Participant Information Sheet

Clozapine and risperidone for the treatment of secondary progressive multiple sclerosis (CRISP)

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INTRODUCTION

You are invited to take part in a study on the use of medicines for the treatment of secondary progressive multiple sclerosis. Whether or not you participate in the study is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive.

This information sheet will help you decide if you'd like to participate in the study. You do not have to decide today and are welcome to talk about the study with other people, such as family, whānau, friends, or healthcare providers, before you decide.

This document is 8 pages long, including the consent form. Please make sure you have read and understood all the pages. You will be given a copy of the information sheet and the consent form to keep.

WHAT IS THE PURPOSE OF THE STUDY?

Clozapine and risperidone are medicines that are currently used to treat mental illnesses. These medicines have been shown to have anti-inflammatory effects in the brain and therefore may also be useful for treating multiple sclerosis (MS). At the dose used in patients with mental illnesses clozapine and risperidone can have a range of side effects, but research has shown that a lower dose may be suitable for treating MS.

The main purpose of this study is to assess the safety and acceptability of treatment with a low dose of clozapine or risperidone in patients with secondary progressive MS by comparing their use to people given a placebo (inactive medicine). The study will also look at whether these medicines can reduce the symptoms of MS, and how they might affect the immune system. This information will help determine if one or both of these medicines should be further developed as a treatment for MS.

This study has received approval from the Central Health and Disability Ethics Committee, reference (15/CEN/216) and the Standing Committee on Therapeutic Trials (15/SCOTT/177).

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

You have been chosen to participate in this study because you:

- Have secondary progressive multiple sclerosis
- Are aged 18 – 70 years
- Have an expanded disability status score of 3.5 to 6.5

There are a number of reasons you might not be able to participate in the trial and the neurologist will discuss these with you.

If you choose to participate in the study, you will be randomly selected to receive either clozapine, risperidone, or a placebo (an inactive treatment). These medicines are not currently prescribed to patients as a treatment for MS, therefore it is unlikely that you would be offered these medicines if you were not in the trial. The patients and trial staff will not know which treatment each patient is taking. Study participation takes a total of 32 weeks (about 7 months), with regular visits to Wellington Hospital.

During the first visit you will be assessed to see if you meet the requirements for being in the study and to collect information about your health. This will involve answering questions and performing a range of simple tasks (such as walking a short distance), a blood test, and having the electrical activity and function of your heart checked by an electrocardiogram (ECG) and echocardiogram.

The blood sample will be taken by inserting a small needle into a vein in your arm and collecting up to 33 mLs (2 tablespoons). A sample of the blood will be stored and analysed at the Wellington Hospital and Victoria University Laboratories. These blood tests will include routine blood tests to assess health and immune function. We will look at white blood cell function and evaluate changes in specific white blood cell types. Additionally, we will measure immune related factors. These tests will be done during the study period. Samples will also be stored until the 5 years after the end of the study in case we need to re-do any of the tests and then they will be destroyed. These tests will not include testing for drugs of abuse.

The ECG will involve attaching electrodes to your chest, arms, and legs, and the echocardiogram is performed by having a gel spread over your chest and an instrument called a transducer moved over the skin to scan the heart. Both procedures are non-invasive and completely painless. This first study visit will take up to 3 hours.

If you consent to being in the study, you will come back to the hospital one week later to receive your first doses of medicine. Before you receive the first dose, you will have a magnetic resonance imaging (MRI) scan. The MRI uses a magnetic field and radio waves to produce an image of the brain. The scan is a painless procedure and takes between 30 and 60 minutes.

After the MRI, you will be given the first dose of study medicine. Because the medicines can cause low blood pressure and dizziness in some people, a nurse will monitor you for 4 hours after you have taken the medicine each day, for the first five days. If you do experience side effects during these visits the nurse may arrange for you to have further monitored visits at Wellington Hospital or to contact you each morning for a further five days in your own home. The medicine will be started at a very low dose and slowly increased over two weeks, which lowers the risk of experiencing side effects. After you have taken your first doses with the nurse, you will be given instructions on how much medicine to take at home and when to take it.

