Analysis of liver infiltrating lymphocytes in primary sclerosing cholangitis
by fine needle aspiration of the liver.

Patient Information Sheet
PSC Cohort

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1. Invitation
You are invited to take part in an educational clinical research study carried out by the University of Oxford in conjunction with the Gastroenterology Unit at The John Radcliffe Hospital. Before you decide whether or not you wish to take part, you should read the information provided in this leaflet carefully and if you wish, discuss it with your family, friends or GP. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you – this process is known as ‘Informed Consent’.

2. Why is this study being done?
Despite encouraging advances in our understanding of primary sclerosing cholangitis (PSC), we still do not fully understand the cause of the disease, nor is there a beneficial medical treatment to slow its progression.
PSC is an immune-mediated disease. Immune cells called “lymphocytes” are thought to play a key role in its development. Lymphocytes that usually reside in the gut are also in the liver of people with PSC but not in the liver of people with other liver diseases. It is thought that the migration of these lymphocytes from the gut to the liver contributes to the development of PSC. However, research to date has focused on lymphocyte activity only in people with advanced PSC.

To address this further, we need to analyse the lymphocytes which are present in the liver in PSC in all stages of the disease, and compare them with liver lymphocytes from people without PSC. The only way to obtain lymphocytes from the liver is to take a sample directly. This may be done through a very low risk procedure called fine needle aspiration with minimal to no side effects to the patient.

A range of experiments will then be carried out on the samples obtained to better understand the mechanisms that lead to the development and progression of PSC. This study is educational in nature and will help us learn more about these causative processes, which could potentially enable us to design and target better therapies for PSC.

3. Why have I been invited?

You have been invited because you have been diagnosed with Primary Sclerosing Cholangitis. We are inviting up to 50 patients with PSC to take part, as well as 50 control patients who do not have PSC (but have some other form of chronic liver disease).

4. Do I have to take part?

No. It is up to you to decide as to whether or not to take part. Not participating will have no effect on your future care.

You may change your mind at any time, before the start of the study or even after you have commenced the study, for whatever reason, without having to justify your decision. This too will have no negative impact on the care you receive.
5. What will happen to me if I decide to take part?

If you decide to take part, we will arrange for you to have a Study Visit with us to obtain samples (detailed below). Prior to that we will check that you have had a recent abdominal ultrasound (in the last year) as well as a recent routine blood test (in the last three months). If you have not had these done recently, we will arrange for you to have these done before taking part in the study. These are part of your routine clinical care, and can be done local to you (e.g. GP surgery) or at the hospital.

We will contact you via phone or email to set up a time for your Screening Visit and Study Visit 1. We want to try and minimise the amount of time you have to come to the hospital, so usually these two visits could occur on the same day (immediately one after the other). But, if you wish, we can organise the Screening Visit on an earlier date, so you can talk through the trial with us in person before entering the study, and thereby leaving some time between entering the study and Study Visit 1.

**Screening Visit**

This will be a one-on-one consultation with one of the investigators, who is also a medical doctor. You will have an opportunity to ask questions about the study and then if you are happy to participate, you will sign the Informed Consent Form to confirm you have entered the study. The investigator will go through your past medical history with you and check your recent blood tests and ultrasound, and confirm whether you are eligible for the trial. You have not yet had the relevant blood tests and ultrasound, these may be ordered at this stage (blood test can be taken at this appointment).

We expect this Screening Visit would take approximately half an hour, and it would occur at the John Radcliffe Hospital (or, rarely, at an alternative site of Oxford University Hospitals).

**Study Visit 1**

This may occur straight after the Screening Visit if all the investigations are done, or else on a separate date. At this visit, a sample of blood will be taken – around 25ml, which is approximately 5 teaspoons worth. You will then undergo fine needle aspiration of the liver (further details below), and be observed for an hour afterwards. If you are fine at this stage, you would then be free to go home. We anticipate that Study Visit 1 would take around 1.5-
2 hours in total, though occasionally it may be slightly longer. You will be able to drive and resume work immediately after this visit.

**Telephone follow-up 1**

You will be called on the telephone one month later to check how you have been since Study Visit 1.

We will also ask you whether you are happy to be contacted at a later date (within one year) to consider having a repeat Study Visit (for another blood sample and a second fine needle aspiration of the liver). This is completely optional, and you will only have to decide about this at the telephone follow up, as by this stage you will have more of an idea of what the study visit (and there for the fine needle aspiration of the liver) entails. If you decline contact with regards to a further Study Visit (which is perfectly fine, and you would not need to give an explanation), then this would be the end of your trial involvement.

