
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30 377 unblinded data grouped by intervention throughout the trial and make recommendations to
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32
33 378 the trial's steering committee who would only become unblinded in the event of a serious
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35 379 event.

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38 381 **Participant timeline**

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43 382 The time schedule for enrolment, interventions and assessments is given in table 1.

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47 48 49 384 **Statistical Considerations**

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52 53 54 386 **Sample Size**

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56 387 The primary outcome variable is verbal memory , assessed as part of WMS-IV. In one
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59 388 published series of adults who survived HSV encephalitis, 19 of 22 had memory impairment
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3 389 evident at follow up, with verbal memory being most severely affected ¹². In that study the
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6 390 mean (standard deviation, SD) verbal memory score was 88.9 (18.9) compared with the
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8 391 population mean (SD) of 100 ¹⁵. This score can only be assessed in survivors, we estimate
9
10 392 approximately 10% of patients in the trial will die before assessment of the primary
11
12
13 393 outcome^{8,41,42}. In instances where the death is judged to be associated with encephalitis the
14
15 394 verbal memory score is recorded as 40, (the lowest possible value which would be obtained
16
17 395 even where a patient recorded no recall of any of the items administered in the memory
18
19 396 subtests). Where the cause of death is thought to be independent of having encephalitis,
20
21 397 those patients will be recorded as lost to follow up. Similarly, for patients who are too unwell,
22
23 398 due to encephalitis, to undergo the assessment, the score is recorded as 40. Decisions as to
24
25 399 whether the reasons for death or non-completion of the measures were due to encephalitis
26
27 400 will be made by an independent committee blinded to dexamethasone allocation. Adjusting
28
29 401 the estimate of mean and standard deviation from survivors, to include the 10% of patients
30
31 402 with the lowest possible value of 40, gives a total population mean of 84.8, with a standard
32
33 403 deviation of 23.1. A final sample size of 36 participants per group allows us to detect a
34
35 404 clinically meaningful difference of 15.5 on the verbal memory score with 80% power, at a two-
36
37 405 sided significance level of 0.05. Allowing for up to 20% dropout gives an initial target sample
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39 406 size of 45 participants per group, for a total of 90.
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408 **Statistical analysis**

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52 409 For the primary outcome, participants are included in the analysis based on the intention-to-
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54 410 treat principle. Verbal memory score will be compared between groups using linear
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56 411 regression. The model will be adjusted for pre-specified variables which are judged to be
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3 412 potentially related to the outcome, including age and admission Glasgow coma scale score.
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6 413 No interim analysis is planned, but there is regular monitoring by the IDSMC.
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11 415 As there may be some missing primary outcome data due to death, inability to complete the
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13 416 assessment, or loss to follow up, a sensitivity analysis will be carried out. All randomised
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15 417 patients will be included in this analysis.
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20 419 For continuous secondary outcome variables, comparisons between groups will be analysed
21

22 420 as per the primary outcome. The results for residual viral presence in the CSF at 2 weeks will
23

24 421 be reported with a 95% confidence interval for the difference in proportions between groups.
25
26

27 422 Time to event outcomes will be analysed using Kaplan-Meier curves, log rank tests and Cox
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29 423 Proportional Hazards models. Binary secondary outcomes will be analysed using logistic
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31 424 regression.
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37 38 426 **Trial Promotion and engagement** 39

40 427 Considerable effort is maintained to keep the principal investigators, research nurses and the
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42 428 community engaged in the trial. The trial is being publicised using public forums, the
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44 429 Encephalitis Society website and newsletter, social media, patient journey articles and work
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46 430 with newspapers and TV. To promote site engagement, study days are arranged for research
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48 431 teams to attend, along with scheduled research nurse teleconferences to allow ideas on
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50 432 maximising recruitment and updates on trial progress to be shared. Sites are also kept
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52 433 updated through our website (www.dexenceph.org.uk), newsletters and an innovative sticker
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54 434 chart, whereby a sticker is sent out to every site each time a patient is recruited (Figure 2).
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3 435 The Encephalitis Society are playing a key role in providing additional support to the patients
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5
6 436 and their families aside from their work for the trial.
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10 11 438 **Publication and Dissemination**

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13 439 The results from different centres will be pooled for analysis and published as soon as the
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16 440 analysis is complete. They will be presented at the annual conference organised by the
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18 441 Encephalitis Society and at other meetings.
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22 23 24 443 **Trial Closure**

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27 444 The end of the trial is defined to be the date on which data for all participants is frozen and
28
29 445 data entry privileges are withdrawn from the trial database. The trial may be closed
30
31 446 prematurely by the trial steering committee, on the recommendation of the IDSMC if there is
32
33 447 sufficient evidence of risk to patient safety.
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36 37 448 **Pharmacovigilance**

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40 449 Oversight of the trial is provided by the trial steering committee, which meets at least annually
41
42 450 to review trial progress, safety, and adverse events. The committee is also informed of any
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44 451 protocol changes by the clinical trial research unit.
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46

47
48 452 The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions are
49
50 453 used for Adverse Event (AE), Adverse Reaction (AR), Unexpected Adverse Reaction (UAR),
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52 454 Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected
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54 455 Serious Adverse Reaction (SUSAR).
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59 456 Depending on the nature of the event the reporting procedures below are followed:
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3 457 1. Serious adverse events occurring up to 30 days after randomisation are reported through
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6 458 a Serious Adverse Event Form (if serious) or in the 30 day/discharge case record forms (CRF)
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8 459 if they are a notable event (Positive PCR in CSF at 2nd lumbar puncture, gastrointestinal bleed,
9
10 460 hyperglycaemia requiring change in medical management, opportunistic infections,
11
12
13 461 unexpected/severe neuropsychiatric events).

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16 462 2. Serious adverse events occurring after 30 days from randomisation are monitored through
17
18 463 reporting in the CRFs with safety data collected in the 26 week and 78-week CRFs if serious.

19
20
21 464 The research investigator at each study site (or designated other) assesses all adverse events
22
23 465 for seriousness, causality and severity. The Chief Investigator (or designated other) assesses
24
25 466 all adverse drug reactions for expectedness from known side effects of the use of
26
27 467 Dexamethasone.⁴³ All serious ARs, AEs and SUSARs occurring up to 30 days from
28
29 468 randomisation (apart from death unless the investigator suspects causality) require reporting
30
31 469 to the clinical trials unit, within 24 hours of the site becoming aware of the event. In the case
32
33 470 of death of a patient causality will be assessed by the trial steering committee.

34
35
36 471 The clinical trials unit will notify the Medicines and Healthcare products Regulatory Agency
37
38 472 and main research ethics committee of all SUSARs that occur during the study according to
39
40 473 the following timelines; fatal and life-threatening within 7 days of notification and non-life
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42 474 threatening within 15 days. All investigators are informed of all SUSARs occurring throughout
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44 475 the study.

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47 476 SAEs occurring after 30 days from randomisation are monitored by the clinical trials unit via
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49 477 the 26 week and 78week CRFs. These CRFs need to be received at the clinical trials research
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51 478 unit by 4 weeks after the 26 and 6 weeks after 78week time points.
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3 479 Safety data is provided to the IDSMC, who are responsible for safeguarding the interests of
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6 480 trial participants and assessing the safety of the interventions during the trial; the IDSMC
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8 481 ensures action is taken as needed should they become aware of trends in reported AEs that
9
10 482 raise safety concerns.
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16 484 **Ethical Considerations**

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18 485
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21 486 The trial falls within the remit of the EU Directive 2001/20/EC, transposed into UK law as the
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23 487 UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations
24
25 488 2004 as amended. This trial is registered with the MHRA and granted Clinical Trial
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27 489 Authorisation (CTA). The EUDRACT number for CTA reference is 2015-001609-16. Ethical
28
29 490 approval has been obtained from a multi-centre research ethics committee familiar with the
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31 491 principals of the Mental Capacity Act 2005 guidance for sites in England and Wales and the
32
33 492 Adults with Incapacity Act 2008 for sites in Scotland as the principals are relevant to a clinical
34
35 493 trial of investigational medicinal products (CTIMP). Clinical Research Governance approval
36
37 494 was given through the Sponsor, The University of Liverpool. The trial protocol was approved
38
39 495 by a National Research Ethics Service Committee reference is 2015-001609-16 (Attained
40
41 496 31/03/2016) and underwent independent review at the Research and Development offices
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43 497 at participating sites. This study abides by the principles of the World Medical Association
44
45 498 Declaration of Helsinki (1964) and Tokyo (1975), Venice (1983), Hong Kong (1989) and South
46
47 499 Africa (1996). Due to the nature of this trial it also abides by the Medicine for Human Use
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49 500 (Clinical Trials) regulations 2004 (S.I.2004:1031) and all following amendments which are
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51 501 incorporated into UK law.
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503 **Informed Consent Process**

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

513

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

522

523 As suspected encephalitis is a medical emergency, a deferred consent process is used for the
524 collection and retention of some samples as part of routine clinical management. Using
525 emergency deferred consent for samples involves taking additional samples of blood and CSF
526 only if the procedure is being performed for clinical care. If deferred consent has been used,

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3 527 written consent is requested from either the patient or a legal representative as soon as is
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6 528 possible and appropriate, with samples discarded if this is declined. This approach is based on
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8 529 discussions with patients and the public through the Encephalitis Society.
9

10 530

13 531 **Data Capture Methods**

15 532 Data is stored securely in line with the Data Protection Act 1998. The randomisation system,
16
17 533 data capture form and CRF have been designed to optimally protect participant information
18
19 534 and to maintain confidentiality. Trial data is captured at local sites using paper CRFs. These
20
21 535 are then sent into the clinical trials research unit for data entry into the study specific
22
23 536 database. Completed CRFs are returned to clinical trial research centre within 7 days of
24
25 537 completion. A copy of the CRF sent over to the clinical trials research unit is retained at site.
26
27 538 CRFs and consent forms are stored separately and securely at all times in dedicated areas of
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29 539 the clinical trials research unit.
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37 541 CRFs are checked for data quality by the clinical trials research unit in Liverpool responsible
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39 542 for ensuring data collection and storage.
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44 544 Patients' anonymised and labelled neuroimaging data are put on to discs at site and sent to
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46 545 the clinical trials research unit; the images can also be transferred via the Image Exchange
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48 546 Portal in an encrypted manner. The final dataset will be solely accessible to the central study
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50 547 team at the University of Liverpool for analysis and write up.
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59 550 **Trial Funding and Financial Arrangements**

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6 552 This trial is funded by the NIHR Efficacy and Mechanism Evaluation Programme for the
7
8 553 Department of Health. Contractual agreements are in place between the Sponsor and
9
10 554 collaborating centres that describe financial arrangements. Trial participants are not paid to
11
12 555 participate in the trial but are paid travel expenses for the follow up visits, estimated at £50
13
14 556 per visit. Payments to sites are made per site initiation but the bulk of payments are made
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16 557 per patient recruitment. Sites receive payment for: clinical time oversight, research nurse
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18 558 time, administrative support, magnetic resonance imaging scanning and pharmacy oversight.
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560 **Patient and public involvement**

561 The Encephalitis Society was consulted and provided advice on the design of the trial and the
562 difficulties participants and their families will likely encounter. The Chief Executive of The
563 Encephalitis Society is a co-applicant on the grant application and a co-author on this paper.

564

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

567 The Encephalitis Society will drive forward publication and dissemination of the trial findings
568 among lay, therapeutic and health professionals through the use of web materials,
569 newsletters and guides as well as at conferences and seminars in relation to encephalitis and
570 related fields. All patients and their family/carers will be acknowledged in any outputs from
571 the trial. We also work with The Encephalitis Society on a programme
572 of teaching events and produce guides for healthcare professionals and lay people.

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3 573 In instances where trial participants and their families have ongoing difficulties the central
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6 574 study team seek help for them through the Encephalitis Society and appropriate specialists
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8 575 for further assistance.
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13 577 **Discussion**

15 578

18 579 This protocol describes the design of a randomised controlled trial to demonstrate the utility
19
20 580 of using dexamethasone in the management of individuals with HSV encephalitis. HSV
21
22 581 encephalitis is a rare sporadic acute disease, and the trial has been designed to take this
23
24 582 challenge into account, along with the practicalities of running the trial in a UK National Health
25
26 583 Service setting. In particular lessons were learnt from a previous similar European study, the
27
28 584 German trial of Aciclovir and Corticosteroids in Herpes simplex virus Encephalitis (GACHE
29
30 585 trial), which was stopped early because of recruitment difficulties. Recruitment to the GACHE
31
32 586 trial necessitated patients had focal neurological signs of no longer than five days prior to
33
34 587 admission, whilst DexEnceph has less stringent criteria and reflects the diverse ways in which
35
36 588 HSV encephalitis may present. DexEnceph has been designed to be both practical and
37
38 589 pragmatic, in that patients must be recruited within 7 days of the PCR result becoming
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40 590 available. This allows for occasions where it may take longer to get the PCR performed, and
41
42 591 also allows time for patients admitted to district general hospitals, which may not be study
43
44 592 centres, to be transferred to larger hospitals which are. DexEnceph also has the advantage in
45
46 593 that its recruitment projections were based on preliminary data garnered from the ENCEPH-
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48 594 UK NIHR program (www.encephuk.org) and from a multicentre cohort study of encephalitis
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50 595 in England, run by the Health Protection Agency (fore-runner to the Health Protection
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52 596 Agency).⁹ These two studies provided direct information on the number of HSV encephalitis

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3 597 patients presenting to UK hospitals. Our choice of an open label observer-blind study, rather
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6 598 than a placebo-controlled double-blind trial, avoided the logistic challenges of ensuring
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8 599 blinded study drug was available across the large number of centres, necessitated by a rare
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11 600 sporadic disease, which may also have been a factor in the recruitment difficulties
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13 601 experienced by the GACHE trial. We are confident our robust monitoring and trial promotion
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15 602 ensures the majority of eligible patients are recruited. N- methyl-D-aspartic acid (NMDA)
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17 603 receptor antibody encephalitis (which is treated with corticosteroids and other
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20 604 immunomodulatory therapies) is being recognised increasingly as a late complication of HSV
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22
23 605 encephalitis.^{44,45} DexEnceph may also be able examine whether corticosteroids reduce the
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25 606 incidence of this complication. If there is demonstrable efficacy of corticosteroid in improving
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28 607 neuropsychological, imaging and quality of life outcomes, without compromising patient
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30 608 safety the results will be far reaching.
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36 610 **Collaboration with France**

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40 611 Because we recognised from the start that there may be difficulties keeping to recruitment
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42 612 targets in the DexEnceph study, we worked with colleagues in France to develop a parallel
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45 613 French study (DexEnceph-France). This follows the UK DexEnceph protocol as closely as
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47 614 possible, whilst being pragmatic about the constraints of a different country's health care
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50 615 system. The French trial is based in 10 hospitals with the lead centre being Grenoble Alpes
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52 616 University Hospital and the aim of recruiting 30 patients.
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55 617 The intention is for the two trials to be analysed separately, with the option of also results
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57 618 also combining them into an overall analysis which will give additional power to detect a
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60 619 treatment effect.

