Optimization of the flare management in rheumatoid arthritis (RA) by implementing patient-driven systematic changes to the RA ambulatory care stream

Grant ID: 15322005

Key Project Staff: Eric Matteson MD, MPH; Cynthia Crowson, MS; John Davis III, MD; Sherine Gabriel, MD, MSc; Elena Myasoedova, MD, PhD

Abstract:
Flare is an important aspect of the disease experience for patients with rheumatoid arthritis (RA), having a crucial impact on quality of life and well-being, and associated joint damage and comorbidity. There is a growing appreciation of the benefits of tight inflammation control to improve outcomes in RA, necessitating systematic patient-tailored changes to the RA management plan as outlined by European League Against Rheumatism (EULAR) recommendations and principles of treat-to-target-recommendations in RA. This project is aimed at developing an improved multilevel care process model for the management of RA disease activity by implementing systematic self-monitoring of flare experiences by RA patients, combined with continuous patient-tailored adjustments of treatment modalities by a coordinated team of rheumatology health care providers (RHCPs). The current rheumatology practice will be augmented by a nurse-led, telephone-based, flare management service providing continuous patient-provider communication and triage to prioritize patient appointments with RHCPs, based on the results of the patients' self-assessment of flare using an established self-administered flare assessment in RA questionnaire (FLARE). Random allocation of RA patients to an intervention arm vs. standard of care (SOC) will be used. RA activity measures, including flare rates and flare-to-visit time; patients' and RHCPs satisfaction rates, and costs, will be compared between the baseline, intervention arm, and SOC. Addressing the principles of patient-centeredness, efficiency, effectiveness, and safety, this project is expected to result in improved experiences and satisfaction of RA patients by early, timely, and cost-effective RA flare management, which will be readily reproducible in other rheumatology practice settings.

OVERALL GOALS AND OBJECTIVES

The overall goal of the project is two-fold: to develop an improved multilevel care process model for the management of rheumatoid arthritis (RA) disease activity through the implementation of systematic self-monitoring of the flare experience by patients with RA, combined with continuous patient-tailored adjustment of treatment modalities by different levels of rheumatology health care providers (RHCPs), i.e. nurses, nurse-practitioners (NPs), physician assistants (PAs), and physicians. This project will address an existing gap between patients' perceptions of flare and the availability of immediate professional help, precluding the implementation of patient-tailored changes to the RA management plan as outlined by European League Against Rheumatism (EULAR) recommendations and principles of treat-to-target recommendations (TTT) in RA.[1,2] As the appreciation of tightly controlling RA disease activity grows in the rheumatology community, the gap between successful monitoring and timely patient-tailored treatment changes becomes more apparent, necessitating systematic changes to the RA care process model in order to optimize flare management in RA.

The project is designed to improve RA patients' experiences and satisfaction with the outpatient rheumatology healthcare, both on an individual and cohort level, as well as to evaluate for improved cost-effectiveness of the suggested health care model, which is in line with the principles of the Institute of Health Care Improvement Triple Aim framework.[3] The overall concept of this care process model resides on improvement of three key areas of effective healthcare delivery: speed (efficient workflow, decreased waste), quality (patient safety), and cost. This integrative approach to flare management will serve to optimize outpatient rheumatology workflow by synchronizing patients' needs with access to appropriate medical services, thereby improving disease-related outcomes, including reduction of disease activity. The proposed intervention is expected to be reproducible in other rheumatology practice settings, whether in a community-based practice or an academic medical center, and can be implemented widely in the US and abroad.

Key objectives

1. **To improve monitoring of flares in patients with RA, by:**
    a. integrating an established, self-administered, flare assessment in RA (FLARE) questionnaire[4] into routine rheumatology outpatient care;
    b. developing continuous communication of self-assessment results between patients and RHCPs, facilitating continuous feedback and identification of the patient-centered personalized threshold for flare.

    This objective is intended to address the pressing need for the systematic change in flare management through an improved patient-centered approach to flare monitoring, using a self-administered FLARE questionnaire as a tool for collecting and sharing information on patients' flare experiences for timely identification of flares, tailored to each individual patient's perception of RA activity.

2. **To develop and implement changes to the RA disease activity medical care stream, by:**
    a. introducing a nurse-led, telephone-based, flare management service in order to provide positive behavior support and guidance to self-management;

b. using a nurse-led triage system to prioritize patient appointments with RHCPs, based on the results of the patients' self-assessments of flares;
c. applying patient-oriented, shared decision making strategies to guide personalized, patient-agreed goals of care and RA management plan.

This three-fold objective is intended to further target the need for improved RA flare management by developing a coordinated RHCP-guided network, empowered with nurse-led telephone service, to ensure effective patient triage based on patients' self-perceptions of RA activity/flare and the development of personalized RA management plans. The impact is anticipated to be improvement of patients' experiences and satisfaction with early, timely, and cost-effective RA flare management.

The nurse-led care (NLC) model is an established and rapidly developing model of care for patients with chronic diseases including patients with musculoskeletal conditions such as RA which has been shown to be clinically effective, cost effective, and safe in various health care practices across the world.[5-9] Several studies have shown a beneficial patient satisfaction profile with the NLC model.[7,9,10] The use of this model in rheumatology practices is supported by the EULAR, as reflected in the recent EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis.[11] We believe that the use of the NLC model in our project can be a high-yield intervention resulting in improved RA flare management.

3. To estimate the effectiveness of the suggested RA care model, by:

a. comparing the changes in flare metrics (i.e. flare-to-visit time, flare rates) in patients who used the FLARE intervention vs. those who did not (standard of care [SOC] group);
b. evaluating changes in RA disease activity measures using standard composite indices of RA disease activity, i.e. disease activity score 28 (DAS 28), clinical disease activity index (CDAI) and simplified disease activity index (SDAI) in the intervention and the SOC group;
c. assessing patients' and RHCPs' satisfaction and acceptance of the implemented RA care flow model vs. baseline vs. SOC;
d. comparing direct medical costs in the FLARE intervention group vs. the SOC group.

This objective addresses the question of the value of the project to healthcare and its sustainability for future practice by evaluating the clinical benefits and economic costs of the NLC approach to RA flare management. The results will inform rheumatology practice and will assist in shaping an improved flare management workflow.

