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Low-dose **I**ntravenous Immunoglobulin Treatment for Complex Regional **P**ain **S**yndrome

The LIPS Trial

Patient Information Sheet

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Dear patient,

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

Chief investigator:

Dr. Andreas Goebel, Consultant in Pain Medicine, University of Liverpool

Principal investigator:

What is the purpose of the study?

Complex Regional Pain Syndrome (CRPS) is often a distressing condition, which in many cases is difficult to treat.

Intravenous immunoglobulin (IVIG) is a drug, which has been used for over 30 years to effectively treat other health conditions, but has only recently been researched as a treatment for pain such as yours. We think that IVIG may be effective in CRPS because IVIG affects the immune system and we know that the immune system is involved in pain such as yours.

In this study our aim is to find out if intravenous immunoglobulin can relieve chronic pain better than a dummy drug.

The duration of the main study is 12 weeks, and involves four visits. The main study is followed by an optional 'open label' study, which lasts a further 12 weeks and involves one more visit.

What is the drug or procedure that is being tested?

Immunoglobulin is purified from plasma from the blood of more than 1000 donors. Plasma is the fluid portion of the blood from which the cells have been removed. It contains 'immunoglobulin molecules' that are substances which normally fight infections and control inflammation but can sometimes cause disease. Immunoglobulin is used to treat other conditions where the immune system is thought to be causing disease. It is given by infusion through a small plastic needle inserted into a vein usually in the forearm (intravenous infusion).

Why have I been chosen?

- Because you suffer from a particular type of pain, which is called "Complex Regional Pain Syndrome (CRPS)", and
- Because you feel that your pain medication and physiotherapy do not reduce your pain enough.
- We wish to study a total of 108 patients with pain such as yours in research centres across the UK.

Do I have to take part?

No, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

You will be given intravenous infusions on day 1 and day 22. The infusions will either be the true treatment (immunoglobulin), or dummy treatment, which looks the same but is actually a harmless inactive substance (placebo).
You may have further infusions of true treatment on day 43 and day 64, if you wish. You can participate in the trial without having these further infusions on day 43 and 64, if you do not want them. All infusions are given in hospital and take about five hours. You will need to keep pain diaries and answer questionnaires as in the next section.

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What do I have to do?

- We need you to complete pain diaries and questionnaires at the times described in the study-plan attached.
- We will also need to interview you at the agreed times. You will have to come to the clinic at least four times (for the durations of each visit see study-plan)- and up to five times in total should you decide to receive the optional infusions on days 43 and 64, see below.
- We will also ask you to give blood on two separate occasions: Before you receive your first infusion (40 ml in total, which is about 8 teaspoons. Of this 30 ml is for research purposes and 10 ml is for routine blood tests), and at the end of the trial (30 ml for research purposes). Please note the blood is not taken from your CRPS affected limb (unless in exceptional circumstances where we cannot reasonably get blood in another way). We will examine your research bloods for substances which may explain why you have CRPS, or which may help us to understand your condition better. The types of substances, which we may examine include, but are not limited to antibodies, cytokines and mediators. If you prefer not to provide blood samples for research, you can still participate in the clinical trial but we would still need to do the routine blood tests before your first infusion, to make sure there is no medical reason for you not to have the infusion.
- You will not have to stop any of your prescribed medications. Should you feel that the dose of your prescribed medications should be changed, we are asking you to please discuss this with your study doctor. This includes for example increases of your study medication in case of a flare up, or reduction of your study medication in case that you have less pain.

- You should preferably not start any new treatment for your pain during the study. If during the study you feel you need to seek a new treatment we ask that you speak to your study doctor first.
- Immunoglobulin may be less effective for the treatment of pain when patients develop a common cold or flu. Please avoid contact with friends or relatives who have a cold or flu if at all possible. However if you feel you have caught a cold or flu, please tell us. This will not exclude you from the study.

What are the alternatives for diagnosis or treatment?

