PROTOCOL

Oral Versus Intramuscular Steroid Use to Control Rheumatoid Arthritis Flares: A Pragmatic Randomized Clinical Trial

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SPONSOR STATEMENT OF COMPLIANCE

This study will comply with the International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), World Medical Organization Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements.

Personnel listed below are authorized to sign the protocol and any subsequent protocol on behalf of the sponsor:

Name:

Title:

Signature:

Date of Approval:
(yyyy-mmm-dd)

PROTOCOL SIGNATURE PAGE

I have read this protocol in its entirety and its appendices. I agree to comply with the requirements of the study protocol and procedures for data recording/reporting and acknowledge my responsibility for the well-being of each research participant, and to ensure that all persons involved in study activities are adequately informed about the protocol, the investigational product, and their trial-related duties. The signature below constitutes the agreement to conduct this study in accordance with the Research Ethics Board (REB) approved protocol, GCP, and applicable regulatory requirements, including confidentiality, ethical guidelines, and regulations regarding the conduct of research in humans.

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Name & Title:
(print)

Institution:
(print)

Signature:

Date of Signature:
(yyyy-mmm-dd)

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LIST OF ABBREVIATIONS

The following abbreviations describe terms, documents and study personnel used in the conduct of this study protocol.

ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% response criteria
AE	Adverse Event
CATCH	Canadian Early Arthritis Cohort study
csDMARD	Conventional Synthetic Disease Modifying Anti-Rheumatic Drug
CDAI	Clinical Disease Activity Index
CRF	Case Report Form
DAS28	Disease Activity Score 28 Joints
DMARD	Disease Modifying Anti-Rheumatic Drug
eCRF	Electronic Case Report Form
ESR	Erythrocyte Sedimentation Rate
EULAR	European Alliance of Associations for Rheumatology
GC	Glucocorticoid
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire Disability Index
HCQ	Hydroxychloroquine
PHIPA	Personal Health Information Protection Act
ICF	Informed Consent Form
ID	Identification
IM	Intramuscular
MCID	Minimally Clinically Important Differences
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
OMERACT	Outcome Measures in Rheumatology

PROMIS	Patient-Reported Outcomes Measurement Information
PHI	Personal Health Information
PO	Per Oral
RA	Rheumatoid Arthritis
RA-FQ	Rheumatoid Arthritis Flare Questionnaire
RCT	Randomized Controlled Trial
REB	Research Ethics Board
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SSZ	Sulfasalazine
tREACH	Rotterdam Early Arthritis Cohort study
TSQM	Treatment Satisfaction Questionnaire for Medication

PROTOCOL SUMMARY

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in Canada. The disease course is at times marked by periods of disease flares, during which patients experience acute joint swelling and pain, leading to decreased quality of life. When multiple joints are involved and when the flare is severe, the treating rheumatologist may begin treatment with glucocorticoids (GC), which can be given via oral (PO) or intramuscular (IM) routes, in conjunction with other disease modifying anti-rheumatic drugs (DMARDs). The main goal of treating RA flares is to quickly improve symptoms, while minimizing exposure to GC, as long-term use and higher doses are associated with numerous side effects.

In practice, the treating rheumatologists decide the chosen route of GC administration for the treatment of RA based upon clinical experience, anecdotal evidence, and established practice patterns. Currently, there is a lack of high-quality evidence to guide the optimal route of GC administration. This uncertainty was reinforced by a survey our research group conducted amongst the rheumatologists at the University of Toronto, which indicated significantly varying practice patterns pertaining to the optimal route of GC administration, with 58.8% voting for the PO route as opposed to IM administration. Furthermore, there is minimal evidence in the literature to guide the best method of administering GC in patients with RA flares in terms of safety and efficacy; prior studies mainly focused on clinical outcomes, lacking information on GC associated morbidity and patient related satisfaction/preference as key outcome measures. Additionally, information is lacking on cumulative GC exposure and whether a specific route corresponds to easier discontinuation of GC or equally importantly, steroid associated side effects. Lastly, prior trial designs also used doses of GC that were much higher than what is used in contemporary practice (due to increased recognition of steroid toxicities in recent years).

In this study, we aim to compare the differences in terms of patient perspectives, satisfaction, side effects, cumulative steroid dosages and clinical efficacy between the IM and PO routes of steroid administration in patients with RA flares. We will perform a pragmatic randomized controlled trial at University of Toronto affiliated teaching hospital-based rheumatology clinics, where we will randomize patients with RA flares to either IM or PO steroid arms. We will follow up with visits conducted both in person and virtually for 12 weeks to assess the differences between our chosen outcomes. Lastly, we will conduct an interview with patients enrolled in the study to highlight their experiences with IM or PO steroids.

Through this study, we hope to explore the question on the optimal route of steroid administration to treat RA flares and importantly include patient perspectives within our study design. We wish to determine whether PO versus IM steroids are preferable in terms of patient reported outcomes (PROs), clinical efficacy, and side effect profiles. This is a novel, impactful and highly relevant clinical question that we hope to answer which has the potential to drastically inform how we treat patients with RA in the future.