TECHNICAL APPROACH

Current Assessment of Need in the Target Area

Quantitative baseline data summary. Flare is an important aspect of RA patients' disease experiences, with a crucial impact on quality of life and well-being, associated with joint damage and comorbidity.[12-14] Despite the clear benefits of tight inflammation control, there is a significant discordance between the objective need for treatment and successful implementation of the TTT strategies in an individual patient.[2] The shortage of readily available specialized help is one of the reasons for the lack of the treatment success, suggesting that

extending the rheumatology workforce by actively engaging nurses and mid-level RHCPs in triage and routine treatment decision-making may help to address the existing problem.[15]

There is currently no uniform tool for characterizing an RA flare. However, there are a growing number of established approaches for evaluating flare experiences in RA, including the OMERACT 9 definition of flare[16] and the FLARE questionnaire.[4] The FLARE self-assessment questionnaire is an established tool for the detection of flares based on joint symptoms (e.g. joint pain, swelling, morning stiffness, or use of antirheumatic drugs) and the systemic impact of RA disease (e.g. signs of fatigue and depression). This tool has good content validity and reproducibility, and has been shown to reliably identify RA flares in the European population.[17]

Preliminary Data

Identification of RA flare using the FLARE Questionnaire in a US population of patients with RA. We have recently tested the FLARE questionnaire in our ongoing NIH-funded prospective cohort study of patients with RA in the Olmsted County, MN [R01AR46849]; we aimed to assess the performance of FLARE questionnaires in relation to clinical and laboratory measures of RA disease activity/severity in RA patients. The study included 160 RA patients (mean age 62.6 years; 74% female; mean RA duration 14.7 years) who completed the FLARE and Bristol Rheumatoid Arthritis Fatigue (BRAF) questionnaires, as well as the Health Assessment Questionnaire (HAQ) with visual analogue scale for pain (VAS pain) on a 100 mm scale during a study visit (2012-2014), and submitted a blood sample for C-reactive protein (CRP) and interleukin-6 (IL6) assessment. Retrospective electronic medical records (EMR) reviews were performed to collect prior history of flares (as per OMERACT 9 definition), as well as physician clinical assessments (PCAs) and patient global assessments (PGAs) of RA disease activity on a 100 mm scale for the most recent clinical visits prior to the study visits. The previously validated RA medical records-based index of severity (RARBIS) and the claims-based index of RA severity (CIRAS) were used to estimate RA severity, based on the recent year of data on RA disease characteristics and medications.[18-20] Data on joint surgeries, erosions, extra-articular manifestations, RA flares, morning stiffness, rheumatoid factor (RF), acute phase reactants, and antirheumatic drugs were gathered to calculate RARBIS, with and without the optional medication scale. Claims data were used to calculate the CIRAS based on the number of rheumatology and rehabilitation visits, tests for inflammatory markers, RF, platelet counts, and chemistry panels. Pearson's correlation was used to examine the relationships between the variables.

The mean (standard deviation [SD]), of the overall FLARE score was 2.47 (2.54) on the 0-10 scale; 1.82 (2.43) for the systemic subscale; and 3.26 (3.08) for the joint subscale. Other mean (SD) measurements were: CRP, 4.15 (5.8) mg/L; IL6, 3.48 (5.52) pg/mL; HAQ, 0.64 (0.62); VAS pain, 28.6 (24.6). Table 1 summarizes the results of the correlation analysis. The FLARE score overall and both subscales were statistically significantly correlated with BRAF, HAQ, VAS pain, IL6 and PGA, but not PCA. CRP was significantly correlated with the overall FLARE score and the systemic, but not joint subscale. There was a statistically significant correlation of FLARE overall and its joint subscale with RARBIS, but not CIRAS. No significant correlation of FLARE was found with any history of prior flares. In a subset of patients (n=28) who had a clinical visit within 3

months of the study visit, being in a flare at that visit correlated with FLARE overall (r=0.41, *P*=.03) and joint subscale (r=0.51, *P*=.006), but not systemic subscale (r=0.26, *P*=.18).

Table 1. Correlation of the FLARE questionnaire results with characteristics of RA activity, severity, and fatigue.[a]

Characteristics		FLARE questionnaire subscales		
		joint	systemic	overall
BRAF score subscales	overall	0.44 <.001	0.71 <.001	0.61 <.001
	physical fatigue	0.46 <.001	0.71 <.001	0.62 <.001
	living with fatigue	0.46 <.001	0.71 <.0001	0.62 <.001
	cognitive fatigue	0.31 <.001	0.50 <.001	0.43 <.001
	emotional fatigue	0.29 <.001	0.62 <.001	0.48 <.001
HAQ score, 0-3 points		0.52 <.001	0.50 <.001	0.55 <.001
VAS RA Pain rating within last week, 0-100mm		0.66 <.001	0.59 <.001	0.67 <.001
IL6, pg/mL		0.24 .003	0.17 .04	0.22 .006
CRP, mg/L		0.10 .22	0.24 .004	0.18 .03
VAS Patient Global Assessment, 0-100mm		0.62 <.001	0.68 <.001	0.69 <.001
VAS Physician Clinical Assessment, 0-100mm		0.16 .20	0.17 .18	0.17 .17
RARBIS, 0-18 points		0.27 .006	0.17 .09	0.23 .016
CIRAS, 0-11 points		0.06 .53	0.14 .16	0.11 .28
Any history of prior flare		0.12 .20	0.08 .42	0.11 .26

[a] The results are presented as Pearson correlation coefficients with *P*-values below.

In summary, the FLARE score was highly correlated with other measures of RA patients' self-report, i.e. BRAF, HAQ, VAS pain and PGA, with systemic inflammatory markers, RARBIS and flare at the most recent visit. Our findings suggest that the FLARE questionnaire may be a

reliable tool for RA flare detection, reflecting clinical and laboratory aspects of RA disease activity [unpublished data, abstract submitted to the upcoming American College of Rheumatology (ACR) 2014 annual scientific meeting].

Work to develop a decision threshold (i.e., cut-off value) for flare is ongoing. The optimal flare definition threshold is important to standardize as it will impact the optimal cost-benefit management, including the need for office visits, changes in medication, laboratory monitoring, and related healthcare resource use, which will result in consequences for both patients and the healthcare system. The studies to determine the minimal clinically important difference in FLARE scores to assess changes in flare levels are underway in collaboration with the developers of the FLARE questionnaire in Europe. While this work is ongoing and the current study will be useful to help refine an optimal definition, we also need guidelines to use in the interim to determine when patients need to be seen. Similar to the EULAR definition of response, these criteria will be based on both the absolute level of the FLARE score and on the change in FLARE score from one assessment to the next. We will define the preliminary threshold for flare at a FLARE score of ≥5 units. This corresponds to 1 SD above the mean for our preliminary data and is comparable to the high disease activity state defined for DAS28 of ≥5.1. Furthermore, we will also consider patients with a change between consecutive assessments of the FLARE score of ≥1.6 units to be in flare, as 1.6 is the smallest detectable difference (unpublished data).

Evaluation of the dynamics of RA flares and measures of RA disease severity over time. In a population-based inception cohort of patients with incident RA (as per the 1987 ACR Criteria) seen at Mayo Clinic from 1988-2007 with follow up until 7/1/2012, we examined RA flare rates and the changes in the CIRAS and RARBIS scores as measures of RA disease severity over time. RA flare was defined as any worsening of RA activity leading to initiation/change/increase of therapy (OMERACT 9).

