ImmunoglobuliN in the Treatment of Encephalitis
The IgNiTE Study

A study testing a new treatment for children with encephalitis.

Parent/Guardian Study Information Booklet

You are invited to take part in this research study. The reason for this study is to find out whether a treatment called intravenous immunoglobulin has any benefit for children with encephalitis.

The study has been funded by the National Institute for Health Research (Efficacy and Mechanism Evaluation programme). The study is being run by the Department of Paediatrics, University of Oxford and will be taking place in up to 40 hospitals across the United Kingdom.

Before you decide whether your child should take part, it is important for you to understand what the study is about and what participation would involve for you and your child. This leaflet describes the study.

Please take time to read the information carefully, and discuss with others if you wish. If anything is unclear or you would like further information please contact the study team (details below).

Thank you for taking the time to consider taking part in the study.

Contact Details

Oxford Vaccine Group
Centre for Clinical Vaccinology and Tropical Medicine (CCVTM)
Churchill Hospital
Old Road, Headington
Oxford. United Kingdom OX3 7LE

Telephone (01865) 611400
Facsimile 01865 289695
Email info@ovg.ox.ac.uk

Why have I been given this leaflet?

You have been given this leaflet because of one of the following reasons:

(a) your child has recently been diagnosed with encephalitis or has symptoms that suggest s/he may have encephalitis, and because s/he is between 6 weeks and 15 years old and is too young to consent to take part in research.
(b) your child has recently been diagnosed with encephalitis or has symptoms that suggest s/he may have encephalitis and is 16 years old but is unable to give consent because s/he is unwell.

What is encephalitis?

Encephalitis means inflammation of the brain and there are lots of different causes. Encephalitis could be caused by an infection (*infectious encephalitis*) or by the body's immune system turning against itself (*immune mediated encephalitis*) by producing proteins that attack the brain called auto-antibodies. Viruses are the most common bugs that cause infectious encephalitis within the United Kingdom, and of these the most commonly identified is the Herpes simplex virus (which causes cold sores). In approximately two thirds of children with encephalitis, the cause is unknown.

The inflammation of the brain that happens in encephalitis is what makes children with the illness unwell. The amount of swelling is different for each child. For many children the brain inflammation resolves and affected children come through the illness with little or no difficulties. In other situations, it can lead to a number of problems including behavioral difficulties, problems with learning, seizures, physical disability and can be life-threatening. It is not possible to tell beforehand what the exact outcome for an affected child will be and some affected children who recover quickly or appear to have made full recovery while in hospital might still experience difficulties months to years later. If you would like more information on encephalitis, you should discuss this with the hospital doctors who are taking care of your child.

Doctors can tell if someone has encephalitis by testing the fluid that covers the brain and spinal cord otherwise called cerebrospinal fluid or CSF. Doctors obtain this fluid by doing a test called lumbar puncture. They can also see if there is any swelling of the brain by taking special pictures called *MRI scans.*

What is this study about?

There is some evidence that a treatment called intravenous immunoglobulin (IVIg) may benefit children with encephalitis. However, the evidence is based on a small number of children and in some cases only studied children with certain types of encephalitis. There are no research studies that have looked at the effect of IVIg when used in a large number of children, regardless of the type of encephalitis that they have. Also, although some doctors may use IVIg to treat children with encephalitis, this is often given late in the illness so we do not know the effect of IVIg when used early after diagnosis.

In this study, we would like to find out whether IVIg can help children with encephalitis get better quicker if given early during the hospital admission. To do this we want to compare the recovery of children who receive IVIg to those who do not. Since children and young people who have been affected by encephalitis but appear to have made good recovery while in hospital could still have difficulties later on due to the illness, it is important that in the study we include those who have recovered very quickly and those who have not.

What is intravenous immunoglobulin (IVIg)?

IVIg is a collection of proteins called antibodies. Antibodies are made by the body's immune system and help to fight infections. IVIg is obtained from blood donations and comes in a liquid form to be given through an intravenous 'drip'. IVIg is approved for use in treating children with certain medical conditions however it is currently not approved for use in children with encephalitis.