1.0 BACKGROUND AND RATIONALE

Rheumatoid arthritis (RA) is a chronic and progressive autoimmune disease characterized by symmetrical polyarthritis with a global prevalence of 460 per 100,000 (1). It is the most common autoimmune inflammatory arthritis in Canada. RA flares are common in persons with RA and is often characterized by joint swelling, pain and fatigue (2). RA is a disease marked by recurrent flares, with prior observational data indicating that upwards of 57% of patients having flares during a 6-month span (3). RA flare has been defined as 'a cluster of symptoms of sufficient duration and intensity that cannot be self-managed by the patient and require initiation, change or increase in therapy' (4). There is evidence that flares contribute to worsening cardiovascular morbidity, joint damage, and other long-term outcomes (5). Fear of flares may induce wide-ranging behavioral modifications, including retreat from social life and reductions in physical activities over long periods of time (6).

RA flares can be treated with systemic glucocorticoids (GC) alongside changes to disease modifying anti-rheumatic drugs (DMARDs). Treatment goals for patients with RA in the short term is to decrease disease activity and achieve clinical remission, and in the medium term to limit or prevent structural progression, disability, and systemic manifestations (7). Disease modifying anti-rheumatic drugs (DMARDs) have shown their efficacy and form the backbone of long-term treatment in RA. However, their clinical effect may take upwards of several months to become apparent. Consequently, short-term systemic GC are sometimes necessary to alleviate symptoms prior to DMARDs' onset of action. While GC use has been associated with many adverse effects - cardiovascular diseases, infections, gastrointestinal diseases, psychological disorders, endocrine pathologies, dermatological issues, musculoskeletal disorders (including osteoporosis) and ophthalmological diseases (8), GC therapy has also been shown to be an effective short-term option to treat RA flares irrespective of DMARD therapy modification, especially when multiple inflamed joints are involved. The European Alliance of Associations for Rheumatology (EULAR) guidelines suggest short-term GC as a bridging therapy option when starting or changing conventional synthetic (CS) DMARD therapy, with subsequent rapid tapering of GC to discontinuation as fast as clinically feasible (9). Regarding flare management, the EULAR Task Force suggests that GC are appropriate flare medications (9) which is further concordant with the Canadian Rheumatology Association Living Guidelines for RA (10).

Systemic GC used in the treatment of RA flares can be administered either orally (PO) or via intramuscular (IM) routes. However, there is a paucity of evidence to guide the optimal method of GC administration for RA flare management. Specifically, the differences in terms of clinical efficacy, safety profile or patient preference are unknown. Given how commonly GC are used to RA flares, there is a need to investigate the comparative effectiveness of PO versus IM GC using a randomized controlled trial (RCT) design.

Clinical efficacy of systemic corticosteroids as bridging therapy

Systemic GC have an inherent risk of toxicity with safety risks correlated with increasing doses and/or duration. This limits their role as a long-term agent to treat RA (11). Despite their safety

concerns, GC continue to be used due to their effectiveness in controlling disease activity. The efficacy of GC has been studied in RA. A recent clinical trial randomized patients with early RA to treatment with methotrexate (MTX) and hydroxychloroquine (HCQ), and either prednisone (low dose GC) (initial dose 10 mg/day) or placebo. Patients who were started on MTX with HCQ with low-dose GC showed greater short-term improvement in American College of Rheumatology 20 (ACR20) response, disease activity score (DAS) 28-ESR, and health assessment questionnaire-disability index (HAQ-DI) at 3 and 6 months compared to those started on the placebo (7). The combined treatment regimen also helped control the radiological progression of the joint, especially bone erosion, with a certain overall improvement in radiological signs. The efficacy of initial GC bridging was also studied in the CareRA trial (12). The CareRA trial was an RCT that investigated the use of MTX with additional DMARD and bridging glucocorticoids as initial treatment for patients with early RA. The trial studied initial GC bridging (COBRA slim, MTX+GC initial dose 30 mg/day) versus MTX tight step-up treatment with no oral GC allowed. Those in the oral GC bridging group had lower values of DAS28 and were less likely to receive GC intra-articular injections.

Routes of glucocorticoid administration

While intra-articular steroids may be appropriate for one or two swollen joints, when multiple joints are involved, GC are commonly used and can be given either PO or via IM administration. However, there is no consensus regarding the optimal route of GC administration as bridging therapy or for flare management. This stems from a paucity of evidence to guide the most appropriate route, either in terms of clinical efficacy, safety profile or patient preference.

A two-year RCT of IM steroids versus placebo in patients with established RA who showed an incomplete response to DMARDs, demonstrated an improvement in disease activity in the short term and produced a small reduction in bone erosion at the cost of a significant increase in adverse events (13).

