Low-dose Interleukin-2 for Treg Expansion after induction therapies in

Multiple Sclerosis (LITMUS)

INFORMATION SHEET FOR PARTICIPANTS WHO

HAVE RECEIVED ALEMTUZUMAB

We would like to invite you to take part in our research study. This study is being carried out partly to fulfil an educational qualification and is funded by a Wellcome Trust Clinical PhD Fellowship award.

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. Talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear.

Part 1

1. What is the purpose of the study?

Alemtuzumab is a highly effective treatment for multiple sclerosis (MS). It works by depleting immune cells (lymphocytes) which normally fight infections but which mistakenly attack nerves in MS. Following treatment the immune system grows back, but without the immune cells which cause MS. Although effective, alemtuzumab has side effects, in particular 4 in 10 patients develop a new autoimmune disease after treatment. In other words, as their immune system grows back, it begins to attack other parts of their body; most commonly the thyroid gland.

We think that increasing a special type of immune cell, called a T-regulatory cell (Treg), whose job is to control the rest of the immune system, might help reduce the risk of this complication. In this study, we would like to see whether we can increase Tregs after alemtuzumab treatment without

impacting other immune cells. To do this, we will use an injectable medicine called IL-2 (Interleukin-2, Proleukin).

2. Why have I been invited?

You have been invited to take part because you have MS and have already been treated with alemtuzumab as part of your routine NHS care. We are inviting patients who were treated with alemtuzumab at least 6 months ago, but no longer than 24 months ago, and who are not currently taking any other medications for MS.

3. Do I have to take part?

No, participating in this study is completely voluntary. It is up to you to decide whether or not you would like to take part. If you do, you will be given this information sheet to keep and will be asked to sign a consent form. However, you will still be free to withdraw from the study at any time, without giving a reason. A decision to withdraw, or not to take part, will not affect the care you receive or your involvement with any other study.

4. What will happen to me if I take part?

You will not be re-treated with alemtuzumab, or any other MS therapy, on this study. Taking part in this study will not affect the treatment of your MS in any way, and you will continue all of your usual medications. You will remain under the care of your usual NHS doctors and GP throughout the study. We will communicate test results with your GP, neurologist or other hospital specialist where needed. We will review parts of your past medical records relevant to taking part in the study (such as your recent blood test results and other medical conditions).

5. What does taking part involve?

Taking part in the study takes between 8 and 12 weeks in total. During this time, you will see the research team face-to-face 6 times. There is a diagram explaining the visits below. Each of these appointments will typically last 20 minutes, except the first two visits, which will take between 1 and 2 hours.

During this study, you will take an injection of IL-2, given under the skin using a small needle twice a week for 3 weeks (6 injections in total). We will teach you how to do the injections yourself. You will do most of them at home. If you prefer, we can teach someone you live with to help you.

You will also give blood on 4 occasions (twice before, and twice after you've started the injections of IL-2).

The last visit on this study is 4 weeks after you have finished taking IL-2.

6. What is IL-2 (Proleukin)?

IL-2 is a natural immune cell growth factor. Treg cells are very sensitive to IL-2, which causes them to increase in number.

IL-2 is available as a licensed drug in the UK, called Proleukin, which closely resembles the natural growth factor. Proleukin was originally designed as an immune-boosting anti-cancer therapy, used at very high doses. Scientists later worked out that at very low doses IL-2 mainly affects Tregs, instead of boosting the rest of the immune system. In this study, we will use IL-2 at a very low dose that preferentially acts on Tregs.

7. What happens at the different visits if I take part?

Visit 1 (screening, approximately 1 hour):

At this visit, you will have a chance to ask further questions about taking part. If you are happy to proceed with the study, you will provide written consent. We will ask some questions about your general health and the medications that you are currently on. We will check your regular medications at every visit of the study, in case of any changes. We will check that you are generally well, by asking a few questions and measuring your pulse, blood pressure, and temperature (your vital signs). We will test a urine sample for infection, and also do a urine pregnancy test (if relevant). This is all to check you are eligible to participate in the study. We will also measure your height and weight (to work out the dose of IL-2 you will need).

Last of all, we will take some blood samples (approximately two tablespoonful's): for screening blood tests (e.g. blood counts, kidney function, liver function); and to measure your Treg cells in the lab.

Visit 2 (start of dosing, approximately 2 hours):

This visit will take place within 1 to 4 weeks of your first visit (but not earlier than 1 week after your first visit).