The study included 525 patients (mean age 55; 71% female) who had 15,649 clinical visits (mean 30 visits per patient) within an average of 10.3 years of follow-up. The mean (SD) RARBIS score at RA incidence was 3.3 (1.4) and the CIRAS was 4.5 (1.9). There was an increase in both CIRAS and RARBIS scores during the first year of disease (**Figure 1**). Thereafter, the CIRAS scores tended to decrease, but the RARBIS

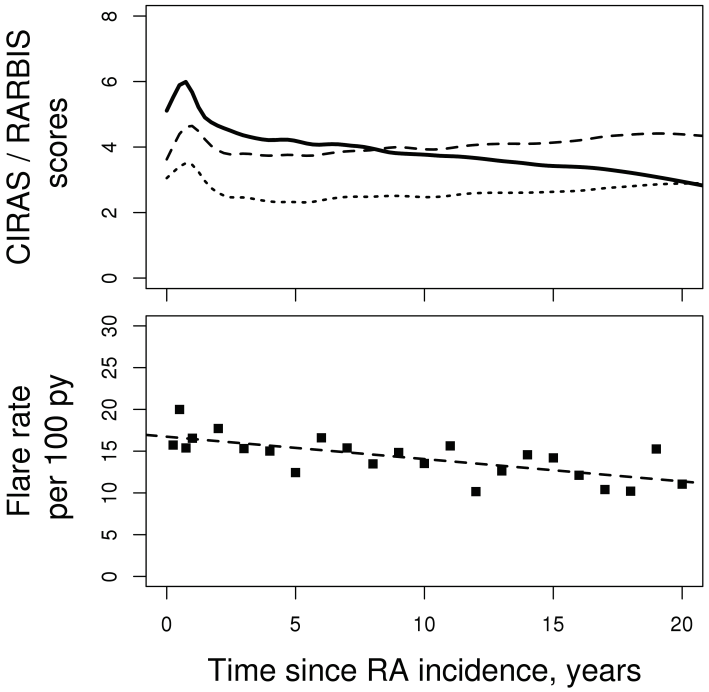


Figure 1. Trends in CIRAS (solid line), RARBIS with medications (dashed line), RARBIS without mediations (dotted line) [upper panel], and flare rate [lower panel].

values showed little change over the disease course. The flare rate decreased significantly during the follow-up by 0.3 per 100 person-years each year (*P*<.001).

In summary, the uniform increase in CIRAS and RARBIS values during the first year after index date may reflect an initial spike of RA activity and an initial extensive workup of RA disease. The subsequent decline in CIRAS scores is concordant with decreasing flare rates, and could be due to the gradual decrease in the need for a comprehensive laboratory workup and decreased frequency of rheumatology visits in patients with established disease.

The Impact of RA Flare on the Risk of Cardiovascular Disease (CVD). We have examined the impact of RA flare, remission, and cumulative burden of RA severity on the development of CVD. In a population-based cohort of patients with RA (per the 1987 ACR criteria), age ≥30 years, who were seen from 1988-2007, and had no history of CVD, we performed a retrospective EMR review of each clinical visit to estimate flare/remission status. An RA flare was defined based on the OMERACT 9 definition. Remission was defined as the absence of disease activity (i.e., tender joint count [TJC] = 0 + swollen joint count [SJC] = 0 + erythrocyte sedimentation rate [ESR] ≤10 mm/hr) (OMERACT 7). The RARBIS and CIRAS were used to estimate RA severity. The comparison cohort included age- and sex-matched non-RA subjects without CVD from the same underlying population. Data on CVD risk factors and incidents (e.g., myocardial infarction, cardiovascular death, angina, heart failure, stroke, intermittent claudication) were collected. All subjects were followed until death, migration, or 7/1/2012. The association of RA activity/severity measures with CVD was examined using Cox models with time-dependent covariates, adjusting for age, sex, calendar year of RA, CVD risk factors, and antirheumatic drug use.

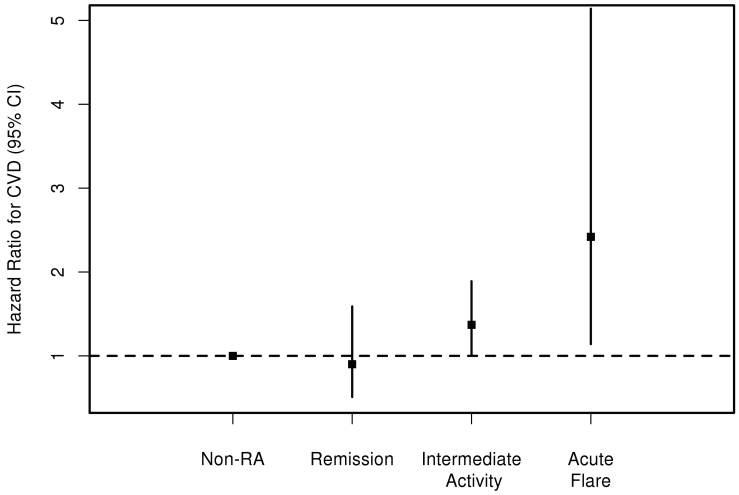


Figure 2. CVD risk depending on the level of rheumatoid arthritis (RA) disease activity in patients with RA as compared to the non-RA subjects adjusted for age, sex, calendar year of RA, and cardiovascular risk factors.

The study included 525 RA patients and 524 non-RA subjects (mean age 54.5 years; 71% female in both groups). During the mean follow-up of 10.3 years in the RA cohort and 8.8 years in the non-RA cohort, 129 RA patients and 77 non-RA subjects developed CVD. There was a significant increase in CVD risk (hazard ratio [HR]) in RA per each acute (6-week) flare vs. remission (HR 1.07; 95% CI, 1.01-1.15). The CVD risk for RA patients during remission was not significantly different from the non-RA subjects adjusting for age, sex, calendar year of RA, and CVD risk factors (HR 0.90; 95% CI, 0.51-1.59). However, patients with RA had an increased risk of CVD during intermediate activity (HR 1.37: 95% CI, 1.01-1.89) and during acute flare (HR 2.42; 95% CI, 1.14-5.14) compared to the non-RA subjects, adjusting for age, sex, calendar year of RA, and CVD risk factors (**Figure 2**). Increased cumulative

moving average of daily RARBIS (HR 1.16; 95% CI, 1.03-1.30) and CIRAS (HR 1.38; 95% CI, 1.12-1.70) was associated with CVD. The RA patients who spent more time in medium- and high-CIRAS tertiles tended to have higher CVD risk vs. those in the lower tertile (HR 1.08; 95% CI 0.98-1.20 and HR 1.18; 95% CI 1.06-1.31, respectively, per 1 year increase).