- Pain such as yours may be amenable to an operation called 'Spinal Cord Stimulation', where an electrical lead is placed close to the nerves in your back. You should have discussed this option with your consultant or the study doctor before entering the trial.
- Physiotherapy is an important part of treatment for your condition and if you are seeing a physiotherapist you should continue this during the trial.

What are the side effects of any treatment received when taking part?

A. Side effects from the drug

A common side effect is an increase in the intensity of your pain. This may occur in up to 30% of patients both after immunoglobulin or the dummy drug. It rarely lasts longer than three days. Headaches are also common. Occasional side effects include short lasting nausea, vomiting and dizziness, chills, fever, nose bleed, a runny nose, tummy pain short-lasting back- and joint pains, coughing, low blood pressure and an allergic reaction such as a short-lasting skin rash. Rarely meningism can occur, that is an irritation of the lining of the brain causing severe headache.

With larger doses than used in this trial, very rare effects include acute kidney failure, and deep vein thrombosis (clotting of the deep veins in the leg). These latter side effects are not expected with the low dose being used in this trial.

Very rarely, a patient may develop a severe allergic reaction to the drug while the drug is infused. This can be a life-threatening situation, which may need immediate attention by your doctor.

Finally: The effectiveness of live vaccines such as measles, rubella, mumps and chicken pox may be reduced if you receive such vaccines within 3 months of receiving immunoglobulin treatment. For this reason, you should inform the investigator if you intend to have any vaccines during this time period.

Immunoglobulin is derived from human blood and there is a theoretical possibility of transmitting known or unknown infective agents, such as the hepatitis, AIDS and CJD (mad cow disease) viruses. There are no reports of any of the immunoglobulin being used in this trial causing any of these virus infections but the possibility cannot be completely excluded.

B. Side effects from intravenous infusion and blood donation:

The insertion of the needle or cannula for the infusion or blood donation may cause slight pain at the time and mild bruising afterwards. Please note we will not insert any needle or cannula into your CRPS-affected limb unless in exceptional circumstances where we cannot find another vein. Very rarely needle/cannula insertion might cause inflammation of the vein. Some people feel faint when they have an injection: please tell us if this applies to you and we will take special precautions.

We will provide a special space in your diary where we ask you to note any side effects, which you experience. If, after having received the drug, you have any concerns please contact your pain research centre and speak to the research doctor or nurse in working hours.

You will also be given an emergency contact phone number when you receive your first infusion at the Pain Clinic. This number can be used 24 hours a day in the case of a medical emergency, where your GP or another doctor needs to urgently know whether you have been given IVIG or the dummy medication.

What are the disadvantages of taking part?

Women who wish to take part must not be pregnant, or plan to become pregnant during the study. If you are at risk of becoming pregnant you must use an effective contraceptive during the course of the study. Appropriate methods of contraception include barrier contraception such as condoms or hormonal contraception such as the oral contraceptive pill. You may be asked to have a pregnancy test to exclude the possibility of a pregnancy. If any woman finds that she has become pregnant once starting the study she must tell her research doctor immediately.

Litigation: If you are in on going litigation with respect to the injury, which triggered your CRPS, and your trial infusion leads to strong on going pain relief and improved function, this might affect the level of compensation which you would receive for future losses.

Other trials: You will usually not be able to participate in other research trials within three months from the time of your second study visit – you would be able to participate in such trials thereafter. If you wish to participate in additional trials, please contact your study doctor.

What are the possible benefits of taking part?

You may get better with either immunoglobulin, or the dummy-drug. However, this cannot be guaranteed. The information we get from this study will help us and other researchers to understand and eventually treat your pain syndrome (CRPS) better.

What happens when the research study stops?

This is a research study. Should the treatment prove to be effective in this trial, we intend to pursue this research to make this treatment available under the NHS. However it will not be available in the near future.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?