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11 624**Trial status**12
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14 625 The trial has been open across the UK since August 2016, and as of July 2019 is open at 4515
16 626 NHS trusts; 71 patients have been randomised (of the total target of 90) meaning that we17
18 627 have recruited 79% of the patients are recruiting at just over 80% of the target recruitment19
20 628 rate. The trial was due to complete recruitment later in 2020 with 6 months follow up and 321
22 629 months post trial closure for write up. Though recent COVID-19 pandemic has placed23
24 630 difficulties in conducting trials and paused recruitment, the primary outcome has not been25
26 631 missed in any existing DexEnceph recruit, this has been achieved by conducting27
28 632 neuropsychology assessment by either telephone or online video discussion, thus avoiding29
30 633 any risk of transmission. DexEnceph-France study, which opened in 2018 has recruited 1031
32 634 patients from 10 sites.33
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36 636 If you are interested to find out more information or to see if your trust is involved visit37
38 637 www.dexenceph.org.uk or for more information please email: dexenceph@liverpool.ac.uk.39
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47 639 **Dissemination**48
49 64050
51 641 The results of the DexEnceph trial will be published in a high impact journal in a timely manner52
53 642 to present the findings to front-line clinicians. Authorship of the final papers will be54
55 643 determined in accordance with the international committee of medical journal editors'56
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3 644 guidelines. The investigators will be involved in the preparation and drafting of the
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5 645 manuscripts. There is no intended use of professional writers.
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10 647 **Declaration of Interest**

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12
13 648 TS is supported by the National Institute for Health Research (NIHR) Health Protection
14
15 649 Research Unit in Emerging and Zoonotic Infections (Grant No. IS-HPU-1112-10117), NIHR
16
17 650 Global Health Research Group on Brain Infections (No. 17/63/110), and the European Union's
18
19 651 Horizon 2020 research and innovation program ZikaPLAN (Preparedness Latin America
20
21
22 652 Network), grant agreement No. 734584.
23
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26
27 654 **Author Statement**

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29
30 655 All authors were consulted and inputted into the article, below lists the particular role
31
32 656 within DexEnceph

33
34
35 657 TW: Clinical research fellow, CF: Clinical research fellow, KDavies: trials manager, SD: contributor to
36
37 658 trial design and running, MG: Clinical and laboratory biomarkers lead, CH: Neuropsychology
38
39 659 researcher, RT: trial pharmacist, GB: Trial statistician, AR-H: trial statistician, PM: Neuropsychology
40
41 660 lead, KDas: Neuroimaging lead, MZ: Virology, LP: Neuroimaging, SK: Neuroimaging, NR:
42
43 661 Neuroimaging, EA: Encephalitis Society Chief Executive advisor, RK: Clinical lead brain infections UK,
44
45 662 TS Chief Investigator
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50 664 **Data Statement**

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53 665 There are currently no current plans to publish the data
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58 667 **References**
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35 801 **Table 1: Time scale for patients Randomised in the DexEnceph study**
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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	

Procedures	Follow-up Schedule						
	Screening	Baseline	2 weeks	Discharge or Day 30 of admission (whichever is sooner)	26 weeks	78 weeks	Premature Discontinuation
Magnetic resonance imaging (MRI) scan		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 quality of life 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 randomised controlled trial

*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 prior to randomisation, daily for the first 14 days and then weekly until Discharge/30 days (whichever sooner)

(X) – As indicated/appropriate

Author Statement

Figure 1: Schematic Design of Randomised controlled trial

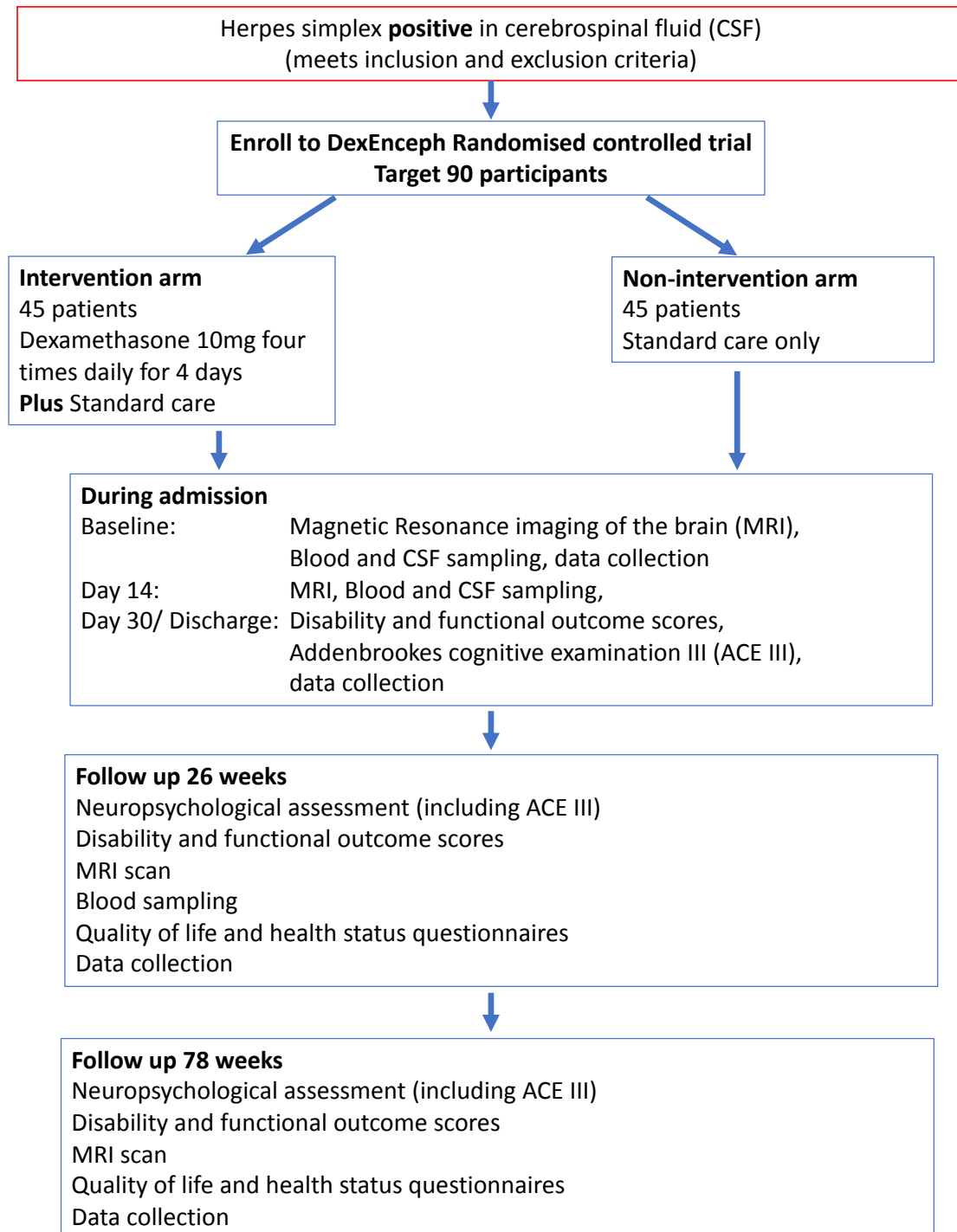




Figure 2: DexEnceph Trial recruitment poster

303x426mm (72 x 72 DPI)



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?

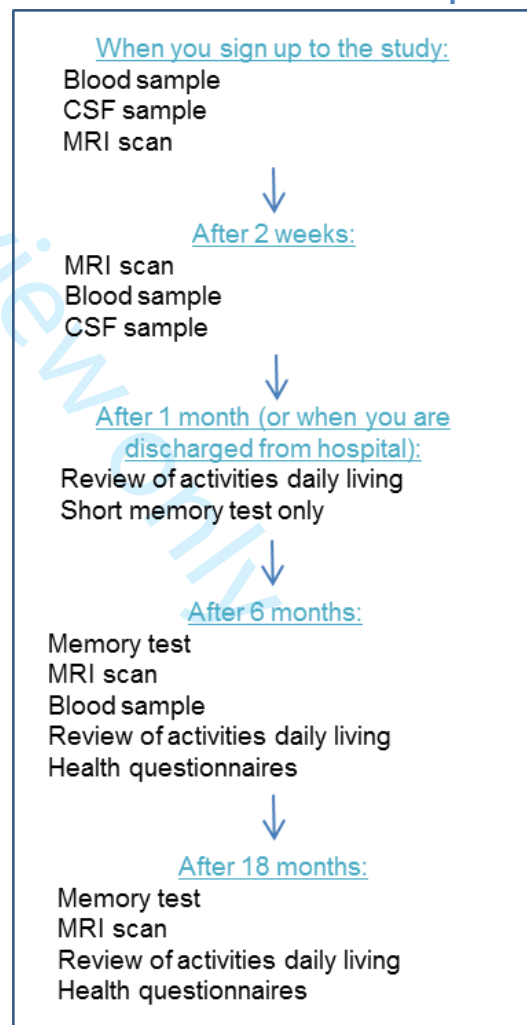
All patients in the study will receive aciclovir. This is standard treatment for HSV encephalitis.

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?



All the tests done when you sign up to the study and the CSF tests after 2 weeks will

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.

Other things to consider

14. Do I have to take part?

No, taking part is voluntary. If you agree, we will ask you to sign a consent form.

If you agree to take part you are free to change your mind at any time, without giving a reason. You may decide to have only some tests in the study without having to drop out of the study altogether. This will not affect the standard of care you receive.

If you withdraw from the study we will stop collecting data. We will ask you if we can use the information and samples we have gathered up to the point that you withdraw.

15. What happens if there is a problem?

If you have any concerns about any part of this study, please speak with your hospital doctor (consultant) or one of your research team.

If you remain unhappy and wish to complain formally you can do this using the NHS Complaints Procedure. You can get information on how to do this from the Patients Advice Liaison department (PALS) in your hospital.

If you suffer harm from taking part in this study, there are no special compensation arrangements. If harm occurs to you and it is due to someone's negligence, you may have grounds for legal action for compensation against the NHS hospital where you are being treated but you may have to pay your legal costs.

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.

Benefits and risks

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:

Centre Code:

Name of Principal Investigator:

Study Number:

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

YES**NO**

1. I confirm I have read and understand the Information Leaflet (dated DD/MMM/YYYY) for the above study, and have had the opportunity to ask questions and have these answered satisfactorily.	INITIAL IF YES	INITIAL IF NO
2. I agree to take part in this study.	INITIAL IF YES	INITIAL IF NO
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.	INITIAL IF YES	INITIAL IF NO
4. I agree for my consent form and contact details to be passed to the University of Liverpool for the administration of the study.	INITIAL IF YES	INITIAL IF NO
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.	INITIAL IF YES	INITIAL IF NO
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.	INITIAL IF YES	INITIAL IF NO

7. I agree to have MRI scans as part of the trial.

INITIAL
IF YES

INITIAL
IF NO

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

INITIAL
IF YES

INITIAL
IF NO

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.

INITIAL
IF YES

INITIAL
IF NO

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).

INITIAL
IF YES

INITIAL
IF NO

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

INITIAL
IF YES

INITIAL
IF NO

Name of Participant
(Please print)

Signature

Date (DD/MM/YYYY)

Researcher*

Signature

Date (DD/MM/YYYY)

* **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).

BMJ Open

Protocol for DexEnceph; a randomised controlled trial of dexamethasone therapy in adults with Herpes Simplex Virus Encephalitis

Journal:	<i>BMJ Open</i>
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1 **Protocol for DexEnceph; a randomised controlled trial of dexamethasone therapy in adults**
2 **with Herpes Simplex Virus Encephalitis**

3 The study is funded by the National Institute for Health Research's Efficacy and Mechanism
4 Evaluation (EME) programme.

5
6 The trial sponsor is the University of Liverpool, who are responsible for all aspects of study
7 design, implementation, analysis and write up (sponsor@liverpool.ac.uk).

8
For peer review only

9 **Abstract**

10 **Introduction**

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

19 **Method**

20 DexEnceph is a pragmatic multicentre, randomised, controlled, open label, observer-blind
21 trial to determine whether adults who receive dexamethasone alongside standard
22 treatment with aciclovir for HSV encephalitis have improved clinical outcomes compared
23 with those who receive standard treatment alone. Overall, 90 patients with HSV
24 encephalitis will be recruited from a target of 90 recruiting sites; patients will be
25 randomised 1:1 to the dexamethasone or control arms of the study. The primary outcome
26 measured is verbal memory as assessed by the Weschler Memory Scale fourth edition
27 Auditory Memory Index at 26 weeks post randomisation. Secondary outcomes are
28 measured up to 72 weeks include additional neuropsychological, clinical and functional
29 outcomes as well as comparison of neuroimaging findings. Patient safety monitoring occurs
30 throughout and includes the detection of HSV DNA in cerebrospinal fluid 2 weeks after
31 randomisation, which is indicative of ongoing viral replication.

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3 32 **Discussion**
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9 34 DexEnceph aims to be the first completed randomised controlled trial of steroid therapy in
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11 35 HSV encephalitis. The results will provide evidence for future practice in managing adults with
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14 36 the condition and has the potential to improve outcomes in a life-changing disease.
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19 38 **Ethics and dissemination**
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21 39 The trial has ethical approval from the UK National Research Ethics committee (Liverpool
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23
24 40 Central, REF: 15/NW/0545, 10/08/2015). Protocol version 2.1 July 2019 The results will be
25
26 41 published and presented as soon as possible on completion.
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31 43 **Registration numbers**
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34 44 ISRCTN11774734, EUDRACT 2015-001609-16
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40 47 Key words: Herpes simplex, Encephalitis, Dexamethasone, Steroid, Verbal memory
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3 49 **Article Summary**
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5 50 **'Strengths and limitations of this study'**, and containing up to five short bullet points, no
6 51 longer than one sentence each, that relate specifically to the methods.
7
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- 9
10 53 ▪ DexEnceph will be the first completed randomised controlled trial of steroid in herpes
11 54 simplex virus encephalitis, examining the utility and safety of steroid use.
12
13 55
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15 56 ▪ DexEnceph's primary end point is verbal memory score recorded at 26 weeks post
16 57 randomisation, this represents the most common area of the brain to be affected.
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18 58
19 59
20 60 ▪ The recruitment target is informed by the recent Enceph-UK programme grant of
21 61 encephalitis in the UK; the trial is currently open and has recruited 71 patients of a
22 62 target 90.
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27 64 ▪ Concentration on site engagement with innovative, bespoke methods are key to
28 65 identifying and recruiting patients to ensure trial success.
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30 66
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32 67 ▪ The pragmatic open label, observer blind design of the trial is ensuring successful
33 68 recruitment to date.
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19 106 **Introduction**
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22 107 Herpes simplex virus infection (HSV) is the most commonly identified viral cause of
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24 108 encephalitis, inflammation and swelling of the brain caused by a virus or the body's immune
25
26 109 system, in the UK as in most western industrialised nations.¹⁻⁴ The incidence has been
27
28 110 estimated at 1 in 250,000-500,000,² with evidence this may be higher.⁴ Although a rare
29
30 111 disease, HSV encephalitis has a disproportionately large impact due to its devastating long
31
32 112 term neuro-psychological sequelae . These can have a marked impact on the quality of life of
33
34 113 the patient and their family and high health economic and social costs.^{5,6}
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40 114 Since the introduction of the antiviral drug aciclovir in the 1970s the mortality of HSV
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42 115 encephalitis has reduced from around 70% to 5.5-12%.⁷⁻⁹ However, survivors are commonly
43
44 116 left with neurological impairment; less than 20% of patients are able to return to work and
45
46 117 48% are classed as moderate to severely disabled.¹⁰ Even when obvious disabilities have not
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48 118 occurred, families often report personality changes – the person they take home from
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50 119 hospital is simply not the same as the one before the illness. ^{6,11}
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55 120 HSV encephalitis can cause a broad range of cognitive impairments, but impaired memory,
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57 121 especially verbal memory, is the most common and likely relates to the viral predilection for
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1
2
3 122 the temporal lobe of the brain.^{12,13} The verbal memory deficits manifest as difficulties
4
5 123 remembering names of objects and people, as well as listening to and recalling spoken
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8 124 information such as conversations.^{14,15} In addition to memory problems, difficulties in
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10 125 processing speed, concentration, language and executive function are also common amongst
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13 126 survivors of HSV encephalitis, along with fatigue, poor concentration, anxiety and depression.