We will ask a few questions to ensure you are well, measure your vital signs, and do a urine test for infection (and pregnancy test if relevant). We will go through your regular medications again. This is all to check you are well enough to start the IL-2 injections the same day.

We will then take a research blood sample. The amount of blood taken will be based on your weight, but it will typically be around 80 to 90ml, which is less than a small teacup.

We will teach you (or a family member, if you prefer) how to give yourself an injection under the skin. You will practice dummy injections on artificial skin, then when you feel confident we will watch you give yourself the first IL-2 injection.

As with all new drugs, it is possible (but very rare) to have an unexpected reaction or allergic reaction, so we will observe you for an hour after the injection before you go home.

You will receive a cool-bag containing the next injection of IL-2 and a small “sharps” bin to safely dispose of the needles, to take at home. You will keep the sharps bin until you have finished all the injections. At your penultimate visit, you will return the sharps bin to us for safe disposal.

Visit 3 (dispensing visit, approximately 20 minutes or less):

This visit is exactly 7 days after your first IL-2 dose. We will ask you how you feel, check the injection sites, and go through your regular medications. If you have any unused IL-2 injections, please ensure you bring them with you.

You will take away the third and fourth dose of IL-2 to have at home. If you are not feeling confident, we can watch you give yourself the third dose in clinic instead.

Visit 4 (dispensing visit, approximately 20 minutes or less):

This visit is exactly 14 days after your first IL-2 dose. The visit has the same format as visit 3. Again, please ensure you bring any unused IL-2 injections with you.

Visit 5 (end-of-dosing visit, approximately 20 minutes):

This visit takes place 2-4 days after your last injection of IL-2. We will check how you feel, check the injection sites and go through your regular medications again. We will take research blood samples. As before, the volume of blood will be around a small tea-cup full, based on your weight.

Please bring any unused IL-2 injections with you, as well as the sharps bin.

Visit 6 (follow-up visit, approximately 20 minutes):

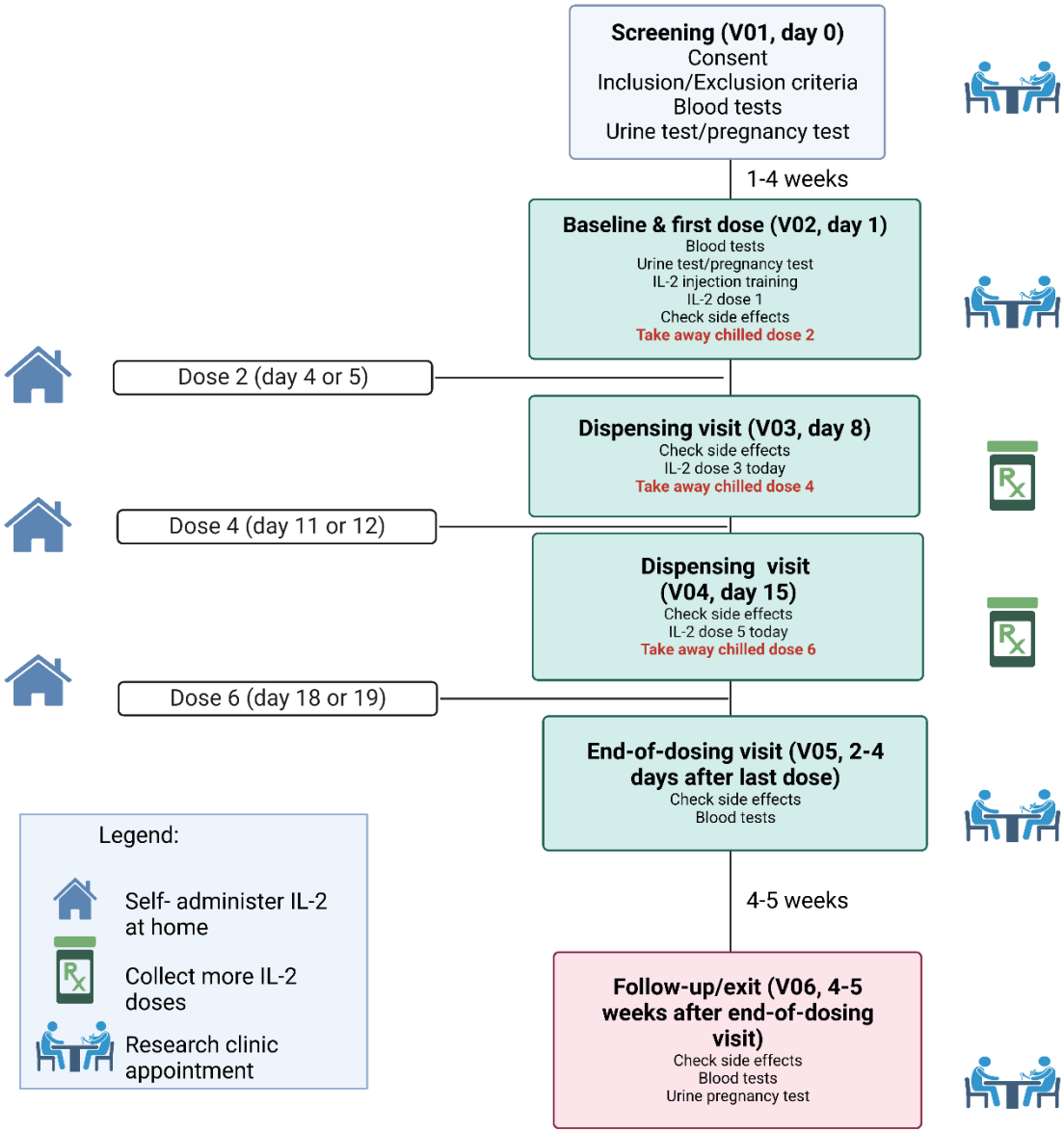
This visit will be around 4 to 5 weeks after the previous visit. Its purpose is to check how you feel and to ensure your blood tests and Treg cells are going back to their pre-study levels.

