



Participant Information Sheet

IL-6 Inhibition in Patients with Depression and Low-grade Inflammation: The Insight Study

Thank you for your interest in this study, which is investigating the role of immune system, particularly inflammation, in depression. Before you decide whether you wish to participate, 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 with others if you wish. Let us know if you have any questions or need further information.

Part 1 tells you the purpose of the study and what will happen if you decide to take part. Part 2 gives more detailed information about the study.

Part 1

What is the purpose of this study?

Depression causes suffering to millions of people and a considerable proportion of people who take antidepressants do not get better. Research suggests that low-grade inflammation (overactivity of one aspect of immune system, which can be measured by a blood test) may play a role in the development and persistence of depressive symptoms. Inflammation may also make it difficult for patients to get better despite taking antidepressant treatment.

The aim of this study is to test the effects of a single dose of an anti-inflammatory drug called tocilizumab on mood, attention, memory, and a number of blood biomarkers in patients with depression who show evidence of low-grade inflammation. We are interested to examine whether reducing inflammation with this drug can help reduce symptoms of depression. We will be looking at biochemical changes related to the inflammation level as a result of taking this drug to see if these changes could influence certain symptoms of depression. Another purpose of this study is to compare patients with depression who have evidence of inflammation with those who do not, in order to understand whether these groups of people are different from each other.

The study will give us more insights into whether inflammation plays a role in causing depression and whether anti-inflammatory drugs may be used for treating some patients with depression in future.

Why am I being invited to take part?

You have been chosen because you are receiving treatment for depression.

Do I have to take part?

No – participation is entirely voluntary, and if you decide not to take part it will not affect your usual medical care.

Who can participate in this study?

People with depression aged 20-65 years who are taking an antidepressant, have evidence of inflammation (this will be confirmed by a blood test), and who are safe to receive a single dose of an anti-inflammatory drug called tocilizumab can participate in this study.

Specifically, we are looking for people who meet the following criteria:

- Currently meet criteria for diagnosis of depression, and taking an antidepressant medication for at least four weeks
- Aged 20-65 years
- Able to understand written and spoken English
- Willing and able to provide blood samples
- Willing and able to give informed consent for participation in the study, including consent to share information with GP and to access GP records to establish eligibility
- Willing to abstain from strenuous exercise for 72 hours prior to assessment
- *Do not* have Tuberculosis, Hepatitis B, Hepatitis C and HIV (confirmed by blood test and chest X-ray)
- *Not* currently pregnant or breast feeding
- *No* history of infection requiring hospitalization or treatment with intravenous antibiotics in the month prior to eligibility assessment
- *No* history of serious liver, heart or kidney disease or certain other medical disorders
- *Not been* previously diagnosed with bipolar disorder, psychosis, eating disorder, or emotionally unstable personality disorder (borderline personality disorder)

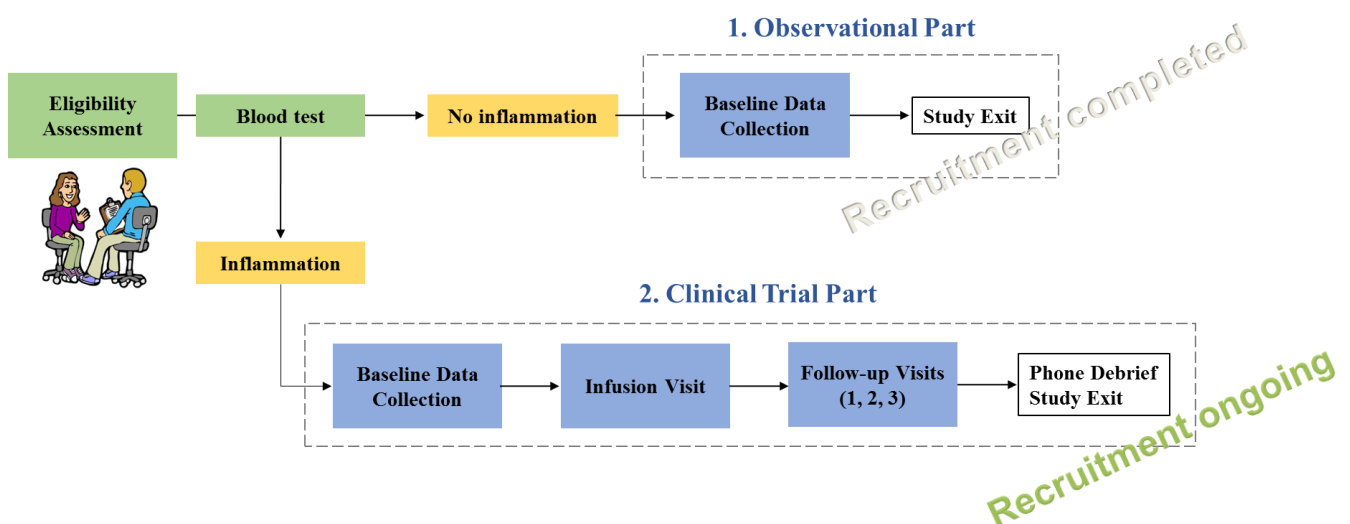
What will happen if I agree to participate in this study?