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15 127 7,16,17
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19 128 The pathogenic mechanisms in HSV encephalitis are not fully understood. The evidence
20
21 129 suggests that in addition to direct viral pathogenesis, inflammation of the brain in response
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24 130 to the virus is a key component of the disease process.^{18–21} This is supported by the
25
26 131 observation that in the cerebrospinal fluid (CSF), higher levels of proinflammatory
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28
29 132 chemokines, especially monocyte chemoattractant protein (MCP)-1, interferon γ and interleukin
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31 133 6 (IL-6) are associated with a worse prognosis.^{22,23} Poor prognosis is also associated with the
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33
34 134 extent of inflammation seen on neuroimaging,²⁴ and the degree of temporal lobe swelling is
35
36 135 correlated with the severity of verbal memory impairment.²⁵
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40 136 Control of the inflammation in HSV encephalitis may improve outcome, as shown in mouse
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42 137 models of the disease.^{26–28} Before the availability of aciclovir, corticosteroids were also used
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44
45 138 routinely as a treatment in humans with HSV encephalitis,^{29,30} and more recently both
46
47 139 cerebral oedema on imaging and cerebrospinal fluid IL-6 levels were shown to be reduced in
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50 140 patients given corticosteroids.²³ However, because corticosteroids cause
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52 141 immunosuppression which in theory facilitates increased viral replication, their role is
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54 142 uncertain.³¹
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57 143 In other brain infections, including bacterial meningitis and tuberculous meningitis the benefit
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60 144 of corticosteroids has been demonstrated in large clinical trials.³² For HSV encephalitis the

1
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3 145 potential benefit of using corticosteroid as an adjunct to aciclovir therapy has been suggested
4
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6 146 from small case series and retrospective comparisons, but there has been no prospective
7
8 147 randomised study reported.^{33–38} One study, the German trial of Aciclovir and Corticosteroids
9
10 148 in Herpes simplex virus Encephalitis (the GACHE trial) was stopped early because of poor
11
12
13 149 recruitment rates.³⁹ However, there is clearly a need for a study to assess this question. The
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15 150 DexEnceph Study, a randomised controlled trial of dexamethasone in HSV encephalitis, aims
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18 151 to achieve this.

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22 23 24 153 **Trial design**

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27 154 DexEnceph is a pragmatic, multicentre, randomised, controlled, observer-blind trial to
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29
30 155 determine whether the addition of dexamethasone to standard aciclovir treatment improves
31
32 156 clinical outcomes (in particular verbal memory score) for adults with HSV encephalitis.
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34 157 Additionally, neuroimaging and biomarkers will be assessed along with detection of HSV in
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37 158 the cerebrospinal fluid at 2 weeks post randomisation to monitor for difference in viral
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39 159 replication between the two groups.

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43 44 45 161 **Primary objective**

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48 162 To determine whether a short course of intravenous dexamethasone, in addition to standard
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51 163 care, improves verbal memory score in adults with HSV encephalitis at 26 weeks post
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53 164 treatment compared to standard care alone.

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57 58 59 166 **Secondary objectives**

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3 167 Secondary objectives include the following:
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6 168 To determine whether dexamethasone therapy has an effect on other neuropsychological,
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9 169 cognitive, clinical, disability and functional outcomes in HSV encephalitis.

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12 170 To assess the effect of dexamethasone therapy on brain swelling assessed by neuroimaging
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14 171 imaging.

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17 172 To determine whether dexamethasone therapy affects clearance of HSV from cerebrospinal
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20 173 fluid, the emergence of anti-N-Methyl-D Aspartic acid (NMDA) receptor antibody or causes
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22 174 any changes in transcriptomic and proteomic profiling in the CSF and blood.
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27 176 A more comprehensive list of measures is detailed in the outcomes section.
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32 33 178 **Methods and analysis**

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36 179 DexEnceph is an observer blind, open label, prospective, randomised, controlled trial of
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38
39 180 dexamethasone at 10mg four times daily for 4 days, versus no dexamethasone, in adults with
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41 181 HSV encephalitis.
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43 44 182 **Research setting**

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47 183 The trial is being conducted in up to 45 NHS trusts, with a recruitment target of 0-2 patients
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49
50 184 per site per year. A full list of sites involved in DexEnceph can be obtained from
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52 185 www.dexenceph.org.uk
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54 55 186 **Eligibility criteria**

56 57 58 187 **Inclusion Criteria** 59 60

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3 188 Enrolled patients fulfil all of the following criteria:
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8 190 1. Suspected encephalitis defined as: new onset seizure or new focal neurological signs or
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10 191 alteration in consciousness, cognition, personality, or behaviour. Personality / behaviour
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12 192 change includes agitation, psychosis, somnolence, insomnia, catatonia, mood lability, altered
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14 193 sleep pattern.
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20 195 2. A positive HSV DNA polymerase chain reaction (PCR) result from CSF, reported not more
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22 196 than 7 days prior to randomisation.
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28 198 3. Receiving intravenous aciclovir administered as 10mg/kg three times daily or at a reduced
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30 199 dose if clinically indicated.
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35 201 4. Age \geq 16 years.
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40 203 5. Written informed consent given by the patient or their legal representative⁴⁰
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46 205 **Exclusion Criteria**
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49 206 Patients are excluded if they have any of the following:
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52 207 1. Have received oral or injectable corticosteroid therapy in the 30 days prior to the day of
53
54 208 admission to hospital. This does not apply to topical/ inhaled corticosteroids. [Patients who
55
56 209 have received oral or injectable corticosteroid therapy AFTER their admission to hospital will
57
58 210 not be excluded from the study if they consent to trial participation].
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6 212 2. History of hypersensitivity to corticosteroids.
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8 213
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10 214 3. Immunosuppression secondary to:
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13 215 a. Known HIV infection and CD4 white cell count under 200/mm³
14
15 216 b. Currently taking biologic therapy or other immunosuppressive agents [e.g.
16
17 azathioprine, methotrexate, ciclosporin]
18 217
19
20 218 c. Previous solid organ transplant and currently on immunosuppression
21
22
23 219 d. Previous bone marrow transplant
24
25 220 e. Currently undergoing a course of chemotherapy or radiotherapy
26
27
28 221 f. Known primary immunodeficiency syndrome
29
30 222 g. Known current haematological malignancy
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35 224 4. Pre-existing indwelling ventricular devices.
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40 226 5. Peptic ulcer disease in the last 6 months, defined as a peptic ulcer seen at endoscopy or
41
42 227 an upper gastrointestinal bleed causing a ≥ 2 unit haemoglobin drop, in the last 6 months.
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47 229 6. Antiretroviral regime containing rilpivirine as current treatment [Levels of rilpivirine are
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49 230 known to significantly decrease in co-administration with dexamethasone, a switch to a
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51 suitable alternative can facilitate trial entry].
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57 233 **Intervention**
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3 234 Participants are randomised in a 1:1 ratio to dexamethasone four times daily for four days
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6 235 alongside standard care, or standard care alone (Figure 1). Standard care includes intravenous
7
8 236 aciclovir for a minimum of 14 days based on an ideal body weight at 10mg/kg every 8 hours,
9
10 237 unless dose adjustment to account for renal impairment is necessary. Participating clinicians
11
12
13 238 remain free to modify or discontinue the dexamethasone administration or to give alternative
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15 239 treatments at any stage, if this is judged to be in the best interest of the patient.
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20 241 Participants assigned dexamethasone receive 10 mg equivalent of ordinary ward stock,
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22 242 prescribed by an authorised member of the local study team, given intravenously four times
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24 243 daily for four days (16 doses in total) starting within 24 hours of randomisation.
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29
30 245 The University of Liverpool employs a clinical trials unit to be responsible for screening, and
31
32 246 monitoring data collection, quality and completeness. As there is a low number of
33
34 247 participants to be recruited, the trials unit are able to liaise regularly with each site following
35
36 248 randomisation to ensure all follow up data are collected. Primary outcome is recorded by a
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38 249 centrally employed roving neuropsychologist, who collects the neuropsychological outcomes
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40 250 at 26 and 72 weeks.
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14 262 **Outcome measures**
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17 263 **Primary Outcome**
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20 264 Verbal memory score, determined by the Wechsler Memory Scale 4th edition (WMS-IV)
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22 265 Auditory Memory Index, at 26 weeks after randomisation.
23
24
25 266 **Secondary Outcomes**
26
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28 267 Other neuropsychological outcome measures [at 26 weeks and 78 weeks after
29
30
31 268 randomisation]:
32
33
34 269 • Verbal memory score, determined by the WMS-IV, Auditory Memory Index, at 78
35
36 270 weeks after randomisation.
37
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39 271 • Visual, Immediate and Delayed Memory by Indexes of the WMS-IV, processing speed
40
41 272 and working memory subscales from the Wechsler Adult Intelligence Scale Fourth
42
43 273 Edition.
44
45
46 274 • Higher executive function using the Trail Making Test.
47
48
49 275 • Anxiety and Depression symptom levels by the Beck Depression Inventory and Beck
50
51 276 Anxiety Inventory.
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53
54 277 • Subjective cognitive complaints using the Perceived Deficits Questionnaire.
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56 278 Cognitive Outcome Measures [at discharge or 30 days if still in hospital, 26 weeks and 78
57
58 279 weeks]
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2
3 280 • Addenbrooke's Cognitive Assessment III.
4

5
6 281 Clinical Outcomes
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- 8 282 • Incidence of epilepsy.
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11 283 • Time to hospital discharge.
12
13 284 • Requirement of high dependency unit or Intensive care unit admission up to 30 days
14
15 285 post randomisation.
16
17
18 286 • Time taken to be free of ventilatory support for 14 days [if any].
19
20
21 287 • Time to reach maximum recorded Glasgow coma scale score.
22
23 288 • Survival.
24

25 289 Disability & Functional Outcomes [at discharge or 30 days if still in hospital, 26 weeks and 78
26
27 weeks]:
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30 291 • Modified Rankin Score, Barthel Index, Liverpool Outcome Score and Glasgow
31
32 Outcome Scale Extended.
33 292

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35 293 Imaging Outcomes: Change from Baseline at 2 weeks, 26 weeks and 78 weeks
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38 294 • Temporal lobe volume (as % of intra-cranial volume).
39
40 295 • Whole brain volume (as % of intra-cranial volume).
41
42
43 296 • Volume of affected region as seen on fluid-attenuated inversion recovery (FLAIR)
44
45 297 image (as % of intra-cranial volume).
46
47
48 298 • Volume of affected region as seen on diffusion-weighted image (as % of intra-cranial
49
50 299 volume).
51

52 300 Biomarker Outcomes:
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55 301 • Transcriptomic and proteomic profiling on blood at convalescence (2 weeks and 26
56
57 302 weeks), compared to acute baselines, and on CSF at 2 weeks compared to acute
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59 303 baseline.
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3 304 • Anti-NMDA receptor antibody testing at 26 weeks.
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6 305 Safety Outcomes:
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- 8 306 • Proportion of patients with detectable HSV in CSF by PCR at 2 weeks.
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11 307 Health Status and Quality of Life [at 26 and 78 weeks]:
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- 13 308 • Measured by the EuroQoL-5 Dimension-5 Level quality of life scale (EQ-5D-5L) and 36
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15 309 item short form survey (SF-36) self-completed questionnaires.
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21 311 **Screening**
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23 312 The majority of potential patients are identified by the local research team through
24
25 313 identifying patients with a relevant clinical presentation suspicious of HSV encephalitis and/or
26
27 314 detection of HSV in a CSF sample. A screening log is completed for all potential patients. A
28
29 315 strong link with the local laboratory is essential as a key factor in ensuring eligible patients are
30
31 316 not missed by the investigative team. Investigators for the local research team include
32
33 317 neurologists, infectious disease clinicians, microbiologist and virologists.
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39
40 319 Because this is an uncommon disease, extra measures have been taken to try and maximise
41
42 320 recruitment. On identifying a suitable patient, sites are able to contact the trial management
43
44 321 team for intensive support via a dedicated telephone hotline, email, or an app. Short videos
45
46 322 which explain the trial to patients, families and to health care workers also support
47
48 323 recruitment. Every month, the trial management group monitor the screening reports of each
49
50 324 site for the previous 3 months, to ensure they are actively looking for patients. Lower than
51
52 325 expected screening is followed up by the central study team making contact with the study
53
54 326 site to review their screening methodology and offer support.
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8 329 **Randomisation**

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10 330 Participants are randomised using a 24-hour secure web-based programme, which is centrally
11
12 331 controlled by the clinical trials research centre. Designated members of the trial team at the
13
14 332 site (detailed on the delegation of responsibilities log) are provided with a unique username
15
16 333 and password which is required to access the web-based randomisation system. In the event
17
18 334 of system failure, the patient can be randomised centrally electronically or through secure
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20 335 envelopes. Each participant is allocated a unique study number (randomisation number), the
21
22 336 primary identifier for all the participants in this study.

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29 338 The neuropsychologist collecting the primary outcome and other outcome assessors such as
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31 339 radiologists and those responsible for paper authorship are blinded to randomisation during
32
33 340 the trial. Trial participants and local site study teams, as well as the trial manager and trial
34
35 341 data manager at the clinical trials unit are aware of what treatments have been allocated. The
36
37 342 independent data safety and monitoring committee (IDSMC) and statisticians have access to
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39 343 unblinded data grouped by intervention throughout the trial and make recommendations to
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41 344 the trial's steering committee who would only become unblinded in the event of a serious
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43 345 event.

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49 347 **Participant timeline**

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52 348 The time schedule for enrolment, interventions and assessments is given in table 1.

