Participant Information Sheet – Patients
Psychosis Immune Mechanism Stratified Medicine Trial: The PIMS Trial

This document was prepared in collaboration with people with lived experience of psychosis.

Thank you for your interest in this study, which is investigating the role of the immune system, particularly inflammation, in psychosis. 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?
Psychotic disorders, like schizophrenia, cause suffering to millions of people, but not everyone who takes antipsychotic medication gets better. Research suggests that low-grade inflammation (overactivity of one aspect of the immune system, which can be measured by a blood test) may play a role in the development and persistence of psychotic symptoms. Inflammation may also make it difficult for patients to get better despite taking antipsychotic medication.

The aim of this study is to examine the role of inflammation in psychosis. This will be done by testing the effects of reducing inflammation levels in the body, using a single dose of an anti-inflammatory drug called tocilizumab, on psychotic symptoms, mood, cognition, and a number of blood biomarkers in patients with psychosis who show evidence of low-grade inflammation. We are interested in examining whether reducing inflammation with this drug can help reduce symptoms of psychosis. We will be looking at biochemical changes related to inflammation levels as a result of taking this drug to see if these changes could influence certain symptoms of psychosis. Another purpose of this study is to compare patients with psychosis who have evidence of inflammation with 1) those who do not have evidence of inflammation, and 2) those who do not have any mental illness, in order to understand whether these groups of people are different from each other.

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

Why am I being invited to take part?
You have been chosen to take part because you have a current diagnosis of psychosis.

Do I have to take part?
No – participation is entirely voluntary. If you decide not to take part, it will not affect your usual medical care.

Who can participate in this study?
We are looking for people aged 18-40 years that fit into one of the following 3 categories:

(1) Psychosis with inflammation: People with psychosis who are within the first 3 years of diagnosis, who have evidence of inflammation (this will be confirmed by a blood test), and who are safe to receive the anti-inflammatory drug, tocilizumab.

(2) Psychosis without inflammation: People with psychosis who are within first 3 years of diagnosis and who do not have evidence of inflammation (confirmed by a blood test).

(3) Healthy comparison group: People that do not have a history of any psychiatric illness. ← Recruited separately

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

- Currently meet criteria for diagnosis of schizophrenia/related psychosis and are within 3 years of first diagnosis
- Aged 18-40 years
- Able to understand written and spoken English
- 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 and able to provide blood samples
- Willing to abstain from strenuous exercise for 72 hours prior to assessment
- *Do not* have a body mass index (BMI) above 35
- *Do not* have Tuberculosis, Hepatitis B, Hepatitis C, or HIV (confirmed by blood test and chest X-ray for participants entering the clinical trial part of the study; see below)
- *Do* have evidence of antibodies against varicella-zoster virus (VZV) and SARS-CoV-2 (confirmed by a blood test for participants entering the clinical trial part of the study; see below)
- *Not* currently pregnant or breast feeding
- *No* history of antisocial personality disorder, autism or other neurodevelopmental disorder, or major traumatic brain injury
- *No* current diagnosis of eating disorder
- *No* current infection
- *No* history of infection requiring hospitalisation 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
- *No* history of substance use disorder within the past 6 months

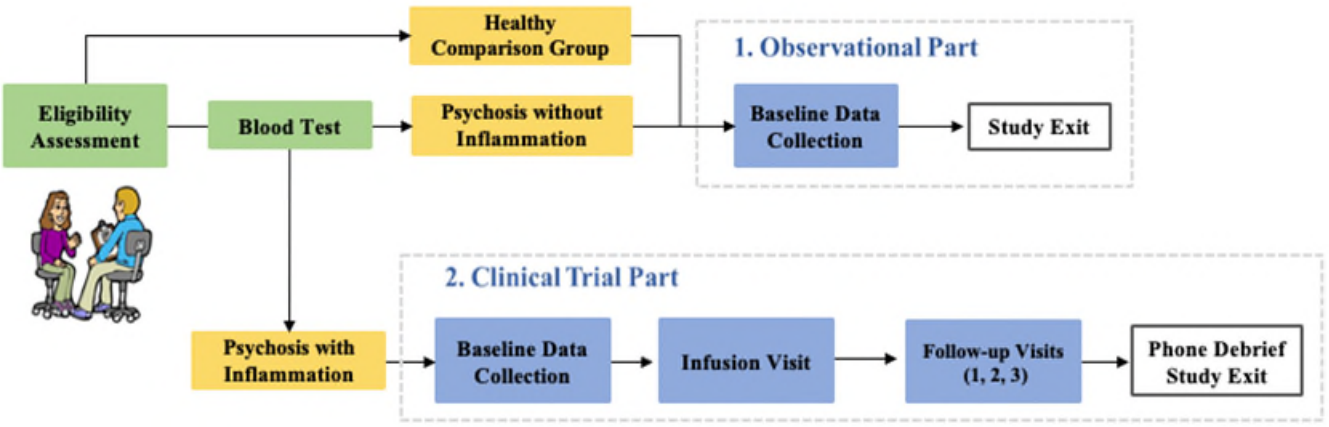
What will happen if I agree to participate in this study?

