Informed Consent Form for Participation in a Research Study

Study Title: *Oral Versus Intramuscular Steroid Use to Control Rheumatoid Arthritis Flares: A Pragmatic Randomized Clinical – Clinical Component*

Site-lead Study Doctor:

Sponsor/Funder(s): *PSI Foundation*

Emergency Contact Number (24 hours / 7 days a week):

INTRODUCTION

You are being invited to participate in a clinical trial (a type of study that involves research). You are invited to participate in this trial because you have rheumatoid arthritis and are experiencing a disease flare. This consent form provides you with information to help you make an informed choice. Please read this document carefully and ask any questions you may have. All your questions should be answered to your satisfaction before you decide whether to participate in this research study.

The study staff will tell you about the study timelines for making your decision.

Taking part in this study is voluntary. You have the option to not participate at all or you may choose to leave the study at any time. Whatever you choose, it will not affect the usual medical care that you receive outside the study

IS THERE A CONFLICT OF INTEREST?

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

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

You are being asked to participate in the study because you have been identified as a patient with rheumatoid arthritis who is currently experiencing a flare.

Glucocorticoids (“steroids”) are frequently used to treat rheumatoid arthritis flares because they work quickly to reduce flare symptoms of pain, stiffness, fatigue and disability. This research study will help determine which is the best and safest method of taking steroids for flares: by pill form for a few weeks (oral route) or as a single injection into the muscle (intramuscular). Currently, both oral and injected steroids are used in routine care. We will evaluate which route of steroid administration is more effective at alleviating symptoms, minimizing side effects, and which may be easier and preferable from a patient perspective.

Potential advantages and disadvantages of intramuscular versus oral steroids are listed below

	Intramuscular Glucocorticoid	Oral Glucocorticoid

Potential Advantages	Single injection in clinic Fast onset of action	No injection required Fast onset of action Dose can be adjusted or changed once given if experiencing side effects
Potential Disadvantages	Pain or redness at injection site Immediate side effects: flushing, insomnia, high blood pressure, increased appetite, mood changes Dose cannot be adjusted or changed once given	Pills have to be accurately counted each day and reduced according to schedule Potential nausea or stomach upset due to pill format Immediate side effects: flushing, insomnia, high blood pressure, increased appetite, mood changes

This is a randomized clinical trial which means you will receive either intramuscular steroid as a single injection (Methylprednisolone 120 mg) or oral steroids (Prednisone 15 mg daily tapered over 21 days).

The standard or usual treatment for rheumatoid arthritis flares includes steroids.

WHY IS THIS STUDY BEING DONE?

Rheumatoid arthritis (RA) is the most common type of inflammatory arthritis affecting Canadians. It causes painful swelling in the joints, making it hard to move and reducing quality of life. Nearly all individuals living with RA will have at least one severe flare-up in their lifetime and require medical treatment to treat the flare. When flares happen, rheumatologists often prescribe steroids to quickly ease the symptoms. These steroids can be taken as pills (e.g. prednisone) tapered over a few weeks or as a single steroid dose injected into the muscle (intramuscular). Steroids can be very effective, but here's the catch: rheumatologists are not sure which method works best, which may be safer or which formulation is preferred by patients.

We will conduct a randomized clinical trial at several hospitals across the University of Toronto. We will randomize RA patients with flares (and who have not had any steroids in the previous 4-weeks) to either take steroids by mouth over 3-weeks, or receive it as a single intramuscular injection. Then, we will follow patients over time to determine which method of steroids is better for improving flare symptoms (at week-6) and monitor side effects and treatment satisfaction. In summary, the goal of this study is to find out which way of giving steroids works best for RA flares and to make sure we are considering what patients want.

WHAT OTHER CHOICES ARE THERE?

You do not have to take part in this study in order to receive treatment or care. Other options (in addition to the standard or usual treatment described above) may include, but are not limited to:

- no therapy to treat the flare at this time
- standard treatment for flare management with steroids (if clinically appropriate) can and will also be offered to those not participating in the study

Please talk to your usual doctor or the study doctor about the known benefits and risks of these other options before you decide to take part in this study. Your usual doctor or the study doctor can also discuss with you what will happen if you decide not to undertake any treatment at this time.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

It is anticipated that about 220 people will take part in this study, from research sites located in Toronto, Canada.

This study should take 2 years to complete and the results should be known in about 3 years.

WHAT WILL HAPPEN DURING THIS STUDY?

Assignment to a Group

If you decide to participate then 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.

WHAT IS THE STUDY INTERVENTION?