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350 **Statistical Considerations**

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352 **Sample Size**

353 The primary outcome variable is verbal memory , assessed as part of WMS-IV. In one
354 published series of adults who survived HSV encephalitis, 19 of 22 had memory impairment
355 evident at follow up, with verbal memory being most severely affected ¹². In that study the
356 mean (standard deviation, SD) verbal memory score was 88.9 (18.9) compared with the
357 population mean (SD) of 100 ¹⁵. This score can only be assessed in survivors, we estimate
358 approximately 10% of patients in the trial will die before assessment of the primary
359 outcome^{8,41,42}. In instances where the death is judged to be associated with encephalitis the
360 verbal memory score is recorded as 40, (the lowest possible value which would be obtained
361 even where a patient recorded no recall of any of the items administered in the memory
362 subtests). Where the cause of death is thought to be independent of having encephalitis,
363 those patients will be recorded as lost to follow up. Similarly, for patients who are too unwell,
364 due to encephalitis, to undergo the assessment, the score is recorded as 40. Decisions as to
365 whether the reasons for death or non-completion of the measures were due to encephalitis
366 will be made by an independent committee blinded to dexamethasone allocation. Adjusting
367 the estimate of mean and standard deviation from survivors, to include the 10% of patients
368 with the lowest possible value of 40, gives a total population mean of 84.8, with a standard
369 deviation of 23.1. A final sample size of 36 participants per group allows us to detect a
370 clinically meaningful difference of 15.5 on the verbal memory score with 80% power, at a two-
371 sided significance level of 0.05. Allowing for up to 20% dropout gives an initial target sample
372 size of 45 participants per group, for a total of 90.

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3 374 **Statistical analysis**
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6 375 For the primary outcome, participants are included in the analysis based on the intention-to-
7
8 376 treat principle. Verbal memory score will be compared between groups using linear
9
10 377 regression. The model will be adjusted for pre-specified variables which are judged to be
11
12 378 potentially related to the outcome, including age and admission Glasgow coma scale score.
13
14
15 379 No interim analysis is planned, but there is regular monitoring by the IDSMC.
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20 381 As there may be some missing primary outcome data due to death, inability to complete the
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22 382 assessment, or loss to follow up, a sensitivity analysis will be carried out. All randomised
23
24 383 patients will be included in this analysis.
25

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30 385 For continuous secondary outcome variables, comparisons between groups will be analysed
31
32 386 as per the primary outcome. The results for residual viral presence in the CSF at 2 weeks will
33
34 387 be reported with a 95% confidence interval for the difference in proportions between groups.
35
36 388 Time to event outcomes will be analysed using Kaplan-Meier curves, log rank tests and Cox
37
38 389 Proportional Hazards models. Binary secondary outcomes will be analysed using logistic
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40 390 regression.
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48 392 **Trial Promotion and engagement**
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51 393 Considerable effort is maintained to keep the principal investigators, research nurses and the
52
53 394 community engaged in the trial. The trial is being publicised using public forums, the
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55 395 Encephalitis Society website and newsletter, social media, patient journey articles and work
56
57 396 with newspapers and TV. To promote site engagement, study days are arranged for research
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3 397 teams to attend, along with scheduled research nurse teleconferences to allow ideas on
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6 398 maximising recruitment and updates on trial progress to be shared. Sites are also kept
7
8 399 updated through our website (www.dexenceph.org.uk), newsletters and an innovative sticker
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10 400 chart, whereby a sticker is sent out to every site each time a patient is recruited (Figure 2).
11
12
13 401 The Encephalitis Society are playing a key role in providing additional support to the patients
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15 402 and their families aside from their work for the trial.

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18 405 **Trial Closure**

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24 406 The end of the trial is defined to be the date on which data for all participants is frozen and
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26 407 data entry privileges are withdrawn from the trial database. The trial may be closed
27
28 408 prematurely by the trial steering committee, on the recommendation of the IDSMC if there is
29
30 409 sufficient evidence of risk to patient safety.

31 410 **Pharmacovigilance**

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34 411 Oversight of the trial is provided by the trial steering committee, which meets at least annually
35
36 412 to review trial progress, safety, and adverse events. The committee is also informed of any
37
38 413 protocol changes by the clinical trial research unit.

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41 414 The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions are
42
43 415 used for Adverse Event (AE), Adverse Reaction (AR), Unexpected Adverse Reaction (UAR),
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45 416 Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected
46
47 417 Serious Adverse Reaction (SUSAR).

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49 418 Depending on the nature of the event the reporting procedures below are followed:
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3 419 1. Serious adverse events occurring up to 30 days after randomisation are reported through
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6 420 a Serious Adverse Event Form (if serious) or in the 30 day/discharge case record forms (CRF)
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8 421 if they are a notable event (Positive PCR in CSF at 2nd lumbar puncture, gastrointestinal bleed,
9
10 422 hyperglycaemia requiring change in medical management, opportunistic infections,
11
12
13 423 unexpected/severe neuropsychiatric events).

14
15
16 424 2. Serious adverse events occurring after 30 days from randomisation are monitored through
17
18 425 reporting in the CRFs with safety data collected in the 26 week and 78-week CRFs if serious.

19
20
21 426 The research investigator at each study site (or designated other) assesses all adverse events
22
23 427 for seriousness, causality and severity. The Chief Investigator (or designated other) assesses
24
25
26 428 all adverse drug reactions for expectedness from known side effects of the use of
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28
29 429 Dexamethasone.⁴³ All serious ARs, AEs and SUSARs occurring up to 30 days from
30
31 430 randomisation (apart from death unless the investigator suspects causality) require reporting
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33
34 431 to the clinical trials unit, within 24 hours of the site becoming aware of the event. In the case
35
36 432 of death of a patient causality will be assessed by the trial steering committee.

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39 433 The clinical trials unit will notify the Medicines and Healthcare products Regulatory Agency
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41 434 and main research ethics committee of all SUSARs that occur during the study according to
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43
44 435 the following timelines; fatal and life-threatening within 7 days of notification and non-life
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46 436 threatening within 15 days. All investigators are informed of all SUSARs occurring throughout
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48
49 437 the study.

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52 438 SAEs occurring after 30 days from randomisation are monitored by the clinical trials unit via
53
54 439 the 26 week and 78week CRFs. These CRFs need to be received at the clinical trials research
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57 440 unit by 4 weeks after the 26 and 6 weeks after 78week time points.
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3 441 Safety data is provided to the IDSMC, who are responsible for safeguarding the interests of
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6 442 trial participants and assessing the safety of the interventions during the trial; the IDSMC
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8 443 ensures action is taken as needed should they become aware of trends in reported AEs that
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11 444 raise safety concerns.

12 13 445 **Trial Funding and Financial Arrangements**

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18 447 Contractual agreements are in place between the Sponsor and collaborating centres that
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20
21 448 describe financial arrangements. Trial participants are not paid to participate in the trial but
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23
24 449 are paid travel expenses for the follow up visits, estimated at £50 per visit. Payments to sites
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26 450 are made per site initiation but the bulk of payments are made per patient recruitment. Sites
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28 451 receive payment for: clinical time oversight, research nurse time, administrative support,
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31 452 magnetic resonance imaging scanning and pharmacy oversight.

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34 35 454 **Patient and public involvement**

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38 455 The Encephalitis Society was consulted and provided advice on the design of the trial and the
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41 456 difficulties participants and their families will likely encounter. The Chief Executive of The
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43 457 Encephalitis Society is a co-applicant on the grant application and a co-author on this paper.

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48 459 The Encephalitis Society has also provided patient representatives at our trial steering
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51 460 committee and assisted in the production and dissemination of trial promotional materials.

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53 461 The Encephalitis Society will drive forward publication and dissemination of the trial findings
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55 462 among lay, therapeutic and health professionals through the use of web materials,
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58 463 newsletters and guides as well as at conferences and seminars in relation to encephalitis and
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3 464 related fields. All patients and their family/carers will be acknowledged in any outputs from
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6 465 the trial. We also work with The Encephalitis Society on a programme
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8 466 of teaching events and produce guides for healthcare professionals and lay people.
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10 467 In instances where trial participants and their families have ongoing difficulties the central
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12
13 468 study team seek help for them through the Encephalitis Society and appropriate specialists
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15 469 for further assistance.
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22 23 472 **Ethics and Dissemination**

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28 474 The trial falls within the remit of the EU Directive 2001/20/EC, transposed into UK law as the
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31 475 UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations
32
33 476 2004 as amended. This trial is registered with the MHRA and granted Clinical Trial
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35 477 Authorisation (CTA). The EUDRACT number for CTA reference is 2015-001609-16. Ethical
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37 478 approval has been obtained from a multi-centre research ethics committee familiar with the
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39 479 principals of the Mental Capacity Act 2005 guidance for sites in England and Wales and the
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41 480 Adults with Incapacity Act 2008 for sites in Scotland as the principals are relevant to a clinical
42
43 481 trial of investigational medicinal products (CTIMP). Clinical Research Governance approval
44
45 482 was given through the Sponsor, The University of Liverpool. The trial protocol was approved
46
47 483 by a National Research Ethics Service Committee reference is 2015-001609-16 (Attained
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49 484 31/03/2016) and underwent independent review at the Research and Development offices
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51 485 at participating sites. This study abides by the principles of the World Medical Association
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53 486 Declaration of Helsinki (1964) and Tokyo (1975), Venice (1983), Hong Kong (1989) and South
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3 487 Africa (1996). Due to the nature of this trial it also abides by the Medicine for Human Use
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5 488 (Clinical Trials) regulations 2004 (S.I.2004:1031) and all following amendments which are
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7
8 489 incorporated into UK law.
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10 490

13 491 **Informed Consent Process**

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18 493 In obtaining and documenting informed consent, the investigators adhere to National
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20 494 Institute for Health Research (NIHR) Good Clinical Practice (GCP) guidelines and the ethical
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22 495 principles derived from the Declaration of Helsinki. Staff delegated by the principal
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24 496 investigator and appropriately trained with experience in obtaining informed consent, discuss
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26 497 the objectives, risks and inconveniences of the trial and the conditions under which it is to be
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28 498 conducted with the patient or if the patient lacks capacity with a legal or professional
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30 499 representative. Trial information documents and points of contact for further information are
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32 500 provided and the potential participants are given adequate time to consider their
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34 501 decision(supplementary file 1).
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42 503 As this is a CTIMP, the clinical trial regulations for incapacitated adults are followed
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44 504 (Medicines for Human Use Clinical Trial Regulations 2004 and amendments). When a legal
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46 505 representative has given consent for a patient to participate in the trial and the patient
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48 506 subsequently regains capacity, the research team will provide the patient information sheet
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50 507 and request consent from the participant. Patients are allowed to withdraw from the study
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52 508 at any point and may request withdrawal of their data collected until this point. Prospective
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54 509 consent can also be obtained prior to a positive PCR result so participants may have adequate
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56 510 time for contemplation.
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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.

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520 **Data Capture Methods**

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Data is 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 is 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.

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

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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

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3 535 Portal in an encrypted manner. The final dataset will be solely accessible to the central study
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6 536 team at the University of Liverpool for analysis and write up.
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10 538 **Dissemination**

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14
15 540 The results of the DexEnceph trial will be published in a high impact journal in a timely manner
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17 541 to present the findings to front-line clinicians. They will be presented at the annual conference
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19 542 organised by the Encephalitis Society and at other meetings. Authorship of the final papers
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21 543 will be determined in accordance with the international committee of medical journal editors'
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23 544 guidelines. The investigators will be involved in the preparation and drafting of the
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25 545 manuscripts. There is no intended use of professional writers.
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39 550 **Discussion**

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45 552 This protocol describes the design of a randomised controlled trial to demonstrate the utility
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47 553 of using dexamethasone in the management of individuals with HSV encephalitis. HSV
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49 554 encephalitis is a rare sporadic acute disease, and the trial has been designed to take this
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51 555 challenge into account, along with the practicalities of running the trial in a UK National Health
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53 556 Service setting. In particular lessons were learnt from a previous similar European study, the
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55 557 German trial of Aciclovir and Corticosteroids in Herpes simplex virus Encephalitis (GACHE
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58 558 trial), which was stopped early because of recruitment difficulties. Recruitment to the GACHE
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3 559 trial necessitated patients had focal neurological signs of no longer than five days prior to
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6 560 admission, whilst DexEnceph has less stringent criteria and reflects the diverse ways in which
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8 561 HSV encephalitis may present. DexEnceph has been designed to be both practical and
9
10 562 pragmatic, in that patients must be recruited within 7 days of the PCR result becoming
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13 563 available. This allows for occasions where it may take longer to get the PCR performed, and
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15 564 also allows time for patients admitted to district general hospitals, which may not be study
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18 565 centres, to be transferred to larger hospitals which are. DexEnceph also has the advantage in
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20 566 that its recruitment projections were based on preliminary data garnered from the ENCEPH-
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22
23 567 UK NIHR program (www.encephuk.org) and from a multicentre cohort study of encephalitis
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25 568 in England, run by the Health Protection Agency (fore-runner to the Health Protection
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28 569 Agency).⁹ These two studies provided direct information on the number of HSV encephalitis
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30 570 patients presenting to UK hospitals. Our choice of an open label observer-blind study, rather
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33 571 than a placebo-controlled double-blind trial, avoided the logistic challenges of ensuring
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35 572 blinded study drug was available across the large number of centres, necessitated by a rare
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38 573 sporadic disease, which may also have been a factor in the recruitment difficulties
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40 574 experienced by the GACHE trial. We are confident our robust monitoring and trial promotion
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42 575 ensures the majority of eligible patients are recruited. N- methyl-D-aspartic acid (NMDA)
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45 576 receptor antibody encephalitis (which is treated with corticosteroids and other
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47 577 immunomodulatory therapies) is being recognised increasingly as a late complication of HSV
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49 578 encephalitis.^{44,45} DexEnceph may also be able examine whether corticosteroids reduce the
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52 579 incidence of this complication. If there is demonstrable efficacy of corticosteroid in improving
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55 580 neuropsychological, imaging and quality of life outcomes, without compromising patient
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57 581 safety the results will be far reaching.