Comparative effectiveness between routes of administration

There is a paucity of data on head-to-head comparisons between routes of administration of GC. A small trial of 43 RA patients in 1993 who were started on sodium aurothiomalate were randomized to receive three doses of either 500 mg methylprednisolone orally and a placebo injection or 120 mg of IM depot methylprednisolone acetate and oral placebo tablets at 4-weekly intervals. At 16 weeks, the IM route showed greater improvement on pain, ESR and HAQ score (14). However, it is worth noting that the high doses of GC used in the trial are seldom used today with increased recognition of the toxicities of high dose and prolonged steroids.

The Rotterdam Early Arthritis Cohort (tREACH) trial, a stratified single-blinded trial in the Netherlands, compared patients with very early RA the 1-year clinical efficacy of initial triple DMARD therapy with initial MTX monotherapy, unbiased by GC and, different GC bridging therapies: oral versus a single intramuscular injection. Patients received either MTX monotherapy or MTX+sulfasalazine (SSZ)+HCQ and oral GC started at 15 mg/day and tapered

during 10 weeks versus MTX+SSZ+HCQ plus an initial IM pulse of GC (15). GC were given either IM (methylprednisolone 120 mg or triamcinolone 80 mg) or in an oral tapering scheme (weeks 1–4: 15 mg/day, weeks 5–6: 10 mg/day, weeks 7–8: 5 mg/day and weeks 9–10: 2.5 mg/day). The two groups did not differ at 1 year in clinical response, structural progression, or safety. This suggested that both GC bridging therapies were equally effective clinically. However, it is worth noting that this study protocol dictated 10 weeks of oral GC exposure. Moreover, the two dosing regimens were non-equivalent, with patients in the oral arm exposed to a higher cumulative GC dose. This raises the possibility (though not explicitly studied) that IM steroids may yield similar clinical responses at a lower dose. However, whether each route led to further steroid sparing effects after the trial period was not studied.

Knowledge gaps

There is currently clinical equipoise and lack of high-quality evidence on the optimal route of steroid administration to treat RA flares. Previous trials have used antiquated dosing regimens that are no longer used in routine contemporary practice (i.e., too high of a dosage). Further, prior studies assessing IM versus oral GC such as in the tREACH trial use protocolized treatment regimens in patients newly diagnosed with RA. However, in clinical practice patients with flares are typically not in patients newly diagnosed with RA initiating DMARD therapy, but rather, those with established disease who may flare and require bridging therapy while DMARD therapy is being intensified or changed. Lastly, prior studies have mainly focused on clinical outcomes and have failed to provide information on corticosteroid associated morbidity and patient related satisfaction/preference as key outcome measures. Hence, there is a lack of high-quality evidence looking at whether PO or IM GC are better in terms of symptom relief, disease progression, side effects and patient preference. Additionally, information is lacking on whether a specific formulation corresponds to easier tapering of GC. Given how commonly GC are used in clinical practice, there is a need for research looking into the comparative effectiveness of PO versus IM GC. This trial aims to determine the optimal method of administering GC.

2.0 HYPOTHESES

We hypothesize that IM GC offer an effective and safer option, with lower cumulative dose and potential short-term toxicity when compared to PO GC used to treat active RA. Specifically, we hypothesize that IM GC may have advantages in terms of GC toxicity, patient satisfaction and be associated with a lower cumulative steroid dosage, in addition to being non-inferior to PO GC in patient reported outcomes and yield comparable clinical efficacy.

3.0 STUDY OBJECTIVE

Our main objective is to identify the optimal route of steroid administration to treat RA flares. We wish to determine whether PO versus IM steroids are preferred in terms of efficacy, while

minimizing patient exposure to GC and its associated side effects. We also aim to understand which route of GC administration is preferred in terms of patient satisfaction.

3.1 Specific Aims and Objectives

Specific aims:

1. To assess the comparative effectiveness of IM versus PO GC in the treatment of RA flares. Specifically, to assess whether IM administration of GC is non-inferior to PO GC for RA flare symptom improvement;
2. To determine whether clinical efficacy, health related quality of life, treatment satisfaction, safety profile and cumulative GC dose over time differ for IM vs PO GC;
3. To qualitatively describe and thematically analyze patient perspectives on receiving either PO versus IM steroids for RA flares.

Objective 1: To compare whether IM administration of GC is non-inferior to PO GC for RA flare symptom improvement

Hypothesis 1: Compared to patients receiving PO GC, the improvement in RA flare symptoms will be non-inferior to those receiving IM GC

Objective 2: To assess whether treatment satisfaction, safety profile, clinical efficacy and cumulative GC dose over time differ for IM versus PO GC administration for RA flares

Hypothesis 2: IM GC may have advantages in terms of GC toxicity, patient satisfaction and be associated with a lower cumulative steroid dosage, and yield comparable clinical efficacy to PO GC.

Objective 3: To highlight the views and perspectives of RA patients using either IM or PO GC to treat flares.

4.0 PRELIMINARY WORK

Needs-based survey

To gauge current practice patterns from faculty members within the Division of Rheumatology at the University of Toronto, we prepared a survey assessing current practices for GC use in RA.