We will check how you feel, and will review the injection sites, and go through your regular medications. We will take a small amount of blood (around two tablespoonfuls). We will do a pregnancy test where relevant. This is the last visit on the study.

Please note that if for any reason you are unable to complete the full set of 6 IL-2 injections (but you are happy to continue in the study), we would strongly encourage you to let us know and to still attend for visits 5 and 6. They would be at the same intervals from your last dose that we have specified above. It is important to attend because it enables us to monitor your safety. As a secondary consideration, this is also helpful to the study: in many cases, we can still gain useful information from your participation to date.

Of course, if at any point you decide that you no longer want to take part in the study altogether, you are free to do so- please see Part 2, Section 1 about this.

Here is a diagram of the study visits.



8. What are the possible disadvantages and risks of taking part?

Attending appointments:

You will need to attend the research facility six times.

Some of the appointments are not flexible i.e. you need to attend on a specific day. This is because some of our immunology tests are time-dependent in relation to the injections, which are also on fixed days. We understand this can be inconvenient so we have tried to be as flexible as we can where possible.

Blood tests:

Blood tests can cause mild bruising and slight discomfort on the skin. The total volume of blood taken over the course of the study is less than one single blood donation session and will not have any significant effect on you (we check your blood tests before starting the study to ensure this).

Subcutaneous injections of IL-2:

The injections are given under the skin, in a fleshy area such as the abdomen (tummy). They often cause slight discomfort (a pinch), redness and a temporary lump under the skin at the injection site. This happens in most people, but not necessarily after each injection, and it goes away on its own in a few days.

Side effects from taking low-dose IL-2:

Low-dose IL-2 is very safe and usually only causes mild side effects - these are listed below.

Risks of targeting immune cells in MS:

We are giving a small number of IL-2 injections in this study and we think this is very safe to do in MS.

IL-2 has been given to patients with other (non-MS) autoimmune diseases in many studies without causing any significant problems. In particular, there have been no reports of worsening autoimmune disease, or increased infections.

IL-2 has not been widely given after alemtuzumab. So it is possible that we could see some unexpected and unintended effects on increasing non-Treg immune cells. However, previous studies have shown that the effects of IL-2 wear off within a few weeks of stopping the injections. Thus, we are confident that any unexpected effects would not be lasting.

9. What are the side effects of IL-2 (Proleukin)?

Proleukin, when given at low doses (like in our study), is usually very safe and well tolerated. The side effects of low-dose Proleukin are typically non-serious, mild, and fully resolve by themselves.

Very common (more than 10 in 100 patients):

- Injection site reactions, e.g. local redness and a non-painful lump at the injection site. This disappears soon afterwards.
- Tiredness- usually not severe.

Common (5 to 10 in 100 patients):

- Cold or flu-like symptoms. This can include e.g. sore muscles, shivers, a high temperature, a runny nose or sore throat. Paracetamol helps control these symptoms, but you may not need it. Most people experience mild symptoms.
- Nausea, lack of appetite, diarrhoea or abdominal (stomach) pain. If these do happen, they tend to be quite brief, rather than the whole time you are taking IL-2.