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 an eligibility assessment to confirm whether you are eligible to take part in this study.

The study has two parts: (1) observational part, and (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 when taking part in the study.

Throughout the study, we will endeavour that the time and place of assessments suits you and all visits will be scheduled based on your availability. You are welcome to have someone accompany you to all appointments. Refreshments will be available for you during each study visit.

Figure 1: Overview of Study Visits



Taking part in the study involves the following steps:

1) Eligibility assessment

At this meeting, a member of the research team will meet you to answer any questions you may have. If you decide to proceed, they will take your consent for participating in the study. This assessment will last up to 60 minutes. We will ask you to complete a few questionnaires, including one to confirm whether you currently meet criteria for diagnosis of schizophrenia or a related psychosis. You will also be asked to provide a blood sample, which will be used to measure your 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 regarding this study.
2. You are eligible to take part in the psychosis without inflammation group: you will be invited to take part in the observational part of the study (see below).
3. You are eligible to take part in the psychosis with inflammation group: you will be invited to take part in both the observational and clinical trial parts (see below).

2) Observational Part

This will involve one assessment, called the "baseline data collection" assessment. This visit will last about four hours; you will be welcome to take breaks. All eligible participants take part in this assessment. During this visit, we will ask you to:

- complete questionnaires (such as psychiatric symptoms and sociodemographic information)
- complete a few cognitive tests (such as memory and attention tasks)
- provide blood samples
- have an MRI brain scan (optional).

If you are taking part in the observational part only (i.e., psychosis without inflammation group), your participation in the study will end after this visit.

3) Clinical Trial Part

All participants taking part in the clinical trial part of the study will complete the observational part of the study (see above). In addition, the clinical trial part will include four meetings: the 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 and follow-up 3), and four hours (follow-up 2).

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 approved clinical research facilities in Bristol, Birmingham, or Cambridge.

During this visit, you will:

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

This is a double-blind study which means that neither you nor the study team will know whether you have received tocilizumab or normal saline. At the end of the entire study, you will have the option to know whether you received the drug or placebo. You are welcome to

bring along a mobile phone, book, etc., and a friend/family member for support during this visit. Refreshments will be provided.

Follow-up Visits:
These meetings will take place approximately 7, 14, and 28 days after the infusion. These visits will be similar to the baseline data collection assessment. During these visits, we will ask you to:

- complete questionnaires
- provide blood samples
- complete a few cognitive tests, as before (only on day 14)
- have an MRI brain scan, as before (only on day 14; optional).

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. This will be your final contact with the study team and you will exit the study.

Possible Change in Study Activities due to Covid-19 Outbreak

We will take a number of steps to minimise the risk of infection to study participants and research staff in line with government and local guidelines. For instance, we will do the following:

- Evidence of COVID-19 immunity will be required before the infusion visit. A blood test will be performed to check antibody levels against SARS-CoV-2 to ensure participants are likely to be protected against severe COVID infection/complications.
- Data collection for all sessions will be carried out remotely, e.g., via telephone, email, or video conference, as much as possible.
- Face-to-face visits will be limited to only those which are necessary, e.g., blood collection, chest X-ray, infusion visit, cognitive testing, and brain scan.

When face-to-face visits are required, appropriate measures will be taken to minimise risk of infection to participants and research staff, in line with the Universities of Bristol, Birmingham, and Cambridge, and NHS guidelines. These measures may include:

- A brief telephone call 24-48 hours before all face-to-face visits to assess COVID-19 symptoms.
- Handwashing and use of hand sanitiser, face mask, and other PPE as appropriate by study participants and research staff throughout the study visit.
- Maintaining social distance throughout the visit, where possible.
- As per standard operating procedures for the research facilities we use, all workspaces and clinic areas will be cleaned before and after individual use.
- Participants and staff will be encouraged to use personal transport. If necessary, a taxi will be provided for participants to attend the appointment.
- Participants will be encouraged not to bring anyone to the appointment.
- When access to the hospital environment is required (i.e., for chest X-ray or infusion visit), we will follow NHS guidance on COVID-19 safety including use of PPE.