Preliminary results suggested an interest in this topic as well as variability in current practice patterns. Stakeholders raised ideas that also informed proposed research study design.

Out of 17 respondents, 15 (88.24%) reported the use of steroids in the treatment of RA flares. There was clinical equipoise in terms of the most requested route of GC administration with 10 (58.82%) voting for the PO route. No respondent believed that there was sufficient data in the literature to guide the effectiveness/safety of IM vs. PO steroids for RA flares. Lastly, 13 (76.5%)

physicians expressed interest in participating in a clinical trial on PO versus IM steroid administration in RA flares.

5.0 METHODOLOGY

5.1 Study Design and Overall Summary

This study will be two-armed pragmatic RCT enrolling patients who have a RA flare, as determined by the treating rheumatologist, where systemic steroids are indicated. The study will compare the use of IM GC and PO GC to treat active RA flares. The main outcome of interest is the patient reported benefit of steroid therapy in the form in the Rheumatoid Arthritis Flare Questionnaire (RA-FQ).

This study will take place at five University of Toronto affiliated teaching hospital-based rheumatology clinics (Women's College Hospital, Sunnybrook Health Sciences Centre, Mount Sinai Hospital, University Health Network, and St. Michael's Hospital) in Toronto, Ontario, Canada. We will enroll and randomize 220 participants with active RA to two arms of the study - IM vs. PO GC where they will receive either IM or PO GC.

In the PO arm, participants will receive oral prednisone that will be fully tapered off in 3 weeks. The dose of the PO prednisone will be 15 mg tapered over 21 days. In the IM arm, participants will receive 120 mg of IM methylprednisolone.

This project will be carried out by a multidisciplinary team that includes investigators, collaborators from different disciplines, e.g., front-line clinicians, advanced nurse practitioners, managers, and data scientists.

The study is not blinded.

5.2 Participant Eligibility

Inclusion criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

- Rheumatologist verified RA diagnosis
- Patients are allowed to be on non-steroidal anti-inflammatory drugs (NSAIDs) prior to randomization, but the dosages must be stable for ≥2 weeks prior to randomization.
- Patients must be on stable doses of conventional synthetic disease-modifying antirheumatic drugs (csDMARD), targeted synthetic disease-modifying antirheumatic drugs (tsDMARD), biologics for ≥8 weeks prior to randomization.
- Willing and able to provide informed consent

Exclusion criteria

Any individual who meets any of the following criteria will be excluded from participation in this study:

- Allergies, intolerances or contraindications to systemic steroids
- Patients with active malignancy, are pregnant or breastfeeding
- Patients who have received systemic GC within 4-weeks of randomization
- Patients who have received intra-articular GC within 4-weeks of randomization

5.3 Participant Recruitment and Consent Procedures

Potentially eligible patients will be identified by the physicians at each site. The study will then be introduced to the potentially eligible participants by the treating rheumatologist during their regular clinic visit. If the patient wishes to consider participating in the study, they will be directed to the study coordinator/assistant who will then provide a detailed description of the study and complete the consent process should the patient wish to enroll in the study. All patients will receive detailed information about the study prior to signing an informed consent form. Informed consent will be obtained from participants in-person. Participants will have the opportunity to leave the study at any time.

The Informed consent process will be documented using the study's database on REDcap by filling out a form that will indicate the consent version, date, consent options and choices, as well as the person obtaining consent. No study procedures will be undertaken until this in-person visit has occurred and consent is obtained and documented from the participant. A copy of the signed informed consent form (ICF) will be provided to the participant during that same visit (electronic or paper). The original copy (paper or electronic) of the signed ICF will be filed in the Informed Consent binder (separate from the participant's research records).

A copy of the signed ICF will be provided to the participant via paper copy, in accordance with the participant's wishes. The original copy of the signed ICF will be filed in the Informed Consent binder (separate from the participant's research records).

The consent form will disclose to participants that they will be randomized to the IM GC arm, or the PO GC arm. The treatment team will be aware of the randomization group.

Withdrawal Procedures

Participants may choose to withdraw from participation in the study at any time. Participants can inform the research staff of their withdrawal via email, telephone, or in-person. The research

staff will be responsible for recording their withdrawal in the study log and in REDCap. Participants do not have to provide a reason for their withdrawal. There will be no consequences for withdrawing from the study.

5.4 Randomization

Participants will be randomized in a 1:1 fashion and will receive either IM GC or PO GC.

Randomization at the participant level will be under the supervision and control of the study biostatistician. The general features of the design of the assignment process include:

- Use of a centrally administered, computer-based generation scheme, stratified by site.
- Release of assignments only after eligibility has been determined, consent obtained and required baseline data collected and recorded.
- Inability to predict future assignments from past assignments.
- Creation of an audit trail for the assignment process (electronic and paper-based).
- A software system using Balanced Random Assignments to Treatment will be used to generate treatment assignment schedules in a random permuted block design. When a participant is ready to be randomized the treatment team will access the randomization ID and will access the treatment allocation.