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56 583 **Collaboration with France**
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9 584 Because we recognised from the start that there may be difficulties keeping to recruitment
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11 585 targets in the DexEnceph study, we worked with colleagues in France to develop a parallel
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13 586 French study (DexEnceph-France). This follows the UK DexEnceph protocol as closely as
14
15 587 possible, whilst being pragmatic about the constraints of a different country's health care
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17 588 system. The French trial is based in 10 hospitals with the lead centre being Grenoble Alpes
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19 589 University Hospital and the aim of recruiting 30 patients.
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24 590 The intention is for the two trials to be analysed separately, with the option of also results
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26 591 also combining them into an overall analysis which will give additional power to detect a
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28 592 treatment effect.
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4041 597 **Trial status**
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43 598 The trial has been open across the UK since August 2016, and as of July 2019 is open at 45
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45 599 NHS trusts; 71 patients have been randomised (of the total target of 90) meaning that we
46
47 600 have recruited 79% of the patients are recruiting at just over 80% of the target recruitment
48
49 601 rate. The trial was due to complete recruitment later in 2020 with 6 months follow up and 3
50
51 602 months post trial closure for write up. Though recent COVID-19 pandemic has placed
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53 603 difficulties in conducting trials and paused recruitment, the primary outcome has not been
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55 604 missed in any existing DexEnceph recruit, this has been achieved by conducting
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3 605 neuropsychology assessment by either telephone or online video discussion, thus avoiding
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6 606 any risk of transmission. DexEnceph-France study, which opened in 2018 has recruited 10
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8 607 patients from 10 sites.
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13 609 If you are interested to find out more information or to see if your trust is involved visit
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15 610 www.dexenceph.org.uk or for more information please email: dexenceph@liverpool.ac.uk.
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27 28 29 30 616 **References**

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Authors' Contributions

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2
3 749 All authors were consulted and inputted into the article, below lists the particular role
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6 750 within DexEnceph
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8 751 TW: Clinical research fellow, CF: Clinical research fellow, KD: trials manager, SD: contributor to trial
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10 752 design and running, MG: Clinical and laboratory biomarkers lead, CH: Neuropsychology researcher,
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12 753 RT: Trial pharmacist, GB: Trial statistician, AR-H: trial statistician, PM: Neuropsychology lead, KDas:
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14 754 Neuroimaging lead, MZ: Virology, LP: Neuroimaging, SK: Neuroimaging, NR: Neuroimaging, EA:
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16 755 Encephalitis Society Chief Executive advisor, ST: Study co-ordinator France, RK: Clinical lead brain
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18 756 infections UK, JPS: Principle investigator France, TS: Chief Investigator responsible for the trial
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761

762 **Declaration of Interests**

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768 Other authors: non declared

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770 **Data Statement**

771 There are currently no current plans to publish the data, data is available on reasonable request.

772

773 **Word count:** 4900 words

774 **Figure Legends**

775

776 **Figure 1: Schematic design of DexEnceph randomised controlled trial**

777 **Figure 2 : DexEnceph Recruitment poster**

778 **Supplementary file 1: DexEnceph Information and Consent form**

779 **Table 1: Time scale for patients Randomised in the DexEnceph study**

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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	
Magnetic resonance imaging (MRI) scan		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 quality of life questionnaires					X	X	

Procedures	Follow-up Schedule						
	Screening	Baseline	2 weeks	Discharge or Day 30 of admission (whichever is sooner)	26 weeks	78 weeks	Premature Discontinuation
Clinical Laboratory: Haematology, Biochemistry		X α					
Assessment of Adverse Events			(X)	(X)	(X)	(X)	(X)

781 † Only applicable when patients are prospectively consented for the randomised controlled trial

782 *Procedures required before randomisation.

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

784 γ Diagnostic lumbar puncture for clinical purposes done prior to randomisation

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

786 ∞ Recorded prior to randomisation, daily for the first 14 days and then weekly until Discharge/30 days (whichever sooner)

787 (X) – As indicated/appropriate

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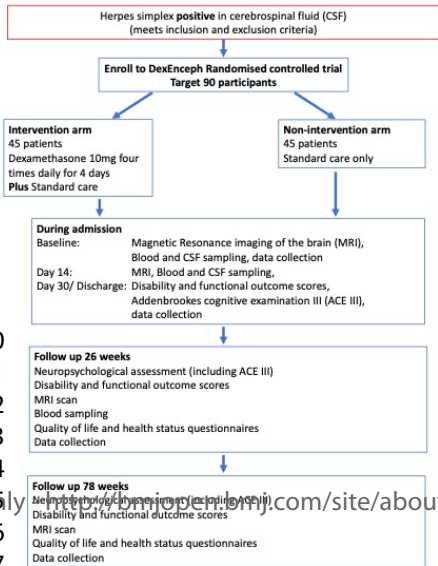
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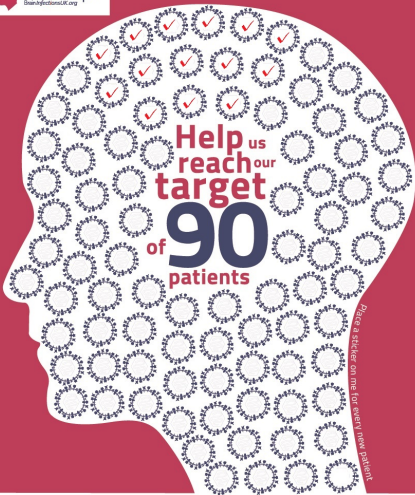
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Figure 1: Schematic Design of DexEnceph randomised controlled trial





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Place a sticker on me for every new patient.

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National Institute for Health Research



A Randomised Controlled Trial
Dexamethasone
in Herpes Simplex Virus Encephalitis

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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?

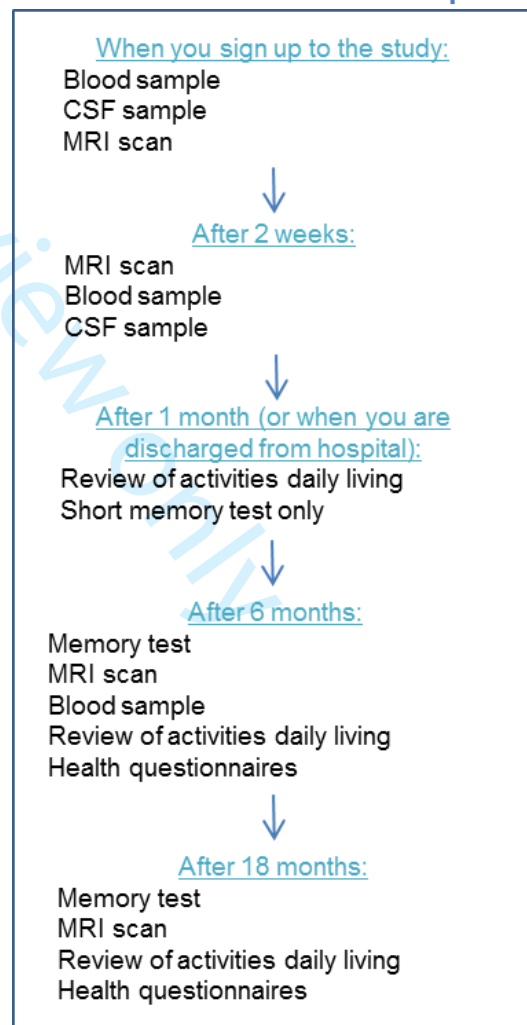
All patients in the study will receive aciclovir. This is standard treatment for HSV encephalitis.

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?



All the tests done when you sign up to the study and the CSF tests after 2 weeks will

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.

Other things to consider

14. Do I have to take part?

No, taking part is voluntary. If you agree, we will ask you to sign a consent form.

If you agree to take part you are free to change your mind at any time, without giving a reason. You may decide to have only some tests in the study without having to drop out of the study altogether. This will not affect the standard of care you receive.

If you withdraw from the study we will stop collecting data. We will ask you if we can use the information and samples we have gathered up to the point that you withdraw.

15. What happens if there is a problem?

If you have any concerns about any part of this study, please speak with your hospital doctor (consultant) or one of your research team.

If you remain unhappy and wish to complain formally you can do this using the NHS Complaints Procedure. You can get information on how to do this from the Patients Advice Liaison department (PALS) in your hospital.

If you suffer harm from taking part in this study, there are no special compensation arrangements. If harm occurs to you and it is due to someone's negligence, you may have grounds for legal action for compensation against the NHS hospital where you are being treated but you may have to pay your legal costs.

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.

Benefits and risks

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:

Centre Code:

Name of Principal Investigator:

Study Number:

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

YES**NO**

1. I confirm I have read and understand the Information Leaflet (dated DD/MMM/YYYY) for the above study, and have had the opportunity to ask questions and have these answered satisfactorily.	INITIAL IF YES	INITIAL IF NO
2. I agree to take part in this study.	INITIAL IF YES	INITIAL IF NO
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.	INITIAL IF YES	INITIAL IF NO
4. I agree for my consent form and contact details to be passed to the University of Liverpool for the administration of the study.	INITIAL IF YES	INITIAL IF NO
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.	INITIAL IF YES	INITIAL IF NO
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.	INITIAL IF YES	INITIAL IF NO

7. I agree to have MRI scans as part of the trial.

INITIAL
IF YES

INITIAL
IF NO

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

INITIAL
IF YES

INITIAL
IF NO

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.

INITIAL
IF YES

INITIAL
IF NO

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).

INITIAL
IF YES

INITIAL
IF NO

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

INITIAL
IF YES

INITIAL
IF NO

Name of Participant
(Please print)

Signature

Date (DD/MM/YYYY)

Researcher*

Signature

Date (DD/MM/YYYY)

* **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).

BMJ Open

Protocol for DexEnceph; a randomised controlled trial of dexamethasone therapy in adults with Herpes Simplex Virus Encephalitis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041808.R2
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1 **Protocol for DexEnceph; a randomised controlled trial of dexamethasone therapy in adults**
2 **with Herpes Simplex Virus Encephalitis**

3 The study is funded by the National Institute for Health Research's Efficacy and Mechanism
4 Evaluation (EME) programme.

5
6 The trial sponsor is the University of Liverpool, who are responsible for all aspects of study
7 design, implementation, analysis and write up (sponsor@liverpool.ac.uk).

8
For peer review only

9 **Abstract**

10 **Introduction**

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

19 **Method**

20 DexEnceph is a pragmatic multicentre, randomised, controlled, open label, observer-blind
21 trial to determine whether adults who receive dexamethasone alongside standard
22 treatment with aciclovir for HSV encephalitis have improved clinical outcomes compared
23 with those who receive standard treatment alone. Overall, 90 patients with HSV
24 encephalitis will be recruited from a target of 90 recruiting sites; patients will be
25 randomised 1:1 to the dexamethasone or control arms of the study. The primary outcome
26 measured is verbal memory as assessed by the Weschler Memory Scale fourth edition
27 Auditory Memory Index at 26 weeks post randomisation. Secondary outcomes are
28 measured up to 72 weeks include additional neuropsychological, clinical and functional
29 outcomes as well as comparison of neuroimaging findings. Patient safety monitoring occurs
30 throughout and includes the detection of HSV DNA in cerebrospinal fluid 2 weeks after
31 randomisation, which is indicative of ongoing viral replication.

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3 32 **Discussion**
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9 34 DexEnceph aims to be the first completed randomised controlled trial of steroid therapy in
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11 35 HSV encephalitis. The results will provide evidence for future practice in managing adults with
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14 36 the condition and has the potential to improve outcomes in a life-changing disease.
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19 38 **Ethics and dissemination**
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21 39 The trial has ethical approval from the UK National Research Ethics committee (Liverpool
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23
24 40 Central, REF: 15/NW/0545, 10/08/2015). Protocol version 2.1 July 2019 The results will be
25
26 41 published and presented as soon as possible on completion.
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31 43 **Registration numbers**
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34 44 ISRCTN11774734, EUDRACT 2015-001609-16
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40 47 Key words: Herpes simplex, Encephalitis, Dexamethasone, Steroid, Verbal memory
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3 49 **Article Summary**

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5 50 **'Strengths and limitations of this study',**

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8 52 ▪ DexEnceph will be the first completed randomised controlled trial of steroid in herpes
9 53 simplex virus encephalitis, examining the utility and safety of steroid use.

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14 55 ▪ DexEnceph's primary end point is verbal memory score recorded at 26 weeks post
15 56 randomisation, this represents the most common area of the brain to be affected.

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19 59 ▪ The recruitment target is informed by the recent Enceph-UK programme grant of
20 60 encephalitis in the UK; the trial is currently open and has recruited 71 patients of a
21 61 target 90.

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25 63 ▪ Concentration on site engagement with innovative, bespoke methods are key to
26 64 identifying and recruiting patients to ensure trial success.

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30 66 ▪ The pragmatic open label, observer blind design of the trial is ensuring successful
31 67 recruitment to date.

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18 19 105 **Introduction**

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22 106 Herpes simplex virus infection (HSV) is the most commonly identified viral cause of
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24 107 encephalitis, inflammation and swelling of the brain caused by a virus or the body's immune
25
26 108 system, in the UK as in most western industrialised nations.¹⁻⁴ The incidence has been
27
28 109 estimated at 1 in 250,000-500,000,² with evidence this may be higher.⁴ Although a rare
29
30 110 disease, HSV encephalitis has a disproportionately large impact due to its devastating long
31
32 111 term neuro-psychological sequelae . These can have a marked impact on the quality of life of
33
34 112 the patient and their family and high health economic and social costs.^{5,6}

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37 113 Since the introduction of the antiviral drug aciclovir in the 1970s the mortality of HSV
38
39 114 encephalitis has reduced from around 70% to 5.5-12%.⁷⁻⁹ However, survivors are commonly
40
41 115 left with neurological impairment; less than 20% of patients are able to return to work and
42
43 116 48% are classed as moderate to severely disabled.¹⁰ Even when obvious disabilities have not
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45 117 occurred, families often report personality changes – the person they take home from
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47 118 hospital is simply not the same as the one before the illness.^{6,11}

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50 119 HSV encephalitis can cause a broad range of cognitive impairments, but impaired memory,
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52 120 especially verbal memory, is the most common and likely relates to the viral predilection for
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3 121 the temporal lobe of the brain.^{12,13} The verbal memory deficits manifest as difficulties
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5 122 remembering names of objects and people, as well as listening to and recalling spoken
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8 123 information such as conversations.^{14,15} In addition to memory problems, difficulties in
9
10 124 processing speed, concentration, language and executive function are also common amongst
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12
13 125 survivors of HSV encephalitis, along with fatigue, poor concentration, anxiety and
14
15 126 depression.^{7,16,17}

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19 127 The pathogenic mechanisms in HSV encephalitis are not fully understood. The evidence
20
21 128 suggests that in addition to direct viral pathogenesis, inflammation of the brain in response
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23
24 129 to the virus is a key component of the disease process.^{18–21} This is supported by the
25
26 130 observation that in the cerebrospinal fluid (CSF), higher levels of proinflammatory
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29 131 chemokines, especially monocyte chemotactic protein (MCP)-1, interferon γ and interleukin
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31 132 6 (IL-6) are associated with a worse prognosis.^{22,23} Poor prognosis is also associated with the
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33
34 133 extent of inflammation seen on neuroimaging,²⁴ and the degree of temporal lobe swelling is
35
36 134 correlated with the severity of verbal memory impairment.²⁵

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40 135 Control of the inflammation in HSV encephalitis may improve outcome, as shown in mouse
41
42 136 models of the disease.^{26–28} Before the availability of aciclovir, corticosteroids were also used
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45 137 routinely as a treatment in humans with HSV encephalitis,^{29,30} and more recently both
46
47 138 cerebral oedema on imaging and cerebrospinal fluid IL-6 levels were shown to be reduced in
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50 139 patients given corticosteroids.²³ However, because corticosteroids cause
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52 140 immunosuppression which in theory facilitates increased viral replication, their role is
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54 141 uncertain.³¹

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57 142 In other brain infections, including bacterial meningitis and tuberculous meningitis the benefit
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60 143 of corticosteroids has been demonstrated in large clinical trials.³² For HSV encephalitis the

