FACULTY OF MEDICINE | UNIVERSITY OF CALGARY

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CONSENT TO PARTICIPATE IN A RESEARCH STUDY

TITLE: Cardiac Sarcoidosis Multi-Center Randomized Controlled Trial (CHASM CS-RCT)

Sponsor: University of Ottawa Heart Institute Research Corporation
Funder: Canadian Institutes of Health Research (CIHR).
Principal Investigator: F. Russell Quinn M.D. 403-220-5500

INTRODUCTION

Dr. Russell Quinn from the Cumming School of Medicine at the University of Calgary is conducting a research study.

This consent form is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something described here, or information not included here, please ask. Take the time to read this carefully and to understand any accompanying information. You will receive a copy of this form for your records.

You were identified as a possible participant in this study because you have been diagnosed with Cardiac Sarcoidosis. Sarcoidosis is a disease of unknown cause where small areas of inflammation and/or scarring can affect many organs and tissues of the body. When this is found in the heart it is called Cardiac Sarcoidosis (CS)..

Taking part in this study is voluntary. Deciding not to take part or deciding to leave the study later will not result in any penalty or affect current or future health care.

Researcher Conflict of Interest
There are no conflicts of interest to declare related to this study.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to compare the effects of low dose prednisone combined with methotrexate to see if it will be as effective and better tolerated than the standard dose of prednisone taken alone for the treatment of cardiac sarcoidosis.

Over the years there have been improvements in the diagnosis and treatment for cardiac sarcoidosis (CS). At present, treatment options for CS are based on expert opinion and vary from hospital to hospital. There are no published clinical trials looking at the treatment of CS. A clinical trial will help to answer and guide important patient care questions.

The usual treatment for cardiac sarcoidosis is a medication called prednisone (steroid therapy). However, there is not enough good information on the best dose, length of treatment, or method to assess the effectiveness of the treatment. Another drug called methotrexate is often used in patients who do not respond to steroid therapy or who have significant side effects from steroid therapy.

The study doctors want to determine if a low dose of prednisone given *with* methotrexate will be as effective as the standard dose of prednisone taken alone. The study will also investigate which of the two treatments has less side effects. The study doctors believe the two treatments will have similar effectiveness, and the combined prednisone/methotrexate treatment may lead to fewer side effects.

Prednisone and Methotrexate are widely used as a treatment for many forms of sarcoidosis, including cardiac sarcoidosis. Health Canada has allowed methotrexate and prednisone to be used in this study. You will receive a written prescription for the study drugs from your study doctor, which you will take to your pharmacy.

The effect of the medication therapy on your cardiac sarcoidosis will be assessed after 6 months of therapy using FDG-PET (Fluorodeoxyglugose Positron Emission Tomography) scan imaging.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

It is anticipated that about 194 people will take part in this study, from research sites located in Canada, the USA and Japan. We hope to enroll 20 subjects at the University of Calgary site.
This study should take 4 years to complete, and the results should be known in about 5 years. Your participation would last for 6 months.

This study is funded by the Canadian Institutes of Health Research (CIHR). The Coordinating Centre for the study is located at the University of Ottawa Heart Institute.

WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

If you decide to participate, you will be "randomized" into one of the groups described below. Randomization means that you are put into a group by chance (like flipping a coin). There is no way to predict which group you will be assigned to. You will have an equal chance of being placed in either group. Neither you, the study staff, nor the study doctors can choose what group you will be in. You will be told which group you are in.

If you are assigned to Group 1 you will be asked to return to the clinic for up to 5 study visits.
If you are assigned to Group 2 you will be asked to return to the clinic for up to 4 study visits.

Group 1 (Experimental/Study Specific intervention):
Standard intervention: Prednisone, *plus experimental intervention*: methotrexate and folic acid
If you are randomized to this group, you will be prescribed:

- Prednisone 20mg orally daily for 1 month then decreasing until stopped after 3 months
  AND
- Methotrexate orally or by injection, once a week for 6 months (see below)
  AND
- Folic acid orally per day for 6 months

Methotrexate will be started at a low dose once per week and increased after 4 weeks, if tolerated. The method of taking the methotrexate (by mouth or injection) will be at the discretion of the study doctor. Folic acid will be taken to reduce the chance of side-effects from the Methotrexate. Methotrexate and folic acid will be taken for a total of 6 months.

Group 2 (Non-Experimental/Standard Care Intervention):
Standard intervention: prednisone therapy alone.