Our calculated sample size (see Statistical Plan section) will be 101 patients per group. Assuming approximately 10% attrition, we aim to recruit 220 patients. We will use block randomization within the 5 sites with random block sizes (16). Study visits will be in-person at randomization and week-6 with virtual, and telephone-based visits at weeks 1, 2, 4 and 12 to collect information on patient reported outcome measures and continued use of GC beyond the trial period (Appendix 2). We will collect data from clinicians at each in-person clinical visit on adverse events (AEs). Serious AEs will be defined according to the Medical Dictionary for Regulatory Activities (MedDRA) (17).

For the qualitative component, we will recruit and conduct a semi-structured interview at week-6 among patients involved in the trial using an interview script. Patients will be recruited by convenient sampling. We will use qualitative description to identify commonalities and thematic patterns across participants' perspectives, characterizing each theme in a theoretically useful manner to influence clinical practice. Recruitment will be guided by conceptual thematic saturation; we estimate including 20 participants (10 per group). We will use a qualitative description approach with concurrent data collection and analysis in an iterative process (18). Specifically, we are interested in characterizing patient preferences/treatment priorities surrounding GC use in RA flares. We will further explore the perceived advantages/disadvantages of IM versus PO GCs and trade-offs between the benefits of treatment and potential for side effects.

5.5 Study Interventions

Participants will be randomized in a 1:1 fashion.

- PO GC arm: Prednisone 15 mg/day for a week, reducing by 5 mg/day every 7 days until off.
- IM GC arm: Single dose 120 mg IM methylprednisolone.

Treating rheumatologists will be allowed to add, switch, or change doses of any DMARD therapy or non-steroidal anti-inflammatory drugs (NSAID) as per usual care.

5.6 Study Assessments

All virtual study assessments will be completed on REDCap. Participants will be sent email links that will direct them to the assessments on REDCap. The assessments will take approximately 5 minutes to complete during each assessment.

The in-person assessments will take place during visits to the University of Toronto affiliated teaching hospital-based rheumatology clinics. The in-person assessments will be conducted by trained study personnel.

Rheumatoid Arthritis Flare Questionnaire (RA-FQ)

The Rheumatoid Arthritis Flare Questionnaire (RA-FQ) was constructed out of the Outcome Measures in Rheumatology (OMERACT) Rheumatoid Arthritis (RA) Flare Group in 2016 and has undergone psychometric analysis on content and construct validity (19). The RA-FQ encompasses five items which involve patients rating their pain, physical function, stiffness, fatigue, and participation over the past week using 11-point NRS (0 = none to 10 = severe). The output is a summative score across items, yielding an interval score (0–50) where higher scores reflect worsening disease activity. Although thresholds to identify meaningful change vary, minimal worsening and improvement are generally associated with a mean 4.7 and − 1.8 change in RA-FQ, respectively (20).

Health Assessment Questionnaire – Disability Index (HAQ-DI)

The Health Assessment Questionnaire – Disability Index (HAQ-DI) is a component of the HAQ questionnaire that specifically measures physical disability. The questionnaire can be completed by the patient in approximately five minutes. It evaluates a patient's functional abilities, focusing on fine motor skills of the upper extremities, mobility of the lower extremities, and activities involving both upper and lower limbs. The HAQ-DI consists of 20 questions across 8 categories, which cover a broad range of everyday routine activities: dressing, rising, eating, walking, hygiene, reaching, gripping, and performing usual activities. Responses are rated on a 4-point scale from zero (no disability) to three (completely disabled) (21). Average scores that have been reported are 0.49 for the general population, and 1.2 in RA patients (21). In RA patients, the minimal clinical important difference most often used is ≥0.22 units (22).

Clinical Disease Activity Index (CDAI)

The Clinical Disease Activity Index (CDAI) is a composite measure incorporating swollen, tender joints as well as patient and physical global assessments to assess disease activity in RA. It is endorsed in clinical practice guidelines to guide treatment to targeted disease states (23). A prior study using data from Canadian Early Arthritis Cohort patients examined absolute changes in CDAI to determine minimally clinically important differences (MCID) and have suggested cut points for improvement were 12 (patients starting in high disease activity, CDAI>22), 6 (moderate, CDAI 10–22), and 1 (low disease activity, CDAI <10) (24).

Treatment Satisfaction Questionnaire for Medication

The Treatment Satisfaction Questionnaire for Medication (TSQM) v1.4 is a tool to assess patients' treatment satisfaction related to chronic disease treatments (25). Incorporated domains include: Effectiveness, Side Effects, Convenience, and Global Satisfaction domains, with scores ranging from 0 (poor satisfaction) to 100 (perfect satisfaction) (26). It has been incorporated in RA patients in observational studies.

Absence of continued steroid use beyond 6 weeks

The goal in RA pharmacotherapy is treatment to target disease activity, all the while minimizing the use of GC, which harbor multiple deleterious side effects. We will also measure the continued use of GC beyond 6 weeks (to 12-weeks) post-randomization as a secondary outcome measure.