In summary, there was a meaningful 7% increase in CVD risk with exposure to each acute flare, but not remission, in RA vs. the general population, highlighting the pivotal role of RA flares in shaping CVD risk in RA. Higher long-term burden of RA severity was associated with significantly increased CVD risk in RA, suggesting accrued detrimental impact of RA severity over time. These findings imply important cardiovascular benefits associated with improved flare management and tight inflammation control in RA [results were partially presented at the EULAR 2014 meeting: Myasoedova E. et al., Ann Rheum Dis 2014;73(Suppl2); abstract submitted to the upcoming American College of Rheumatology annual scientific meeting; a manuscript describing the results is in its final stage of preparation for submission].

How this project builds upon existing work and ongoing projects. This project builds upon the well-established rheumatology clinical practice at Mayo Clinic (see methods section for details) and the long-standing experience of the investigative team in conducting epidemiological and translational studies of patients with RA in Olmsted County, MN. Our ongoing studies of the use of the FLARE questionnaire in RA will directly inform and facilitate the progress of the proposed initiative. In addition, we have established an association with the developers of the FLARE questionnaire in France, which will enhance the interpretation of the results.

Primary Target Audience

The primary target audience includes patients with RA and RHCPs (nurses, nurse-practitioners [NP], physician assistants [PA] and physicians) involved in routine care of these patients. Patients with RA will directly benefit from this initiative through improved flare monitoring and tailored management of RA activity. Currently about 3,000 unique RA patients are seen yearly at Mayo Clinic. Using a sample size of approximately 150 RA patients, we anticipate that the proposed patient-oriented approach for flare management will result in development of an improved care process model for the management of RA activity, which can be then disseminated to other healthcare systems on a national and international level. Successful implementation of thethis model is expected to improve patients' satisfaction with their RA disease management service and positively affect the overall practice of flare management in RA, thus addressing the existing gap in management of active disease.

Innovation

Increasing evidence supports a sizable mismatch at the national level between rheumatology service demand and provider supply, suggesting that the needs of the patients with rheumatic conditions, are insufficiently addressed.[21] This lack of resources makes the implementation of the TTT strategy as per the EULAR recommendations and principles of TTT in RA extremely challenging for many practitioners.[1] One suggested approach to improving the efficiency of rheumatology service is to increase the role of mid-level providers (NPs and PAs).[15] However, the evidence supporting this approach is lacking. This project is designed to address this gap by actively integrating the mid-level RHCPs in the rheumatology ambulatory workflow. This award

will enable us to develop and refine this innovative and original RA ambulatory care model that can then be disseminated widely to other rheumatology sites.

Project Design and Methods

Summary of the SOC (current state) model. The Division of Rheumatology conducts over 27,000 patient visits per year, including over 3,000 unique patients with RA per year (using ICD-9 code 714.9). Last year (2013) there were 27,132 patient visits to rheumatology including 3,182 unique patients with RA (68% female, 93.4% white), with 6,840 total visits. Forty eight percent of these patients (mainly patients living within 120 miles of the Mayo Clinic) were seen at least twice in 2013.

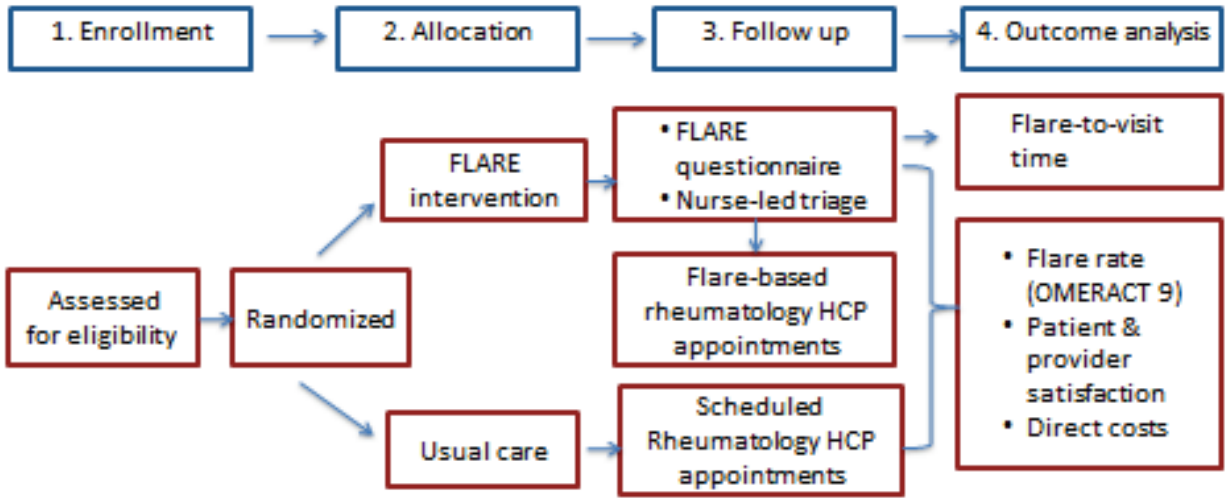
Patients with RA are seen in the outpatient Rheumatology Clinic (Division of Rheumatology, Department of Internal Medicine) for routine follow-up an average of every 6 months. Patients with a new onset of RA and those with moderate- or high-disease activity may require follow-up visits at shorter intervals than the current average of 6 months, per the discretion of the practice and rheumatologist availability. As part of the visit, the patients complete the following self-reported measures of RA disease activity: the HAQ and VAS for both pain and the PGA of RA disease activity. A RHCP (MD/PA/NP) performs a clinical examination of the patient, including assessment of swollen and tender joint counts as well as completion of a PCA of RA disease activity using the VAS scale. The results of the patients' self-reports and provider evaluations of RA disease activities are then entered into the Clinical Document Management (CDM) report, a specialized document comprising a part of the EMR, which documents the details of the history and physical examination at follow-up visits. Laboratory measures of RA disease activity (i.e., ESR, CRP) are pulled into the CDM report from laboratory databases for calculation of composite measures of RA disease activity, such as the DAS28-CRP, DAS28-ESR, CDAI, or SDAI. Based on the calculated score, the patients are classified as being in remission, low-, moderate-, or high-disease activity. These results are longitudinally tracked at each visit to facilitate TTT. Based on the clinical impression, the results of the evaluation of RA activity level and the patients' preferences for the goals of care, the patients and RHCP jointly devise the management plans, including pharmacological treatment and an optimal time-frame for follow-up appointments.

Study Design (summarized in **Figure 3**)

Patient enrollment. For this project we will include established patients with RA (2010 ACR criteria for RA) who have had at least 2 rheumatology visits within the past 18 months for the following reasons: 1) RA patients with newly diagnosed RA tend to have high disease activity requiring more frequent rheumatology visits and medications adjustment, suggesting that they need different routine care flow as compared to patients with established disease, who represent the vast majority (90%) of RA patients seen at the outpatient rheumatology clinic. Thus, we chose to not include patients with new onset RA. 2) Some of the patients who come to the Mayo Clinic Rheumatology Clinic, either episodically or for a single visit, are unlikely to return for a follow-up on a regular basis (e.g., patients from foreign countries or from distant parts of the US, those referred for a second opinion who have their primary established rheumatology provider elsewhere, etc.). These patients are unlikely to complete the study and

will not be included. The intervention will focus on patients with RA who have established rheumatology care at Mayo Clinic, with ≥2 rheumatology visits within the past 18 months and who will be most likely to have complete follow-up data for the study.