If you are randomized to this group, you will prescribed:

- Prednisone according to your body weight, taken orally, daily, to a maximum dose of 30 mg daily for 6 months.

If you have side effects while you are on this study, the study doctor may make changes to the experimental intervention.

In addition to the medications, the study will be collecting data from procedures and assessments. They are defined as "standard" (part of your normal CS care) or "experimental" (done for the purposes of our research only).

Study Procedures-Standard Care

The following tests will be done as part of your routine care and will be added to the study data. You may have had many of these procedures already.

- Positron Emission Tomography (FDG PET) scan and myocardial perfusion imaging (MPI)
- Cardiac Magnetic Resonance Imaging (MRI)
- Echocardiography (ultrasound of the heart)
- Electrocardiography (ECG- a test that views the electrical activity of the heart)
- Blood tests-hematology, chemistry, lipids
- Device interrogation-downloading rhythm information from your pacemaker/defibrillator

Study procedures-Experimental

The following tests are considered experimental and will be done for all participants on this study:

- Biomarker Blood Samples: You will have 3 tubes (18 ml or 1 tablespoon) of blood collected at, or close to the date, of each FDG PET scan that is performed to measure certain biomarkers. Biomarkers are proteins or chemical changes seen in the blood which may help us to see how you respond to medications, and which may give us other clues to your condition.

- Skin/muscle strength and neuropsychiatric assessment: Your skin will be assessed by the study doctor for changes (rash, bruising, thinning). Your shoulder muscle strength will be assessed by the study doctor by having you push against his or her hand. The neuropsychiatric assessment looking at your sleep and mood will be measured with questionnaires.

- Bone mineral density scan: You will have a computerized x-ray scan done to look for the amount of calcium in your bones or changes in the bones. This test is optional but encouraged.

- Quality of life questionnaires: You will be asked to complete 4 questionnaires about your sarcoidosis symptoms, medication side effects, and your general health and well-being. The questionnaires will take about 30 minutes to complete. The information you provide is for research purposes only. Some of the questions are personal. You can choose not to answer questions if you wish.

- Participant Diaries: You will be asked to keep a diary of when you took your study medication. Please record the time/day of taking each dose every day or every week, as applicable. You will be asked to return the diary to this centre.

PET scan and blood sample sharing

FDG-PET scan images will be collected as part of this study. This is required for central review of the treatment effect for each study group/drug. Copies will be sent to the PET Core lab, located at the University of Ottawa Heart Institute, and kept for 15 years after which they will be destroyed.

To protect your identity, the information that will be on your PET scan image will be limited to the unique study identification number.

MANDATORY BLOOD SAMPLE COLLECTION

The researchers doing this study wish to test blood samples to measure for biomarkers (proteins or chemical changes seen in the blood) which may help us to see how you respond to the study medications and help us understand the prognosis and guide therapy in sarcoidosis.

The collection of these samples is a necessary part of this study. Samples will be used only for these purposes. The samples will not be sold.

Once these tests have been completed, any leftover samples will be destroyed unless you wish to give permission for other future research purposes, in which case you will be given a separate optional consent form to sign.

Reports about any research tests done with your samples will not be given to you, the study doctor(s) or study staff, your doctor, or other health care provider(s). These reports will not be put in your medical records.

Blood samples will be taken by inserting a needle into a vein in your arm by a nurse on the study team. These blood samples will be sent to the biomarker core lab located at the University of Ottawa Heart Institute where they will be tested and stored.

To protect your identity, the information that will be on your samples will be limited to the unique study identification number.

Despite protections being in place, there is a risk of unintentional release of information. Due to technological advances in genetics, there may be a risk that the genetic information in the samples could be linked back to you.

If you no longer want your samples to be used in this research, you should tell the study doctor/research study staff, who will ensure the samples are destroyed.

If tests have already been done on your sample(s) it will not be possible to withdraw those results. However, no further testing will be done.

If you choose to participate in this study, you will be expected to:

- Tell the study doctor about your current medical conditions.
- Tell the study doctor about all prescription and non-prescription medications and supplements, including vitamins and herbals, and check with the study doctor before starting, stopping or changing any of these. This is for your safety as these may interact with the study medication.
- Tell the study doctor if you are thinking about participating in another research study

- Take the prescribed study medication as directed
- Return any unused study medication and the study medication diary at each visit.
- Return any questionnaires, that you take home to complete
- Tell the study doctor if you become pregnant or father a child while participating on this study
- Avoid drinking milk products and alcohol (methotrexate group)
- The prescribed prednisone, methotrexate and folic acid is for you alone, and must not be shared with others. If someone accidentally takes your prescribed prednisone, or methotrexate they should immediately go to the nearest emergency department.