5.7 Outcome Measures

Primary outcomes:

1. RA flare questionnaire (RA-FQ) score change from baseline to 6-weeks

Secondary outcomes:

1. Clinical Disease Activity Index (CDAI) score change at 6-weeks
2. Health Assessment Questionnaire – Disability Index (HAQ-DI) score change at 6-weeks
3. GC use between 6- and 12-weeks (in prednisone equivalents)
4. Treatment Satisfaction Questionnaire for Medication (TSQM) score change at 6-weeks
5. Qualitative assessment of patient views and perspectives on RA flare management, including glucocorticoid use

5.8 Study Visits

Visit 1 (baseline) will be conducted in person:

- Participant demographics: age, sex, race (patient self report, as per CIHI standards)

- Participant height, weight, blood pressure
- Baseline information: disease duration, tender joint count, swollen joint count, flare duration, prior DMARDs
- Steroid dose administered/prescribed
- Baseline CDAI
- Baseline HAQ-DI
- Baseline RA-FQ
- Baseline TSQM

Visit 2 (interval; administration of questionnaires via email) – week 1

- RA-FQ

Visit 3 (interval; administration of questionnaires via email) – week 2

- RA-FQ

Visit 4 (interval; administration of questionnaires via email) – week 4

- RA-FQ

Visit 5 – week 6 (in person)

- Participant height, weight, blood pressure
- CDAI
- HAQ-DI
- RA-FQ
- TSQM
- *a time window of +/- 2 weeks will be allowed
- *if agreeable, semi-structured interview for qualitative component

Visit 6 – Week 12 (interval), via telephone

- Any use of steroids between week 6 and 12 (any associated dosages)

Interval visits will consist of an email with the questionnaire link for the patient to complete.

Table 1 – summary of study related activities						
RESEARCH VISITS	**Visit 1: Baseline**	**Visit 2: Week 1**	**Visit 3: Week 2**	**Visit 4: Week 4**	**Visit 5: Week 6**	**Visit 6: Week 12**
Virtual/In-person	In-person	Virtual	Virtual	Virtual	In-person	Virtual
Patient consenting	X					
Participant Demographics	X					
Steroid dose administered/prescribed	X					
Participant height, weight, blood pressure	X				X	
Baseline information	X					
Patient questionnaires						
Qualitative interview^					X	
CDAI	X				X	
RA-FQ	X	X	X	X	X	
TSQM	X				X	
HAQ-DI	X				X	
Any use of steroids between week 6 and 12	X	X				X
^optional						

6.0 STATISTICAL ANALYSIS

Patient demographic/clinical characteristics will be summarized by randomization groups descriptively including baseline parameters: age, sex, race, RF/CCP positivity, active joint counts, disease duration, flare symptom duration, current DMARD therapy, CRP and ESR levels.

Our sample size calculation for our primary outcome was based on demonstrating non-inferiority in terms of RA-FQ score changes between the IM and PO groups at 6-weeks. According to observational data from the Canadian Early Arthritis Cohort study (CATCH) cohort, standard of care in early RA results in RA-FQ improvement of 10.0±14.2 before 12-weeks (unpublished). Since there are no prior trials using the RA-FQ, we selected an acceptable change within a non-inferiority margin of 50% or -5.0 in expected change in RA-FQ as compared to usual care, as guided by the Food and Drug Administration (27,28). Assuming an alpha error of 0.05, and one-sided calculation with power of 80%, a sample size of 101 patients per group would be required. Assuming less than 10% attrition (since this a short trial), we aim to recruit 220 patients in total. This power calculation was conducted with input from the study statistician.

We will use an ANCOVA linear model for the primary outcome with intercept and main terms for the treatment assignment and baseline variables, adjusted for baseline RA-FQ scores and

study site (29). Secondary outcome measures including CDAI score, TSQM score, HAQ-DI scores, and use of GC between 6 and 12-weeks will be calculated descriptively. Adverse events related to GC will be analyzed descriptively.

Those receiving additional course(s) of steroids (whether via IM or PO administration) beyond protocol administration, will be labelled as treatment failures. If a patient's flare does not improve adequately, the investigator may initiate a change in DMARD therapy during the study time period. A flare not improving may trigger the introduction of additional steroids; but these patients will remain in the study for safety and secondary outcome analysis only (not primary RA-FQ response). We will use per-protocol analysis with intention to treat analysis as sensitivity analysis (30).

The qualitative component of the study will use qualitative description which aims to provide a detailed account of experiences, maintaining close adherence to the data with minimal interpretation. This approach is particularly useful in studies within medicine that aim to gather insights from individuals who are directly experiencing the phenomenon being examined, such as patients with RA suffering from disease flares. Its philosophical foundation is based on an inductive process, which is used to develop, understand, and describe phenomena. Aligned with an interpretivist perspective, the researcher plays an active role in the research process. We will apply these principles to study the preferences of patients living with RA around treatment of flares, with a focus on use of GC (either IM or PO) (18).