1
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3 144 potential benefit of using corticosteroid as an adjunct to aciclovir therapy has been suggested
4
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6 145 from small case series and retrospective comparisons, but there has been no prospective
7
8 146 randomised study reported.^{33–38} One study, the German trial of Aciclovir and Corticosteroids
9
10 147 in Herpes simplex virus Encephalitis (the GACHE trial) was stopped early because of poor
11
12
13 148 recruitment rates.³⁹ However, there is clearly a need for a study to assess this question. The
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15 149 DexEnceph Study, a randomised controlled trial of dexamethasone in HSV encephalitis, aims
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18 150 to achieve this.
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22 23 24 152 **Trial design**

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27 153 DexEnceph is a pragmatic, multicentre, randomised, controlled, observer-blind trial to
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29
30 154 determine whether the addition of dexamethasone to standard aciclovir treatment improves
31
32 155 clinical outcomes (in particular verbal memory score) for adults with HSV encephalitis.
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34 156 Additionally, neuroimaging and biomarkers will be assessed along with detection of HSV in
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37 157 the cerebrospinal fluid at 2 weeks post randomisation to monitor for difference in viral
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39 158 replication between the two groups.
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43 44 45 160 **Primary objective**

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48 161 To determine whether a short course of intravenous dexamethasone, in addition to standard
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51 162 care, improves verbal memory score in adults with HSV encephalitis at 26 weeks post
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54 163 treatment compared to standard care alone.
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58 59 60 165 **Secondary objectives**

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3 166 Secondary objectives include the following:
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6 167 To determine whether dexamethasone therapy has an effect on other neuropsychological,
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8 168 cognitive, clinical, disability and functional outcomes in HSV encephalitis.
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12 169 To assess the effect of dexamethasone therapy on brain swelling assessed by neuroimaging
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14 170 imaging.
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17 171 To determine whether dexamethasone therapy affects clearance of HSV from cerebrospinal
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19 172 fluid, the emergence of anti-N-Methyl-D Aspartic acid (NMDA) receptor antibody or causes
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21 173 any changes in transcriptomic and proteomic profiling in the CSF and blood.
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27 175 A more comprehensive list of measures is detailed in the outcomes section.
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32 33 177 **Methods and analysis** 34

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36 178 DexEnceph is an observer blind, open label, prospective, randomised, controlled trial of
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38 179 dexamethasone at 10mg four times daily for 4 days, versus no dexamethasone, in adults with
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40 180 HSV encephalitis.
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43 44 181 **Research setting** 45

46
47 182 The trial is being conducted in up to 45 NHS trusts, with a recruitment target of 0-2 patients
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49 183 per site per year. A full list of sites involved in DexEnceph can be obtained from
50
51 184 www.dexenceph.org.uk. The trial uses SPIRIT reporting guidelines,⁴⁰ (supplementary file 1).
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54 55 185 **Eligibility criteria** 56

57 58 186 **Inclusion Criteria** 59 60

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3 187 Enrolled patients fulfil all of the following criteria:
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8 189 1. Suspected encephalitis defined as: new onset seizure or new focal neurological signs or
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10 190 alteration in consciousness, cognition, personality, or behaviour. Personality / behaviour
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12 191 change includes agitation, psychosis, somnolence, insomnia, catatonia, mood lability, altered
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14 192 sleep pattern.
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20 194 2. A positive HSV DNA polymerase chain reaction (PCR) result from CSF, reported not more
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22 195 than 7 days prior to randomisation.
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28 197 3. Receiving intravenous aciclovir administered as 10mg/kg three times daily or at a reduced
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30 198 dose if clinically indicated.
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35 200 4. Age \geq 16 years.
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40 202 5. Written informed consent given by the patient or their legal representative⁴¹
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46 204 **Exclusion Criteria**

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49 205 Patients are excluded if they have any of the following:
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51 206 1. Have received oral or injectable corticosteroid therapy in the 30 days prior to the day of
52
53 207 admission to hospital. This does not apply to topical/ inhaled corticosteroids. [Patients who
54
55 208 have received oral or injectable corticosteroid therapy AFTER their admission to hospital will
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57 209 not be excluded from the study if they consent to trial participation].
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2. History of hypersensitivity to corticosteroids.

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10 213 3. Immunosuppression secondary to:

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13 214 a. Known HIV infection and CD4 white cell count under 200/mm³

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15 215 b. Currently taking biologic therapy or other immunosuppressive agents [e.g.

16
17 216 azathioprine, methotrexate, ciclosporin]

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19 217 c. Previous solid organ transplant and currently on immunosuppression

20
21 218 d. Previous bone marrow transplant

22
23 219 e. Currently undergoing a course of chemotherapy or radiotherapy

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25 220 f. Known primary immunodeficiency syndrome

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27 221 g. Known current haematological malignancy

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31 223 4. Pre-existing indwelling ventricular devices.

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35 225 5. Peptic ulcer disease in the last 6 months, defined as a peptic ulcer seen at endoscopy or

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37 226 an upper gastrointestinal bleed causing a ≥ 2 unit haemoglobin drop, in the last 6 months.

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41 228 6. Antiretroviral regime containing rilpivirine as current treatment [Levels of rilpivirine are

42
43 229 known to significantly decrease in co-administration with dexamethasone, a switch to a

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45 230 suitable alternative can facilitate trial entry].

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49 232 **Intervention**

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3 233 Participants are randomised in a 1:1 ratio to dexamethasone four times daily for four days
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6 234 alongside standard care, or standard care alone (Figure 1). Standard care includes intravenous
7
8 235 aciclovir for a minimum of 14 days based on an ideal body weight at 10mg/kg every 8 hours,
9
10 236 unless dose adjustment to account for renal impairment is necessary. Participating clinicians
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12
13 237 remain free to modify or discontinue the dexamethasone administration or to give alternative
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15 238 treatments at any stage, if this is judged to be in the best interest of the patient.
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20 240 Participants assigned dexamethasone receive 10 mg equivalent of ordinary ward stock,
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22 241 prescribed by an authorised member of the local study team, given intravenously four times
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24 242 daily for four days (16 doses in total) starting within 24 hours of randomisation.
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29
30 244 The University of Liverpool employs a clinical trials unit to be responsible for screening, and
31
32 245 monitoring data collection, quality and completeness. As there is a low number of
33
34 246 participants to be recruited, the trials unit are able to liaise regularly with each site following
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36 247 randomisation to ensure all follow up data are collected. Primary outcome is recorded by a
37
38 248 centrally employed roving neuropsychologist, who collects the neuropsychological outcomes
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40 249 at 26 and 72 weeks.
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14 261 **Outcome measures**
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17 262 **Primary Outcome**
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20 263 Verbal memory score, determined by the Wechsler Memory Scale 4th edition (WMS-IV)
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22 264 Auditory Memory Index, at 26 weeks after randomisation.
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25 265 **Secondary Outcomes**
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28 266 Other neuropsychological outcome measures [at 26 weeks and 78 weeks after
29
30
31 267 randomisation]:
32
33 268 • Verbal memory score, determined by the WMS-IV, Auditory Memory Index, at 78
34
35 269 weeks after randomisation.
36
37
38 270 • Visual, Immediate and Delayed Memory by Indexes of the WMS-IV, processing speed
39
40 271 and working memory subscales from the Wechsler Adult Intelligence Scale Fourth
41
42 272 Edition.
43
44 273 • Higher executive function using the Trail Making Test.
45
46 274 • Anxiety and Depression symptom levels by the Beck Depression Inventory and Beck
47
48 275 Anxiety Inventory.
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50 276 • Subjective cognitive complaints using the Perceived Deficits Questionnaire.
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53 277 Cognitive Outcome Measures [at discharge or 30 days if still in hospital, 26 weeks and 78
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55 278 weeks]
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3 279 • Addenbrooke's Cognitive Assessment III.
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6 280 Clinical Outcomes
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- 8 281 • Incidence of epilepsy.
9
10 282 • Time to hospital discharge.
11
12 283 • Requirement of high dependency unit or Intensive care unit admission up to 30 days
13
14 284 post randomisation.
15
16 285 • Time taken to be free of ventilatory support for 14 days [if any].
17
18 286 • Time to reach maximum recorded Glasgow coma scale score.
19
20 287 • Survival.
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25 288 Disability & Functional Outcomes [at discharge or 30 days if still in hospital, 26 weeks and 78
26
27 weeks]:
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- 30 290 • Modified Rankin Score, Barthel Index, Liverpool Outcome Score and Glasgow
31
32 Outcome Scale Extended.
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35 292 Imaging Outcomes: Change from Baseline at 2 weeks, 26 weeks and 78 weeks
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- 38 293 • Temporal lobe volume (as % of intra-cranial volume).
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40 294 • Whole brain volume (as % of intra-cranial volume).
41
42 295 • Volume of affected region as seen on fluid-attenuated inversion recovery (FLAIR)
43
44 image (as % of intra-cranial volume).
45
46 296
47
48 297 • Volume of affected region as seen on diffusion-weighted image (as % of intra-cranial
49
50 volume).
51
52

53 299 Biomarker Outcomes:
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- 55 300 • Transcriptomic and proteomic profiling on blood at convalescence (2 weeks and 26
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57 weeks), compared to acute baselines, and on CSF at 2 weeks compared to acute
58
59 baseline.
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3 303 • Anti-NMDA receptor antibody testing at 26 weeks.
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6 304 Safety Outcomes:
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- 8 305 • Proportion of patients with detectable HSV in CSF by PCR at 2 weeks.
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11 306 Health Status and Quality of Life [at 26 and 78 weeks]:
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- 13 307 • Measured by the EuroQoL-5 Dimension-5 Level quality of life scale (EQ-5D-5L) and 36
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15 308 item short form survey (SF-36) self-completed questionnaires.
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21 310 **Screening**
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23 311 The majority of potential patients are identified by the local research team through
24
25 312 identifying patients with a relevant clinical presentation suspicious of HSV encephalitis and/or
26
27 313 detection of HSV in a CSF sample. A screening log is completed for all potential patients. A
28
29 314 strong link with the local laboratory is essential as a key factor in ensuring eligible patients are
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31 315 not missed by the investigative team. Investigators for the local research team include
32
33 316 neurologists, infectious disease clinicians, microbiologist and virologists.
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39
40 318 Because this is an uncommon disease, extra measures have been taken to try and maximise
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42 319 recruitment. On identifying a suitable patient, sites are able to contact the trial management
43
44 320 team for intensive support via a dedicated telephone hotline, email, or an app. Short videos
45
46 321 which explain the trial to patients, families and to health care workers also support
47
48 322 recruitment. Every month, the trial management group monitor the screening reports of each
49
50 323 site for the previous 3 months, to ensure they are actively looking for patients. Lower than
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52 324 expected screening is followed up by the central study team making contact with the study
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54 325 site to review their screening methodology and offer support.
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8 328 **Randomisation**

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10 329 Participants are randomised using a 24-hour secure web-based programme, which is centrally
11
12 330 controlled by the clinical trials research centre. Designated members of the trial team at the
13
14 331 site (detailed on the delegation of responsibilities log) are provided with a unique username
15
16 332 and password which is required to access the web-based randomisation system. In the event
17
18 333 of system failure, the patient can be randomised centrally electronically or through secure
19
20 334 envelopes. Each participant is allocated a unique study number (randomisation number), the
21
22 335 primary identifier for all the participants in this study.
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30 337 The neuropsychologist collecting the primary outcome and other outcome assessors such as
31
32 338 radiologists and those responsible for paper authorship are blinded to randomisation during
33
34 339 the trial. Trial participants and local site study teams, as well as the trial manager and trial
35
36 340 data manager at the clinical trials unit are aware of what treatments have been allocated. The
37
38 341 independent data safety and monitoring committee (IDSMC) and statisticians have access to
39
40 342 unblinded data grouped by intervention throughout the trial and make recommendations to
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42 343 the trial's steering committee who would only become unblinded in the event of a serious
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44 344 event.
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52 346 **Participant timeline**

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55 347 The time schedule for enrolment, interventions and assessments is given in table 1.
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349 **Statistical Considerations**

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351 **Sample Size**

352 The primary outcome variable is verbal memory , assessed as part of WMS-IV. In one
353 published series of adults who survived HSV encephalitis, 19 of 22 had memory impairment
354 evident at follow up, with verbal memory being most severely affected.¹² In that study the
355 mean (standard deviation, SD) verbal memory score was 88.9 (18.9) compared with the
356 population mean (SD) of 100.¹⁵ This score can only be assessed in survivors, we estimate
357 approximately 10% of patients in the trial will die before assessment of the primary
358 outcome.^{8,42,43} In instances where the death is judged to be associated with encephalitis the
359 verbal memory score is recorded as 40, (the lowest possible value which would be obtained
360 even where a patient recorded no recall of any of the items administered in the memory
361 subtests). Where the cause of death is thought to be independent of having encephalitis,
362 those patients will be recorded as lost to follow up. Similarly, for patients who are too unwell,
363 due to encephalitis, to undergo the assessment, the score is recorded as 40. Decisions as to
364 whether the reasons for death or non-completion of the measures were due to encephalitis
365 will be made by an independent committee blinded to dexamethasone allocation. Adjusting
366 the estimate of mean and standard deviation from survivors, to include the 10% of patients
367 with the lowest possible value of 40, gives a total population mean of 84.8, with a standard
368 deviation of 23.1. A final sample size of 36 participants per group allows us to detect a
369 clinically meaningful difference of 15.5 on the verbal memory score with 80% power, at a two-
370 sided significance level of 0.05. Allowing for up to 20% dropout gives an initial target sample
371 size of 45 participants per group, for a total of 90.