What happens in the study?

A summary of what the study will involve is shown in the study timeline at the end of this letter.

We are planning to recruit 308 children from up to 40 hospitals in the United Kingdom. There are several aspects in the study and we have divided these into three main parts: (i) before your child begins in the study (ii) after your child is enrolled in the study and (iii) after study treatment.

Part 1: Before your child begins in the study

1.1 Consent

After reading this information leaflet, you will be given the chance to discuss the study in more detail, including the risks and benefits of your child participating in the study. We will also check that the study is suitable for your child. If you were still happy after the discussions, and your child is eligible to take part, you will be required to sign a consent form. Depending on your child's age, and if they are well enough, s/he would also be required to sign an assent form to say that they agree with your decision for them to take part in the study. If your child is unable to sign an assent form at the same time, s/he will be able to do so at a later time. You will be given a copy of the signed consent and assent form to keep.

The decision for your child to take part in the study is entirely voluntary. You can choose to withdraw your child from the study at any point and this will not affect his/her medical care in any way. Also, if at any point in the study your child wishes not to continue, they would be withdrawn.

1.2 Enrolment

Your child will be enrolled to the study if s/he is eligible and you have signed the consent form, unless your child refuses to assent. This means that from this point, they are included in the study and will be allocated a unique study number. The study number will be used in place of your child's name or any other identifiable information for the entire study duration.

Part 2. After your child is enrolled in the study

We will look at your child's medical notes and also collect the results of investigations that they will have had or will be having. This will include blood, CSF test, brain scan images and reports and EEG reports. An EEG is a special brain wave test that doctors sometimes do for children with encephalitis.

2.1 Randomisation and study treatment

Your child will be allocated to one of two study groups. This will be done by a computer programme and allocation of your child to a study group will be by chance, like tossing a coin. This is so that every child has an equal chance of being allocated to each group. It will not be possible for anyone to influence which group your child is allocated to.

The normal care that your child will receive from the hospital doctors will not change but in addition to this, your child will receive one of two study treatments. The study treatment that your child will be given will depend on what group he/she is allocated to. One group will receive IVIg and the other group will receive a placebo (a 'treatment' that looks like IVIg but has no medical effect for encephalitis). You and your child will not know whether they are having IVIg or placebo. Also, the doctors and nurses will not know this.

Your child will be given two doses of the study treatment, 24-36 hours apart and the first dose must be given early during the admission. The amount of study treatment that your child will be given will be worked out according to his/her weight and each dose will be given slowly over several hours, like a 'drip' into your child's vein using a cannula. Since most children treated for encephalitis require a cannula as part of their normal care, it is unlikely that your child will need to have an extra cannula put in solely for this study.

2.2 Sample collection

For many children taking part in the study, there will be blood and CSF remaining from samples collected as part of their routine care. After all necessary tests have been done, these 'surplus' samples are usually stored in the laboratory for a period of time, after which they are discarded. If you give consent for your child to take part in this study, any of your child's blood or CSF remaining after clinical testing will be studied to understand the body's immune response in encephalitis and to look for autoantibodies in blood and CSF. These tests are for research purposes and are not currently available as standard investigations.

3. After study treatment

Your child will remain in the study for around 12 months after receiving the study treatment. Any other routine appointments that your child may require as part of their routine care will not be affected. During this time, we will be collecting information on your child's health and well-being in the following ways:

3.1 Questionnaires

You will be asked to answer some questions about your child's general health and wellbeing after illness. These are easy to complete and form a very important part of the study. The number of questionnaires that you will have to complete will depend on your child's age.