7.0 DATA SAFETY AND ADVERSE EVENTS

7.1 Data and Safety Monitoring Plan

Overall Monitoring Plan

A complete protocol with executive summary and figures for quick access will be available for all investigators and staff. The trial will be conducted and documented in accordance with Good Clinical Practice (GCP). All patients will receive usual standard of care. All staff will be trained on the protocol at least yearly, and a staff training log will be maintained at all sites and centrally. All staff and investigators will have to complete GCP training and present an up-to-date certificate of completion prior to enrollment at that site. We have developed several methods for monitoring the fidelity of the intervention delivery, data collection, data completeness and adherence to GCP.

Responsibility for Conducting the Clinical Monitoring

The investigators will be responsible for monitoring the trial and ensuring the integrity of the interventions and data collected. The individual site PIs and the site coordinators will also monitor quality assurance of the proposed clinical trial. The lead site coordinator will monitor

data capture and overall study activities on a weekly basis. The team will meet at least 1-2 times per month throughout the length of the study with more frequent meetings in the first 6 months.

Data Management Plan

Patients will be identified by a completely numerical code (including a numerical code for hospital; Mount Sinai Hospital: 1, Sunnybrook Health Sciences Centre: 2, Toronto Western Hospital: 3. Women's College Hospital: 4, St. Michael's Hospital: 5) for study ID. The unique study ID number for each patient will comprise of the site identification code followed by the local patient ID number. For instance, study ID 4:17 refers to patient number 17 from the Women's College Hospital (WCH) site. Each site will keep a confidential subject identification code list in a password-protected excel spreadsheet located in the hospital research drive that will only be accessed by the research study team. In case there is missing data, this information will be available locally to resolve data queries.

The Decision Support team at Sunnybrook Health Sciences Centre will serve as the data coordination center for this study. The team will work closely with the study research coordinator and primary investigator to develop electronic case report forms (eCRFs), train study staff, and perform data validation and/or monitoring activities. Sunnybrook Health Sciences Centre employs an industry-leading, web-based, secure database technology (REDCap) which incorporates advanced data validation and reporting tools and allow for faster access to research data than traditional paper-based data collection tools. After clinical data is collected from study participants, recruitment sites will complete electronic data entry into a pooled database in REDCap. All data will be stored on Storage Area Network (SAN) servers at Sunnybrook Health Sciences Centre for 10 years after study completion. The servers are maintained by the Sunnybrook Health Sciences Centre Information Management/Information Technology (IM/IT) team. Only authorized staff members can access this data using usernames and passwords that are unique for each individual. With limited access privileges, 24-hour security and monitoring, the data center is highly secure.

All data will be directly entered into REDCap for all study activities. There will not be paper clinical research forms except for the unlikely circumstance that the server is down. Clinical data collected during the study visits will be directly entered into REDCap. Patient surveys will also be directly entered into REDCap. During the in-persons visits, the patients will complete their questionnaires on a computer or a tablet. For the virtual visits, the participants will receive a REDCap link that will direct them to the assessments on REDCap. The assessments can be completed on a tablet, laptop, or personal computer. Online questionnaires are set up so that study participants can decline to answer questions.

All research data will be submitted to the primary coordinating center without patient identifiers (including only site ID and patient ID), where the data will be stored and analyzed anonymously.

Monitoring of Data Capture and Prevention of Missing Data

Missing data reports and missing data rules are constructed within REDCap. Patients with missing data on virtual assessment questionnaires will be emailed/texted a second time to remind them to complete their assessments (within 1 day). If data is still missing, the site coordinator will call the patient daily until communication is established. The coordinator will also run weekly missing data reports that will be generated for each site and sent to each site weekly to ensure timely and complete data capture.

There are several levels for quality control.

A. Locally

The last question of the e-CRF on REDCap: "Have you checked that the patient has filled in all the questions of their assessments, and have you filled in all the questions of your questionnaire?"

B. Central quality control

The lead site coordinator will check REDCap for each site for quality control.

Data Verification

To ensure accurate data capture, the site PI will be asked to review the complete data entry from the baseline visit to ensure that all data is correct. They may reference the patient's medical record. We will repeat this data check for the first three follow up visits at each site and an additional two more for each site. If data were incorrectly entered within REDCap, a correction will be made through the backend portal with a comment as to why the changes were made.

Process for Locking the Final Trial Dataset

After completion of the last study visit, the database will be checked for missing, incomplete, and incorrect data. Any changes to the database after that time can only be made with the written agreement by Dr. Kuriya. The study will be completed once all enrolled patients have completed the study per the protocol and the clinical database has been locked.

Planned Procedures for Data Access and Sharing

After publication of the results, de-identified datasets will be shared upon request. Written requests for data use, including the planned analyses will be required for data sharing. Additionally, the investigators must agree to the planned analyses.