All information collected about you during the course of the research will be kept strictly confidential. Information held about you includes your medical history and your pain diaries and results from routine blood tests. Dr. Andreas Goebel, the Chief Investigator for this trial (XXXX) together with your study doctor will be responsible for safety and security of your data. Any information about you, which leaves the hospital will contain your initials and date of birth but will have your name, address and all identifiable information (including patient/ hospital/NHS number, and GP details) removed so that you cannot be recognised from it. Data from the study will be stored for at least 20 years with your name and address removed. Your GP will be notified of your participation in the trial if you agree to this.

What will happen to the results of the research study?

Results from this study are likely to be published in a medical journal. If you like you can obtain a copy of published results from your study doctor after the project has finished. If you are interested in feedback as to which treatments you received at which time, we will be able to tell you this after all patients have completed their treatment. You will not personally be identified in any report/publication.

Who is organising and funding the research?

This study is being organised by a team of pain researchers from across the UK, led by Dr Andreas Goebel. The IVIG is supplied by a pharmaceutical company (Biotest UK) and the placebo medication is manufactured by a NHS pharmacy. The Clinical Trials Unit at King's College London is helping with the trial.

The study is funded by the National Institute for Health Research under their EME research programme. Additional financial support is being provided by the Pain Research Foundation in Liverpool.

This is a doctor led study and no doctor or nurse will be paid personally for including you into the study

Reimbursement

We will pay reasonable travel expenses for you to travel to the research related appointments and if you need to be accompanied by a carer, we will also pay their travel

costs. If your travel expenses will be more than £50 per visit please advise us in advance. We will always try to make your visit possible and will also book a hotel for you if needed.

Who has reviewed the study?

The study has been reviewed by the NHS research ethics committee
East of England Hatfield REC (Formally known as: NRES Committee East of England – Welwyn) Room 002, TEDCO Business Centre, Rolling Mill Road, Jarrow, NE32 3DT

Contact for Further Information

In case of any further questions to this study, please do not hesitate to contact your study doctor.

Thank you for reading about this study.

STUDY PLAN:

PART ONE (ENROLMENT)

A First Appointment Time: 3 hours

1. The study will be explained to you in detail and you will be asked to sign a consent form at this stage. If you decide at any time that you do not wish to participate, you can change your mind.

2. You will be examined and asked some questions about your condition and medical history and details of any medications or treatments you currently receive.

3. You will be asked to complete some detailed questionnaires about how you are affected by your condition.

4. The feeling on your skin may be tested using a method called "quantitative sensory testing". This will be explained to you at the appointment and takes about 30min.

5. You will give blood as a gift for research purposes (if you have consented to do so) and for routine clinical testing (40ml, approximately 8 teaspoons).

6. If you are a woman of childbearing age, we will test your urine to exclude that you are pregnant. You should not become pregnant for the duration of this study.

7. First pain diary is given and explained to you
   You will be asked to complete the diary daily until your next appointment, and to telephone your study doctor in about 10 days time. He or she will decide if the study is suitable for you, based on your pain patterns and blood results. If so, an appointment will be made for you to receive IVIG or placebo infusion treatments. Before your appointment, a computer programme will decide which treatment you will receive, but neither you nor your doctor will know which you receive. You will be telephoned the day before your appointment to confirm you will definitely attend, as the pharmacy department will need to prepare the medication the day before your appointment.

8. You will be given the following instructions on the effects from your study medication, and on completing your pain diaries:
   - Both the study drug and the 'dummy drug' may provide important pain relief. We don't know why the dummy drug can provide important pain relief, but we have observed this in earlier trials. I.e. one cannot tell from the pain relief you experience whether you had the study drug, or the 'dummy drug'.

- Both the study drug and the 'dummy drug' may also cause an initial pain increase or other adverse symptoms such as headaches. I.e. one cannot tell from any adverse event you experience whether you had the study drug, or the 'dummy drug'.
- Any pain relief may last as little as a few days, or as long as a month, or even longer in some cases.
- It is important to the success of the trial, **that you record your pain accurately the way you feel it,** whether it is much pain, or little pain – what ever you record is equally valuable to the trial, as long as you record it as you feel it.