The following interventions will be randomized equally to:

- Oral Glucocorticoid arm: Prednisone 15 mg/day for a week, reducing by 5 mg/day every 7 days until off
- Intramuscular Glucocorticoid arm: Single dose 120 mg Intramuscular methylprednisolone

That is, participants will have an equal chance of receiving either the oral or intramuscular formulation of glucocorticoid.

Treating rheumatologists will be allowed to add, switch, or change doses of any disease modifying anti-rheumatic drug therapy or non-steroid anti-inflammatory drug as per usual care.

WHAT ELSE DO I NEED TO KNOW ABOUT THE STUDY INTERVENTION?

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

WHAT ARE THE STUDY PROCEDURES?

As part of routine care, your study physician will perform a physical examination to assess for swollen or tender joints. Study procedures refers to aspects of care that are not routine (e.g. questionnaires sent at set intervals). Specifically, you will complete a series of questionnaires to ask about your symptoms, treatment satisfaction and any side effects from therapy.

A central coordinator will be responsible for follow-up with you.

Questionnaires

You will be provided with a series of questionnaires (see below Study Visit Schedule). The purpose of the questionnaire is to understand how the study intervention and illness affects your quality of life. Each questionnaire will take about 5 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.

Even though you may have provided information on a questionnaire, these responses may not be reviewed by your health care team or study team - if you wish them to know this information please bring it to their attention.

The study will have 5 visits (see Table) during the 6-week study period. The baseline visit and week 6 visit will be in-person, the rest of the visits will be remote. The in-person visits will include all of the standard elements of your clinical visits with your rheumatologist but will take ~30 minutes longer to complete questionnaires. There will be an additional remote visit at 12 weeks to determine if you have used any more steroids to treat your symptoms. We will collect the clinical information of your usual care visit at visit 1 and visit 5 (6 weeks). Various assessments and questionnaires will be done during these study visits to determine which method of steroids is better for improving flare symptoms and to monitor side effects and treatment satisfaction. These questionnaires will be delivered via secure email.

Study Visit Schedule

Visit	Type of Visit	Information Collected	Time Commitment
Visit 1 (baseline)	In-person	Questionnaires Randomized to intramuscular or oral steroid	~ 30 minutes
Visit 2 (week 1)*	Interval	Questionnaires	~20 minutes
Visit 3 (week 2)*	Interval	Questionnaires	~20 minutes
Visit 4 (week 4)*	Interval	Questionnaires	~20 minutes
Visit 5 (week 6)	In-person	Questionnaires	~30 minutes
Visit 6 (week 12)^	Interval	Physician Follow Up	~20 minutes

- *email with questionnaire links only, no physician visit
- ^virtual telephone visit at week 12 with the physician

WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?

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 intervention you receive on this study.
- Tell the study doctor if you are thinking about participating in another research study
- Tell the study doctor if you become pregnant or father a child while participating on this study
- The steroids are for you alone, and must not be shared with others.

HOW LONG WILL PARTICIPANTS BE IN THE STUDY?

See Study Visit Schedule

You may be seen more often if the study doctor determines that this is necessary.

No matter which group you are randomized to, and even if you stop the study intervention early, we would like to keep track of your health for 12 weeks to look at the long-term effects of your participation on this study. We would do this by having someone from this centre call you to see how you are doing.

CAN PARTICIPANTS CHOOSE TO LEAVE THE STUDY?

You can choose to end your participation in this research (called withdrawal) at any time without having to provide a reason. If you choose to withdraw from the study, you are encouraged to contact the study doctor or study staff.

You may be asked questions about your experience with the study intervention, and to have laboratory tests and physical examinations considered necessary to safely stop your study involvement.

You may withdraw your permission to use information that was collected about you for this study at any time by letting the study doctor know. However, this would also mean that you withdraw from the study.

If you decide to leave the study, you can ask that the information that was collected about you not be used for the study. Let the study doctor know if you choose this.

CAN PARTICIPATION IN THIS STUDY END EARLY?

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 research ethics board withdraw permission for this study to continue
- If you plan to or become pregnant

If this happens, it may mean that you would not receive the study intervention 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.

WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?

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.

Risks and side effects related to the experimental of steroids we are studying include:

Intramuscular injections of steroid:

Risks of bruising, pain, or bleeding at site of injection, and rarely infection. We minimize these risks by cleaning the skin carefully before injecting, applying pressure to prevent bruising and having a physician or nurses perform the injection.