Rare (2 in 100 patients or fewer)

- IL-2 can rarely cause a temporary increase in a type of blood cell called eosinophils. This does not cause any symptoms or problems. The eosinophil count typically goes back to normal after 1-2 days. We will check your blood counts at the end of the study for safety.
- Migraine or other headache

Extremely rare (probably <1/1000, or not measured to date):

- As with any new drug, it is possible to have an allergic reaction (including a serious one, such as anaphylaxis) with the drug Proleukin. To date there is only one reported case of this. We will observe you after your first dose, and give you advice on what to do in case of allergic reaction to be on the safe side.
- Skin rashes, including acne

Additionally, IL-2 can cause some white blood cells (specifically, lymphocytes) to move out and then back into the blood circulation in the day after an injection. This can make the lymphocyte count temporarily appear lower than it actually is, usually in the 24 hours after an injection. It is not a side-effect but rather a consequence of how IL-2 works. We are mentioning it to make you and your usual

doctor aware, just in case you have any blood tests outside of the study while taking the IL-2 injections.

10. What are the possible benefits of taking part?

There is no intended therapeutic or other benefit to you from participating in this study. The potential changes to your immune cells are all expected to be temporary. The number of IL-2 injections is too small to cause an effect on your health (such as lowering your chance of getting autoimmunity complications after alemtuzumab). So we are not measuring any clinical effect of IL-2 in our study. However, information collected as part of your participation in this study may benefit patients with MS in the future.

11. What will I need to do when taking part?

We know that taking part in a research study can be quite daunting, so if you decide to take part we will guide you through what is required from you.

During the study, you will remain under the care of your usual neurologist for your MS, and GP for other matters. However, we will support you throughout the study if you have questions or concerns. We can be contacted by phone and e-mail.

The time you spend in the study is relatively short (2-3 months). We anticipate that you would be unlikely to need imminent changes to your MS treatment during this time. However, if at any point your neurologist feels that there is a need to change your MS treatment, or you need to take steroids for a flare of MS, you will be free to do so. We would simply ask you to inform us of any changes first, because they may affect whether you should continue in our study, or how we interpret our results. For this reason, we will be recording the medications you take alongside the study at every visit.

12. Are there any implications from taking part on pregnancy and breastfeeding?

Proleukin is very similar to natural IL-2, but it is still a drug. As with many drugs, it should not be taken by pregnant or breastfeeding patients, because it has not been tested in these settings and we do not know its effects.

You must not participate if you are planning to become pregnant or father a child during the study. We will ask you to use reliable contraception during the study (from our first meeting, until your final visit).

Women who are sexually active and able to have a baby must use one of the following highly effective forms of contraception:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (i.e. it stops an egg being released):
  - Oral (the combined “Pill”)
  - Intravaginal (usually, a ring or other similar device)
  - Transdermal (the “patch”)
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral (the “mini-pill”)
  - Injectable (the contraceptive injection)
  - Implantable (the contraceptive implant)
  - Intrauterine device (IUD) (the coil)

Intrauterine hormonal-releasing system (the “Mirena” coil, or other similar system)

- Bilateral tube occlusion (an operation to “tie the tubes” that carry eggs)

The names in brackets are those you might be more familiar with in everyday speech. We will discuss the options with you if you choose to take part in the study.

Men must use the following effective form of contraception:

- A condom and spermicide (a chemical that kills sperm), even if female partner(s) is using another method of contraception.

Men should also use a condom to protect male partners, or female partners who are pregnant or breastfeeding, from exposure to the IL-2 in semen, and should not donate sperm while on the study.

You do not need to use contraception if:

- You are a woman and you only have one male partner, who has had an operation to cut the tubes that carry sperm (vasectomy).
- You are a woman who cannot become pregnant.
- You practice true abstinence as part of your usual and preferred lifestyle. If you become sexually active during the study, you must use contraception as outlined above.

13. Taking part in research during the COVID-19 pandemic

We have done everything possible to make participation in our research study safe for you.

The situation with COVID-19 can change rapidly, but we have included general precautions and specific adaptations (in case of rising risk in the UK) in our plans.

The number of face-to-face visits is small (six only) but sufficient to support you during the study. You need to be at least 6 months after your latest alemtuzumab infusion to participate, which takes you out of the most vulnerable period for infections. If at any point during the study we feel the risk of face-to-face appointments is too great due to COVID-19, we will be able to safely reduce your face-to-face time with our research team. We will achieve this by reducing the number of times you attend the research facility and using phone/video consultations whenever possible.