If you indicate that you are willing to participate and you are deemed potentially eligible to take part based on your response to screening questionnaires accompanying this information sheet, we will arrange a face-to-face assessment to confirm whether you are eligible to take part in this study.

The study has two parts: (1) observational part, (2) clinical trial part. You may be eligible for the first part of the study only or for both parts. Please see a figure below, which outlines what is involved in taking part in the study.

Throughout the study, we will endeavour that the time and place of assessments suits you, you are welcome to have someone accompany you to all appointments. Some assessments can be done at your home if you so wish. Refreshments will be available for you during each study visit.

Figure: Overview of Study Visits



Taking part in the study involves the following steps:

Eligibility assessment

At this meeting, a member of the research team will meet you to answer any questions you have. They will take your consent for taking part in the study if you decide to proceed. This assessment will last up to 60 minutes. We will ask you to complete a few questionnaires, including one to confirm you currently meet criteria for diagnosis of depression. We will take a blood sample, which will be used to measure the level of inflammation

Based on this assessment and blood test, we will inform you whether you are eligible to take part in the study or not. There are three likely scenarios:

1. You are not eligible to take part: there will be no further contact for the purpose of this study.
2. You are eligible to take part and your blood test shows no inflammation: you will be invited to take part in the observational part of the study (see below).
3. You are eligible to take part and your blood test shows inflammation: you will be invited to take part in both observational and clinical trial parts of the study (see below).

Observational Part

This will involve one face-to-face data collection assessment, called "baseline data collection", lasting up to two hours; you will be welcome to take a break. Participants with and without evidence of inflammation can take part in this assessment. During this visit, we will ask you to:

- complete a few questionnaires (such as depressive symptoms, sociodemographic information)
- complete a few cognitive tests (such as memory, attention)
- provide a blood sample.

If you are taking part in the observational part only, your participation in the study would end after this visit.

Clinical Trial Part

All participants taking part in the clinical trial part will complete a face-to-face data collection assessment initially, which will be the same as baseline data collection (see above). In addition, the clinical trial part will include four meetings: infusion session, follow-up 1, follow-up 2, and follow-up 3. The duration for each of these sessions will vary: approximately two and half hours (infusion session), one hour (follow-up 1), two hours (follow-up 2), one hour (follow-up 3).

We will do further blood tests and a chest X-ray prior to the infusion session to make sure it is safe for you to receive the anti-inflammatory drug tocilizumab.

Infusion Session:

The infusion session will take place at Addenbrooke's hospital in Cambridge. During this visit, you will:

- receive an intravenous infusion of either tocilizumab (anti-inflammatory drug) or normal saline (placebo or dummy drug) over an hour
- have your pulse and blood pressure checked occasionally
- complete a few questionnaires to assess how you feel

Follow-up Visits:

These meetings will take place approximately about 7, 14, and 28 days after the infusion. These visits will be similar to the initial face-to-face data collection assessment (baseline data collection). During these visits, we will ask you to:

- complete a few questionnaires
- complete a few cognitive tasks as before (only on day 14)
- provide a blood sample.

Approximately 42 days after infusion, a member of the study team will contact you by telephone to provide a final debrief and answer any questions you may have. That would be your final contact with the study team and your exit from the study.

Expenses and Payments

You will be compensated for your time and inconvenience: £100 for the baseline data collection meeting, £50 for the infusion session, £75 for follow-up 1, £100 for follow-up 2, and £75 for follow-up 3. You will also be reimbursed for your travel expenses for each visit. The study team can arrange and pay for train tickets, if required. Please note the payment constitutes declarable income for tax and benefit purposes. If you are a benefit claimant and would like advice about this, we can provide you with the contact details.