Oral steroid:

A buildup of fluid, causing swelling in your lower legs, high blood pressure, problems with mood swings, memory, behavior, and other psychological effects, such as confusion or delirium, upset stomach, weight gain in the belly, face and back of the neck may occur. We will minimize these risks by rapidly lowering the dose of prednisone over 3 weeks.

WHAT ARE THE REPRODUCTIVE RISKS?

Steroids have been shown to have a 6% increase in the risk of cleft palates to the fetus. We will not include pregnant patients in this study or those planning on pregnancy during the study time period.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

We hope the information learned from this study will help other people with rheumatoid arthritis in the future.

HOW WILL PARTICIPANT INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, the study doctors and study staff will only collect the information they need for this study. 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.

In order to maintain confidentiality during the study and analysis, all personal identifiers will be removed and a unique identifier will then be assigned to each participant. The central coordinator will have access to a separate list, partitioned from other study data that lists emails and phone number along with their unique identifiers for the purpose of follow-up.

The de-identified data will be stored and analyzed in REDCap, a password, firewalled and encrypted secure system located at Sunnybrook Health Sciences Centre. No Personal Health Information (other than phone number and email for the purpose of follow-up) will be shared with the coordinating site (Sunnybrook Health Sciences Centre).

10 years after study completion, the data will be deleted permanently from the servers by the Information Management/Information Technology team.

Authorized representatives of the following organizations may look at your original (identifiable) medical/clinical study records 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 research ethics board who oversees the ethical conduct of this study in Ontario
- This institution and affiliated sites, to oversee the conduct of research at this location

Information that is collected about you for the study (called study data) may also be sent to the organizations listed above. Representatives of Clinical Trials Ontario, a not-for-profit organization, may see study data that is sent to the research ethics board for this study. Your name, address, email, or other information that may directly identify you will not be used. The records received by these organizations may contain your disclose identifiers e.g., participant code, initials, sex, and date of birth. The data will be stored in a secure server.

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 voluntary.

Communication via e-mail is not absolutely secure. We do not recommend that you communicate sensitive personal information via e-mail.

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during this study will be used in analyses and will be published/ presented to the scientific community at meetings and in journals.

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.

<u>WILL FAMILY DOCTORS/HEALTH CARE PROVIDERS KNOW WHO IS PARTICIPATING IN</u>

THIS STUDY?

Your family doctor/health care provider will not be informed by the study team that you are taking part in the study. You can choose to let your family doctor/health care provider know, if you like.

WILL INFORMATION ABOUT THIS STUDY BE AVAILABLE ONLINE?

A description of this clinical trial 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.

WHAT IS THE COST TO PARTICIPANTS?

The costs of your medical treatment will be paid for by your provincial medical plan to the extent that such coverage is available.

ARE STUDY PARTICIPANTS PAID TO BE IN THIS STUDY?

There is no compensation for this study.

In the case of research-related side effects or injury, medical care will be provided by your doctor or you will be referred for appropriate medical care.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study.

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of the results of this study, please contact the study doctor.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form you do not give up any of your legal rights against the study doctor, sponsor or involved institutions for compensation, nor does this form relieve the study doctor, sponsor or their agents of their legal and professional responsibilities.

You will be given a copy of this signed and dated consent form prior to participating in this study.

WHAT IF RESEARCHERS DISCOVER SOMETHING ABOUT A RESEARCH PARTICIPANT?

During the study, the researchers may learn something about you that they didn't expect. For example, the researchers may find out that you have another medical condition.

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

WHOM DO PARTICIPANTS CONTACT FOR QUESTIONS?

If you have questions about taking part in this study, or if you suffer a research-related injury, you can talk to your study doctor, or the doctor who is in charge of the study at this institution. That person is:

Dr. Timothy Kwok, Telephone: 416-480-4580 Ext: 3

If you have questions about your rights as a participant or about ethical issues related to this study, you can talk to someone who is not involved in the study at all. That person is:

Chair, Mount Sinai Hospital Research Ethics Board

Phone: 416-586-4875

SIGNATURES

- All of my questions have been answered,
- I understand the information within this informed consent form,
- I allow access to medical records and related personal health information as explained in this consent form,
- I do not give up any legal rights by signing this consent form,
- I understand that my family doctor/health care provider may be informed of study participation
- I agree, or agree to allow the person I am responsible for, to take part in this study.

_____	_____	_____
Signature of Participant	PRINTED NAME	Date

_____	_____	_____
Signature of Person Conducting the Consent Discussion	PRINTED NAME & ROLE	Date

☐ The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to the participant, and any questions have been answered.

_____	_____	_____
PRINT NAME of witness	Signature	Date

_____
Relationship to Participant