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3 **373 Statistical analysis**
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6 374 For the primary outcome, participants are included in the analysis based on the intention-to-
7
8 375 treat principle. Verbal memory score will be compared between groups using linear
9
10 376 regression. The model will be adjusted for pre-specified variables which are judged to be
11
12
13 377 potentially related to the outcome, including age and admission Glasgow coma scale score.
14
15 378 No interim analysis is planned, but there is regular monitoring by the IDSMC.
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20 380 As there may be some missing primary outcome data due to death, inability to complete the
21
22 381 assessment, or loss to follow up, a sensitivity analysis will be carried out. All randomised
23
24 382 patients will be included in this analysis.
25

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30 384 For continuous secondary outcome variables, comparisons between groups will be analysed
31
32 385 as per the primary outcome. The results for residual viral presence in the CSF at 2 weeks will
33
34 386 be reported with a 95% confidence interval for the difference in proportions between groups.
35
36 387 Time to event outcomes will be analysed using Kaplan-Meier curves, log rank tests and Cox
37
38 388 Proportional Hazards models. Binary secondary outcomes will be analysed using logistic
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40 389 regression.
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48 **391 Trial Promotion and engagement**
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51 392 Considerable effort is maintained to keep the principal investigators, research nurses and the
52
53 393 community engaged in the trial. The trial is being publicised using public forums, the
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55 394 Encephalitis Society website and newsletter, social media, patient journey articles and work
56
57 395 with newspapers and TV. To promote site engagement, study days are arranged for research
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3 396 teams to attend, along with scheduled research nurse teleconferences to allow ideas on
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6 397 maximising recruitment and updates on trial progress to be shared. Sites are also kept
7
8 398 updated through our website (www.dexenceph.org.uk), newsletters and an innovative sticker
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10 399 chart, whereby a sticker is sent out to every site each time a patient is recruited (Figure 2).
11
12
13 400 The Encephalitis Society are playing a key role in providing additional support to the patients
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15 401 and their families aside from their work for the trial.
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20 21 22 23 24 404 **Trial Closure**

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27 405 The end of the trial is defined to be the date on which data for all participants is frozen and
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29 406 data entry privileges are withdrawn from the trial database. The trial may be closed
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31 407 prematurely by the trial steering committee, on the recommendation of the IDSMC if there is
32
33 408 sufficient evidence of risk to patient safety.
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37 409 **Pharmacovigilance**

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40 410 Oversight of the trial is provided by the trial steering committee, which meets at least annually
41
42 411 to review trial progress, safety, and adverse events. The committee is also informed of any
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44 412 protocol changes by the clinical trial research unit.
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48
49 413 The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions are
50
51 414 used for Adverse Event (AE), Adverse Reaction (AR), Unexpected Adverse Reaction (UAR),
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53 415 Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected
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55 416 Serious Adverse Reaction (SUSAR).
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59 417 Depending on the nature of the event the reporting procedures below are followed:
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3 418 1. Serious adverse events occurring up to 30 days after randomisation are reported through
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6 419 a Serious Adverse Event Form (if serious) or in the 30 day/discharge case record forms (CRF)
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8 420 if they are a notable event (Positive PCR in CSF at 2nd lumbar puncture, gastrointestinal bleed,
9
10 421 hyperglycaemia requiring change in medical management, opportunistic infections,
11
12 422 unexpected/severe neuropsychiatric events).

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14
15
16 423 2. Serious adverse events occurring after 30 days from randomisation are monitored through
17
18 424 reporting in the CRFs with safety data collected in the 26 week and 78-week CRFs if serious.

19
20
21 425 The research investigator at each study site (or designated other) assesses all adverse events
22
23 426 for seriousness, causality and severity. The Chief Investigator (or designated other) assesses
24
25 427 all adverse drug reactions for expectedness from known side effects of the use of
26
27 428 Dexamethasone.⁴⁴ All serious ARs, AEs and SUSARs occurring up to 30 days from
28
29 429 randomisation (apart from death unless the investigator suspects causality) require reporting
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31 430 to the clinical trials unit, within 24 hours of the site becoming aware of the event. In the case
32
33 431 of death of a patient causality will be assessed by the trial steering committee.

34
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36 432 The clinical trials unit will notify the Medicines and Healthcare products Regulatory Agency
37
38 433 and main research ethics committee of all SUSARs that occur during the study according to
39
40 434 the following timelines; fatal and life-threatening within 7 days of notification and non-life
41
42 435 threatening within 15 days. All investigators are informed of all SUSARs occurring throughout
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44 436 the study.

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47 437 SAEs occurring after 30 days from randomisation are monitored by the clinical trials unit via
48
49 438 the 26 week and 78week CRFs. These CRFs need to be received at the clinical trials research
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51 439 unit by 4 weeks after the 26 and 6 weeks after 78week time points.
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3 440 Safety data is provided to the IDSMC, who are responsible for safeguarding the interests of
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6 441 trial participants and assessing the safety of the interventions during the trial; the IDSMC
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8 442 ensures action is taken as needed should they become aware of trends in reported AEs that
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11 443 raise safety concerns.

12 13 444 **Trial Funding and Financial Arrangements**

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18 446 Contractual agreements are in place between the Sponsor and collaborating centres that
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20
21 447 describe financial arrangements. Trial participants are not paid to participate in the trial but
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24 448 are paid travel expenses for the follow up visits, estimated at £50 per visit. Payments to sites
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26 449 are made per site initiation but the bulk of payments are made per patient recruitment. Sites
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28 450 receive payment for: clinical time oversight, research nurse time, administrative support,
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31 451 magnetic resonance imaging scanning and pharmacy oversight.

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33 452

34 35 453 **Patient and public involvement**

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38 454 The Encephalitis Society was consulted and provided advice on the design of the trial and the
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41 455 difficulties participants and their families will likely encounter. The Chief Executive of The
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43 456 Encephalitis Society is a co-applicant on the grant application and a co-author on this paper.

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48 458 The Encephalitis Society has also provided patient representatives at our trial steering
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51 459 committee and assisted in the production and dissemination of trial promotional materials.

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53 460 The Encephalitis Society will drive forward publication and dissemination of the trial findings
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56 461 among lay, therapeutic and health professionals through the use of web materials,
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58 462 newsletters and guides as well as at conferences and seminars in relation to encephalitis and
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3 463 related fields. All patients and their family/carers will be acknowledged in any outputs from
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6 464 the trial. We also work with The Encephalitis Society on a programme
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8 465 of teaching events and produce guides for healthcare professionals and lay people.
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10 466 In instances where trial participants and their families have ongoing difficulties the central
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12
13 467 study team seek help for them through the Encephalitis Society and appropriate specialists
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15 468 for further assistance.
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22 23 471 **Ethics and Dissemination**

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28 473 The trial falls within the remit of the EU Directive 2001/20/EC, transposed into UK law as the
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31 474 UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations
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34 475 2004 as amended. This trial is registered with the MHRA and granted Clinical Trial
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36 476 Authorisation (CTA). The EUDRACT number for CTA reference is 2015-001609-16. Ethical
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39 477 approval has been obtained from a multi-centre research ethics committee familiar with the
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41 478 principals of the Mental Capacity Act 2005 guidance for sites in England and Wales and the
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43 479 Adults with Incapacity Act 2008 for sites in Scotland as the principals are relevant to a clinical
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45
46 480 trial of investigational medicinal products (CTIMP). Clinical Research Governance approval
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48 481 was given through the Sponsor, The University of Liverpool. The trial protocol was approved
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50
51 482 by a National Research Ethics Service Committee reference is 2015-001609-16 (Attained
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53 483 31/03/2016) and underwent independent review at the Research and Development offices
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56 484 at participating sites. This study abides by the principles of the World Medical Association
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58 485 Declaration of Helsinki (1964) and Tokyo (1975), Venice (1983), Hong Kong (1989) and South
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3 486 Africa (1996). Due to the nature of this trial it also abides by the Medicine for Human Use
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6 487 (Clinical Trials) regulations 2004 (S.I.2004:1031) and all following amendments which are
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8 488 incorporated into UK law.
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10 489

13 490 **Informed Consent Process**

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18 492 In obtaining and documenting informed consent, the investigators adhere to National
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20 493 Institute for Health Research (NIHR) Good Clinical Practice (GCP) guidelines and the ethical
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23 494 principles derived from the Declaration of Helsinki. Staff delegated by the principal
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25 495 investigator and appropriately trained with experience in obtaining informed consent, discuss
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27
28 496 the objectives, risks and inconveniences of the trial and the conditions under which it is to be
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30 497 conducted with the patient or if the patient lacks capacity with a legal or professional
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33 498 representative. Trial information documents and points of contact for further information are
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35 499 provided and the potential participants are given adequate time to consider their
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37 500 decision(supplementary file 2).
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42 502 As this is a CTIMP, the clinical trial regulations for incapacitated adults are followed
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44 503 (Medicines for Human Use Clinical Trial Regulations 2004 and amendments). When a legal
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47 504 representative has given consent for a patient to participate in the trial and the patient
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50 505 subsequently regains capacity, the research team will provide the patient information sheet
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52 506 and request consent from the participant. Patients are allowed to withdraw from the study
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55 507 at any point and may request withdrawal of their data collected until this point. Prospective
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57 508 consent can also be obtained prior to a positive PCR result so participants may have adequate
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59 509 time for contemplation.
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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.

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519 **Data Capture Methods**

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Data is 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 is 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.

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

532 Patients' anonymised and labelled neuroimaging data are put on to discs at site and sent to
533 the clinical trials research unit; the images can also be transferred via the Image Exchange

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3 534 Portal in an encrypted manner. The final dataset will be solely accessible to the central study
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6 535 team at the University of Liverpool for analysis and write up.
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10 537 **Dissemination**

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15 539 The results of the DexEnceph trial will be published in a high impact journal in a timely manner
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18 540 to present the findings to front-line clinicians. They will be presented at the annual conference
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20 541 organised by the Encephalitis Society and at other meetings. Authorship of the final papers
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22 542 will be determined in accordance with the international committee of medical journal editors'
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24
25 543 guidelines. The investigators will be involved in the preparation and drafting of the
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28 544 manuscripts. There is no intended use of professional writers.
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39 549 **Discussion**

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45 551 This protocol describes the design of a randomised controlled trial to demonstrate the utility
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48 552 of using dexamethasone in the management of individuals with HSV encephalitis. HSV
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50 553 encephalitis is a rare sporadic acute disease, and the trial has been designed to take this
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53 554 challenge into account, along with the practicalities of running the trial in a UK National Health
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55 555 Service setting. In particular lessons were learnt from a previous similar European study, the
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57 556 German trial of Aciclovir and Corticosteroids in Herpes simplex virus Encephalitis (GACHE
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60 557 trial), which was stopped early because of recruitment difficulties. Recruitment to the GACHE

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3 558 trial necessitated patients had focal neurological signs of no longer than five days prior to
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6 559 admission, whilst DexEnceph has less stringent criteria and reflects the diverse ways in which
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8 560 HSV encephalitis may present. DexEnceph has been designed to be both practical and
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11 561 pragmatic, in that patients must be recruited within 7 days of the PCR result becoming
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13 562 available. This allows for occasions where it may take longer to get the PCR performed, and
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15 563 also allows time for patients admitted to district general hospitals, which may not be study
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17 564 centres, to be transferred to larger hospitals which are. DexEnceph also has the advantage in
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20 565 that its recruitment projections were based on preliminary data garnered from the ENCEPH-
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22 566 UK NIHR program (www.encephuk.org) and from a multicentre cohort study of encephalitis
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24 567 in England, run by the Health Protection Agency (fore-runner to the Health Protection
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26 568 Agency).⁹ These two studies provided direct information on the number of HSV encephalitis
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28 569 patients presenting to UK hospitals. Our choice of an open label observer-blind study, rather
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30 570 than a placebo-controlled double-blind trial, avoided the logistic challenges of ensuring
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32 571 blinded study drug was available across the large number of centres, necessitated by a rare
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34 572 sporadic disease, which may also have been a factor in the recruitment difficulties
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36 573 experienced by the GACHE trial. We are confident our robust monitoring and trial promotion
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38 574 ensures the majority of eligible patients are recruited. N- methyl-D-aspartic acid (NMDA)
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40 575 receptor antibody encephalitis (which is treated with corticosteroids and other
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42 576 immunomodulatory therapies) is being recognised increasingly as a late complication of HSV
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44 577 encephalitis.^{45,46} DexEnceph may also be able examine whether corticosteroids reduce the
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46 578 incidence of this complication. If there is demonstrable efficacy of corticosteroid in improving
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48 579 neuropsychological, imaging and quality of life outcomes, without compromising patient
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50 580 safety the results will be far reaching.
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56 582 **Collaboration with France**
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9 583 Because we recognised from the start that there may be difficulties keeping to recruitment
10 584 targets in the DexEnceph study, we worked with colleagues in France to develop a parallel
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12 585 French study (DexEnceph-France). This follows the UK DexEnceph protocol as closely as
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16 586 possible, whilst being pragmatic about the constraints of a different country's health care
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18 587 system. The French trial is based in 10 hospitals with the lead centre being Grenoble Alpes
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21 588 University Hospital and the aim of recruiting 30 patients.

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24 589 The intention is for the two trials to be analysed separately, with the option of also results
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26 590 also combining them into an overall analysis which will give additional power to detect a
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28 591 treatment effect.
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40 596 **Trial status**
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43 597 The trial has been open across the UK since August 2016, and as of July 2019 is open at 45
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45 598 NHS trusts; 71 patients have been randomised (of the total target of 90) meaning that we
46
47 599 have recruited 79% of the patients are recruiting at just over 80% of the target recruitment
48
49 600 rate. The trial was due to complete recruitment later in 2020 with 6 months follow up and 3
50
51 601 months post trial closure for write up. Though recent COVID-19 pandemic has placed
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53 602 difficulties in conducting trials and paused recruitment, the primary outcome has not been
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55
56 603 missed in any existing DexEnceph recruit, this has been achieved by conducting
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3 604 neuropsychology assessment by either telephone or online video discussion, thus avoiding
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6 605 any risk of transmission. DexEnceph-France study, which opened in 2018 has recruited 10
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8 606 patients from 10 sites.
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13 608 If you are interested to find out more information or to see if your trust is involved visit
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15 609 www.dexenceph.org.uk or for more information please email: dexenceph@liverpool.ac.uk.
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30 615 **References**
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11 751 **Authors' Contributions**

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13
14 752 All authors were consulted and inputted into the article, below lists the particular role

15
16 753 within DexEnceph

17
18 754 TW: Clinical research fellow, CF: Clinical research fellow, KD: trials manager, SD: contributor to trial

19
20 755 design and running, MG: Clinical and laboratory biomarkers lead, CH: Neuropsychology researcher,

21
22 756 RT: Trial pharmacist, GB: Trial statistician, AR-H: trial statistician, PM: Neuropsychology lead, KDAs:

23
24 757 Neuroimaging lead, MZ: Virology, LP: Neuroimaging, SK: Neuroimaging, NR: Neuroimaging, EA:

25
26 758 Encephalitis Society Chief Executive advisor, ST: Study co-ordinator France, RK: Clinical lead brain

27
28 759 infections UK, JPS: Principle investigator France, TS: Chief Investigator responsible for the trial

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35 761 **Trial Funding statement**

36
37 762 This trial is funded by the NIHR Efficacy and Mechanism Evaluation Programme for the

38
39 763 Department of Health reference 12/205/28.

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45 765 **Declaration of Interests**

46
47 766 TS is supported by the National Institute for Health Research (NIHR) Health Protection

48
49 767 Research Unit in Emerging and Zoonotic Infections (Grant No. IS-HPU-1112-10117), NIHR

50
51 768 Global Health Research Group on Brain Infections (No. 17/63/110), and the European Union's

52
53 769 Horizon 2020 research and innovation program ZikaPLAN (Preparedness Latin America

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55 770 Network), grant agreement No. 734584.