In rare cases, the medicines used in the study can affect the number of white blood cells in your body or have other side effects. For this reason, once a week for the first 18 weeks of the study you will need to have a blood test and answer some questions from the nurse about how you are feeling. If the nurse has any concerns about your health they will ask the neurologist to examine you. You will need to come to Wellington Hospital for these visits at least once per fortnight, but on the other weeks you may go to your local Southern Community Laboratories site to have the blood test and the nurse will call you to discuss how you are feeling. After 18 weeks, these visits will only be needed once every 4 weeks until 1 month after you have finished taking the study medicine. If you have any kind of infection, fever, sore throat, or other flu like symptoms in between these visits you should contact the study neurologist immediately, using the contact details at the top of this form.

After you have been taking the study medicine for 3 months, and again after 6 months, you will have a clinical visit with the neurologists and nurse. These visits will be similar to the first study visit and will involve answering questions about your health and how you feel about taking the medicine, performing some simple tasks, and having blood tests and an ECG. At the six-month visit, you will also have a further MRI scan. These visits may take up to 4 hours each. In between the 3-month and 6-month clinical visits, you will be asked to increase the dose of medicine you are taking. This will involve slowly taking more of the medicine each day over 2 weeks, and will be done at home.

If you need any other medical treatment while you are in the study then it is important that the person treating you knows that you may be taking one of the study medicines. For this reason, the lead neurologist will have access to your medical records so that he can add a note that you are participating in the study. We will also notify your general practitioner that you are taking part in the study.

The table below summarises the visits to the hospital required for the study, and the maximum time that each visit may take.

Study Week:	**Key Study Visits:**
0	Screening visit *(3 hours)*
1	First dose-monitoring visit (*up to 6 hours)*
1	Dose monitoring visits on days 2 – 5 *(up to 4.5 hours each)*
13	3-month clinical visit *(3 hours)*
26	6-month clinical visit *(4 hours)*
	Other Visits:
2 to 18	Weekly blood test and talk with the nurse *(30 mins)*
22 and 32	4-weekly blood test and talk with the nurse *(30 mins)*

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

This study will provide knowledge about the use of clozapine and risperidone in patients with secondary progressive MS. Treatment with these medicines in patients with mental illness has been associated with a range of side effects. Whether these side effects will affect people with secondary progressive MS who are using the medicines at lower doses is not clear, and is one of the reasons the study is being performed. For this reason you will be closely monitored during the study to ensure your wellbeing. If at any time the neurologist feels it is important for your treatment to know which medication you are receiving, your treatment can be revealed.

The most common side effects occurring in more than 1 in 10 patients taking clozapine or risperidone are drowsiness, sedation, dizziness, weight gain, increased heart rate, vomiting, nausea, dry mouth, constipation, anxiety, and increased salivation. Less common side effects include thrombocytopenia (loss of a type of blood cell known as platelets), intestinal obstruction, fever, high blood sugar, changes to the heart rhythm, blood clots, myocarditis and cardiomyopathy (inflammation and changes to the heart muscle), involuntary movements, increased levels of the prolactin hormone, seizures, liver disease, difficulty swallowing, and neuroleptic malignant syndrome.

The small risk of these side effects will be managed during the study in three ways. First, people having a medical history that increases the chance of them having any of these side effects will not be included in the study. Second, you will be monitored at Wellington Hospital when taking the first five doses of the medicine. Third, you will have regular blood tests and consultations with the nurse, and additional tests performed during the clinical visits, which will all be used to monitor your health and quickly detect any concerns. If the neurologist believes the study medicine is having a negative impact on your health for any reason during the study he may decide to stop the treatment.

In rare cases these medicines can cause granulocytopenia or agranulocytosis, which is the loss of a type of white blood cell that is important for fighting off infections. The risk of granulocytopenia in patients taking clozapine is 3%, and the risk of agranulocytosis is 0.7%. Agranulocytosis occurs in less than 1 in 10,000 people taking risperidone. This condition can be serious if not detected, but is reversible once the treatment is stopped. For this reason, blood tests will be collected weekly for the first 18 weeks of the study and your white blood cell numbers will be closely monitored.

