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Imperial College London

CALMED

Clinical Effectiveness and Cost Effectiveness of Clozapine for inpatients with Borderline Personality Disorder

Patient Information Sheet

- We would like to invite you to take part in our research study
- Before you decide, it is important that you understand why the research is being done and what it would involve for you
- Please take time to read the following information carefully. A member of our team will go through the information sheet with you and answer any questions you may have. Discuss it with your friends, family or doctor if you wish.
- You are free to choose whether you would like to take part. If you decide not to take part, it will not affect any care you may be receiving
- Thank you for taking the time to read this information. If you decide to take part, please keep this information sheet
- 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 this study?

Over a million people are affected by borderline personality disorder in Britain. People with these problems experience sudden and distressing changes in mood, negative feelings about themselves and difficulties in relationships with others. People with borderline personality disorder sometimes act in ways which pose risks to themselves or to others, which can lead to an admission to hospital. Even though there are no approved drugs for the disorder, many patients are treated with large amounts of medication, with unknown long-term effects. In recent years, clinicians have tried prescribing a drug called clozapine, but it is not clear how helpful this is.

The purpose of this study is to find out whether clozapine improves mental health and quality of life for people with borderline personality disorder. We are also looking to find out whether adding clozapine to usual treatment reduces time spent in hospital and decreases use of other types of medication. Our aim is to recruit 222 participants over 18-months.

2. Why have I been approached?

You are a patient who has been receiving treatment for borderline personality disorder, and we believe you have not responded well to your current care. For this reason, we would like to invite you to take part in the study.

3. Do I have to take part?

No, it is up to you to decide. We will describe the study, go through this information sheet with you, and then give you a copy to keep. Even if you do agree to take part, you are free to withdraw at any time without giving a reason. If you choose not to take part or later withdraw, our researchers may ask the reason for this so that we can understand people's thoughts on the study. You do not have to answer, and if you do, nothing you say will affect the care that you are entitled to and the standard of care you receive.

4. What will happen if you agree to take part?

If you are interested in learning more about the study, we will arrange a meeting with a researcher to discuss taking part and give you the opportunity to ask any questions. If you are happy to take part in the study the researcher will ask you to complete and sign a consent form to say that you would like to be included.

With your permission, we would also like to have contact details of a relative or friend that the research team could contact if they were unable to get in contact with you directly. If you would rather we didn't contact a relative or friend, you do not have to give us their details.

The treatment

If the checks show the study is suitable for you, you will be randomly assigned by a computer to one of two groups, meaning that you will have a 50:50 chance of being in either group. One group will receive clozapine capsules (the study drug) and the other group a placebo (a dummy capsule). Placebo capsules look exactly like the clozapine capsules, but do not contain any medication. You, your doctor and the researchers you meet will not know whether you are being given the placebo or the clozapine capsules. This allows for a fair assessment of the effectiveness of clozapine. Your doctor will be able to find out quickly which treatment you are receiving if s/he needs to. Taking part in the study will not stop your doctor changing your other treatments or adding new medication if this is considered the best thing for you.

You will be asked to take study capsules twice a day for 6 months. We will start you on a low initial dose of 12.5mg, which will be gradually increased to 300mg depending on how well you feel. The reason the dose is adjusted is to keep the side effects to a minimum. If there is a need for a higher dose, you may be prescribed a maximum dose of 400mg.

Blood monitoring

Everyone that takes part in the study will be asked to provide a blood sample at the start of the study and regularly throughout the study. This is because clozapine can cause a significant reduction in white blood cells, a condition known as agranulocytosis. Our white blood cells are responsible for fighting infection and having less of these cells means a minor infection could develop into a more serious one. For this reason, everyone who takes part in the study must have their blood monitored to make sure they are able to start and continue taking the study medication.

