ENCEPH-IG Trial

Intravenous Immunoglobulin in Autoimmune Encephalitis in Adults

Participant Information Sheet v4.0 28.04.2022

You are being invited to take part in a research trial on autoimmune encephalitis. This condition 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 trial would involve and answering any questions.

TRIAL SUMMARY

- This is a trial for patients with autoimmune encephalitis (swelling of the brain) caused by the body's own immune system attacking the brain in error.
- Encephalitis can make you confused, drowsy, behave out of character, affect your memory and mood, or may cause you to have seizures (fits).
- Autoimmune encephalitis is usually treated with steroids to reduce the inflammation and swelling in the brain.
- If patients are not improving, a protein product (immunoglobulin, sometimes abbreviated to IVIG) is given by drip (inserted into your vein), usually after a few weeks.
- We want to find out if early treatment with intravenous immunoglobulin (IVIG) leads to an improved recovery.
- In the trial there will be two groups of patients, one that receives IVIG and one that does not but receives an inactive version (placebo). Both groups will receive steroid treatment.
- The treatment will be given for 5 days in hospital.
- Both groups will have the same investigations to see if IVIG has been of benefit.
- IVIG is a drug that is currently used for autoimmune conditions. Like all medicines, IVIG has side-effects, some of which can be serious. We will explain further in this leaflet what these are.
- You will be asked to donate some blood and cerebral spinal fluid samples, and to complete some questionnaires about your recovery
- Throughout the trial, doctors will also assess your recovery by looking at your clinical condition.

WE WOULD LIKE TO INVITE YOU TO TAKE PART IN A RESEARCH TRIAL

- 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 information sheet and ask you to sign a consent form.

There are two sections to this information sheet:

Section 1: Tells you the purpose of the trial and what will happen to you if you take part

Section 2: Gives you more detailed information about the conduct of the trial

PART 1. PURPOSE OF THE TRIAL AND WHAT WILL HAPPEN

WHAT IS AUTOIMMUNE ENCEPHALITIS?

Autoimmune encephalitis is inflammation and swelling of the brain caused by the body's own immune system attacking the brain in error. Encephalitis can make you confused, drowsy, behave out of character, affect your memory and mood or may cause you to have seizures (fits). Some patients recover completely, but some have ongoing memory loss and other problems.

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

WHY ARE WE DOING THIS TRIAL?

Currently, IVIG is given to about half of the patients with autoimmune encephalitis. Some doctors think that if IVIG is used from the start of treatment, patients may recover more quickly and have better outcomes. However, as with all drugs, IVIG has side effects. We are doing this trial to find out whether, in patients with autoimmune encephalitis, early treatment with IVIG leads to earlier recovery and/or improves outcomes for patients. We also want to understand more about autoimmune encephalitis and how IVIG affects the disease process.

WHY HAVE I BEEN INVITED TO TAKE PART?

You have been invited to take part because your doctor has diagnosed you with autoimmune encephalitis or thinks autoimmune encephalitis is the most likely cause of your illness. The trial will involve 356 adults with autoimmune encephalitis from about 50 hospitals across the UK.

DO I HAVE TO TAKE PART?

No. It is up to you if you decide to take part in this trial. Participation is entirely voluntary. A member of the team will describe the trial and go through this information sheet. If you decide to take part, you will be given the information sheet to keep and you will be asked to sign a consent form. Please feel free to talk about the trial with your family, friends or others before you decide to take part.

You are free to withdraw from the trial at any time, without giving a reason. A decision to withdraw at any time or a decision not to take part will not affect the standard of medical care you receive.

WHAT WILL HAPPEN TO ME DURING THE TRIAL?

All patients in the trial will receive steroid treatment. This is standard treatment for autoimmune encephalitis. In addition, if you decide to take part in the trial, you may be given a short course of IVIG or a product which looks identical (a placebo), but which does not contain the active protein. This will be decided at random by a computer. This is so that neither you, your doctor, nor the research team, can choose whether you receive IVIG or not. Neither you nor your doctor will know whether you have received the IVIG or not during the trial.

Half of the people in the trial will receive IVIG and half will receive the placebo. We use a placebo in trials like this so we can accurately see what effects are caused by the drug and what effects happen by chance or are unrelated to the drug. The placebo in this trial will be made from a salt and water (saline) solution so that it looks like the trial medication but will not contain the active ingredient. The trial treatment (IVIG or placebo) will be given by drip once a day for 5 days.

WHAT TESTS WILL BE DONE IF I TAKE PART?

SAMPLES

As part of your medical care your doctor will already have done a lumbar puncture (LP) to take a sample of fluid. This fluid is called CSF (cerebrospinal fluid). The doctor uses a small needle to take a sample from the lower part of the back. If you agree to take part in the trial the CSF sample will also be used for the trial and would be repeated 2 weeks later. The amount of fluid we take is about 5mls (1 teaspoon).

We will also do blood tests as part of the trial. The doctor or nurse will take a blood sample of 21mls (4 teaspoons) when you join the trial, and at 2 weeks, and again 3 months after you joined.

All the samples will be taken while you are still in hospital or when you come back to hospital for clinical assessments. You will also be given the option to donate one additional CSF sample and 2 additional blood samples, or any combination of the two, for research purposes. Should you consent to provide additional samples for research, we will ask for blood and CSF samples at 2 weeks and for you to donate a blood sample at 3 months when you attend your hospital visit. The samples will be used to measure any changes in your immune system and to explore how IVIG may work to change recovery time from the illness.

When you join the study	At 2 weeks	Every fortnight	At 3 months	Monthly	At 12 months
• clinical assessment • assessment of recovery • CSF samples • blood test	• clinical assessment • assessment of recovery • CSF samples • blood test	• assessment of recovery	• clinical assessment • assessment of recovery • blood test	• assessment of recovery (if ongoing)	• clinical assessment • assessment of recovery (if ongoing)

ASSESSMENTS

Clinical assessments will include your current clinical condition carried out by a member of the hospital care team, and an assessment of your recovery (Glasgow Outcome Scale – Extended or sometimes abbreviated to GOSE) which is completed by you or someone else if you are not able to. A baseline assessment of your recovery will be carried out when you join the trial and then every 2 weeks until 3 months after joining. This assessment will be repeated regularly for one year after you join. There will be two additional assessments when you reach key recovery milestones. Some participants will be asked to undergo annual assessments until the end of the trial. You will need to complete these online assessments at home once you leave the hospital. To remind you to complete the questionnaires, we will be collecting your contact details including your name, email address, telephone and mobile numbers, and address so that we can send you a link to the questionnaire either by email or text message. We may also send out a letter asking about your recovery if we can't get a hold of you. We may also call you to ask you to complete the questionnaire the phone. Your personal details will be securely stored on a password protected database and will only be accessed by the trial team at the Centre for Trials Research.

In addition, some participants will be asked to complete questionnaires about their general health and wellbeing. A member of the trial team will be available to assist you. We will ask you to complete these questionnaires at 3 months after you join the trial, and then 12 months after you joined. Some participants will be asked to complete them annually until the end of the trial.

Some participants will be asked to undergo a series of tasks (neuropsychology assessments) that measure different brain functions for example, memory, planning, and language skills one year after joining the trial.

The trial will not require additional hospital visits over and above the standard of care. The questionnaires are not part of the standard of care. You will be asked to complete them at either your clinical follow up visit or we will send them to you.

We will also be asking someone close to you to act as a study partner. We will collect their contact details including their name, email address and telephone number and with your

permission we will contact them in the event that we are not able to contact you after you have been discharged from hospital. We may also ask them to complete the GOSE questionnaire, on your behalf if you are unable to. The GOSE, and other questionnaires are only available in English. The study partner can also help you complete the GOSE or any of the other questionnaires if there are any difficulties with reading or understanding the questions.

We will also ask your permission to use information in your health records after the trial to look at your longer-term recovery. With your consent we will also share your date of birth, full name, and NHS number with NHS Digital (the group that manages electronic patient records) or an equivalent medical data provider, so we can collect data on how you are recovering and if you are suffering any lasting consequences from the autoimmune encephalitis over the longer term without having to ask you to come back to the hospital.

WHAT WILL HAPPEN TO THE SAMPLES COLLECTED?

All samples will be taken at your hospital and then transported to the University of Liverpool, University of Oxford, and University College London laboratories supporting the trial. These samples will be analysed to tell us more about the disease and how the drug is working. You will not be told the results of any of the tests performed on your samples.

The samples will not have any of your personal information written on them but they may be linked back to your clinical data. Both your samples and clinical data will be identified by your unique trial reference number only. They will be stored in a secure building.

Some of your samples may be left over following this research. We will ask you if they can be stored and used for future research in combination with your clinical data. Your samples and clinical data may be shared with researchers in the UK and abroad, including academic institutions or commercial companies. If you agree, the samples will be stored securely in a biobank approved by the University of Liverpool (Trial Sponsor). The samples will be identified by a unique code and your personal details will not be released. Care will be taken by Cardiff University and the University of Liverpool to ensure that data may not be used to identify you. If you don't want your samples stored for future research they will be destroyed at the end of the trial.

WILL ANY GENETIC TESTS BE DONE?

We will be collecting DNA from blood samples to do genetic tests to look at any similarity in the genes of patients with autoimmune encephalitis and how those genes might affect patient outcomes. You will not be told the results of any of the tests performed on your

samples. The results of these tests may be published in scientific journals but you will not be identified from these.

WHAT WILL THE ASSESSMENTS AND QUESTIONNAIRES INVOLVE?

The assessment of recovery (Glasgow Outcome Scale – Extended) has been used in many previous studies. It can be completed by telephone or postal questionnaires, and for this trial we have converted it to a web-based format. It should take about 5-10 minutes to complete.

The questionnaires ask about your general health and wellbeing and have been used in many previous studies. The questionnaires you will be asked to complete at 3 months after you enter the trial will take about 10-15 minutes to complete. If you are one of the ones asked to complete questionnaires and the neuropsychological tasks 12 month after you enter the trial, they will take about 2 hours to complete. Ideally, these will be completed in one session but if necessary, you can complete them over several sessions.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

There is no guarantee that this trial will help you. You may benefit from receiving IVIG, however we will not know this until the end of the trial.

The information we get from this trial will help us understand more about autoimmune encephalitis and IVIG as a treatment for it. We hope that this will benefit patients in the future.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?

The disadvantage in taking part in this trial may be the risk of having the side-effects of IVIG (this will not be the case if you are in the group that does not have IVIG).

The adverse events of IVIG are well-known and may be serious. Normally these reactions will occur within 72 hours of your first dose. We will monitor carefully for these.

Common Side Effects (affecting somewhere between 1/10 and 1/100 people):

- Allergic reactions, like rashes, swelling, itchy skin, redness, and hives
- Damage to red and white blood cells, and platelets. Symptoms include very pale or yellow skin and eyes, fever, and weakness
- Abnormal movements, like muscle spasms, stiffness or weakness
- Nausea, vomiting, diarrhoea
- Dizziness
- Headaches
- Changes in blood pressure
- Fatigue
- Difficulty breathing

- Pain, typically in the back, neck, face, chest, in the abdomen, and around the injection site

Uncommon side effects (affecting somewhere between 1/100 and 1/1000 people)

- Inflammation of the meninges, or membrane surrounding the brain and spinal cord. This can feel like a headache, stiffness in the neck, and becoming sensitive to light.
- Blood clots. Symptoms include swelling redness, and depending where the blood clot is, breathlessness, or a tight chest
- Abnormal heart rhythms
- Seizures
- Tremors
- Issues with your kidneys. Symptoms include water retention,

Your Trial Doctor may well be able to prescribe medication to ease these effects to make you more comfortable. In exceptional circumstances your Trial Doctor may decide to stop the treatment.

Please tell your research nurse or doctor about any prescribed or other medications you are taking at any stage of the trial as there are some restrictions regarding other medications which might make you unsuitable for this trial. Your Trial Doctor will discuss these with you.

There is the inconvenience of having the IVIG through the drip when you are in hospital. There is also the discomfort of having a lumbar puncture to collect the CSF sample and having additional blood tests. The most common side effect of a lumbar puncture is a headache, but it can normally be treated with painkillers and staying well hydrated. Once you leave hospital there will be travelling to hospital for assessments, undergoing the clinical assessments, and completing questionnaires.

If you are pregnant or breastfeeding there are risks associated with steroid treatments. Steroids are routinely given during pregnancy and to those who are breastfeeding but there is a small chance that they may negatively impact your baby's development or be passed to your baby through your breast milk. During the trial, your baby's development and health will be closely monitored. You should make sure to discuss the risks and benefits to joining the trial with the treating physician before you make a decision.

WILL I BE PAID FOR TAKING PART IN THE TRIAL?

You will not be paid for taking part in the trial.

This completes Part 1 of the Information Sheet

If the information in Part 1 has interested you and you are considering taking part, please continue to read the additional information in part 2 before making any decision.

PART 2. DETAILED INFORMATION ON TRIAL CONDUCT

WHAT WILL HAPPEN IF I DON'T WANT TO CARRY ON TAKING PART IN THE TRIAL?

Taking part in the trial is entirely voluntary. If you decide to take part you may withdraw from the trial, at any time, without affecting the standard of care you receive. You can withdraw from different parts of the trial, like withdrawing from trial treatment, or from provision of samples for future research, or from provision of questionnaires only. Your care team will go through these options with you.

If you wish to stop taking part in the trial completely, we may need to see you one last time for an assessment and tests. This will be for your own safety. If you are taking steroids, your trial doctor will discuss this treatment with you. **You must not suddenly stop taking the steroids if you withdraw from this trial**.

If you are suffering a serious reaction to the trial treatment when you decide to stop, we will need to continue to collect information about you for as long as the reaction lasts.

The trial doctor may decide to withdraw you from the trial if he/she feels it is in your best interests or if you have experienced a serious side effect.

Even if you stop taking part in the trial, the information we have recorded about you and the samples you have provided whilst you were in the trial may still be used. You can ask for these to be destroyed but please consider, and perhaps discuss with us, how valuable these are to our research before making your decision.

In some circumstances, it will not be possible to destroy your data for example, if the analysis has already been conducted or if reports/publications have been written. All safety reports will also need to be retained.

It may not be possible to destroy samples and associated data that have already been used for research as we may not be able to identify them after they have been anonymised

WHAT IF RELEVANT NEW INFORMATION BECOMES AVAILABLE?

Sometimes over the course of a research trial, new information about the treatment becomes available. If this happens, your trial doctor will tell you about it as soon as reasonably possible and discuss whether you should continue in the trial. If you decide not to carry on, your trial doctor will make arrangements for your care to continue. If you decide to continue in the trial, they may ask you to sign a new consent form.

WHAT IF THERE IS A PROBLEM AND I WISH TO COMPLAIN?

If you have a concern about any aspect of this trial, you should contact the researchers who will do their best to answer your questions EncephIG@Cardiff.ac.uk and sponsor@liverpool.ac.uk. If you remain unhappy and wish to complain formally, you can do

this by contacting a NHS complaints advocate. Details can be obtained from https://www.nhs.uk/using-the-nhs/about-the-nhs/how-to-complain-to-the-nhs/]

In the event that something does go wrong, and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against University of Liverpool but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

WILL MY TAKING PART BE KEPT CONFIDENTIAL?

All information collected about you will be kept strictly confidential in accordance with applicable Data Protection laws. Once you have been registered onto the trial, you will be assigned a unique trial reference number and this number will be used for the collection and recording of all trial related information to preserve your anonymity. The information collected will be primarily to do with the treatment you receive, any side effects that you have during treatment and your long-term state of health. When completing the GOSE at home we will collect your device's IP address (your device's unique address when connected to a network) to ensure network and information security. However, we will not link your device's IP address to other data which we are collecting. Nor will we analyse the data unless we have specific reason to look at an individual IP address. The personal data collected will be kept separate from any data about your condition, treatment, and recovery. It may become necessary to discuss your condition, recovery, and trial participation with a relative or friend if you are no longer able to make decisions about your continued involvement in the trial.

Information recorded in your medical records may need to be seen by authorised members of the research team (including staff from the trials co-ordination unit), and the sponsor organisation to verify the data collected. In addition, different regulatory bodies such as the Medicines and Healthcare products Regulatory Agency (MHRA) may require access to your medical records to ensure that the trial is being run in accordance with UK law.

All trial data will be kept securely with restricted access.

WILL MY GP BE INFORMED I AM TAKING PART?

If you decide to take part in the trial, with your consent your GP will be notified that you are taking part. We may also contact your GP if we are not able to contact you or your study partner and we have concerns about your wellbeing.

WHAT ARE THE DATA PROTECTION ARRANGEMENTS?

University of Liverpool is the sponsor for this trial based in the United Kingdom. We will be using information from you and your medical records in order to undertake this trial and will act as the data controller for this trial. This means that we are responsible for looking after

your information and using it properly. As part of that, a data protection impact assessment has been done. University of Liverpool and Cardiff University will keep the research data from this trial for 15 years after the trial has finished. After this time, they will destroy all the information they have saved.

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 trial, 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 https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection and https://www.liverpool.ac.uk/legal/data_protection/

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH?

At the end of the trial the results will be analysed and published in recognised medical journals and presented at scientific meetings. You will not be identified in any publication or presentation about the trial. At the end of the trial, you will be able to see a summary of the results here: https://www.cardiff.ac.uk/centre-for-trials-research/research/studies-and-trials/view/enceph-ig.

WHO IS ORGANISING AND FUNDING THE RESEARCH?

This trial is sponsored by University of Liverpool and is being organised and monitored by the Centre for Trials Research at Cardiff University. Funding for the trial has been provided by the National Institute for Health Research.

WHO HAS REVIEWED THE TRIAL?

All research is looked at by an independent group of people, called a Research Ethics Committee to protect your interests. This trial has been reviewed and approved by Wales REC 3.

CONTACT FOR FURTHER INFORMATION

If you have any questions or would like further information about the trial please contact EncephIG@Cardiff.ac.uk or your hospital trial team

<LOCAL SITE CONTACT DETAILS>

Thank you for reading this information and considering taking part in this trial.