Some visits (most notably the first two), and some activities (such as collecting blood tests) cannot be done remotely. So the study would still require some face-to-face contact, but we would aim to keep it as brief and safe as possible. Your follow-up and support would not be compromised as a result.

The research facility is on the Addenbrooke's site but physically separate from Addenbrooke's Hospital itself, and participants will not have to enter the hospital during study visits. The research team and the research facility staff adhere to hospital COVID-19 safe protocols.

We understand that you may feel uncertain about participating in a study involving the immune system at this time. At present, we have no reason to believe that low-dose IL-2 will make you any more susceptible to infection, or vulnerable to severe COVID-19 disease. Patients in previous studies similar to ours have not reported frequent or severe infections.

If you are due to have a vaccine (including COVID-19 vaccine), we ask that you wait at least 4 weeks after vaccination to participate in our study. This helps to ensure that our intervention does not

interfere with your vaccine response, and that (in turn) a recent vaccine does not confuse our immunology test results.

14. What happens to my personal identifiable information if I take part?

Your participation in this study will be kept confidential. We will follow ethical and legal practice and all information about you will be handled in confidence- please see Part 2 for more information.

While you are taking part in the study, we will securely hold information such as your contact details, name, date of birth, and so on, for the purpose of running the study.

This information will be kept on a secure University server, separate from your clinical data (which will be held on the secure hospital IT system), and your study results (which will be held on University computers in an anonymous form, but can be linked back to your personal data).

15. Expenses and payments?

You will not receive any payment for participating in this study. However, we will reimburse any reasonable travel costs for any extra visits made to the Addenbrooke's site, above and beyond those required for routine medical care, as a result of taking part in this study.

It is important that you keep any travel-related receipts and request a claim form at your visit, if appropriate. Details of how and when payments will be made are available from the study team.

All payments are made electronically via BACS payment, and so in order to process any travel claims we will need your bank account number and sort code. These will be kept confidential and only used for the purpose of reimbursing you for your travel expenses.

This completes Part 1.

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

Part 2

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

Taking part in this study is entirely voluntary. You are free to come off the study at any time without giving a reason and without affecting your future care or medical treatment. If you decide not to participate any further, you will no longer receive the IL-2 injections. No further tests will be performed on you and no further research samples will be collected. Any data already collected or results from tests already performed on your samples will continue to be used in the study analysis.

In the unlikely event that during the study you lose the ability to consent (i.e. to understand the study, weigh the pros and cons of taking part, and communicate with us), we would withdraw you from the study. In this situation, we will not collect any new data from you after this point, including any data that already exists in your medical records. However, we will retain and use data and samples that we have already obtained. They may be used in this study, or in future ethically approved studies (only if you have consented to this option).

2. What if there is a problem?

If you have a concern regarding any aspect of this study please ask us and we will do our best to answer your questions. If you remain unhappy, and wish to formally complain, you can do so through the NHS complaints procedure.

In the event that something does go wrong and you are harmed by taking part in the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Cambridge University Hospitals NHS Foundation Trust. If your claim is successful, your legal costs will be met. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

The University has obtained insurance which provides no-fault compensation i.e. for non-negligent harm, you may be entitled to make a claim for this.

The NHS does not provide no-fault compensation i.e. for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent harm. They are able to consider an ex-gratia payment in the case of a claim.

3. Involvement of your General Practitioner/ Family doctor (GP) and sharing of medical information across platforms

We will inform your GP that you are involved in this study, and keep them informed of your progress on the study. We believe it is important for your GP to be kept informed. As your family doctor they are your first line of care and they are likely to be involved in your treatment. Your GP will not be sent details of our research test results.

We may access your medical records to look up selected test results or relevant medical history (e.g. past medication). We may communicate with your neurologist or other hospital clinicians involved in your care, only when this is relevant to your health, or to the study.

4. How will we use information about you?

Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge are the Sponsors for this study. In this section, “we” refers to the Sponsors and the site (the research team).