In order for us to monitor your blood we are using an independent monitoring service who will keep your doctor informed of your blood results. You will be asked to give about a teaspoon of blood (4.5 ml) on a weekly basis for 18 weeks, and then every two weeks for the following 14 weeks to check your full blood count. The way your doctor will know if your blood result has the normal number of white blood cells in your blood is by a traffic light system (green, amber or red). The study medication will be given to participants with a 'green' result. An 'amber' result on a blood test indicates that the white blood cell count has dropped, in which case, we will revert to weekly blood tests, until the result is 'green' again. Whilst a blood test result is 'amber' participants may continue taking study medication.

About 1 in 100 people who take clozapine will get a 'red' result. A 'red' test result indicates that the white blood cell count is unsafe and study medication will be stopped. If this happened, participants

would need to have daily blood tests to monitor for signs of infection, normally no longer than two or three days. Any person who gets a 'red' test result on a blood test will not be given any more study medication but can continue with study visits.

Study visits

At the beginning of the study we will gather some information from you e.g. date of birth, gender and ethnicity, what medication you are currently taking or have previously taken and complete some questionnaires with you about your current mental health. We will also look at your most recent blood test to confirm that your white blood cells count is in the normal range. If you have not had a blood test within the last 10 days, we will arrange for you to have one.

Before you can start taking study medication, your health team will measure your blood pressure, temperature and pulse. This will then be repeated daily for at least three weeks, but could be more often, even up to one month. We will check if you have had your weight and blood sugar (glucose) checked within the last month, if not, these will also be done. Checking blood sugar level can be done in two ways; either a small device is put on your finger which pricks your skin, and a drop of blood is collected and gives an immediate result on blood sugar level. Or you may be required to give a blood sample, only about a teaspoon of blood would be taken. Your weight and blood glucose measurements will be repeated within three months of you taking the first dose of study medication.

Depending on your health, your doctor may ask you to have additional blood tests done, such as liver function tests or more frequent blood sugar level tests. Liver function tests give your doctor information that your liver is working properly. Only a small amount of blood is needed for these tests, again approximately a teaspoon.

It will take about two hours of your time to complete questionnaires, have your physical health checks done, and give blood (if required) and breaks can be taken if needed.

We will contact you again at 3 months to check we have your current contact details and complete some questionnaires with you. We will complete the same questionnaires again with you at 6 months. Each study visit will take just under 2 hours to complete.

With your permission we would like to collect information from your clinical records on use and type of inpatient treatment, use of community services and quantity and type of medication that you take every six months for a total period of 18 months after you entered the study.

Further research

If you agree, we would like to contact you again in a few years to check your contact details are correct and check on your long-term health by asking you some of the same questions we asked you during the study. We would also like to check your medical records to add to the information we already know about you. You would be given an Information Sheet detailing the additional research and a Consent Form. If you decided, you do not want to take part in this additional research it would not affect your participation in the study.

5. What is the medicine that is being tested?

Clozapine belongs to a group of medicines called second generation antipsychotics, which are thought to be safer than older versions of psychiatric drugs. Clozapine is normally prescribed for people with schizophrenia that have not responded well to other medication. It is believed clozapine works by re-balancing chemicals in the brain that influence the way we feel, act and react.

6. What are the possible benefits of taking part?

By taking part in this study, you will help us find out whether clozapine helps to improve the mental health of people who suffer from borderline personality disorder, and whether it reduces the time people spend in hospital.

7. What are the possible disadvantages or risks of taking part?

If you decide to take part, one disadvantage is the possible risk of a side effects from the study treatment (list of side effects is in a table on the following two pages). Your doctor and the researcher during study visits will ask about any side effects that have developed. If the side effects are serious your doctor may decide to stop study medication.

Another disadvantage is that you will be asked to give blood on weekly basis for 18 weeks, and then every two weeks for the following 14 weeks. Only a small amount of blood is needed for these tests (about a teaspoon) and will only be taken by a trained health care professional. Taking blood can sometimes cause minor bruising and carries a small risk of infection. However, the possibility of developing a local infection is low.

Important things to tell your doctor

Please tell your doctor immediately if you feel feverish, have a sore throat or other flu-like symptoms.