Figure 3. Study design flow chart.



Patient allocation and follow-up. All RA patients who qualify for the study will be provided an opportunity to participate. Patients who agree to participate will meet with a study coordinator and will sign a consent form for study participation. Computer-based randomization will be used to allocate the patients to one of the two arms. **Arm 1: FLARE intervention.** This group will undergo FLARE monitoring through a telephone-based NLC-service accessible during the business hours, 5 days/week (Monday through Friday). At the first study appointment, the patients will be given copies of the FLARE questionnaire requiring monthly completion. The patients will be instructed to complete one copy during the appointment for the baseline assessment to familiarize themselves with the questionnaire format, they will be given an opportunity to ask questions about the questionnaire, if any arise, at that time. Thereafter the patients will be mailed monthly reminders to complete the questionnaire and to report their results, the questionnaire scores, via telephone to the RA care manager (study investigator/registered nurse [RN]) who will determine the need for triage to an outpatient appointment with an RHCP. Our established, secure, online, patient messaging system can be used as an adjunct to telephone-based communication. However, only a minority of patients currently use this patient online service; thus the triage decision will be mainly based on telephone interactions. The triage decision will initially be determined by the decision threshold or if a change in FLARE scores, from the previous assessment, is larger than the minimal clinically important difference. Individual FLARE decision thresholds and associated important differences in the FLARE score will be further defined based on the patients' personalized, agreed-upon goals of care. The patients will be engaged in shared decision making to discuss their management goals, available treatment options, short- and long-term effects, as well as side-effects ,of treatments with respect to their RA disease, and overall well-being. **Arm 2: SOC.** RA patients will receive standard rheumatology ambulatory care with routine practice of

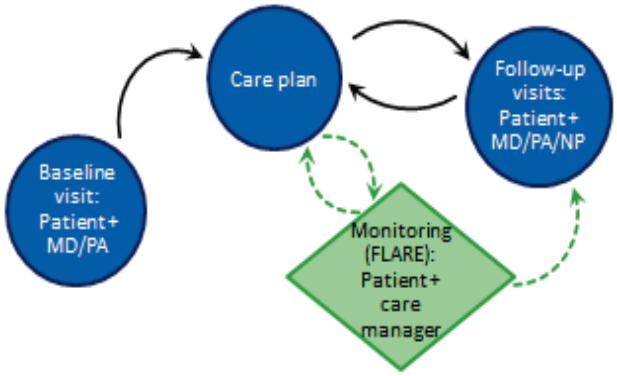


Figure 4. Flare management process map: Current-state SOC RA ambulatory care stream map (blue circles and solid-lined arrows) and a suggested future-state, RA ambulatory care stream map (additional green diamond and dashed arrows).

scheduling follow-up appointments as described above. **Figure 4** summarizes the suggested future-state flare management model vs. the SOC model.

Monitoring of RA disease activity: We will use RA activity scores (i.e., DAS 28, CDAI, SDAI) and self-performed joint counts at baseline and at each subsequent visit to monitor the dynamics of their change over time and to compare the measures at baseline and during the follow-up within each group. Patient-derived joint counts have been shown to have a good agreement with provider-performed joint counts and have been suggested as a reliable adjunct for the assessment of disease activity and clinical response in patients with RA.[22-24] The American College of Rheumatology 20% response (ACR20) criteria[25] will be used at 6-month intervals to evaluate for RA activity improvement in both groups. A standardized musculoskeletal ultrasound with power Doppler will be used at 6-month intervals to compare the activity of synovial inflammation in the joints of hands and knees between the groups. Musculoskeletal ultrasound measures have been suggested as measures of therapeutic response in patients with RA, and can be used to objectively compare the extent of synovial inflammation in the two groups.[26,27] This will be done for research purposes only and is not expected to be part of the care model at the stage of dissemination.

Outcomes Analyses

Primary outcomes. The occurrence of flares over the follow-up time (flare rate) and flare-to-visit time will be estimated, with a goal of 7 days from the detection of a FLARE score above the determined threshold requiring RHCP evaluation. The OMERACT 9 definition of flare will be applied to both groups to determine how many occurrences indicate worsening of disease activity, leading to initiation, change, or increase of therapy by RHCPs.[16] This definition will allow for parallel comparisons of flare rates in both groups. In addition, baseline (pre-intervention) flare rates over the past year will be compared to the flare rates at the completion of the project (post-intervention) for the intervention group. Patient-satisfaction and provider satisfaction surveys will be developed and provided to the patients and RHCPs at baseline and on every subsequent visit to the rheumatology outpatient clinic.

Secondary outcomes. Direct per-person and aggregate annual medical costs, including overall healthcare costs and rheumatology specific costs, will be estimated and compared in the two groups, using the data from the Olmsted County Healthcare Expenditure and Utilization Database (OCHEUD) regarding resource use and associated charges from Mayo Clinic. This claims-based database includes data on healthcare utilization, associated charges, and nationally representative unit costs for patients who receive their care at Mayo Clinic. It has

been previously used by our team to estimate healthcare costs in patients with chronic rheumatic conditions.[28]

Evaluation Design

Table 2 summarizes the measures which we plan to collect at baseline and during the follow-up. Decreased time-to-visit and improved measures of RA disease activity (i.e. flare rate, composite scores of RA activity and measures of self-report and ACR20 response criteria)[25] in FLARE management group as compared to baseline and to the usual care group will imply that the targeted gap of disconnect between patient perception of flare and availability of immediate professional help to initiate patient-tailored changes to their RA management is being addressed. Non-inferiority of the cost-effectiveness in the intervention vs. control group would suggest its potential value to the health-care system and sustainability of the project.

Table 2. Collected measures and timeline from RA patients in FLARE intervention and SOC groups.

	Standard of Care	FLARE Intervention
At Baseline & Follow-up Appointments	DAS28, CDAI, SDAI, HAQ, VAS pain, PGA, PCA, TJC, SJC, self-performed joint counts; patient and RHCP satisfaction surveys	
Monthly	None, except as may be required as part of SOC	Patient-initiated telephone call with FLARE score report
At 6-month Intervals	• ACR20 response criteria • Musculo-skeletal ultrasound with Doppler	
12-month Outcomes	**Primary:** • Flare-to-visit time • Flare rate (OMERACT 9) • Patient and provider satisfaction **Secondary:** • Direct costs	

Statistical analysis plan. Descriptive statistics (means, percentages, etc.) will be used to summarize the data for the two study arms. Changes in disease activity measures (e.g., DAS28, HAQ) over time will be compared in the two study arms using repeated measures analyses. Generalized estimating equations (GEE) will be used to accommodate a varying number of observations for each individual and account for the clustering of repeated measures within individuals. Flare rates will also be compared in the two study arms using GEE models assuming the flare rates will follow a Poisson distribution.