Currently, clozapine and risperidone are not thought to be suitable for use in pregnant or breast feeding women. Women wishing to breast feed or become pregnant during the study will not be included, and contraception should be used by female study participants to avoid pregnancy during the course of the study. However, because clozapine can interact with some oral contraceptives, women using oral contraceptives will not be included this study.

Clozapine and risperidone have not been used to treat MS previously; therefore, there are no confirmed benefits from taking these medicines for this purpose. However, previous research suggests that these medicines may reduce the symptoms and progression of MS, and this will be looked at during the study. If either clozapine or risperidone is found to be appropriate for use in patients with MS from the results of this trial, it will be further developed as a treatment for MS. This would be particularly beneficial to people having secondary progressive MS since there are no alternative treatments currently available.

WHO PAYS FOR THE STUDY?

There are no direct costs for you involved in taking part in this study. Because the study involves many visits to Wellington Hospital, participants will be compensated for their time and travel expenses with $20 petrol or food vouchers per routine study visit to Wellington Hospital.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you would be eligible **to apply** for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT ARE MY RIGHTS?

Your participation in this study is entirely voluntary. If you do agree to take part in the study but change your mind later, you are free to withdraw from the study at any time without having to give a reason. If you decide not to participate in the study, or to

withdraw from the study, this will have no impact on your future care. Participation in this study will be stopped if the investigators feel it is not in your best interests to continue. You will be told if any new information about clozapine or risperidone that may affect your health becomes available during the study.

WHAT HAPPENS AFTER THE STUDY?

At the end of the study the treatment will be stopped. You will slowly reduce the dose of study medicine you are taking over 2 weeks and will have the last blood test to check your blood cell levels 4 weeks after you have finished the medicine.

No material that could personally identify you will be used in any reports on this study. Records will be stored in a locked cupboard or on a password protected computer and will only be available to those involved in the study. At the end of the study, data will be stored in a secure archive for 15 years and then destroyed. Some of the blood collected during your first study visit and at the 3 and 6 month clinical visits will be transported to Victoria University Laboratories for analysis and stored for up to 5 years. These samples will not be labeled with personal identifying information, and will be disposed of according to MPI regulations at the completion of the study. If you would like a karakia to be performed during this process, you may select this option on the consent form.

The results of this study will be published in a medical research journal. There may be a delay of a year or more between data collection and publication of results. If you would like, you can receive a written summary of the study findings after completion.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact the lead investigators using the contact details at the top of page 1 of this form.

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Free phone : 0800 555 050
Free fax : 0800 2 SUPPORT (0800 2787 7678)
Email : advocacy@hdc.org.nz

If you want to talk to someone regarding issues specific to Māori, you can contact the Research Advisory Group – Māori (RAG-M) on:

Phone : 04 806 2524
Address: Māori Health Development Group,
Level 11, Grace Neil Building
Wellington Regional Hospital
Email : ragm@ccdhb.org.nz

You can also contact the health and disability ethics committee that approved this study:

Free phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz

Participant Consent Form

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Please tick to indicate you consent to the following:

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.	
I have been given sufficient time to consider whether or not to participate in this study.	
I have had the opportunity to use whanau/ family support or a friend to help me ask questions and understand the study.	
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.	
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.	
I consent to the research staff collecting and processing my information, including information about my health.	
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐ No ☐
I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study.	
I understand that there may be risks associated with female participants becoming pregnant during the study. If necessary, I agree to take responsibility for the prevention of pregnancy.	
I understand the compensation provisions in case of injury during the study.	
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.	

I agree to my blood samples being transported to and stored at Victoria University for 5 years and I am aware that these samples will be disposed of using established guidelines for discarding biohazard waste.		
I would like an appropriate karakia to be performed before disposal of any remaining samples at the end of the study.	Yes ☐	No ☐
I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.		
I know who to contact if I have any questions about the study.		
I understand my responsibilities as a study participant.		
I wish to receive a summary of the results from the study.	Yes ☐	No ☐

Declaration by participant:
I hereby consent to take part in this study.

Participant's name:

Signature: Date:

Name of general practitioner:

General practitioner's contact address:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature: Date: