A. Cover Page

Title:
Utilizing a Patient Navigator to Improve Oral DMARD Medication Adherence among Rheumatoid Arthritis Patients at an Academic Medical Center

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Abstract: (250 words)

Non-adherence to disease modifying antirheumatic drugs (DMARDs) is common and associated with several modifiable patient and system factors, including lack of patient education, side effects, disease activity, perceptions about medication effectiveness, attitudes towards medication use, self-efficacy regarding medication adherence and health system barriers. The overall goal of this intervention is to utilize a patient navigator, a layperson trained to guide patients through the health care system based on their individual needs, to reduce oral DMARD non-adherence among rheumatoid arthritis (RA) patients. The navigator model has been used to improve cancer screening and chronic disease management and to reduce health disparities. The "DMARD Adherence Navigator" that we proposed will address both patient-centered and system-level factors that contribute to oral DMARD non-adherence.

To achieve the overall goal, we propose two key objectives: 1) To implement a patient navigator intervention specifically to reduce oral DMARD non-adherence, and 2) To test the feasibility and effectiveness of the DMARD Adherence Navigator in a controlled trial.
In current work, we have developed a navigator model to improve patients' access to rheumatology care and will now re-focus the navigator's role to improve oral DMARD adherence. We will train the navigator and provide supporting educational materials through a collaborative process with key stakeholders. The intervention will be tested in a busy rheumatology practice at Brigham and Women's Hospital (BWH). The intervention will compare results of the primary outcome – oral DMARD adherence – at BWH with several satellite practices that are comparable to BWH.

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C1. OVERALL GOAL AND OBJECTIVES: Non-adherence to disease modifying antirheumatic drugs (DMARDs) is common and associated with several modifiable patient and system factors, including lack of patient education, side effects, disease activity, perceptions about medication effectiveness, attitudes towards medication use, self-efficacy regarding medication adherence and health system barriers.(1) The overall goal of this intervention is to utilize a patient navigator, a layperson trained to guide patients through the health care system based on their individual needs,(2) to reduce oral DMARD non-adherence among rheumatoid arthritis (RA) patients. The navigator model has been used to improve cancer screening and chronic disease management and to reduce health disparities.(2, 3) The "DMARD Adherence Navigator" that we proposed will address both patient-centered and system-level factors that contribute to oral DMARD non-adherence.

The DMARD Adherence Navigator model that we will develop and test will have substantial potential for dissemination. Navigators are becoming commonplace in the health care system, especially in cancer care.(4) Furthermore, medication non-adherence has been identified as the single largest driver of avoidable US health care costs. A recent report suggests that non-adherence to medications for several chronic conditions accounted for $105.4B in 2012.(5) Current interventions produce slight improvements in medication adherence, but few have produced substantial gains. Thus, the use of DMARD Adherence Navigators has the potential to increase medication adherence, reduce associated health care costs and is a simple strategy which can be disseminated widely within the current health care system.

Key Objectives: To achieve the overall goal, we propose the following key objectives.
1. To implement a patient navigator intervention specifically to reduce oral DMARD non-adherence. In current work, we have developed a navigator model to improve patients' access to rheumatology care and will now re-focus the navigator's role to improve oral DMARD adherence. We will develop and implement a navigator training program with supporting patient educational materials through a collaborative process with key stakeholders, including RA patients, providers (rheumatologists and nurses), and pharmacists.

2. To test the feasibility and effectiveness of the DMARD Adherence Navigator in a controlled trial. After developing the training materials and recruiting/training the DMARD Adherence Navigator, we will implement and test the intervention in a busy academic rheumatology practice at Brigham and Women's Hospital (BWH). The practice cares for approximately 3,500 patients with RA seen at least annually and has a long track record of successful patient recruitment.(6) We will test whether the navigator program improves the primary outcome of oral DMARD adherence, as well as several secondary endpoints, including patient self-efficacy for disease control, knowledge, and satisfaction with care. The intervention will compare results of the primary outcome – oral DMARD adherence – at BWH with several satellite practices. These control sites are ideal because the same rheumatologists practice at BWH and the affiliated sites (on different days) and the data collection system (a system-wide electronic medical record) is uniform. In addition, patient populations at BWH and the affiliated practices are very similar.

C2. TECHNICAL APPROACH

C2a. Current Assessment of Need in Target Area: The Funding Announcement already describes the need for improved medication adherence. This section focuses on further information that specifically supports the intervention proposed herein.