Clozapine causes constipation in some people, which can sometimes lead to severe stomach issues. Please tell your doctor if you are unable to poo, if you experience cramping pain, vomiting, or regularly pass wind.

If you are a smoker and are thinking of giving up or have quit, it is important that you tell your doctor as s/he may need to change your dose slightly. Similarly, if you drink caffeinated drinks such as coffee or Coca-Cola and suddenly stop, you should tell your doctor as well. This is because caffeine and nicotine effects the amount of medication in your body. Also, if you are taking hormonal contraceptives or would like to start whilst you are in the study please let your doctor know, as this may again require a change to your dose.

We also advise against drinking alcohol whilst you are taking study medication. As the medication may make you feel sleepy, it is best to avoid driving or operating machinery as well.

Side Effects

As with any medicine, side effects are possible with clozapine, however, not everyone who takes the medication will experience problems. To reduce the risk of side effects, you will be given a low dose of the study medication and your doctor will increase it slowly.

The most serious side effect of clozapine is agranulocytosis and for this reason, you are required to have regular blood tests as mentioned above.

If you have any worries about side effects, you can speak with your doctor or a member of the research team (contact details are on the last page). If you feel unwell whilst taking part in the study and seek medical advice, you should tell your doctor that you are taking part in this study. If you experience side effects whilst taking study medication it is important to let your doctor or nurse know. They can advise you if any action needs to be taken and they will report the issue to the Trial Office on your behalf.

Side Effects	What is it?
Uncommon side effects (between 1 in 100 and 1 in 1000 people will experience these)	
agranulocytosis	severe lack of infection-fighting white blood cells
dysphemia	stammering or stuttering
neuroleptic malignant syndrome	severe fever, fast heart rate and stiffness in arms and legs
Very Common side effects (more than 1 in 10 people will experience these)	
drowsiness	strong desire to sleep
dizziness	feeling lightheaded
tachycardia	abnormally fast heart rate
constipation	infrequent bowel movements
hypersalivation	increased production of spit
Common side effects (between 1 in 10 and 1 in 100 people will experience these)	
nausea/vomiting	feeling sick/being sick
leukopenia/neutropenia	when you have low white blood cells in your blood
weight gain	when you put on weight
dysarthria	when you have difficulty speaking
seizures	fits
convulsions	sudden/violent/ irregular movement of the body
myoclonic jerks	involuntary jerking of a muscle
extrapyramidal symptoms	movement disorders
akathisia	restlessness
tremor	shaking
rigidity	stiffness
headache	when your head is painful and pounding
blurred vision	things look fuzzy and you can't focus properly
ECG changes	changes in the heart's rhythm
postural hypotension	dizziness when you stand up
Hypertension	high blood pressure
anorexia	loss of appetite
syncope	fainting
dry mouth	dry mouth
elevated liver enzymes	indicate problems with liver
urinary retention	inability to empty bladder
urinary incontinence	loss of bladder control
hyperthermia	raised body temperature
disturbance in sweating	sweating more than usual
fever	raised temperature
fatigue	feeling tired