PART TWO (TREATMENT)

B Second Appointment (2-3 weeks after the first appointment)

Time: 6 hours in total
½ hour tests
4.5 hours 1st infusion
1 hour observation

1. You will be asked to complete some more detailed questionnaires, as you did on the previous visit.
2. If anything has changed since your last appointment, we will need to know the details – for example if you have been unwell or seen your doctor or if you have started or stopped taking any medications
3. Your first dose of the study or dummy drug will be given to you through a cannula (a small needle) into your vein, over a period of 4.5 hours. Both before and after your infusion, and at regular intervals during the infusion, your blood pressure and pulse will be checked. During the infusion you are allowed to move around, go to the toilet, eat and drink.
4. Your second pain diary will be given and explained to you
5. The second appointment is over and you can leave after 1 hour. Because you may experience rare side effects such as nausea, which could interfere with your driving ability, you will not be able to drive a car home after this first infusion and you will need an escort to travel with you if you are walking or taking public transport. You are expected be able to drive as normal from the day after your infusion. If you feel well after your infusion, then for your next infusion in three weeks time you are not expected to need an escort, and you are expected to be able to drive.
6. The research nurse or doctor will speak to you by telephone twice in the next week to check if you are having any difficulties completing

your pain diary, and if you have any side effects or concerns you can discuss them during these telephone calls. You can also telephone the research nurse if you are worried about anything between appointments.

7. If you have a mobile phone, you will be texted every day from the day after this visit to the last study day, to remind you about the requirement to enter your average 24h pain intensity into your paper pain diary. You can opt out from this service. If you participate, you are encouraged to also text your average pain intensity to a free phone number especially set up for this trial once per day on each study day. If you have agreed to this, and we don't hear from you for a while we may call you to enquire whether everything is ok.

C Third Appointment (3 weeks after 2nd appointment) Time: 5.5 hours

1. You will be asked to complete some more detailed questionnaires, as you did on the previous visit.
2. If anything has changed since your last appointment, we will need to know the details – for example if you have been unwell or seen your doctor or if you have started or stopped taking any medications
3. Your second dose of the study or dummy drug will be given to you through a cannula (a small needle) into your vein, over a period of 4.5 hours. During the infusion, your blood pressure and pulse will be checked regularly.
4. Your third pain diary will be given and explained to you
5. The third appointment is over and you can leave after 1 hour. You are expected to be able to drive a car home after this infusion, and you are expected to not need an escort should you choose to either walk or make use of public transport.
6. The research nurse or doctor will speak to you by telephone twice in the next week to check if you are having any difficulties completing your pain diary, and if you have any side effects or concerns you can discuss them during these telephone calls. You can also telephone the research nurse if you are worried about anything between appointments.

D After Infusions

1. You will continue on your normal pain medication**. Please note that between visit 1 and visit 4 you will not be able to start any new treatments for your pain. Such new treatments might**

interfere with the study and render the results worthless. However you can adjust your usual medications, should you need to. Your welfare always has priority. Should you feel, that you need to start new treatment for your pain, please contact the study team.

PATIENTS WHO CHOOSE **NOT** TO RECEIVE OPEN LABEL IVIG INFUSION (if you wish to receive the open label infusion, please go to section F):

E Fourth Appointment (3 weeks after last infusion) Time: 1 ½ hours

1. You will be examined again and asked to complete some more detailed questionnaires, as you did on the first visit, and if you had been tested with "quantitative sensory testing" on visit 1, this will be repeated now. You will also give 30ml of blood for research purposes if you have agreed to this (however you can withdraw your consent to give blood at any time).