The questionnaires will be completed at the following time points:

(i) around 4-8 weeks from the time when your child's routine treatment for encephalitis has been completed

(ii) around six months after the study treatment

(iii) around 12 months after the study treatment

The questionnaires that you will complete at the first and third time points above could take up to 90 minutes to complete, while the six month questionnaire could take up to 15 minutes. You will be given contact details of a member of the study team should you need help with completing the questionnaires. You will be provided with pre-paid envelopes to return the questionnaires to the Department of Paediatrics, University of Oxford. If we have not received the questionnaires after a period of time, you will be contacted by a member of the research team to offer help or remind you to return the questionnaires.

3.2 Neuropsychology assessment

Around 12 months after study treatment, all children in the study will be assessed by a child neuropsychologist (an expert whose interest is in understanding how the brain works and how this affects people's behaviours). The assessment will be done at your home and will take up to 90 minutes to complete.

Optional Parts of the Study

There are other aspects of the study that you may be happy for your child to take part in, but if you do not want them to do these you can say no and they can still participate in the main study.

(i) Collection and storage of extra samples

We would like to carry out further tests to improve our understanding of encephalitis, especially how the body responds in encephalitis, and how the study treatment may affect this. We can know this by looking at levels of special proteins and cells in the blood and by looking at which genes are activated ('switched on') and which ones are not ('switched off'). We can also get additional information about encephalitis by looking at the DNA. DNA is like an instruction booklet that tells which characteristics a child is likely to get from their parent. In addition, we would like to test for auto-antibodies and to understand how their levels in the blood and/or CSF change with the study treatment.

In order to do the necessary tests, we would like to obtain extra blood and/or CSF samples from children in the study. These extra samples that are collected solely for the study are called research samples. Providing research samples is an optional part of the study and if you do not want your child to do this that is fine. Please put NO against the relevant question on the consent form.

Most children with encephalitis would have several tests done as part of their routine care. Therefore, if you agree to your child providing research samples, we would ask your child's doctors to take extra amounts of blood and/or CSF at the time of routine testing/lumbar puncture. We might also obtain blood sample by doing extra blood tests only if you agree to this. In order to minimise any distress from any extra blood test, depending on your child's age and their preference (where appropriate), we would use a special cream to help numb the skin around where the blood is taken to make it as comfortable as we can. We will not perform an extra lumbar puncture (and thus additional CSF sampling) solely for the purpose of this study.

(ii) Brain magnetic resonance imaging (MRI) scan

We would like to see whether the study treatment has any effect on the swelling that may have occurred in the brain by performing a brain scan around six months after the study treatment to compare with any previous scans that your child may have had while in hospital.

An MRI scan is harmless and uses magnetic and radio waves to produce detailed pictures of the brain and can take up to 60 minutes. The MRI would be done in hospital. Having a brain scan for the study (research scan) is optional and you do not have to agree to this if you do not want to and your child will still be able to take part in the study.

Sometimes, children with encephalitis may require a follow up brain MRI scan as part of their routine care, after they are discharged from hospital. If this is the case for your child, depending on the timing of the routine scan, your child may not need to have a research scan. However with your consent, we would use your child's routine scan pictures for the study. If this was done in another hospital and you give consent, we will contact the hospital doctors to request transfer of your child's scan pictures to the study team.

If you agree for your child to have a research scan, you will have the chance to discuss what this would involve and any questions you may have before the scan. You would also be asked some questions to make sure that it is safe for your child to have the scan.

During the scan, it is important that your child keeps still or else the pictures will be fuzzy. Sometimes, this may not be possible and your child may be given some medicine called 'anaesthetic' to make them sleep for long enough to help get a clear picture. The anaesthetic may make your child wobbly on their feet. Therefore, if your child requires an anaesthetic, he/she will be monitored for a short while in hospital after the scan. This is to make sure that he/she has completely recovered from the anaesthetic before being allowed home.

All of the scans used in the study will be sent to specialists in London who will interpret the results. Your child's name and personal details will be removed from the scan pictures before we do this.

(**iii**) **Sharing information with your child's hospital doctors/GP**

Your child's confidentiality will be maintained at all times during the study. We may want to obtain information on your child's health from their hospital doctor or GP where this is relevant to the study. For example, if we wanted to find the name and dose of any new medicines that your child may have started after discharge from hospital. We would only do this where you have given your consent. We would therefore require you to inform the study team of any change to your contact details during the study period. With your permission, we may contact your GP and/or child's hospital doctor to obtain your contact details if we have been unable to contact you.