Side Effects	What is it?
Rare side effects (between 1 in 1000 and 1 in 10000 people will experience these)	
anaemia	low number of red blood cells
diabetes mellitus	high blood sugar level
hypertriglyceridemia	high level of a type of fat molecule in the blood
agitation	nervousness
restlessness	when you are unable to relax
confusion	your mind is all mixed up
arrhythmias	irregular heartbeat
pericarditis/pericardial effusion	fluid around the heart
circulatory collapse	failure of circulation to maintain oxygen and nutrient supply
myocarditis	when heart muscle swells and is less able to pump blood
thromboembolism	when blood vessels get blocked by blood clots
aspiration of ingested food	inhaling food into your lungs
nasal congestion	blocked nose
pleural effusion	fluid on the lungs
sleep apnoea syndrome	pauses in breathing during sleep usually accompanied by loud snoring
respiratory depression/arrest	rate or depth of breathing is lower, or stops
parotid gland enlargement	cavity in your mouth or face that holds saliva is swollen
pneumonia	chest infection
dysphagia	discomfort in swallowing
pancreatitis	inflamed/swollen pancreas
hepatitis	painful swelling of the liver
cholestatic jaundice	liver disease
thrombocytopenia	low blood platelets (help blood clot)
thrombocythemia	more blood platelets than normal
hyperosmolar coma	abnormally increased body fluids
ketoacidosis	too much harmful substances called ketones in the body
hyperglycaemia	too much sugar in your blood
hypercholesterolemia	too much cholesterol in your blood
obsessive compulsive symptoms	repeating things over and over again
tardive dyskinesia	involuntary repetitive body movements
cardiomyopathy/cardiac arrest	heart attack
Intestinal obstruction/faecal impaction	not being able to poo, this may be too big for you to push out and is serious if you don't get medical help
paralytic ileus	the bowel muscle stops working
fulminant hepatic necrosis	liver failure
interstitial nephritis	kidney problems
priapism	persistent and painful erection of the penis
skin reactions	problems with skin
sudden unexplained death	death without a known medical cause

Side Effects	What is it?
Side effects that we don't know how frequently they occur from the available data	
megacolon	large bowel is swollen
diarrhoea	frequent runny or watery poo
intestinal infarction	loss of blood supply to the small bowel
abdominal discomfort/heartburn	sore or swollen tummy or burning feeling in the chest
colitis	inside of the large bowel is swollen
hypotension	low blood pressure
hepatic steatosis	fat in the liver
hepatic necrosis	part of the liver dying
hepatotoxicity	liver damage with a chemical cause
hepatic fibrosis	extra connective tissue builds up in the liver
hepatic cirrhosis	liver stops working properly
other liver disorders including liver failure	other liver problems
renal failure	kidney stops working
nocturnal enuresis	night time bed wetting
cholinergic syndrome (after abrupt withdrawal)	symptoms including profuse sweating, headache, nausea, vomiting and diarrhoea
EEG changes	changes in the pattern of brain ctivity
pleurothotonus	a rare disorder where the muscles tighten uncontrollably
restless leg syndrome	irresistible urge to move your legs or arms,
pigmentation disorder	discolouration of the skin
chest pain/angina pectoris	chest pain
palpitations	rapid, strong or irregular heatbeat
retrograde ejaculation	semen goes into the bladder rather than out the penis at orgasm
polyserositis	swelling of layer that surrounds the heart, lungs or abdomen with fluid build up

8. What happens when the research study stops?

When your participation in the study finishes (6 months after you first started taking the study medication), your doctor will receive a letter telling her/ him whether you were taking clozapine or placebo capsules. If you want to know which one you have been taking, you will be able to discuss this during an appointment with your doctor, who can give you this information at this stage. At the end of your participation you could discuss with your doctor if you want to continue with or start taking clozapine.

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

Imperial College London is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Imperial College London will keep identifiable information about you for 10 years after the completion of the study.

You can find out more about how we use your information here:
http://www.imperial.ac.uk/admin-services/legal-services-office/data-protection/

Your usual statutory rights to access, change or move your information are limited, because of exceptions applicable to some types of research, and also because we need to manage your information in specific, lawful ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

As a university we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

[NHS/other site] will collect information from you and your medical records for this research study in accordance with our instructions.

[NHS/other site] will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Imperial College London and regulatory organisations may look at your medical and research records to check the accuracy of the research study. [NHS/other site] will pass these details to Imperial College London along with the information collected from you and your medical records. The only people in Imperial College London who will have access to information that identifies you will be people who need to audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

[NHS/ other site] will keep identifiable information about you from this study for 10 years after the study has finished.

After testing, the blood samples will be destroyed within 6 weeks. They will not be used for any other purpose.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/).

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance. In the event that a researcher wishes to replicate the study or elaborate on its findings, only anonymised data will be provided with prior permission from the Chief Investigator (Professor Mike Crawford).