2. If you are a woman of childbearing age, we will test your urine to exclude that you are pregnant.

3. If anything has changed since your last appointment, we will need to know the details – for example if you have been unwell or seen your doctor or if you have started or stopped taking any medications

4. You will be asked to complete a simplified pain diary once a week for the next 3 weeks. At the end of the 3 weeks, the study nurse or doctor will speak to you by telephone to check this information but you will not need to attend the clinic again for the study. During this telephone call, you will also be asked about any new medications you may be taking or any changes to your usual medications and you will be asked about any side effects you may have experienced after the last infusion. If you have any ongoing problems, the research doctor or study nurse may wish to arrange to speak to you again. If not, this will be the end of the study. Thank you.

PATIENTS WHO CHOOSE TO RECEIVE 'OPEN LABEL' IVIG INFUSION

F Fourth Appointment (3 weeks after last infusion) Time: 6 hours

1. You will be examined again and asked to complete some more detailed questionnaires, as you did on the first visit, and if you had been tested with 'quantitative sensory testing' on visit 1, this will be repeated now. You will also give 30ml of blood for research purposes

if you have agreed to this (however you can withdraw your consent to give blood at any time). The blood can usually be drawn from the same vein through which you will receive your infusion (i.e. you will usually only require one puncture of your skin).

2. If you are a woman of childbearing age, we will test your urine to exclude that you are pregnant. You should not become pregnant for the duration of this study.

3. If anything has changed since your last appointment, we will need to know the details – for example if you have been unwell or seen your doctor or if you have started or stopped taking any medications

4. Your first dose of the 'open label' IVIG will be given to you through a cannula (a small needle) into your vein, over a period of 4.5 hours. Both before and after the infusion, and a few times during the infusion your blood pressure and pulse will be checked

5. Your fourth pain diary will be given and explained to you.

6. The fourth appointment is over and you can leave after 1 hour. Because you may have received IVIG at this infusion for the first time, you will not be able to drive a car home after this first infusion and you will need an escort to travel with you if you are walking or taking public transport. You are expected be able to drive as normal from the day after your infusion. If you feel well after your infusion, then for your next infusion in three weeks time (should you decide to receive it) you are not expected to need an escort, and you are expected to be able to drive.

7. If you have any side effects or concerns you can telephone the research nurse between now and your next appointment.

8. If you decide at any time between now and 3 weeks from now *not* to receive a second open label infusion (see next section), we will then also sent you additional diaries to complete once a week through the post.

PATIENTS WHO CHOOSE TO RECEIVE SECOND 'OPEN LABEL' IVIG INFUSION

G Fifth Appointment (3 weeks after last infusion) Time: 6 hours

1. You will be asked to complete some more detailed questionnaires, as you did on the previous visit.

2. If anything has changed since your last appointment, we will need to know the details – for example if you have been unwell or seen your doctor or if you have started or stopped taking any medications

3. Your second dose of the open label IVIG will be given to you through a cannula (a small needle) into your vein, over a period of 4.5 hours. Both before and after the infusion, and a few times during the infusion your blood pressure and pulse will be checked

4. Your fifth set of pain diaries will be given and explained to you.

5. The fifth appointment is over and you can leave after 1 hour. You will be able to drive a car home after this infusion, and you will not need an escort should you choose to either walk or make use of public transport.

6. If you have any side effects or concerns you can telephone the research nurse between now and your next appointment.

7. The pain diaries you are given at this visit will be slightly different. You will now be asked to complete your pain diary as usual for 3 weeks and then you will be telephoned to check your pain levels. After that, you will be asked to complete your pain diary only once a week for another 9 weeks. The doctor or nurse will telephone you again when these diaries are complete to check the levels of pain. Both sets of diaries will be given to you today and you will not need to visit the clinic again for the research study. Twelve weeks after today's visit will be the end of the pain diaries and that will be the end of the study. Thank you.

General information on the return of Pain diaries

At the end of the study, although we will collect pain diary results by telephone, the pain diaries will also need to be returned by post (a stamped, addressed envelope will be provided for this) at the appropriate times. The research nurse or doctor will let you know when this needs to be done.

Thank you for reading about this study