Patient and provider satisfaction surveys will be collected throughout the study in the FLARE intervention and the SOC arm. Time trends in patients and provider satisfaction will be assessed using GEE models to determine whether satisfaction increases over time compared to baseline, as well as comparison of the survey results between the study arms. Healthcare costs during the study period will be aggregated for each patient and divided by the length of follow-up to create a rate of costs per unit of time, since the follow-up will vary for each patient. Both total costs and costs directly associated to rheumatologic care will be assessed. Comparison of costs per unit of time between the two study arms will be performed using Wilcoxon rank sum tests, recognizing that the cost data will not be normally distributed. For all analyses, distributional assumptions will be assessed with data transformations or non-parametric methods used as appropriate. Missing values will be handled using multiple imputation methods. In all cases, two-tailed tests will be used. Unless otherwise noted, test statistics with $P<.05$ will be

considered statistically significant. All analyses will be conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Power/Sample size. A sample-size of N=150 subjects randomized into 2 groups is proposed. In general, for a repeated measures analysis (e.g., paired t-test) a sample size of N=75 per group will provide statistical power (two-tailed, alpha=0.05) of 80% to detect a difference of 0.33 SD. Therefore, the proposed sample size will provide sufficient statistical power to address the study objectives.

Quantifying the amount of change expected from this project. Based on literature data using NLC services to guide disease management, we expect a high patient-satisfaction rate (>90%) in the FLARE intervention arm,[29] and anticipate an increase in patient satisfaction rates (from baseline) of 20-30%. We anticipate that the cost-effectiveness of this intervention will not be inferior to the SOC. In fact, based on the prior studies of specialist nurse-led clinics in diabetes care, the likelihood of cost-effectiveness may be as high as 99%.[30] As far as improvement of RA disease activity measures, we will aim for a ≥20% improvement in the main RA activity measures from baseline, including TJC and SJC, and at least 20% improvement in 3 out of 5 of the following: PGA, PCA, VAS pain, HAQ, and an acute phase reactant, as per ACR20 response criteria, which have been shown to be highly specific measures of RA activity improvement as judged by patients.[25,31] Similarly, previous studies conducted in other settings show that nurse-led triage can decrease waiting times[32] We anticipate a decrease in time-to-visit to ≤7 days from baseline.

Quantifying the degree of involvement of the target audience. Patient and provider satisfaction surveys will be administered on every follow-up visit, including the questions on experience with the intervention and the likelihood of continuing participation. In addition, to assess adherence to the study we will track the FLARE questionnaire response rates.

Dissemination of the project results. Upon the conclusion of the project, the results will be submitted for presentation to international annual rheumatology conferences (ACR and EULAR annual meetings); and manuscripts summarizing the results will be submitted for publication in peer-reviewed journals. Information on the care process model for flare management in RA will be publicly available online on the Mayo Clinic Rheumatology website, as well as on the ACR website in the form of written and video communication. The results of the study will be summarized in a press release. Additionally, in our continuing communication with the developers of the FLARE questionnaire we plan to explore more opportunities for the dissemination of the results in Europe.

DETAILED WORK PLAN AND DELIVERABLES SCHEDULE

The initial start-up activities, including IRB approval, creating a data analysis plan, and study coordinator and RN care manager training will be conducted at the initiation of the project 10/2014 – 12/2014 (**Table 3**). Collection and analysis of the baseline data for each patient, including the summary of RA disease activity over the past year of follow-up (as outlined in the methods section and summarized in **Table 2**) and the results of the baseline surveys for patients and RHCPs, will take place during the period of patient recruitment and consent

(through 9/2016). Pre-intervention surveys will be sent out to RA patients who enroll in the study and RHCPs starting in early 2015 to assess the baseline satisfaction with the current rheumatology practice. The study intervention is expected to be implemented in early 2015. Data collection will continue through 9/2016, ensuring on average of one year of patient follow-up (minimum of 6 months, maximum of 1.5 years). Analysis of data will be conducted in late 2016 – early 2017, which will allow for early dissemination of the results (**Table 3**). **Table 4** summarizes the project deliverables and the schedule for completion of each deliverable.

Table 3. Project timeline: October 2014 – April 2017.

Activity	**2014**	**2015**				**2016**				**2017**
	Q4	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**
Develop study protocol										
Develop informed consent document										
Subspecialty group approval										
Rheumatology Research Committee approval										
IRB approval										
Create study database										
Study coordinator training										
Nurse care manager training										
Nurse training										
Implement patient recruitment plan										
Mail-out pre-intervention surveys										
Collection and analysis of baseline data										
Follow-up, ongoing data collection and monitoring										
Statistical analysis and data interpretation										
Dissemination of results										

Table 4. Milestones/Deliverables schedule

Project Tasks	**Estimated Completion Dates**
1. Deliver final study protocol, IRB approval and complete study personnel training	12/31/2014
2. Implementation of the intervention, recruitment of the first 50 subjects	09/01/2015
3. Completion of patient recruitment and analyses of baseline data	11/01/2016
4. Completion of all data analysis and delivery of final report for all study aims	02/01/2017
5. Submission of abstracts to clinical meeting and manuscript to peer-reviewed journal	04/01/2017

ORGANIZATIONAL DETAIL

Leadership and Organizational Capability

Mayo Clinic is a large, academic, multi-group-practice medical center, with fully integrated research, education, and clinical missions and programs. Mayo Clinic investigators hold over 250 NIH R01 grants contributing to a research portfolio that spans major areas of biomedical science. Extramural support is supplemented with intramural resources invested in research training and biomedical research. This project will be conducted on the Mayo Clinic campus in Rochester, MN.

The Division of Rheumatology at Mayo Clinic in Rochester, Minnesota, ranks consistently among the top centers in the nation for the treatment of rheumatic disease by *US News and World Report*. It has been a leader in clinical practice and research at Mayo Clinic since the time of Dr. Philip S. Hench, who shared the Nobel Prize for Medicine in 1950 for the discovery and use of cortisone in the treatment of RA. In 2013, the total research expenditure for the Division of Rheumatology was $2.9 million, including $1.86 million from extramural sources.

The leadership of the Division of Rheumatology includes Dr. Eric L. Matteson (Division Chair), Dr. Thomas G. Mason (Vice Chair and Education Chair), Dr. Kenneth J. Warrington (Practice Chair), Dr. John M. Davis (Research Chair), and Mr. Robert Warda (Division Administrator). Both Dr. Matteson and Dr. Davis are project co-investigators, hence their leadership roles will facilitate the successful completion of the proposed project. These individuals comprise the Executive Committee, which meets at least quarterly to discuss strategic priorities. These committee meetings will be an ideal venue for communications between the Practice and Research Chairs, serving the integration of this project in the usual process of clinical care.