What is Tocilizumab?

Tocilizumab is an anti-inflammatory drug. It is licensed in the UK for treatment of rheumatoid arthritis and juvenile idiopathic arthritis. It is not currently licensed as a treatment for depression. Tocilizumab blocks one of the main pathways involved in inflammation called interleukin 6 receptor. By blocking this receptor, it reduces the activity of an inflammatory protein called interleukin 6 (IL-6). As a result, treatment with this drug leads to a reduction in the level of inflammation in our body.

What are the risks of participating in the Insight study?

You will be required to donate blood samples, which will be collected by trained staff. This will involve the use of a needle; some people may feel some discomfort and some people might develop a temporary bruise. We will make sure you are as comfortable as possible; you will be able to lie down during blood collection.

As part of the safety screening for taking part in the study, you will have a chest X-ray to check that you do not have Tuberculosis. The X-ray uses ionising radiation. The dose of radiation received during X-ray is equivalent to that received, on average in the UK, from natural sources of radiation in the environment every three to ten days. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. However, we are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this study will only add an extremely small chance (less than 1 in 1.5 million) of this happening to you.

The study will involve a single intravenous infusion of tocilizumab (anti-inflammatory drug) or normal saline (placebo/dummy drug) administered continuously over an hour. You will be required to sit or lie-down during the infusion. Infusion will take place in Addenbrooke's Hospital under supervision of a doctor; a member of the study team will be with you at all times.

As with all medications, there is always a chance of side effects. According to clinical trials in patients with rheumatoid arthritis, the most common side effects of treatment with tocilizumab are respiratory and other infections (about 7%). Other common side effects

include headache (7%), hypertension (6%), altered liver enzymes (6%), nausea (6%), and diarrhoea (5%). The proportion of patients who discontinued treatment due to any side effects in clinical trials was 5% for those taking tocilizumab and 3% for those taking placebo (dummy pill).

To minimize risk of infections, we will not include people who have a history of repeated infections, recent serious infection. We will exclude people who have Tuberculosis, HIV, Hepatitis B, Hepatitis C, VZV, other serious physical illness, and pregnant/breast feeding women, and those with uncontrolled blood pressure and other physical illness.

Serious allergic reactions (anaphylactic reactions) such as shortness of breath, swelling of lips can occur during or after infusion, but these are rare. Occurrence of such severe reactions leading to discontinuation of treatment has been reported in 0.1% (3/2644) in the 6-month, controlled trials and in 0.2% (9/4009) in the all-exposure population. These reactions were generally observed during the second to fourth infusion of tocilizumab, so are unlikely to occur after a single dose (as used in this study). We will give you written information about how to seek help should any adverse effects occur. We will also record any adverse effects during follow-up assessments.

In order to prevent any possible risk of the drug affecting pregnancies, we will ask all participants who are sexually active to use contraception for six weeks after infusion. We will ask male participants not to donate sperm samples for six weeks after infusion.

Why do we collect blood samples?

Blood samples will be used to measure the level of inflammation, and to make sure people with certain conditions for whom it is not safe to receive tocilizumab are not included in the study (Tuberculosis, HIV, Hepatitis B, Hepatitis C, VZV). We will use blood samples to measure particular biomarkers (e.g., inflammatory markers, lipids, proteins, genes, immune cells) to gain a better insights into the links between our immune system and depression.

What are the possible benefits of taking part?

There is no direct benefit to participating in the study. However, we hope that the study will enhance our understanding of the causes of depression particularly whether inflammation plays a role in causing depression. The findings may suggest new treatment directions for some patients with depression. By taking part, you will find out whether there is evidence of low-grade inflammation in your body. The level of inflammation that we are interested in (serum/plasma high sensitivity CRP concentration 3mg/L or higher) is seen in about 40% of the general population, so if your blood test shows evidenced of inflammation it is not necessarily a cause for concern. Reasons for elevated CRP in the absence of an inflammatory illness could include obesity, smoking, alcohol use, lack of exercise, so knowledge of the level of inflammation might prompt participants to adopt a healthier lifestyle.

Part 2

What will happen if I want to withdraw from the study?

You are free to withdraw from the study at any time, without giving a reason. Your usual medical care will not be affected, if you decide not to continue with the study.

Will my taking part be kept confidential?