This section explains what will happen to your information if you take part in the study. We will need to use information from your medical records for this research project. Personal information will include:

Your initials
NHS number and/or hospital number
Name
Date of birth
Contact details

The Sponsors and site will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. For those individuals, your data will have a code instead so they cannot identify you.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. We will not collect new information about you if you stop being part of the study.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at **www.hra.nhs.uk/information-about-patients/**
- from our leaflet, available online at the following addresses:

For Cambridge University Hospitals NHS Foundation Trust

https://www.cuh.nhs.uk/corporate-information/about-us/our-responsibilities/looking-after-your-information

For University of Cambridge

https://www.medschl.cam.ac.uk/research/information-governance/

- by asking one of the research team when you see us.
- by ringing the research team on 01223 216187
- by sending an email to:

Information Governance Lead/ Data Protection Officer Cambridge University Hospitals NHS Foundation Trust Box 153, Hills Road, Cambridge, CB2 0QQ

gdpr.enquiries@addenbrookes.nhs.uk

or

The University of Cambridge Information Governance team

researchgovernance@medschl.cam.ac.uk

5. How will my data be stored?

- While you are taking part in the study, the research team will securely hold information such as your name, date of birth, hospital number, contact details and so on, for the purpose of running the study. This information will be kept for 5 years after the end of this study for safety reasons, on a secure internal University server.
- Your clinical data (e.g. blood test results) will be held on the secure hospital IT system in line with hospital policy.
- Your study test results will be held on University computers in an anonymous form. They can be linked back to your personal data (the linking key is stored separately on the secure internal University server). Study test results will be held for 15 years after the end of the study - in case they need to be interrogated further.

6. What will happen to any samples I give?

We will ask you to donate your samples to the University of Cambridge, Department of Clinical Neurosciences. Your donated samples will be treated as “gifts”, which means that the department will have control over what happens to the samples, how they are used and all rights to any “inventions” (such as drug treatments or tests) which might come out of research performed using your samples.

Some of the blood you donate will be analysed on the day it is taken, but some samples will be frozen for future use on this study. Samples will be kept in a pseudo-anonymous way: they will be labelled with a study-specific number and not directly identifiable as yours. We will share samples with other collaborating academic or industrial third parties that are under contract to carry out sample analysis in agreement with this study’s objectives. Sharing of research samples and data may take place both within and outside the UK and EEA. However, your personal information (such as name or address) will never be shared, so you cannot be recognised.

If there are leftover samples at the end of this study, and if you have consented to this, we will ask for ethical approval to use them in another project. Samples will only be retained if we have appropriate ethical approval from an Ethics Committee to do so. Some leftover samples may be shared with other research centres who are doing very similar research to us, and which has been ethically approved. Research data collected during the study may also be shared in a similar way.

Sharing samples and data can allow more specialised tests to be done which are relevant to the research, but that we might not be able to do locally. We will never share your personal information.

If you do not consent for the use of leftover samples in future research, we will destroy your remaining samples at the end of this study.

7. Will any genetic tests be done?

We would like to look at specific areas in your genetic code (scientists call this your DNA), which would help us study the effects of our study intervention on your immune cells. The tests we would like to do would not produce any information that could affect you as an individual, or affect your family.

DNA can easily be extracted from your blood – you would not need to give an additional sample. We will only look at relevant parts of your genetic code, never the whole thing. We will not feedback any of the results we obtain to you or to anyone else (including your GP). Taking part in this study will not affect any health insurance you may have.

8. What will happen to the results of the research study?

The results of this study may be published in a scientific journal or book, and where appropriate, through formal press releases. Participants will not be identified in any of these reports. You can request a summary of the study findings if you are interested. We will make them available after the study is finished and we have compiled our study report.

9. Who is organising and funding the research?

Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge are jointly sponsoring the study. Our research group receives funding support from various charities such as the MS Society and the Wellcome Trust. This project is specifically funded by a Wellcome Trust Clinical PhD Fellowship award.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee, to protect your interests. This study was reviewed and given favourable opinion by **Wales REC 7.**

10. Further information and contact details

Please feel free to ask questions about this consent form or the study at any time. You may ask questions before you decide to start the study or at any time after the study has started.

If you have any questions about this study please contact:

Joanne Jones	01223 216187	jls53@medschl.cam.ac.uk
Zoya Georgieva	01223 216187	zg248@medschl.cam.ac.uk

If you are unhappy and wish to complain formally, you can do this via the Patient Advice and Liaison Service (PALS):

Tel. 01223 216756

pals@addenbrookes.nhs.uk

In the event of an emergency:

In the event of an emergency please follow your normal emergency procedure. If you need urgent medical attention, go to the nearest nearest accident & emergency (A&E) department.

If you need to contact the study team urgently outside of normal working hours, please contact the Addenbrooke's switchboard on **01223 245151** and ask for a member of **"LITMUS" team.**

Thank you for taking the time to read this document, and for considering taking part in the study.