In the rare event that a person tells us something, which involves a risk to their safety or the safety of someone else, we would talk to them about how to manage this and encourage them to share this information with others involved in their treatment. We would normally only discuss these concerns if a person agrees to us doing this. However, if we judge that there was a major risk to safety we

could be obliged to share this information without their agreement. Under these circumstances we would let the person know of our intention to pass on the information and why we were doing so.

If during the course of the study a member of your clinical team or a study researcher becomes concerned that you seem to be having difficulties understanding information and making decisions, they may decide it is in your best interests to leave the study. In the unlikely event this happens, we would still keep and use the data we have collected from you.

The independent monitoring service we are using (Clozaril Patient Monitoring Service) to monitor your blood will need to have a copy of your personal information (name, date of birth, gender and ethnicity) in order for them to contact your doctor about your blood result. In addition, we are also required to provide your personal details to another organisation (Central Non Re-Challenge Database) that keep a central record of anyone who has an adverse reaction to clozapine to prevent this medication being taken again. The data collected about you may be used in other research in the future, however it would not be possible to identify you from this information.

There may be a requirement to transfer information to countries outside the European Economic Area (for example, to a research partner). Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission (EC) adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient organisation that incorporates EC approved standard contractual clauses that safeguard how your personal data is processed.

If you wish to raise a complaint on how we have handled your personal data or if you want to find out more about how we use your information, please contact Imperial College London's Data Protection Officer via email at dpo@imperial.ac.uk, via telephone on 020 7594 3502 and via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ.
If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO). The ICO does recommend that you seek to resolve matters with the data controller (us) first before involving the regulator.

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

PART 2

1. What if relevant new information becomes available?

If any new information about clozapine becomes available during your participation in the study, a member of the research team will see you and fully explain this newly available information to you. At this point if you wish to continue to be in the study, you may be asked to sign a further consent form. However, if you decide to withdraw from the study treatment your usual care will continue. We will ask you to complete the study visits even if you stop taking the study medication early, but this will also be up to you. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

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

You can withdraw from the study at any time without giving a reason. The information already collected may still be used.

3. What if there is a problem?

Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation. If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Insert name and contact details). The normal National Health Service complaints mechanisms are also available to you; your local PALS can give you information **[Telephone Number here]** or e-mail **[Email Address here]**. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Compliance Office.

4. Involvement of the General Practitioner/ Family Doctor (GP)

With your permission we will notify your GP that you are participating in the study and tell them about the study medication and how long you will be taking this.

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

We will ask you if you would like to be sent a copy of the results at the end of the study and you can choose how you would like to receive them. The results will also be published in scientific journals and presented at conferences.

The reports and presentations we write will not include personal details of the people who take part

6. Who is organizing and funding the research?

The study is organised by Professor Mike Crawford at Imperial College London. Imperial College London is the sponsor of the study. Funding comes from the Health Technology Assessment Programme (HTA), which is part of the Department of Health's NHS National Institute for Health Research (NIHR).

7. Who has reviewed the study?

The National Institute for Health Research reviewed the study before they funded it. Like all research in the NHS, it has been looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by the Wales Research Ethics Committee 1.

8. Expenses and payments

All participants will be offered a voucher or credit of £10 at baseline assessment, £20 at three months and £30 following completion of the six-month follow-up interview. In addition, for participants who have been discharged from hospital during the follow-up period, we will pay for their travel costs.

9. Further information and contact details

If you would like further general information about research and clinical trials, the following websites may be helpful:

- INVOLVE promotes public involvement in the NHS, for more information please visit their website: http://www.invo.org.uk/
- The MRC Clinical Trials Unit provides advice for potential participants and questions that people may wish to ask researchers, for more information please visit their website: http://www.ctu.mrc.ac.uk/about_clinical_trials/

For specific information about this research study, please contact your local study team on (Please enter your local research team contact information here)
These are also the people to contact if you have any concerns during the study.

For advice as to whether you should participate you might want to talk to a member of your clinical team, or [Principal Investigator] who can be contacted on [Insert Number].

Thank you for reading this information.