The division includes 18 practicing rheumatologists, 4-6 rheumatology trainees (two per year), a physician assistant, two nurse practitioners, and four nurses. The allied health staff includes a clinical supervisor, 13 administrative and appointment secretaries, 8 clinical assistants, and 4 nurses. The division occupies 8,615 square feet of clinical space on the east wing of the Mayo Building, 15th floor, including ~50 clinical exam rooms and offices. All offices are equipped with modern computer equipment and network connections.

The division conducts >27,000 patient visits per year, including over 3,000 unique patients with RA (using ICD-9 code 714.9), 80% of whom reside within 250 miles of the clinic. The RA patient population includes patients from rural, farming communities in Minnesota, northern Iowa and western Wisconsin, as well as urban, city dwellers of Rochester, MN; roughly 87% of our patients are Caucasian but have great variability in education and income status. The members of the RA subspecialty group (which includes Dr. Davis and Dr. Matteson) as well as nurses and coordinators dedicated to the RA practice meet on a monthly basis to discuss new and ongoing studies, particularly to address challenges to patient recruitment.

The Rheumatology Research Study Unit (RSU) is conveniently located on the Mayo Building 15th floor in the East corridor, immediately adjacent to the clinical corridors. The mission of the RSU is to provide administrative support and clinical research coordination for studies conducted by rheumatology investigators. Currently, the RSU is successfully managing >50

MAYO CLINIC

200 First Street SW
Rochester, Minnesota 55905
507-284-2511

July 8, 2014

RE: Facilities & Administrative Costs

To whom it may concern:

Facilities & administrative (F&A) costs consist of costs that are incurred by a grantee for common or joint objectives and cannot be identified specifically with a particular project or program. These costs are also known as indirect costs (NIH Grants Policy Statement, 10/20/2011). A partial list of these costs includes Research Administration, Accounting, Materials Management, Space, and Human Resources.

Mayo Clinic is a non-profit organization which follows the cost principles defined by the OMB Circular A-122, "Costs Principles for Non-Profit Organizations." Current Mayo Clinic policy requires that we apply the appropriate F&A rate to all industry-funded agreements. The current rates are based on the classification of the space used to conduct the study. If space is classified as "Clinical," an F&A rate of no less than 30% is applied to the total direct costs. If space is classified as "Research," the most current federally-negotiated F&A rate is applied to the total direct costs.

Total direct costs include all costs incurred, including pass-through payments, with the exception of capital equipment, consortium payments in excess of $25,000 per site (excluding other Mayo Clinic performing sites), and approved start-up fees. Start-up costs include fees for the initial IRB review, IRB continuing review, Clinical Research Unit, pharmacy initiation and maintenance, protocol initiation and maintenance, and radiology.

Best regards,

David Moertel

Director, Office of Sponsored Projects Administration
Institutional Official

REFERENCES

1. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, Combe B, Cutolo M, de Wit M, Dougados M, Emery P, Gibofsky A, Gomez-Reino JJ, Haraoui B, Kalden J, Keystone EC, Kvien TK, McInnes I, Martin-Mola E, Montecucco C, Schoels M, van der Heijde D. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010 Apr;69(4):631-7. PMCID:PMC3015099.
2. Solomon DH, Bitton A, Katz JN, Radner H, Brown EM, Fraenkel L. Review: treat to target in rheumatoid arthritis: fact, fiction, or hypothesis? Arthritis Rheumatol. 2014 Apr;66(4):775-82.
3. Institute for Healthcare Improvement. The IHI TripleAim: better care for individuals, better health for populations, and lower per Capita costs. 2014; Available from: http://www.ihi.org/IHI/Programs/StrategicInitiatives/TripleAim.htm.
4. Berthelot JM, De Bandt M, Morel J, Benatig F, Constantin A, Gaudin P, Le Loet X, Maillefert JF, Meyer O, Pham T, Saraux A, Solau-Gervais E, Spitz E, Wendling D, Fautrel B, Guillemin F. A tool to identify recent or present rheumatoid arthritis flare from both patient and physician perspectives: the 'FLARE' instrument. Ann Rheum Dis. 2012 Jul;71(7):1110-6.
5. Ndosi M, Vinall K, Hale C, Bird H, Hill J. The effectiveness of nurse-led care in people with rheumatoid arthritis: a systematic review. Int J Nurs Stud. 2011 May;48(5):642-54.
6. Primdahl J, Sorensen J, Horn HC, Petersen R, Horslev-Petersen K. Shared care or nursing consultations as an alternative to rheumatologist follow-up for rheumatoid arthritis outpatients with low disease activity--patient outcomes from a 2-year, randomised controlled trial. Ann Rheum Dis. 2014 Feb;73(2):357-64.
7. Koksvik HS, Hagen KB, Rodevand E, Mowinckel P, Kvien TK, Zangi HA. Patient satisfaction with nursing consultations in a rheumatology outpatient clinic: a 21-month randomised controlled trial in patients with inflammatory arthritides. Ann Rheum Dis. 2013 Jun;72(6):836-43.
8. Larsson I, Fridlund B, Arvidsson B, Teleman A, Bergman S. Randomized controlled trial of a nurse-led rheumatology clinic for monitoring biological therapy. J Adv Nurs. 2013 Jun 17.
9. Ndosi M, Lewis M, Hale C, Quinn H, Ryan S, Emery P, Bird H, Hill J. The outcome and cost-effectiveness of nurse-led care in people with rheumatoid arthritis: a multicentre randomised controlled trial. Ann Rheum Dis. 2013 Aug 27.
10. Hill J, Thorpe R, Bird H. Outcomes for patients with RA: a rheumatology nurse practitioner clinic compared to standard outpatient care. Musculoskeletal Care. 2003 Mar;1(1):5-20.
11. van Eijk-Hustings Y, van Tubergen A, Bostrom C, Braychenko E, Buss B, Felix J, Firth J, Hammond A, Harston B, Hernandez C, Huzjak M, Korandova J, Kukkurainen ML, Landewe R, Mezieres M, Milincovic M, Moretti A, Oliver S, Primdahl J, Scholte-Voshaar M, de la Torre-Aboki J, Waite-Jones J, Westhovens R, Zangi HA, Heiberg T, Hill J. EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis. Ann Rheum Dis. 2012 Jan;71(1):13-9.
12. Sariyildiz MA, Batmaz I, Bozkurt M, Bez Y, Cetincakmak MG, Yazmalar L, Ucar D, Celepkolu T. Sleep quality in rheumatoid arthritis: relationship between the disease severity, depression, functional status and the quality of life. J Clin Med Res. 2014 Feb;6(1):44-52. PMCID:PMC3881989.
13. Salaffi F, Carotti M, Gasparini S, Intorcia M, Grassi W. The health-related quality of life in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis: a comparison with a selected sample of healthy people. Health Qual Life Outcomes. 2009;7:25. PMCID:PMC2674445.
14. Wolfe F, Michaud K. Proposed metrics for the determination of rheumatoid arthritis outcome and treatment success and failure. J Rheumatol. 2009 Jan;36(1):27-33.
15. Solomon DH, Bitton A, Fraenkel L, Brown E, Tsao P, Katz JN. The roles of nurse practitioners and physician assistants in rheumatology practices in the US. Arthritis Care Res (Hoboken). 2013 Dec 10.