Adherence to DMARDs in RA patients ranges from 30-80%.(1, 7) Individual-level factors that contribute to DMARD non-adherence include beliefs about RA, concerns about medication side effects, degree of disease activity and health (or functional) literacy.(1) System-level adherence factors include health insurance,drug coverage, and access to providers, necessary tests and medications. In addition, racial, ethnic and socioeconomic differences in both access and adherence to DMARDs contribute to disparities in outcomes.(8) Interventions that attempt a one-size-fits-all approach to adherence have had mixed success whereas patient-centered approaches have been more effective.(9) A DMARD Adherence Navigator, as proposed here, will tailor an adherence strategy to the personal and system-level factors that specifically affect the individual patient with RA.

Table 1: Characteristics of a Sample Cohort of RA Patients at BWH Arthritis Center

Characteristics	"Stoppers" (n=292)	"Non-Stoppers" (n=204)
Follow-up (mean, SD, yrs)	3.8 (1.2)	3.0 (1.6)
Age (mean, SD, yrs)	67.6 (11.4)	70.6 (9.8)
Sex (Female n, %)	246 (84.3)	165 (80.9)
Race/Ethnicity (n, %)		
White	238 (81.5)	180 (88.2)
Black	26 (8.9)	12 (5.9)
Hispanic	14 (4.8)	5 (2.5)
Comorbidities (mean, SD)	2.3 (1.4)	2.0 (1.4)
Index oral DMARD (n, %)		
Methotrexate	175 (59.9)	128 (62.8)
Other oral DMARD	117 (40.1)	76 (37.3)

Notes: Stoppers defined as > 90 days without a prescription. Comorbidities include hypertension, diabetes, hyperlipidemia, tobacco use, obesity, cancer or COPD.

At BWH, of the approximately 3,500 RA patients receiving care, we identified a convenience sample of over 1,700 RA patients and linked their electronic medical records (EMR) to prescribing records. We identified 496 patients with RA who were new users of an oral DMARD (leflunomide, hydroxychloroquine, methotrexate, azathioprine, cyclosporine, or sulfasalazine). "Stoppers" were defined as those without prescription refills for >90 days and "non-stoppers" were those without any gaps in refills during the follow-up period (**Table 1**). Among the 292 "stoppers," 100 patients were randomly selected for detailed chart review (this review has been updated since our LOI submission). Of these patients, 22%% discontinued the oral DMARD because of an adverse event, 26% because the medication was ineffective and 52% because of non-adherence or unknown reasons.

We estimate that with 292 of 496 oral DMARD starters becoming stoppers and 52% of stoppers being non-adherent, baseline "adherence" rates were 69%. Since we have assessed continuation of drug, these rates most closely mirror "persistence" with DMARDs, but

persistence and adherence are typically very similar. These preliminary data help determine the statistical power of our proposed study (see **Sample size/Statistical power section** below).

As well, these data demonstrate the feasibility of the proposed intervention at our site:

a) The BWH Rheumatology practice has a large cohort of patients with RA who start oral DMARDs and will serve as the source of subjects for the proposed intervention;
b) Many of these patients stop oral DMARDs for reasons unrelated to adverse events or lack of effectiveness, suggesting non-adherence; and
c) The investigative team has expertise in tracking drug utilization.(10, 11)

The target population for this intervention will be patients with RA. There is general acceptance that DMARDs are effective in RA and recommended by rheumatology professional organizations.(12) However, many patients do not use them consistently or correctly and thus, do not accrue the recognized benefits.(8, 13, 14) This intervention will focus on the patient and his/her experience with improved adherence. The secondary target population includes providers, health systems, health care insurers, and pharmacy benefits programs. Providers, such as rheumatologists, spend substantial time with patients weighing the benefits and risks of treatment. However, providers are often not skilled in discussing adherence, detecting poor adherence, and in dealing with the myriad causes of non-adherence.(15) Thus, the DMARD Adherence Navigator will assist providers after a prescription for an oral DMARD has been written, freeing providers to focus on clinical issues. The health system is increasingly interested in adherence as more of the financial risk of care is shifted to focus on collaborative care through Accountable Care Organizations and Patient Centered Medical Homes.(16) The health system must make sure that necessary treatments are adhered to avoiding preventable health consequences and disability. Finally, payers want their dollars spent wisely. Health care insurance and pharmacy benefits companies are implementing their own medication adherence programs, documenting their interest in this area.(3)