**Study Visit 2 (optional) – within one year of telephone follow-up 1**

This would be exactly the same as Study Visit 1 – a blood sample and fine needle aspiration of the liver with a short observation period afterwards. As mentioned previously, this second study visit is not routine, and would be an optional extra visit, which you only decide if you want to do at the first telephone follow-up.

**Telephone follow-up 2 (optional - only if Study Visit 2 has occurred)**

You will be called on the telephone one month after Study Visit 2 to check how you have been. This would be the end of your trial involvement.
6. What is involved in a fine needle aspiration of the Liver?

This procedure to obtain cells from the liver has been performed for over 100 years. It originally was designed to take samples to help make a diagnosis of various liver conditions but over the last 12 years, it has been successfully used to obtain lymphocytes from the liver, particularly in order to perform research into specific immune changes associated with specific liver diseases. In over 500 procedures performed for research, no serious complications have occurred. This technique has been used in various liver diseases, particularly Hepatitis C, but never specifically for PSC.

Fine needle aspiration of the liver (FNA liver) is similar to a liver biopsy but is much lower risk as it uses a much finer/thinner needle. You lie down on a bed with your right arm resting above your head. You will be asked to hold your breath out (i.e. exhale) for short amounts of time for some of the following steps of the procedure. An ultrasound would be used to find the best location for the procedure. This is usually between two of your lower ribs on the right-hand side of your upper abdomen.

The area would be cleaned with a sterilising solution and then some local anaesthetic would be injected into the skin and slightly more deeply with a fine needle in this area. This causes a stinging sensation in the area which would last between 10 to 20 seconds. Most patients can tolerate this discomfort fairly well, and the discomfort would then subside.

In the same area, a very fine needle (similar width to a butterfly needle which can sometimes be used when taking blood) will then be inserted through the skin to the edge of the liver. You would not feel any pain from this except for the very rare occasion when the local anaesthetic has not completely numbed the area in which case minor discomfort is experienced. Using suction, the doctor will aspirate cells into a syringe. This will occur twice (without moving the needle) and will take approximately thirty seconds.

The needle is then removed and a bandage is applied to the area with some firm pressure. The whole procedure from the ultrasound to the bandage going on takes around 10-15 minutes. You will then be observed for one hour lying supine on a bed, and have measurements such as blood pressure and heart rate taken. You will be discharged home after one hour after review by the doctor. There are no restrictions on driving or working following the FNA liver. If there are any concerns post-procedure you may be observed for longer, but this is expected to occur only rarely.
7. What are the possible risks of taking part in the study?

The blood samples that you give during this study involve minimal risk but may be associated with minor discomfort, redness or bruising.

Unlike liver biopsy, which carries a 1 in 100 risk of a serious complication, there have been no serious complications reported in the medical literature for FNA liver. Although you may experience some minor discomfort after the local anaesthetic wears off (typically within 30 minutes), this is usually only very mild. If you are in discomfort you will be offered simple analgesia such as paracetamol and occasionally codeine, but actually patients rarely require any pain relief medication.

Despite the very safe track record of FNA liver, there are theoretically very tiny risks of bleeding within the liver, putting a hole (perforation) in a nearby organ (such as the gallbladder, bowel, or lung), injuring a bile duct in the liver, and significant persistent pain. It must be stressed that these complications have never been reported for FNA liver, but you must be aware of the tiny possibility of these. These complications are usually manifested by severe persistent pain in the right upper quadrant of the abdomen, and appropriate clinical care would be implemented either by the investigators of the study or your treating clinician. This would include imaging of the liver (such as a CT scan), pain relief, and sometimes admission to hospital. Surgery is rarely required for these complications – most of them settle with bedrest and observation.

In order to reduce the chance of any complications, the following precautions will be taken:

- An experienced doctor will carry out the procedure under ultrasound guidance.
- The procedure is performed under sterile conditions to ensure minimal risk of infection.
- Your recent blood test will be checked to assess the thinness (clotting) of your blood. If any problems are found in the blood clotting you will not be entered into the study.
- All patients with a known cancer (which can increase the risk of bleeding) will be excluded.
- All patients who have ascites (fluid in the abdominal compartment normally requiring diuretic tablets) will be excluded.
- If you are pregnant, you will not be entered into the study.
8. What are the possible benefits of taking part?

By taking part in this research you are helping to contribute to our understanding of the cause of PSC, and potentially this will help us identify beneficial treatments. You may not benefit yourself directly as a result of this study, but it is hoped the study will benefit future patients with PSC.