What will happen to any samples my child gives?

Blood and CSF samples obtained in this study will be stored at the hospital where your child was treated and then transferred to the University of Oxford where the necessary tests will be performed. Since all samples will be anonymised prior to the testing the study team will not be able to link results back to your child. Anonymised data and samples may be sent to other laboratories for further investigation and analysis if required, including outside the European Union.

Does my child have to take part in the study?

Taking part in research is voluntary. We will help present the details of the study and answer all your questions so you could make an informed decision. If you give consent for your child to take part, you can withdraw this at any time and this will not affect your child's routine care in any way. Whatever you choose, it's important that you are happy with your decision and it is not the role of the study team to help decide for you. You can also choose to withdraw your child from the study at any point and this is OK.

Why is a placebo being used in the study?

We are doing this so that we can compare the recovery of children who receive IVIg to that of those who do not. The questionnaires may be answered differently if people knew that their child received IVIg treatment and this may bias the results. Therefore, it is very important to make sure that people cannot figure this out by having the placebo which looks the same as IVIg and is generally safe. Also, study staff will not know which treatment your child received until after all the samples have been tested and all the results have been analysed to avoid any bias.

At the very end of the study, when the results have been finalised, we can let you know what treatment your child received if you wish to know. This can take several years.

What are the side effects of the study treatment?

The placebo that is used in the study contains a small amount of albumin, which is a type of protein made by the liver. Like IVIg, albumin is obtained from blood donations and is used to treat children with certain other medical conditions.

Both IVIg and placebo are generally safe. As with most treatments, some side effects or reactions may occur. Most of these are not expected to be significant and are usually short lasting. Some children may feel sick, vomit or have a headache at the time of treatment. Other side effects such as increased heart rate, high or low blood pressure and fever may occur. Some children may develop a rash. Most of these symptoms resolve with slowing down the speed of the infusion. 1 out of 500 to 1000 people receiving IVIg treatment, may experience anaphylaxis (a severe allergic reaction that can result in a rash, swelling of the body and breathing difficulties) may occur. Every child will be closely monitored when they are receiving each dose of the study treatment and up to 20 minutes after each dose of study treatment. If need be, medicines to treat or help lessen reactions will be given. Also, after completion of study treatment, your child will continue to be monitored by the hospital team, as part of routine care.

Similar to other blood products, very strict steps are taken to make sure that the blood from which both IVIg and albumin are made from is free from certain viruses such as hepatitis A, B and C (that affect the liver and cause yellowness of the skin, otherwise known as jaundice) and human immunodeficiency virus (HIV) that could be transmitted by receiving blood products. Although transmission of viruses may be possible, the chance of this happening is rare.

When high doses are used, IVIg can cause breakdown of red blood cells causing a drop in the total number of these cells (haemolysis). For this reason, IVIg is made very carefully to help reduce the risk but in a small number of cases, haemolysis can still happen. In mild cases, it resolves quickly once the treatment is stopped. If left too late, it can affect other parts of the body like the kidneys. Therefore, your child's doctors will monitor your child and their blood very closely for signs of haemolysis. To do this a small amount of blood (0.5ml) will be taken from your child 24 to 48 hours after the second dose of the study treatment has been given. If possible this will be taken with routine samples but may need to be taken as an extra blood test if routine samples are not needed at that time. Depending on your child's age and their preference (where appropriate), we would use a special cream to help numb the skin around where the blood is taken to make this as comfortable as we can. Monitoring for signs of haemolysis as we are doing in the study is currently not routine practice in every hospital. People who are in hospital sometimes get moved to another hospital to be looked after there, though this doesn't happen often. If your child is moved to another hospital before the blood test is due, a letter would go with him/her telling the new doctors there about the study and recommending that they do the blood test. However, it will be up to the discretion of the doctors at the new hospital to decide if they wish to do this based on how your child is at that time.