HOW LONG WILL I BE IN THE STUDY?

The study intervention will last for about 6 months.
You will be asked to come back for the visits as described in the schedule of visits table listed above. You may be seen more often if the study doctor determines that this is necessary.

WHAT ARE THE RISKS?

You may experience side effects from participating in this study. Some side effects are known and are listed below, but there may be other side effects that are not expected. You should discuss these with the study doctor.

The study doctor will watch you closely to see if you have side effects. When possible, other medicine will be given to you to make side effects less serious and more tolerable. Many side effects go away shortly after the study intervention is stopped, but in some cases side effects can be serious, long-lasting, permanent, or may even cause death.

Methotrexate

Risks and side effects related to the experimental intervention **methotrexate** include:
MOST Common:

- Gastrointestinal problems, such as nausea, stomach upset, and loose stools
- Soreness of the mouth
- Abnormal liver function or blood count tests
- Suppression of the immune system
- Fatigue, tiredness

LESS Common:

- Skin rash, usually to the extremities
- Headache, fatigue, or impaired ability to concentrate
- Hair loss

Cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported with methotrexate use. PML is a rare disease caused by a specific virus in the nervous system which can be activated by the use of methotrexate as it suppresses your immune system. Your health and study team team will monitor you for signs and symptoms of PML and suspend or stop your use of methotrexate as warranted.

Prednisone

Risks and side effects related to the experimental intervention **prednisone** include:

MOST Common:

- Skin thinning, and/or bruising
- Weight gain, rounder face
- Overall skin/appearance changes
- High blood pressure
- Fluid retention

LESS common:

- Acne
- Abnormal hair growth
- Cataract
- Damage to the optic nerve in the eye (Glaucoma)
- Abnormal lipid blood tests
- Nausea, vomiting, diarrhea, abdominal pain, indigestion
- Bone thinning (Osteoporosis)
- Bone/ joint pain
- Excitement (Euphoria)
- Feeling uneasy/depression
- Inability to sleep (Insomnia)
- Abnormal excitability (Mania)/ false beliefs and hearing and seeing things that do not exist (psychosis)
- High blood sugar/new diabetes
- Increased risk of infections

It is possible that other drugs (prescription and non-prescription), vitamins, or herbals can interact with the study medications. This can result in either the medications not working as expected or side effects, which may severe. It is important to tell your study team ALL products you use.

Bone mineral density scan involves a very small dose of radiation. The amount of radiation involved is less than half that of a chest x-ray and a small fraction of what you are exposed to from natural radiation in the environment each year.

Risk of Insurability:

There is a possibility that participation in research may affect your insurability under certain insurance policies.

WHAT ARE THE REPRODUCTIVE RISKS?

The effects that prednisone or methotrexate may have on an unborn baby (fetus) are birth defects or possible death (methotrexate). You must not become pregnant or father a baby while taking methotrexate and for a minimum of 3 months after the last dose. The study doctor will discuss family planning with you to ensure that you do not become pregnant or father a baby during the study.

Women should not breastfeed a baby while taking prednisone or methotrexate and for a minimum of 3 months after the last dose because the drugs used in this study might be present in breast milk and could be harmful to a baby.

If you become pregnant or father a child while taking prednisone or methotrexate or within 3 months after the last dose, you should immediately notify the study doctor. The study doctor will ask if you/your partner are willing to provide information about the pregnancy as part of this study.

If your partner becomes pregnant, she will be given a separate consent document to sign to give permission for the collection of this information. You or your partner may choose not to give consent for the collection of this information or may withdraw consent at any time without giving a reason. This will not impact your participation on the study and will not result in any penalty or affect your or your partner's current or future health care.

If you are a woman of childbearing age, you will have a pregnancy test done to ensure that you are not pregnant before the study begins.

WILL I BENEFIT IF I TAKE PART?

If you agree to take part in this study, the experimental intervention may or may not be of direct benefit to you. We hope the information learned from this study will help other people with cardiac sarcoidosis in the future.

DO I HAVE TO PARTICIPATE?

No, you do not have to join this study to receive treatment for your condition. Other options (in addition to the standard or usual treatment described above) may include no therapy at this time, or a therapy determined by your usual doctor or the study doctor.