C2b. Intervention Design and Methods

C2b1. Navigator Program: In this section, we describe a current lay navigator program that we have pilot tested and explain the behavioral framework for the proposed DMARD Adherence Navigator.

a. Current Navigator Program: We conducted an initial needs assessment and determined that a patient navigator was a preferred strategy to improve rheumatology care for underserved patients.(17) As a result, we pilot tested a traditional lay navigator program focusing on patients with rheumatic and musculoskeletal conditions. This program employs a trained community health worker whose focus is to help patients “navigate” the health care system. Because of the clear needs identified for underserved populations, the current program is a collaboration between Brigham and Women’s Hospital and the Family Health Center of Worcester (FHCW). The FHCW is a community health center that serves an urban, immigrant population, 95% with income levels below 200% of poverty. FHCW patients often have language, cultural, and economic barriers to receiving appropriate care. The current pilot

navigator program has employed a community health worker to serve as the lay navigator for FHCW patients with rheumatic and musculoskeletal conditions. We trained the navigator through a series of lectures, discussions, and selected readings focused on rheumatic diseases. She also shadowed an existing navigator working on HIV care and received an extensive site-based orientation to familiarize her with available resources. After 4 months of the program, we have served 125 patients and arranged 29 rheumatology consultations. On average, 5 new referrals (range 2-10) are received weekly. Currently, 31 (28%) patients are actively working with the navigator and 81 (72%) patients' primary care doctors were actively in communication with the navigator. Among the 31 actively engaged patients, navigator's services have included direct coordination of appointments and repeated reminders prior to the visit (n=26, 84%), facilitation of communication between providers (n=31, 100%), transportation arrangements (n=7, 23%), financial services including provisions for affordable medications (n=4, 13%) and coordination of live interpreters (n=2, 6%). Of the 29 patients scheduled to see rheumatologists, 14/17 (82%) successfully kept their appointments and 12 appointments are pending.

While the current program is distinct from the DMARD Adherence Navigator that we propose in this application, it provides important experience and proof of concept. *First,* we have trained a lay navigator in rheumatic and musculoskeletal conditions. This required us to develop a curriculum appropriate for her role and level of training, and to support her ongoing education through a back-up system where two rheumatologists are on-call for her at all times. *Second*, we have successfully integrated a lay navigator into a busy medical practice: providers refer patients to and actively engage with the navigator; we have developed charting tools for the navigator to communicate with providers and document her patient interactions; and she effectively works with other practice staff such as financial counselors and social workers. *Third,* we developed and refined a set of assessment tools for patients and providers that the navigator has successfully utilized. These help identify barriers to care and determine the patient experience with the program.

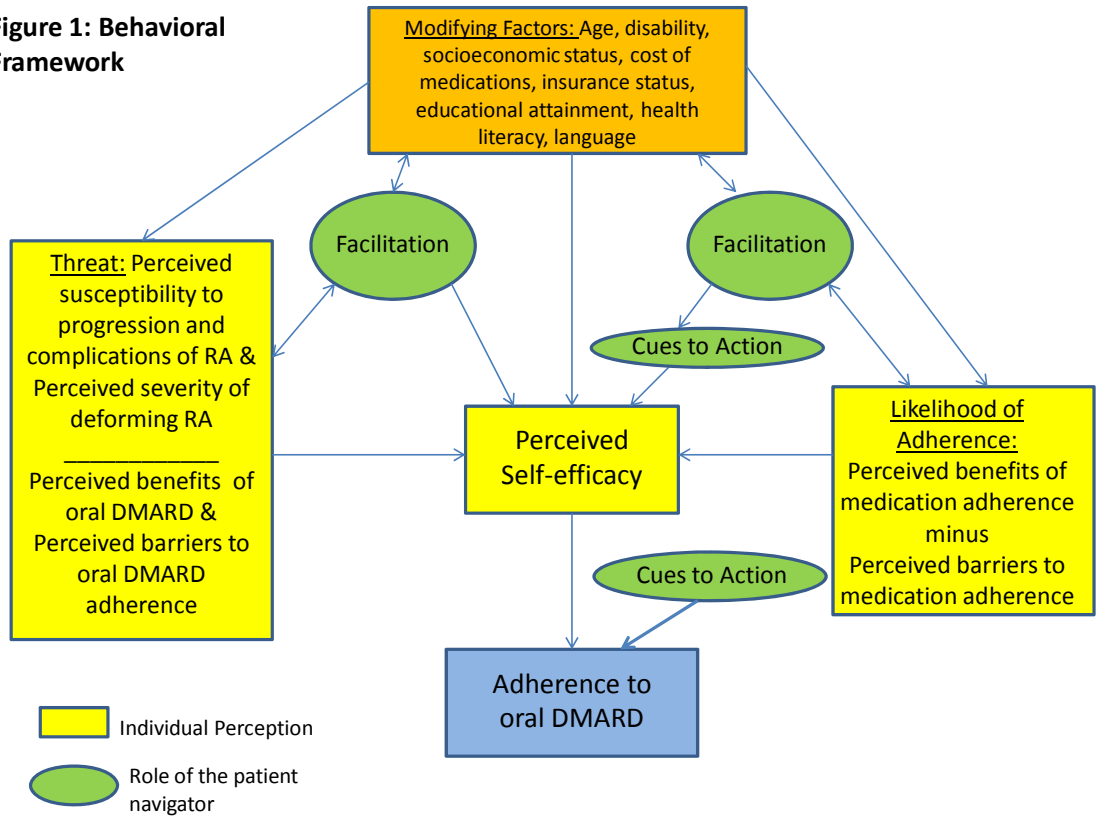
We will build on this experience in the proposed DMARD Adherence Navigator program. The training program will be based on our current curriculum, and we will add relevant DMARD adherence materials (see **Training Program Section** below). The integration into the BWH Rheumatology practice and methods for communication of the DMARD Adherence Navigator will be modeled on the current FHCW navigator. Templates for medical record notes will be used and provider communications will be standardized (see **Appendix A**). Finally, provider and patient assessment tools for the proposed program (see **Appendix B**) will use many of the same questions that have been successfully field-tested in the current program.