16. Bingham CO, 3rd, Pohl C, Woodworth TG, Hewlett SE, May JE, Rahman MU, Witter JP, Furst DE, Strand CV, Boers M, Alten RE. Developing a standardized definition for disease "flare" in rheumatoid arthritis (OMERACT 9 Special Interest Group). J Rheumatol. 2009 Oct;36(10):2335-41.
17. Morel J BJ-M, Constantin A L, De Bandt M, Gaudin P, Vittecoq O, et al Validation Of The FLARE Self-Report Questionnaire For Assessing FLARE Out Of The Clinical Visit In Rheumatoid Arthritis. [abstract]. Arthritis Rheum. 2013;65 Suppl 10:2871.
18. Ting G, Schneeweiss S, Katz JN, Weinblatt ME, Cabral D, Scranton RE, Solomon DH. Performance of a rheumatoid arthritis records-based index of severity. J Rheumatol. 2005 Sep;32(9):1679-87.
19. Ting G, Schneeweiss S, Scranton R, Katz JN, Weinblatt ME, Young M, Avorn J, Solomon DH. Development of a health care utilisation data-based index for rheumatoid arthritis severity: a preliminary study. Arthritis Res Ther. 2008;10(4):R95. PMCID:PMC2575609.
20. Sato M, Schneeweiss S, Scranton R, Katz JN, Weinblatt ME, Avorn J, Ting G, Shadick NA, Solomon DH. The validity of a rheumatoid arthritis medical records-based index of severity compared with the DAS28. Arthritis Res Ther. 2006;8(3):R57. PMCID:PMC1526615.
21. Deal CL, Hooker R, Harrington T, Birnbaum N, Hogan P, Bouchery E, Klein-Gitelman M, Barr W. The United States rheumatology workforce: supply and demand, 2005-2025. Arthritis and rheumatism. 2007 Mar;56(3):722-9.
22. Houssien DA, Stucki G, Scott DL. A patient-derived disease activity score can substitute for a physician-derived disease activity score in clinical research. Rheumatology (Oxford). 1999 Jan;38(1):48-52.
23. Kavanaugh A, Lee SJ, Weng HH, Chon Y, Huang XY, Lin SL. Patient-derived joint counts are a potential alternative for determining Disease Activity Score. J Rheumatol. 2010 May;37(5):1035-41.
24. Figueroa F, Braun-Moscovici Y, Khanna D, Voon E, Gallardo L, Luinstra D, Pina X, Henstorf G, Laurence S, Neiman R, Furst D. Patient self-administered joint tenderness counts in rheumatoid arthritis are reliable and responsive to changes in disease activity. J Rheumatol. 2007 Jan;34(1):54-6.
25. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, Katz LM, Lightfoot R, Jr., Paulus H, Strand V, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis and rheumatism. 1995 Jun;38(6):727-35.
26. Backhaus TM, Ohrndorf S, Kellner H, Strunk J, Hartung W, Sattler H, Iking-Konert C, Burmester GR, Schmidt WA, Backhaus M. The US7 score is sensitive to change in a large cohort of patients with rheumatoid arthritis over 12 months of therapy. Ann Rheum Dis. 2013 Jul;72(7):1163-9. PMCID:PMC3686255.
27. Ramirez J, Ruiz-Esquide V, Pomes I, Celis R, Cuervo A, Hernandez MV, Pomes J, Pablos JL, Sanmarti R, Canete JD. Patients with rheumatoid arthritis in clinical remission and ultrasound-defined active synovitis exhibit higher disease activity and increased serum levels of angiogenic biomarkers. Arthritis Res Ther. 2014 Jan 8;16(1):R5. PMCID:PMC3978423.
28. Kremers HM, Reinalda MS, Crowson CS, Zinsmeister AR, Hunder GG, Gabriel SE. Direct medical costs of polymyalgia rheumatica. Arthritis and rheumatism. 2005 Aug 15;53(4):578-84.
29. Azarmina P, Lewis J. Patient satisfaction with a nurse-led, telephone-based disease management service in Birmingham. J Telemed Telecare. 2007;13:S3-S4.
30. Mason JM, Freemantle N, Gibson JM, New JP. Specialist nurse-led clinics to improve control of hypertension and hyperlipidemia in diabetes: economic analysis of the SPLINT trial. Diabetes Care. 2005 Jan;28(1):40-6.
31. Ward MM, Guthrie LC, Alba MI. Rheumatoid arthritis response criteria and patient-reported improvement in arthritis activity: Is an ACR20 response meaningful to patients? Arthritis Rheumatol. 2014 May 16.
32. Subash F, Dunn F, McNicholl B, Marlow J. Team triage improves emergency department efficiency. Emerg Med J. 2004 Sep;21(5):542-4. PMCID:PMC1726448.

MAYO CLINIC

200 First Street SW
Rochester, Minnesota 55905
507-284-2511

Department of Medicine

July 17, 2014

RE: Support for Grant Proposal:

I give my full and enthusiastic support for the proposed study by Myasoedova et al for the grant titled "Optimization of the flare management in rheumatoid arthritis (RA) by implementing patient driven systematic changes to the RA ambulatory care stream."

Flares are key indicators of active disease, and are associated with poor disease outcomes of the primary disease, as well as being associated with important co-morbidities including cardiovascular disease in patients with rheumatoid arthritis. This proposal, which combines unique strengths of the large integrated practice of rheumatology at Mayo Clinic, with a large local and regional patient base to draw upon for the purposes of this grant, will foster better care for patients with this disease and reduce disease related morbidity.

The study proponents and our clinic are well positioned and trained to successfully pursue this project. The Rheumatology Clinic infrastructure includes 20 rheumatologists, 5 nurses who are active in triage and care management and coordination, and study coordinator, biostatistical, and visit management personnel who are contributing to this project. Standard disease activity assessments captured in the electronic medical record are evaluable for data relevant to this study. As Chair of the Division of Rheumatology, I commit to our clinic and research resources, including space, study coordinator, and management of any overhead shortfall to the successful completion of the study.

Please feel free to contact me with any questions or concerns.

Sincerely

Eric L. Matteson, M.D., M.P.H.
Chair, Division of Rheumatology
Consultant, Divisions of Rheumatology and Epidemiology
Professor of Medicine
Mayo Clinic College of Medicine

Tel: 1-507-284-8450
Fax: 1-507-284-0564
email: matteson.eric@mayo.edu