9. Will my General Practitioner (GP) be informed of my participation?

Yes, we will send a letter to your GP letting them know you are taking part, and what the study involves.

10. Will my taking part in the study be kept confidential?

Every effort is made to keep records of personal information confidential and secure. The information that you give will be stored with a unique study code rather than your name, on a secure computer system, which will only be accessible by the few individuals that are specifically named in this study.

Complete confidentiality is paramount to us, the research team. Personal information will be kept on a computer to which access is limited. You would also be allocated a unique study code that would be used for all of the tests done on your samples.

Nearly all the information necessary for the research will be used through your unique study code. The researchers using this information are aware of the importance of security and confidentiality even though they do not have access to personal information such as your name or address. The small numbers of researchers that do have the key to personal details all are aware of the importance for confidentiality and have been trained in the ways that information is kept secure. These files containing personal details will be destroyed within 3 years of the study ending. We will endeavor to send you a summary of the study findings within this time period.

Responsible members of the University of Oxford and/or Oxford University Hospitals NHS Foundation Trust may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.
11. What will happen to the samples I give?

If the samples reveal anything relevant to your care this will be communicated to your usual treating doctor so that they may discuss this with you.

Any samples collected from you will be labelled with your unique Study ID and contain no personal identifiable information. Most of these samples will be used directly in experiments in secure laboratories within the University of Oxford. If you agree, a small proportion of your samples will be stored anonymously within the University of Oxford laboratories to be used in investigations at a later date. Any unused samples will be destroyed after 5 years.

Your anonymised samples will be used mainly by local researchers at the University of Oxford, but ethically approved research projects may take place in hospitals, universities, non-profit institutions or commercial laboratories worldwide. Any studies carried out on your samples will have appropriate ethical approval.

Some experiments may involve extracting DNA from your sample. The material given to researchers will not have information that identifies you. However, your DNA is unique to you so it can never be completely anonymous.

12. What happens if I don’t want to carry on with the study?

Participation in this study is voluntary and you may change your mind at any time. If this occurs, simply contact us via the details given at the end of this leaflet, and let us know you wish to be withdrawn from the study. You do not have to give a reason, and this will not affect your ongoing clinical care.

If you have undergone a FNA liver, we will still phone you at one month to check you are okay for safety reasons, even if you have withdrawn. We may still use the stored samples and/or the data derived from your samples unless you ask us not to, in which case any existing samples or data related to you will be destroyed.

Please note that it may not be possible in all cases, particularly after much time has passed, to destroy or remove samples such as tissue samples or cell lines derived from these, or data associated with these samples, for instance if these have been transferred elsewhere, or used to generate published data.
13. What if there is a problem?

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study.

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 Dr Kate Williamson (contact details below) or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224, or the head of CTRG, email ctrg@admin.ox.ac.uk.

The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study. If you wish to contact the PALS team please contact ph: 01865 221473 or email: PALSJR@ouh.nhs.uk.

14. 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 participants’ interests. This study has been reviewed and given a favourable opinion by the South Central – Oxford B Research Ethics Committee. In addition, the protocol and study documents have been contributed to and reviewed by the patient charity, PSC Support, and they have formally endorsed this study.

15. Who is organising and funding the study?

The study is sponsored by the University of Oxford and the funding is supplied by an educational grant from the Wellcome Trust. It is being organised by the John Radcliffe Hospital hepatology team and the Keshav and Klenerman laboratory groups in the Translational Gastroenterology Unit.
16. Will I be reimbursed for taking part?

You will be suitably reimbursed for any travel costs incurred for your study visit(s) to the hospital. Otherwise your samples are donated as a gift to the study, and no financial reward will be given for these.

17. What will happen to the results of this study?

The results of this research study may be presented at local, national and international medical and scientific meetings or in publications, and to patient support groups. Some of the research being undertaken will also contribute to the fulfilment of an educational requirement (a doctoral thesis). You will not be identified in any way in publications or reports.

We will list any academic publications derived from this work on the Translational Gastroenterology Unit website available at: http://www.expmedndm.ox.ac.uk/tgu/home.

In addition, a lay report summarising the main results of the study will be sent to you at completion of the study, and will also be published on appropriate departmental and patient websites. You may contact us after you have finished the study to ask about when and where this will be available via the contact information below.

18. Further information and contact details:

For additional information or queries now or at any future time please contact:

Dr Kate Williamson
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Telephone: 01865 227 752 (office hours) or 01865 221185 (out of hours, or emergency)

Thank you for considering taking part in this study. If you are interested in taking part, please contact us via the details given above.