All information collected about you during the course of the study is strictly confidential. Any information that can identify you personally will be stored electronically at University of Cambridge Clinical School computer server in a secure password protected folder. The server is maintained by clinical school IT team. Only the Chief Investigator and his nominated research staff will be able to access this folder using University of Cambridge computers and laptops, which are also password protected. All paper material (e.g., consent forms and forms containing personal information) will be stored in a locked filing cabinet at the University of Cambridge. Paper forms containing personal identifiable data completed at study sites will be securely transported to the University of Cambridge, e.g., in a locked bag. Identifiable data may be stored for up to 12 months after the study has ended. All data are handled in compliance with UK confidentiality and data protection laws. Any information about you that leaves the University Psychiatry department will have personally identifying information (name, date of birth, address) removed so that you cannot be recognized from it. Routinely, only members of the study team will have access to individual level data, who are bound by confidentiality and data protection laws. Rarely, it is necessary to disclose individual information (such as if demanded by a court order or if the study team has concerns that there may be risk of serious harm to a participant and/or other people). In such cases, we will make all reasonable efforts to contact you in advance of disclosing this information to explain why it was being done.

What will happen to my blood samples if I agree to take part?

We will isolate, count and test certain components of your blood such as immune cells, proteins, lipids, metabolites and other biomarkers. We will also isolate DNA/RNA from your samples to help us determine genetic factors that play a role in immune function and depression. All samples will be anonymised before being sent to the laboratory for analysis; sample labels will contain participant ID and minimal personal identifying information (sex, date of birth) so that you cannot be recognized from it. Samples may be stored at the University of Cambridge in a secure freezer for up to 10 years after the completion of the study for additional research. Samples will only be used to understand the role of inflammation in depression, and to develop tests/assays/drugs related to inflammation and/or depression. The research may begin at any time during the study or the post-study storage period. Stored samples will be anonymised throughout the sample storage and analysis process; samples will be labelled with participant ID and date of birth, and no other personal identifiers. You may withdraw consent for your samples to be stored for future research.

What if relevant new information becomes available?

If new information pertaining specifically to your health becomes available, you and your GP will be informed. If the screening tests completed as part of the study produce findings of clinical significance, we will inform you and your GP requesting referral for further investigations. Otherwise, any scientific findings from the research will be published in journal articles, websites and other outlets as usual. We will not include any personal identifiable information in publications.



What will happen to the results of this research study?

We will analyse and write up the results and present them in scientific conferences. We will also publish the findings in scientific journals. However, there will be nothing in published results which could identify individual participants. All data will be stored securely for ten years. If you wish, you will be notified of the study findings when these become available.

Who is organising and funding the research?

The study is being organised jointly by the University of Cambridge, and Cambridgeshire and Peterborough NHS Foundation Trust. The study is supported by funding from the Wellcome Trust. GP practices and mental health services in Cambridgeshire, Suffolk and Norfolk are taking part in this research as recruitment sites.

Who has reviewed this study?

All research in the NHS is approved by a Research Ethics Committee; this is an independent group of people who are there to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by the South Central - Oxford B Research Ethics Committee, reference number 18/SC/0118.

What if there is a problem?

If you have a concern about any aspect of the study, you should ask to speak to the researchers who will do their best to answer your questions. If this is not satisfactory, you are encouraged to speak to The Patient Advice and Liaison (PALS) service, who can offer support and advice regarding complaints. PALS can be contacted on Freephone 0800 376 0775 or by email pals@cpft.nhs.uk

In the unlikely event of anything-untoward happening, insurance has been taken out to cover this study. The University of Cambridge has public liability and professional indemnity insurance in place to cover negligent harm.

Who should I contact for more information?

If you have any questions or require more information about this study, please do not hesitate to contact members of the study team. Contact details:

Bianca Oltean
Research Assistant, Insight Study
Department of Psychiatry, University of Cambridge
Herchel Smith Building for Brain and Mind Sciences
Cambridge Biomedical Campus, Cambridge, CB2 0SZ, UK
Tel: 01223 768503
Email: bo276@medschl.cam.ac.uk

Dr Golam Khandaker
Chief Investigator, Insight Study
Department of Psychiatry, University of Cambridge
Level E4, Addenbrooke's Hospital
Cambridge Biomedical Campus, Cambridge, CB2 2QQ, UK
Tel: 01223 768510
Email: gmk24@medschl.cam.ac.uk

Preferred email contact: insight.study@nhs.net

Thank you for taking the time to consider participating in the Insight Study!