7.2 Adverse Event and Serious Adverse Event Definitions

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness, or experience that develops or worsens in severity during the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance
- leads to an Emergency Department visit
- leads to additional urgent rheumatology visits

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event (SAE)** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event
- cardiovascular events
- pulmonary events
- hospitalizations

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

Recording of Adverse Events

A survey will be available through REDCap should participants experience any AEs related to the study. They will also be asked about AEs during time point surveys.

Plans for Adverse Events

In the unlikely event of an adverse outcome associated with the study protocol, it will be documented and discussed with the research group and reported to the Institutional Review Board (IRB). We will additionally collect information on disease flares.

Plans for Incidental Findings

If a participant reports any concern with the study or distress, the participants will be contacted by the site Principal Investigator to discuss the situation and determine whether the participant should continue or stop with the study. If any medical attention is required, the patient will be instructed to contact their primary care physician or go to the emergency room depending on the nature of the injury.

This is a pragmatic clinical trial. There will only be routine investigations performed on the patients. Hence, the possibility of incidental findings will be low.

If there are any incidental findings, the participants will be contacted by the site Principal Investigator to discuss the situation and determine whether the participant should continue or stop with the study. If any medical attention is required, the patient will be instructed to contact their primary care physician or go to the emergency room depending on the nature of the finding.

8.0 STUDY ADMINISTRATION, DATA HANDLING AND RECORD KEEPING

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the *Personal Health Information Protection Act (PHIPA*). Those regulations require a signed subject authorization informing the subject of the following:

- Information practices include when, how and the purposes for which the investigator routinely collects, uses, modifies, discloses, retains, or disposes of personal health information, as well as the custodian's safeguards with respect to the information
- How to reach the contact person, how to obtain access to or request a correction of a record of personal health information and how to make a complaint to the investigator

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. Participants will sign a combined consent and PHIPA authorization at enrollment.

8.2 Data Collection and Management

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).

One central research coordinator will be responsible for follow-up with all participants across all study sites.

It is important to note that the REDCap database server and individual study databases have never been compromised as a result of the extremely rigorous and secure network firewall technologies.

If this information exists on paper case report forms (CRF), it will be filed under lock and key. No results will be reported in a personally identifiable manner.

All tracking system data will be password-protected with several levels of protection. The first will allow access to the operating system of the computer. The second will allow access to the basic menus of the integrated system; within certain menu options, such as database browsing, a third password will be required. Our prior research employing similar precautions has demonstrated that these techniques are very successful in ensuring the protection of subjects. The same procedure used for the analysis of automated data sources to ensure protection of patient information will be used for the survey data, in that patient identifiers (telephone, email) will be used only to contact patients for relevant study components. The study identification number, and no other identifying information, will be used on all data collection instruments. All study staff will be reminded to appreciate the confidential nature of the data collected and contained in these databases. Each investigator and staff member involved in the proposed study will sign and adhere to a Standard Operating Procedure for managing participant data through the REDCap platform and has participated in required PHIPA compliance training. We will also continue to make use of password protection programs for all computerized records. In no instance will identifying information be publicly disclosed. Prior to conducting any analyses, all identifiers (e.g., names, medical record numbers, health plan enrollee numbers, birth dates, etc.) will be removed. Results from this part of the investigation will be reported in aggregate.

All data will be stored on Storage Area Network servers at Sunnybrook Health Sciences Centre for10 years after study completion. The servers are maintained by the Information Management/Information Technology team. Only authorized staff members can access this data using usernames and passwords that are unique for each individual. With limited access privileges, 24-hour security and monitoring, the data center is highly secure. After

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

In addition, to help maintain confidentiality, all audio recordings will be destroyed immediately following transcription.

Communication with Human Subjects

Individuals are asked to provide their name, an email address (personal), and phone number for the duration of the study. Participants will be sent emails to complete study assessments via REDCap.

9.0 ETHICS CONSIDERATIONS

9.1 Ethical Standard

The investigator will ensure that this study is conducted in accordance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research and codified in the Tri-Council Policy Statement and the ICH E6.

9.2 Research Ethics Board

The protocol, ICF(s), recruitment materials, and all participant materials will be submitted to the REB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the REB before the changes are implemented in the study unless it is to eliminate an immediate hazard.

10.0 PUBLICATION/DATA SHARING POLICY

Publication of results is a critical responsibility that is expected to be carried out in a timely fashion following the completion of the trial; publication should result regardless of the outcome, direction, or nature of the results obtained. All final decisions regarding timing, content, and conclusions of publication rest with the PIs; some of these decisions may be delegated to a publication committee. Publications will be via peer-reviewed journals that allow deposition of the manuscript in PubMed. These results should be published prior to presentation of results, unless agreed-upon by the PIs. All publications should include a list of participating clinical sites and sponsors in an Acknowledgement section.
Authorship on study publications will adhere to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the International Committee of Medical Journal Editors.

These requirements state “Authorship credit should be based on:

1) Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data
2) Drafting the article or revising it critically for important intellectual content; and
3) Final approval of the version to be published

Authors should meet conditions 1, 2, and 3.

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