<u>b. Behavioral Framework:</u> The Health Belief Model (HBM) has been widely applied to a range of health behaviors including adherence to medications, utilization of preventive care services, and participation in health-promoting and health-risk behaviors.(18-20) The original HBM consists of five constructs: perceived susceptibility, perceived severity, perceived benefits, perceived barriers and cues to action. A more recent model incorporates self-efficacy, a key construct of the Social Cognitive Theory. Our proposed framework stems from the HBM and

incorporates two SCT constructs: self-efficacy and facilitation (see **Figure 1**).(21) An understanding of each of these constructs and their interplay will provide the foundation for the navigator intervention.

On the left side of **Figure 1**, perceived susceptibility is defined as a patient's belief about her risk of RA disease progression. In order to be willing to take a medication for RA, a patient must have an understanding of her risk of developing deforming arthritis and subsequent disability. Similarly, perceived severity is a patient's belief in the degree of functional limitation from RA. Together, susceptibility and severity comprise the perceived threat from RA. The navigator will work with patients to educate them about this threat based on the patient's baseline level of understanding and need and help them develop strategies to maintain adherence to the medications.

Figure 1: Behavioral Framework



Also on the left side of **Figure 1**, patient's perceived benefits include her understanding of the short and long-term efficacy of oral DMARDs to reduce pain and disability from RA. This construct is countered by perceived barriers to medication adherence, and the balance between the two results in the likelihood of adherence. Perceived barriers are patient-specific and include financial constraints, insurance status, health literacy, language, side-effect profiles and adverse events. The DMARD Adherence Navigator will help the patient assess and address personal barriers and to enable the patient to see that the benefits of medication adherence outweigh barriers.

As noted in **Figure 1**, self-efficacy can be defined as a patient's belief in his/her ability to engage in the behaviors necessary to adhere to DMARDs.(22) To heighten self-efficacy, the navigator will be trained in Motivational Interviewing techniques to engage the patient in discovering and developing new beliefs, expectations and strategies for overcoming barriers to adherence. Motivational Interviewing is based on Prochaska's Stages of Change and strategies are developed with active engagement of patients to address the patients' current level of readiness for change.(23, 24) This technique has been used successfully in addiction treatment as well as in the management of chronic illness.(25, 26) In addition, the navigator through her knowledge of the health care system may be able to reduce external structural barriers and improve patient knowledge about RA and DMARD use.

Facilitation is defined as the process of providing a patient with important tools and resources necessary to adhere to her medications, and promoting environmental and structural changes to enable this lifestyle change.(21) The DMARD Adherence Navigator will provide a link between the patient, her environment and the healthcare system. The goal of the navigator's work is to address modifiable factors, such as health literacy, language and religious/cultural beliefs, and to manage health care benefits enhancing access. Through these actions, the navigator will increase the likelihood of DMARD adherence. Thus, the navigator's role is both to reduce barriers to adherence and provide patients with skills and resources necessary to adhere to medications after the intervention ends.