You can choose to end your participation in this research at any time without having to provide a reason. If you choose to withdraw from the study, you must contact the study doctor or study staff, who may ask questions about your experience with the study, do laboratory tests and physical examinations considered necessary to safely stop your study involvement.

If you withdraw from the study data collected to that point will be retained, but no further information will be collected or sent to the sponsor after your permission is withdrawn

The study doctor may stop your participation in the study early, and without your consent, for reasons such as:

- The study intervention does not work for you
- You are unable to tolerate the study intervention
- You are unable to complete all required study procedures
- New information shows that the study intervention is no longer in your best interest
- The study doctor no longer feels this is the best option for you
- The Sponsor decides to stop the study
- The Regulatory Authority (Health Canada) or research ethics board withdraw permission for this study to continue
- If you plan to or become pregnant

If any of this happens, it may mean that you would not receive the study medication(s) for the full period described in this consent form.
If you are removed from this study, the study doctor will discuss the reasons with you and plans will be made for your continued care outside of the study.

If any new clinically important information about your health is obtained because of your participation in this study, you will be given the opportunity to decide whether you wish to be made aware of that information.

WILL I BE PAID FOR PARTICIPATING, OR DO I HAVE TO PAY FOR ANYTHING?

You will not be paid to participate in this research study.
The costs of your medical treatment will be paid for by your provincial medical plan to the extent that such coverage is available. Participants are required to pay the costs of the prescribed study medications unless covered by your insurance plan.

Parking costs for study specific visits to the Foothills Medical centre will be covered.

WILL MY RECORDS BE KEPT PRIVATE?

If you decide to participate in this study, the study doctors and study staff will only collect the information they need for this study, including records stored in the EPIC/Connect Care database.

Records identifying you at this centre will be kept confidential and, to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document.

Authorized representatives of the following organizations may look at your original (identifiable) medical/clinical and study records, including ConnectCare, as described above, at the site where these records are held, to check that the information collected for the study is correct and follows proper laws and guidelines.

- The sponsor-Investigator: the Ottawa Heart Institute Research Corporation and its Cardiovascular Research Methods Centre, or his/its designate representatives
- The Conjoint Health Research Ethics Board who oversees the ethical conduct of this study at the University of Calgary
- Health Canada (because they oversee the use of drugs in Canada).

Studies involving humans sometimes collect information on race and ethnicity as well as other characteristics of individuals because these characteristics may influence how people respond to different interventions. Providing information on your race or ethnic origin is required.

If the results of this study are published/presented to the scientific community at meetings and in journals, your identity will remain confidential.
Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated.

A copy of the consent form that you sign to enter the study may be included in your health record/hospital chart.

Your family doctor/health care provider will be informed that you are taking part in this study so that you can be provided with appropriate medical care. If you do not want your family doctor/health care provider to be informed, please discuss this with the study team.

A description of this clinical trial/study will be available on will be available on http://www.clinicaltrials.gov. This website will not include information that can identify you. You can search this website at any time.

This research study can be found on the above listed website by using the clinical trial registration number NCT#03593759.

IF I SUFFER A RESEARCH-RELATED INJURY, WILL I BE COMPENSATED?

In the event that you suffer injury as a result of participating in this research, no compensation will be provided to you by the University of Ottawa Heart Institute, the University of Calgary, Alberta Health Services or the Researchers. Financial compensation for lost wages, disability or discomfort due to an injury or illness is not generally available. You still have all your legal rights. Nothing said in this consent form alters your right to seek damages.

QUESTIONS ABOUT THE STUDY

If you have further questions concerning matters related to this research, please contact:
Dr. F. Russell Quinn (403) 220-5500 OR Jennifer McKeage R.N. (403) 210-6047

If you have any questions concerning your rights as a possible participant in this research, please contact The Chair of the Conjoint Health Research Ethics Board, University of Calgary, at 403-220-7990.

SIGNATURES

- All my questions have been answered,
- I understand the information within this informed consent form,
- I have read, or someone has read to me, each page of this participant informed consent form,
- I allow access to my medical records and specimens as explained in this consent form,
- I do not give up any of my legal rights by signing this consent form,
- I understand that my family doctor/health care provider will be informed of my participation in this study,
- I agree to take part in this study.

Participant's Name (Please print)	Signature and Date
Witness Name	Signature and Date
Investigator/Delegate Name	Signature and Date

The University of Calgary Conjoint Health Research Ethics Board has approved this research study. A signed copy of this consent form will be given to you to keep for your records and reference.