IVIg and albumin have been well studied and the reactions that could occur with both treatments are well known. However, there may be others that we do not know about. Therefore, we will be collecting information on any new reactions to the study treatment that occur during the study.

As we do not know how the study treatment will affect a baby, if your child is a girl and is pregnant, or has just had a baby and is breast-feeding, she would not be able to take part in this study. Also, if she became pregnant during the study, it is very important that you tell the study team. She will no longer be able to continue in the study and will be withdrawn and the study team would inform your GP.

What are the benefits of taking part?

We will not know whether your child will receive IVIg or placebo. If your child were to receive placebo, since this does not contain any active substances, there are no benefits from this treatment. Similarly, if your child were to

receive IVIg, since the use of IVIg in encephalitis is still being studied, we cannot guarantee any direct benefits either because we do not know whether IVIg will work.

Importantly, your child's involvement in the study will help us understand whether children with encephalitis benefit from IVIg. The results of this study may provide guidance on the routine use of IVIg for all children with encephalitis and could benefit other children with encephalitis in the future.

What are the possible disadvantages and risks of taking part?

With the exception of receiving IVIg/Placebo, the care that your child receives in hospital will be exactly the same as any other child with encephalitis who is admitted to the same hospital, regardless of whether s/he is in the study or not.

Some people may find discussing their illness upsetting. The Encephalitis Society are able to offer support and advice and can be contacted on +44 (0) 1653 699599.

MRI is safe and does not involve the use of X-rays. However, because they use a large magnet to work, MRI scans are not suitable for everybody. Because of this, you will be asked some safety questions about your child to help determine if s/he is able to have a MRI scan. You should let the study team know if your child has been fitted with metals such as a pacemaker. Also, some cochlear implants may not be compatible with the MRI scanner.

As some of the scans are noisy, your child will be given earplugs, head padding or headphones to make this quieter. It is important that these are fitted correctly as they are designed to protect the ears. In preparation for the scan and for your child's comfort and safety s/he may be asked to change into pocket less and metal free "pyjama-style" top and trousers, which are available in a range of sizes. Underwear and socks could be left on, but we will ask females to remove underwired bras. A suitable sports type bra may be worn instead. Metal jewellery, including body piercing, must also be removed. Eye shadow and mascara must also be avoided, since some types contain materials that can interact with the magnetic field. If your child wishes to wear eye makeup on the day of the scan we can provide makeup removal wipes but we advise that they bring some makeup to reapply.

While there is no evidence to suggest that MRI is harmful to unborn babies, as a precaution, the Department of Health advises against scanning pregnant women unless there is a clinical benefit. We do not test for pregnancy as routine so if you think your child may be pregnant you should inform a member of the study team as soon as possible as this may make the MRI scan not suitable

Some children may require light anaesthetic. There are risks associated with every anaesthetic. Most of these are mild. Some children may feel sick and some may have a sore throat or headache. Serious complications are rare and the risk of these occurring is very small. 1 in 5,000 to 20, 000 children may have a bad reaction to the anaesthetic medicines. You will have the chance to discuss any specific risks that may relate to your child before the scan.

Would my child's participation in this study be kept confidential?

With your permission we will inform your GP and health visitor that your child was enrolled in this study. All information and blood samples collected from your child will be coded with a study number and kept strictly confidential. Your child's information will be stored on a secure database, and paper notes will be held by the study teams in locked filing cabinets. Only authorised study staff can access your child's data and samples.

Following completion of the study, all study data will be archived for a period of 3 years after the youngest participant turns 18 years. Storage of this data will be reviewed every 5 years and files will be confidentially destroyed if storage is no longer required.

Who else can see my child's study records?

In order to ensure that the study is being conducted correctly, the following groups may inspect the study records without violating your confidentiality:

- Monitors who check that the study is being conducted to a high standard
- The research Sponsor and their representatives
- The National Health Service (NHS) Trust where your child is a patient
- The Medicines and Healthcare products Regulatory Agency (MHRA), who regulate all medicines and vaccines in the United Kingdom.