Expenses and Payments

You will be compensated for your time and effort: £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. In addition, you will be reimbursed for your travel expenses. Please note the payment constitutes declarable income for tax and benefit purposes. We can point you to the right person for more information if this is relevant.

What is Tocilizumab?

Tocilizumab is an anti-inflammatory drug, licensed in the UK for treatment of rheumatoid arthritis. It is not currently licensed as a treatment for psychosis. Tocilizumab blocks one of the main pathways involved in inflammation called the 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 is an MRI scan?

MRI stands for “magnetic resonance imaging”. It is used routinely in modern medicine to take a 3D picture of your brain. MRI will allow us to test directly whether a reduction in inflammation levels in the body after taking the drug, tocilizumab, is also accompanied by a reduction in levels of inflammation in the brain. We will also compare brain images of psychosis patients with and without inflammation with brain images of members of the healthy comparison group to understand how these groups of people are different from each other. MRI involves a strong magnetic field. Therefore, you will need to remove all metal belongings from your person, and you cannot have any metal in your body (e.g., pacemaker, cochlear implant). You will remain clothed throughout, and metal that is part of your clothes (jeans rivets, etc.) is not usually a problem. During the scan, you will lie on a hospital-style bed with your head inside the MRI scanner. To get a good picture of your brain, it is important that you keep your head as still as possible when in the scanner. Scans typically last around 1 hour.

What if the MRI scan suggests something unusual about my brain?

Our research studies are designed to improve our knowledge of the brain. They are not designed to look for any problems in the brain. After your scan, a doctor will examine these pictures, although this will not be done on the day of the study. Minor changes are sometimes found in completely healthy people. You should know that because our pictures are taken for a specific research purpose, not all problems that might be found by other MRI scans are necessarily seen. On rare occasions, we might find something that should be investigated further. If this is the case, we will inform you and your GP so appropriate steps can be taken.

What are the risks of participating in the PIMS Trials?

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 slight discomfort and you may develop a temporary bruise. We will make sure you are as comfortable as possible.

If you take part in this study, you may have a chest X-ray to assess for TB in the lung. All X-rays use ionising radiation to form images of your body. Ionising radiation may cause cancer many years or decades after the exposure. The chance of this happening to you as a consequence of taking part in this study is extremely small (a cancer risk of around 1 in 1.5 million). The amount of radiation you will be exposed to is equivalent to that received, on average in the UK, from natural sources of radiation in the environment every three to ten days.

This study may involve getting an MRI brain scan. Strong magnets used during the scan can affect any metal that may be in your body and so, you will be asked to remove all metal belongings and screened to ensure you have no metal within your body (e.g., pacemaker, cochlear implant). Some discomfort may be caused by the loud noise created by the machine and due to the confined space of the testing area. To minimise discomfort, ear plugs and headphones will be provided to overcome the loud noise and mirrors will be positioned in and outside the machine, allowing you to view outside of the machine. You will also be able to communicate with a trained MRI operator at all times via the headphones provided. Some people experience mild transient vertigo when they are being moved into

the MRI machine. You will be provided with a hand-held alarm that you can squeeze if you become uncomfortable or distressed at any time. This will alert the operator who will remove you from the scanner immediately.

If you take part in the clinical trial part of the study, you will receive a single intravenous infusion of either tocilizumab (an anti-inflammatory drug) or normal saline (a placebo/dummy drug), administered continuously over one hour. You will be required to sit or lie-down during the infusion. Infusion will take place at clinical research facilities under supervision of a doctor, and a member of the study team will be present.

We have taken precautions to make sure it is safe for you to receive an infusion of tocilizumab. However, 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%). Serious allergic reactions (anaphylactic reactions) such as shortness of breath or swelling of lips can occur during or after infusion, but these are rare (0.1% or 3/2644 in 6-month controlled trials). There is also a risk of gastrointestinal perforation, but the risk is relatively low - 2.53/1000 patients per year. 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). Please note, these reactions were generally observed during the second to fourth infusion of tocilizumab. Only one dose of tocilizumab or dummy drug will be given during 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.

To minimize the risk of infection, we will not include people who have a history of repeated infections or recent serious infection. We will exclude people who have Tuberculosis, HIV, Hepatitis B, Hepatitis C, VZV (or do not have VZV antibodies), and those with uncontrolled blood pressure and other serious physical illness. The use of tocilizumab during pregnancy and breastfeeding is limited. Whilst there is no evidence to suggest it might harm the foetus, to eliminate any risk to mother, foetus, or neonate, women who are pregnant or breastfeeding will be excluded from the trial.