771 Other authors: non declared

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773 **Data Statement**

774 There are currently no current plans to publish the data, data is available on reasonable request.

775

776 **Word count:** 4900 words

777 **Figure Legends**

778

779 **Figure 1: Schematic design of DexEnceph randomised controlled trial**

780 **Figure 2 : DexEnceph Recruitment poster**

781 **Supplementary file 1: DexEnceph SPIRIT checklist**

782 **Supplementary file 2: DexEnceph Information and Consent form**

783 **Table 1: Time scale for patients Randomised in the DexEnceph study**

784

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	

Procedures	Follow-up Schedule						
	Screening	Baseline	2 weeks	Discharge or Day 30 of admission (whichever is sooner)	26 weeks	78 weeks	Premature Discontinuation
Magnetic resonance imaging (MRI) scan		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 quality of life 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 randomised controlled trial

*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 prior to randomisation, daily for the first 14 days and then weekly until Discharge/30 days (whichever sooner)

(X) – As indicated/appropriate

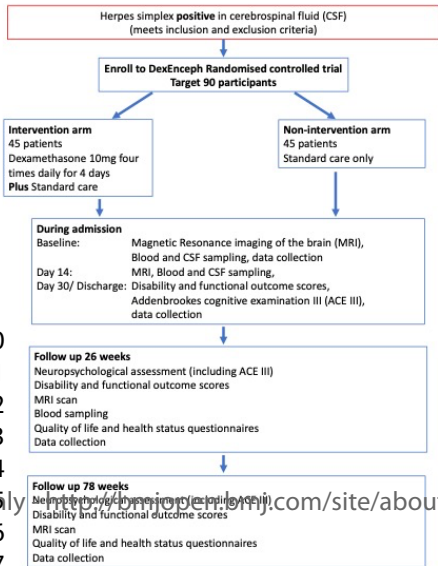
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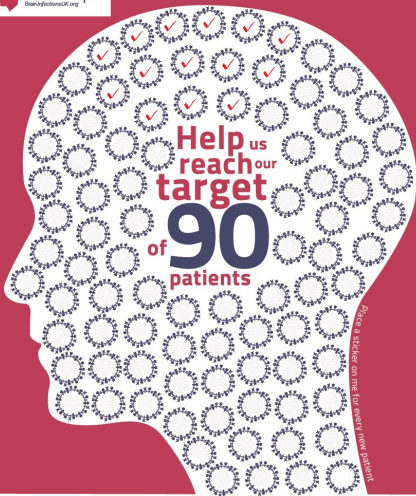
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Figure 1: Schematic Design of DexEnceph randomised controlled trial





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National Institute for Health Research



A Randomised Controlled Trial
Dexamethasone
in Herpes Simplex Virus Encephalitis

Hotline 0300 008 0007
Landline 0151 794 9767

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dexenceph@liverpool.ac.uk

SPIRIT checklist for protocol of the DexEnceph clinical trial.

	Reporting Item	Page Number
Administrative information		
Title	#1 Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3 Date and version identifier	3
Funding	#4 Sources and types of financial, material, and other support	34
Roles and responsibilities: contributorship	#5a Names, affiliations, and roles of protocol contributors	4-5
Roles and responsibilities: sponsor contact information	#5b Name and contact information for the trial sponsor	1, 5
Roles and responsibilities: sponsor and funder	#5c Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	33-34

1	Roles and	#5d	Composition, roles, and responsibilities of the	19-21
2	responsibilities:		coordinating centre, steering committee, endpoint	
3	committees		adjudication committee, data management team, and	
4			other individuals or groups overseeing the trial, if	
5			applicable (see Item 21a for data monitoring committee)	
6				
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8				
9	Introduction			
10				
11				
12	Background and	#6a	Description of research question and justification for	6-9
13	rationale		undertaking the trial, including summary of relevant	
14			studies (published and unpublished) examining benefits	
15			and harms for each intervention	
16				
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18				
19	Background and	#6b	Explanation for choice of comparators	6-9
20	rationale: choice of			
21	comparators			
22				
23				
24	Objectives	#7	Specific objectives or hypotheses	8-9
25				
26				
27	Trial design	#8	Description of trial design including type of trial (eg,	8
28			parallel group, crossover, factorial, single group),	
29			allocation ratio, and framework (eg, superiority,	
30			equivalence, non-inferiority, exploratory)	
31				
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33				
34	Methods:			
35	Participants,			
36	interventions, and			
37	outcomes			
38				
39				
40				
41	Study setting	#9	Description of study settings (eg, community clinic,	9
42			academic hospital) and list of countries where data will	
43			be collected. Reference to where list of study sites can	
44			be obtained	
45				
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47				
48	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	9-11
49			applicable, eligibility criteria for study centres and	
50			individuals who will perform the interventions (eg,	
51			surgeons, psychotherapists)	
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54				
55	Interventions:	#11a	Interventions for each group with sufficient detail to allow	11-12
56	description		replication, including how and when they will be	
57			administered	
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1	Interventions:	#11b	Criteria for discontinuing or modifying allocated	11-12, 20-
2	modifications		interventions for a given trial participant (eg, drug dose	21
3			change in response to harms, participant request, or	
4			improving / worsening disease)	
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8	Interventions:	#11c	Strategies to improve adherence to intervention	12, 18,
9	adherence		protocols, and any procedures for monitoring adherence	
10			(eg, drug tablet return; laboratory tests)	
11				
12				
13	Interventions:	#11d	Relevant concomitant care and interventions that are	11-12
14	concomitant care		permitted or prohibited during the trial	
15				
16				
17	Outcomes	#12	Primary, secondary, and other outcomes, including the	13-15
18			specific measurement variable (eg, systolic blood	
19			pressure), analysis metric (eg, change from baseline,	
20			final value, time to event), method of aggregation (eg,	
21			median, proportion), and time point for each outcome.	
22			Explanation of the clinical relevance of chosen efficacy	
23			and harm outcomes is strongly recommended	
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25				
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28				
29	Participant timeline	#13	Time schedule of enrolment, interventions (including any	Figure 1,
30			run-ins and washouts), assessments, and visits for	Table 1
31			participants. A schematic diagram is highly	
32			recommended (see Figure)	
33				
34				
35				
36	Sample size	#14	Estimated number of participants needed to achieve	16-18
37			study objectives and how it was determined, including	
38			clinical and statistical assumptions supporting any	
39			sample size calculations	
40				
41				
42				
43	Recruitment	#15	Strategies for achieving adequate participant enrolment	18-19
44			to reach target sample size	
45				
46				
47	Methods:			
48	Assignment of			
49	interventions (for			
50	controlled trials)			
51				
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54	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	15-16
55	generation		computer-generated random numbers), and list of any	
56			factors for stratification. To reduce predictability of a	
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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

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7	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, 15-16
8	concealment		central telephone; sequentially numbered, opaque,
9	mechanism		sealed envelopes), describing any steps to conceal the
10			sequence until interventions are assigned
11			
12			
13			
14	Allocation:	#16c	Who will generate the allocation sequence, who will enrol 15-16
15	implementation		participants, and who will assign participants to
16			interventions
17			
18			
19			
20	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, 15-16
21			trial participants, care providers, outcome assessors,
22			data analysts), and how
23			
24			
25	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is 16
26	emergency unblinding		permissible, and procedure for revealing a participant's
27			allocated intervention during the trial
28			
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30			
31	Methods: Data		
32	collection,		
33	management, and		
34	analysis		
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38	Data collection plan	#18a	Plans for assessment and collection of outcome, 16-18,
39			baseline, and other trial data, including any related
40			processes to promote data quality (eg, duplicate
41			measurements, training of assessors) and a description
42			of study instruments (eg, questionnaires, laboratory
43			tests) along with their reliability and validity, if known.
44			Reference to where data collection forms can be found, if
45			not in the protocol
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51	Data collection plan:	#18b	Plans to promote participant retention and complete 18-19
52	retention		follow-up, including list of any outcome data to be
53			collected for participants who discontinue or deviate from
54			intervention protocols
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58	Data management	#19	Plans for data entry, coding, security, and storage, 24
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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

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7	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
8			16-18
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14	Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
15			17-18
16			
17			
18	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)
19			17-18
20			
21			
22			
23			
24			
25	Methods: Monitoring		
26			
27			
28	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
29			17, 19-21
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39	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
40			19-21
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46	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
47			19-21
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53	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
54			19-21
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Ethics and dissemination

1	Ethics and			
2	dissemination			
3				
4				
5	Research ethics	#24	Plans for seeking research ethics committee /	22
6	approval		institutional review board (REC / IRB) approval	
7				
8				
9	Protocol amendments	#25	Plans for communicating important protocol modifications	22
10			(eg, changes to eligibility criteria, outcomes, analyses) to	
11			relevant parties (eg, investigators, REC / IRBs, trial	
12			participants, trial registries, journals, regulators)	
13				
14				
15				
16	Consent or assent	#26a	Who will obtain informed consent or assent from potential	23
17			trial participants or authorised surrogates, and how (see	
18			Item 32)	
19				
20				
21	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
22	ancillary studies		participant data and biological specimens in ancillary	
23			studies, if applicable	
24				
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26				
27	Confidentiality	#27	How personal information about potential and enrolled	24
28			participants will be collected, shared, and maintained in	
29			order to protect confidentiality before, during, and after	
30			the trial	
31				
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34	Declaration of	#28	Financial and other competing interests for principal	34
35	interests		investigators for the overall trial and each study site	
36				
37				
38	Data access	#29	Statement of who will have access to the final trial	34
39			dataset, and disclosure of contractual agreements that	
40			limit such access for investigators	
41				
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43				
44	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for	19,22
45	care		compensation to those who suffer harm from trial	
46			participation	
47				
48				
49	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	21,22
50	trial results		results to participants, healthcare professionals, the	
51			public, and other relevant groups (eg, via publication,	
52			reporting in results databases, or other data sharing	
53			arrangements), including any publication restrictions	
54				
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58	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	25
59				
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1	authorship	professional writers	
2			
3	Dissemination policy:	#31c Plans, if any, for granting public access to the full	34
4	reproducible research	protocol, participant-level dataset, and statistical code	
5			
6	Appendices		
7			
8			
9	Informed consent	#32 Model consent form and other related documentation	Appendix
10	materials	given to participants and authorised surrogates	1
11			
12			
13	Biological specimens	#33 Plans for collection, laboratory evaluation, and storage of	NA
14		biological specimens for genetic or molecular analysis in	
15		the current trial and for future use in ancillary studies, if	
16		applicable	
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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?

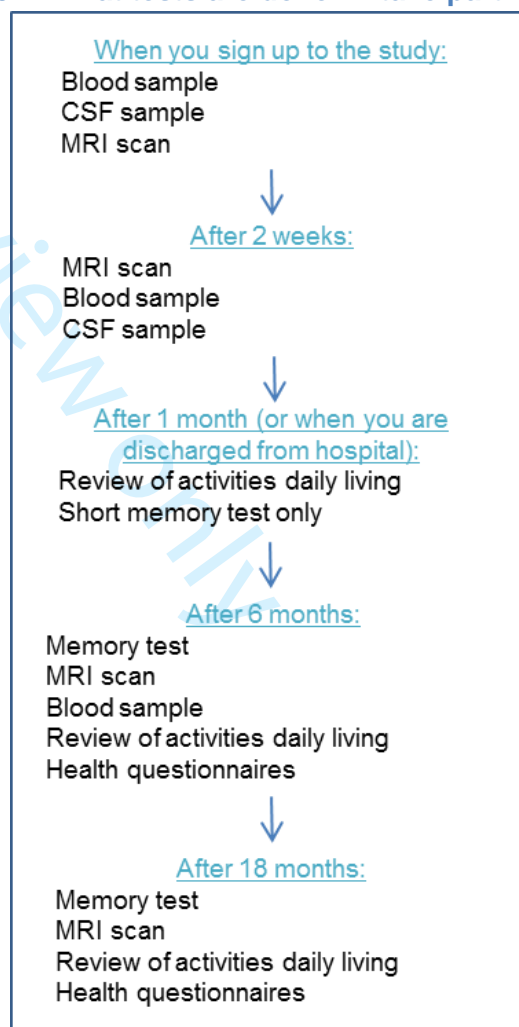
All patients in the study will receive aciclovir. This is standard treatment for HSV encephalitis.

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?



All the tests done when you sign up to the study and the CSF tests after 2 weeks will

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.

Other things to consider

14. Do I have to take part?

No, taking part is voluntary. If you agree, we will ask you to sign a consent form.

If you agree to take part you are free to change your mind at any time, without giving a reason. You may decide to have only some tests in the study without having to drop out of the study altogether. This will not affect the standard of care you receive.

If you withdraw from the study we will stop collecting data. We will ask you if we can use the information and samples we have gathered up to the point that you withdraw.

15. What happens if there is a problem?

If you have any concerns about any part of this study, please speak with your hospital doctor (consultant) or one of your research team.

If you remain unhappy and wish to complain formally you can do this using the NHS Complaints Procedure. You can get information on how to do this from the Patients Advice Liaison department (PALS) in your hospital.

If you suffer harm from taking part in this study, there are no special compensation arrangements. If harm occurs to you and it is due to someone's negligence, you may have grounds for legal action for compensation against the NHS hospital where you are being treated but you may have to pay your legal costs.

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.

Benefits and risks

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

1
2
3 may also benefit from the increased
4 monitoring of having extra scans and
5 memory tests.

6 The information we get from this study
7 may benefit patients in the future.
8
9

10 **18. What are the possible**
11 **disadvantages and risks of taking**
12 **part?**
13

14 The disadvantage in taking part in this
15 study may be the risk of having the side-
16 effects of dexamethasone listed in
17 question 13 (this will not be the case if you
18 are in the group that does not have
19 dexamethasone).
20

21 There is the inconvenience of having
22 the dexamethasone through the drip when
23 you are in hospital. Once you leave
24 hospital there is the inconvenience of
25 travelling to hospital for 2 scans, having
26 the memory tests and completing
27 questionnaires.
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30
31 **Contact details**
32

33 If you have any questions about this study,
34 then please contact the study team
35 members:
36
37

38 Principal Investigator (Doctor leading this
39 study in your hospital):

40 Name: _____
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45 Telephone: _____
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48 Research Nurse:

49 Name: _____
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54 Telephone: _____
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59 Name of your Hospital: _____
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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:

Centre Code:

Name of Principal Investigator:

Study Number:

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

YES**NO**

1. I confirm I have read and understand the Information Leaflet (dated DD/MM/YY) for the above study, and have had the opportunity to ask questions and have these answered satisfactorily.	INITIAL IF YES	INITIAL IF NO
2. I agree to take part in this study.	INITIAL IF YES	INITIAL IF NO
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.	INITIAL IF YES	INITIAL IF NO
4. I agree for my consent form and contact details to be passed to the University of Liverpool for the administration of the study.	INITIAL IF YES	INITIAL IF NO
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.	INITIAL IF YES	INITIAL IF NO
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.	INITIAL IF YES	INITIAL IF NO

7. I agree to have MRI scans as part of the trial.

INITIAL IF YES	INITIAL IF NO
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8. I agree for my GP and hospital doctors to be informed if the scan picks up something unexpected.

INITIAL IF YES	INITIAL IF NO
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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.

INITIAL IF YES	INITIAL IF NO
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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).

INITIAL IF YES	INITIAL IF NO
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11. I agree for my GP to be informed I am taking part in this study.

INITIAL IF YES	INITIAL IF NO
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Name of Participant
(Please print)

Signature

Date (DD/MM/YYYY)

Researcher*

Signature

Date (DD/MM/YYYY)

*** 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).