By signing the consent form for this study, you will be giving permission for these groups to look at your child's medical records; however, they will not be able to remove any information that identified your child from the premises of the hospital where your child is admitted.

What will happen if I don't want my child to carry on with the study?

You are free to change your mind and withdraw your child from the study at any time without giving any reason. If you change your mind and withdraw your child during the study we will use the samples and data we have collected from your child, up until the point you informed us that you wanted to withdraw, but there will be no further samples or visits asked of you.

What will happen at the end of the research study?

At the end of the study, your child may continue under the care of his/her hospital consultant and GP. The results of the research will be published in a scientific medical journal; this may take a few years after the last enrolled participant has completed the study. This could be anywhere between 2 and 5 years from when your child has completed the study. Publications will also appear on the Oxford Vaccine Group website (www.ovg.ox.ac.uk) and the Encephalitis Society website (www.encephalitis.info) and you will receive a letter containing these results. Your child will not be identified in any report or publication. You will be also told what treatment your child received, if you wish to know but this will only be possible after the final study report has been completed.

What if I wish to complain?

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact your local paediatric research team**.** You can also contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or email the head of CTRG, Heather House ctrg@admin.ox.ac.uk

Who is organising and funding the research?

The study is organised by the Department of Paediatrics, University of Oxford and is funded by the National Institute for Health Research (NIHR) and has been reviewed and approved by the South Central - Oxford A Research Ethics Committee [ref: 14/SC/1416], the Research and Development departments of all 40 hospitals participating in

the study and the Medicines in Health Regulatory Authority (MHRA). The IVIg has been provided free of charge by a company called CSL Behring. The placebo has been manufactured by a company in Liverpool, UK. CSL Behring have provided funds for the distribution of the study drugs.

What else do I need to know?

Some of the results from the study will be included in the University degree project (PhD) of one of the study doctors.

You will be given contact details for a member of the study team, should you have any questions relating to the study.

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that your child suffers any harm as a direct consequence of your participation in this study. NHS indemnity will operate in respect to the clinical treatment your child receives.

You may be approached by a member of the study team who will be asking if you would like your child to contribute samples to a separate Biobank study. Details of this will be provided in a separate information sheet after you child is enrolled to the main study. The Biobank study is optional and you can say no to your child taking part, which will not affect his/her participation in the main study. You may also be asked if you would like to be contacted for future research relating to infection and immunity. If you do not want to be contacted, please put NO against the relevant question on the consent form.

You will not be told of the results of the extra blood tests and scan that are done solely for the study. The testing of research samples and examination of the MRI scans may not be done until the end of the study. Given the long gap before we get the results, it is unlikely that the findings would be of any major consequence for your child. However, should any information become available during the course of the study that may affect your child's participation, or in the case of an incidental finding of a possible abnormality, we would inform your child's hospital doctor. If they felt that the abnormality was medically important, you would be contacted directly about the result and what next steps to take.

We will reimburse any extra expenses incurred from travelling for study related investigations only. You or your child will not receive any other payment for taking part in the study.