In order to prevent any possible risk of the drug affecting pregnancies, we will ask all participants who are sexually active to use effective contraception (as defined by the MHRA) for 3 months after infusion (e.g., combined hormonal contraceptives, progestogen-only pills, intramuscular injections, copper intrauterine device, or progestogen implant). We will also ask male participants not to donate sperm samples for 3 months after infusion. At the follow-up 2 visit, we will also perform a physical health screening and take a blood sample to check for any signs of adversity.

Should a participant become pregnant within 30 days after receiving the infusion, the participant's GP will be notified that the participant may have received a single dose of tocilizumab. There are no special interventions required for individuals taking tocilizumab during pregnancy.

Why do we collect blood samples?

Blood samples will be used to measure levels of inflammation. We will also test these samples for evidence of certain conditions (e.g., Tuberculosis, HIV, Hepatitis B, Hepatitis C, VZV) to make sure people with these conditions, for whom it is not safe to receive tocilizumab are not included in the study. We will use blood samples to measure particular biomarkers (e.g., inflammatory markers, lipids, proteins, immune cells) to gain a better insight into the links between our immune system and psychosis. Genes play an important role in whether an individual develops psychosis, as well as partially determining their

prognosis once it has developed. Therefore, blood samples will also be used for genetic analyses.

What are the possible benefits of taking part?

There is no direct benefit to you by participating in the study. However, we hope that the study will enhance our understanding of the causes of psychosis, particularly whether inflammation plays a role. The findings may help to develop new treatments for some patients with psychosis.

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.

Should you lose the capacity to consent during your participation, you will be removed from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected, or any other research procedures carried out.

How will we use information about you?

We will need to use information from you, your medical records, and your GP for this research project. This information will include your name, initials, date of birth, contact details, and NHS number.

People will use this information 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. Your data will have a code number instead. 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 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.
If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

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/
- our leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by sending an email to [email], or
- by ringing us on [phone number].

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. With your permission, we will also isolate DNA and RNA from your samples to help us determine genetic factors that play a role in immune function and psychosis. All samples will be anonymised before being sent to the laboratory for analysis. Sample labels will be stored with unique ID numbers to allow us to link data from your samples to other data about you. Researchers using your samples will not be able to link any of your results to your personal information (e.g., your name, age, date of birth). With your consent, samples may be stored at the Universities of Bristol, Birmingham, and Cambridge in freezers for up to 10 years after the completion of the study for additional future research. This may include use by researchers outside of the UK, EU, and EEA. Your data will be used for research purposes only and we will not sell or make any profit from the samples you donate. Samples will only be used in ethically approved research to understand the role of inflammation in psychosis, and to develop tests/treatments related to inflammation and/or psychosis. The research may begin at any time during the study or during the post-study storage period. Stored samples will be anonymised throughout the sample storage and analysis process. You may withdraw consent for your samples to be stored for future research by contacting a member of the study team.

What if relevant new information becomes available?

If new information pertaining specifically to your health becomes available, you, your GP, and, if necessary, your mental health team 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 investigation. 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 any scientific publications.

What will happen to the results of this research study?

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

Who is organising and funding the research?

The study is being led by the University of Bristol in collaboration with the Universities of Birmingham and Cambridge and the NHS. The study is supported by funding from the UK Medical Research Council. NHS mental health services in Bristol, Birmingham, Cambridgeshire, Suffolk, Norfolk, and Gloucestershire are taking part in this research.

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 **XXX** Research Ethics Committee, reference number **XXX**.

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 073 1778or by emailing awp.pals@nhs.net.

If you have a complaint about how the researchers have handled your information, you should first contact the research team. If the issue is not resolved, you can then contact the

Data Protection Officer. The research team can give you the details for the right Data Protection Officer. If you are not happy with their response or believe they are processing your data in a way that is not right or lawful, you can contact the Information Commissioner's Office (ICO) on 0303 123 1113 or www.ico.org.uk.

In the unlikely event of anything untoward happening, insurance has been taken out to cover this study. The University of Bristol have 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:

Study Team Contact Information

[Name 1]
[Title]
Address:
Tel:
Email:

[Name 2, if necessary]
[Title]
Address:
Tel:
Email:

Chief Investigator Contact Information

Professor Golam Khandaker
Chief Investigator, PIMS Trial
Professor of Psychiatry, Bristol Medical School, University of Bristol
Honorary Consultant Psychiatrist, Avon and Wiltshire Mental Health Partnership NHS Trust
Address: [enter up to date info here]
Tel: [enter up to date info here]
Email: golam.khandaker@bristol.ac.uk

Preferred email address for the trial: [study email address]

Thank you for taking the time to consider participating in the PIMS Trial!