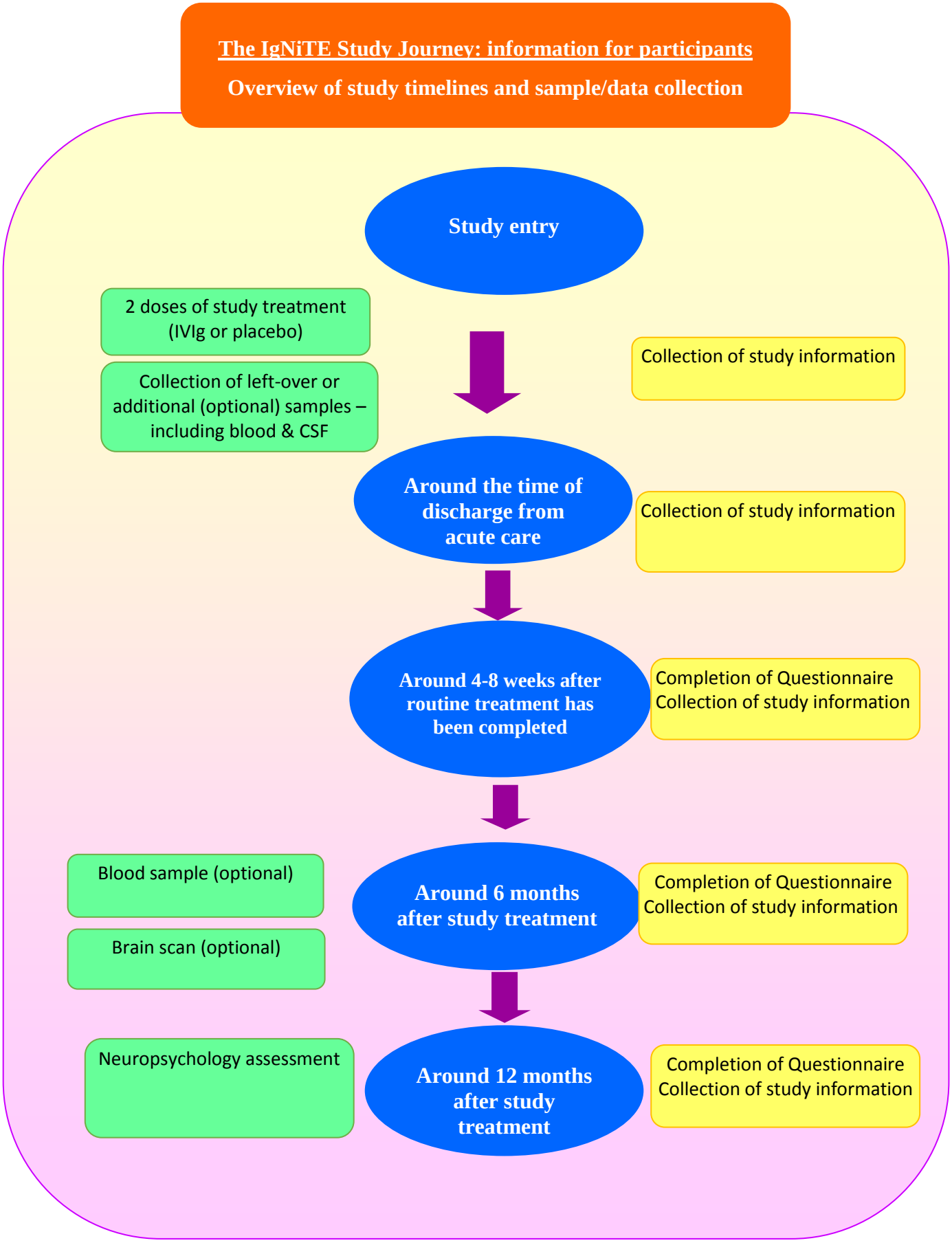
What should I do now if I am happy for my child to take part?

If you have further questions, members of the research team will be happy to answer these. If you would like for your child to take part in the study then please let the research team know and they will ask you to sign a study consent form.

Thank you for considering taking part in this study.

Yours sincerely,

The Oxford Vaccine Group.


The IgNiTE Study Journey: information for participants
Overview of study timelines and sample/data collection
Study entry
2 doses of study treatment (IVIg or placebo)
Collection of left-over or additional (optional) samples – including blood & CSF
Collection of study information
Around the time of discharge from acute care
Collection of study information
Around 4-8 weeks after routine treatment has been completed
Completion of Questionnaire
Collection of study information
Blood sample (optional)
Brain scan (optional)
Around 6 months after study treatment
Completion of Questionnaire
Collection of study information
Neuropsychology assessment
Around 12 months after study treatment
Completion of Questionnaire
Collection of study information