To facilitate change, the navigator will employ cues to action (noted in green in **Figure 1**); positive external techniques to activate readiness to adhere to DMARDs. These cues are individually tailored to the patients' specific needs.(18) The cues will be in the form of emails, text messages or phone calls depending on patient preference. In addition to medication refill reminders, the navigator will provide cues for medication monitoring (i.e. laboratory tests), and for rheumatology appointments.

Overall, this framework described in **Figure 1** allows the navigator to appropriately assess a patient's level of need, her understanding of RA and the prescribed DMARD, barriers to sustained adherence, and her baseline self-efficacy to adhere to medications. Once these factors are delineated, the navigator can work directly with the patient to reduce her personal barriers, provide education and improve self-efficacy to facilitate DMARD adherence.

C2b2. Study Design: We will study the DMARD Adherence Navigator intervention using a controlled trial. This is possible because the BWH Rheumatology practice has several "satellite" (off-campus) locations, allowing comparison with concurrent control subjects who start oral DMARDs at the satellite practice sites without a navigator available. The main campus BWH Rheumatology practice will be the intervention site since it has the largest volume of patients. The other three satellite sites are very similar in almost all respects to the main campus: all of the rheumatologists who practice at the other sites also practice at the main campus; the other sites combined have 7 rheumatologists with large part-time practices seeing approximately 1000 patients with RA each year (compared with 2500 patients with RA at the main campus); the same electronic medical record (EMR) is used at all sites; and the satellite sites are between 2-15 miles from the main campus, so the patient demographics are similar.

We will study individuals in the program and controls for 6 months after the start of the first oral DMARD. Longer term follow-up will be pursued outside of the proposed study.

C2b3. Intervention: This section describes the DMARD Adherence Navigator's training program and role in the intervention.

a. Semi-structured Interviews: Prior to the navigator training and the implementation of the intervention, a series of key informant semi-structured interviews will be held with physicians, nurses, pharmacists and patients. The purpose of these interviews will be to delineate overarching health-system barriers that may need to be addressed prior to initiation. As well, the interviews will help describe the most common questions, concerns and medication-related adverse effects, providing the foundation for the navigator training program.

b. Training Program: The DMARD Adherence Navigator training program will be based on the current navigator curriculum with additional material focused on medication adherence and DMARDs. The DMARD Adherence Navigator will never give specific treatment advice but s/he needs to be able to gain the confidence and respect of patients. Thus, it is critical that the navigator possess a strong working knowledge of RA and its treatment. We have identified several candidate navigators who already have experience working with patients with RA, facilitating training. Drs. Solomon, Feldman and Iversen will provide the training. They will also meet with the navigator weekly for the first several months and then biweekly thereafter during the intervention period to provide ongoing training, supervision, and support. Drs. Solomon and Feldman will be available by beeper for any urgent medical questions that arise.

The educational program is based on the theoretical model for medication adherence (see **Figure 1** above). Medication non-adherence has many root causes, but some of the major issues include: poor patient knowledge about the indication for the medication; concerns about side effects; psychological issues of the patient, including depression and anxiety; as well as health systems issues, such as financing and poor communication.(27) The components of the training program described below target each of these areas so that the navigator can appropriately address common root causes of non-adherence. A draft of the full curriculum can be found in **Appendix C** and we will describe its components and structure in this section.

The components of the training program will be finalized during months 1 and 2 through the semi-structured interviews with patients, providers and pharmacists. These structured interviews will be a way of ensuring that the draft content is comprehensive and patient-centered. We have an RA Patient Advisory Board associated with BWH Rheumatology that will also serve as the patient sounding-board for the training components. As well, we have a large pharmacy staff at BWH who are well versed in adherence counseling and can help ensure that the training program is appropriate. We will also recruit several rheumatology physician colleagues to review the training program.

i. *Component 1 – Rheumatoid arthritis:* The DMARD adherence program will focus on patients with RA. The navigator must be fully conversant in the manifestations of RA, including articular and non-articular symptoms and signs. In addition, functional limitations that occur in patients with RA will be discussed so the navigator can be empathic with the patient experience.

ii. *Component 2 – DMARDs:* The navigator will need to become an expert in all aspects of RA treatment. While the adherence intervention focuses on oral DMARDs, adherence with these agents can best be discussed by a navigator who understands RA treatment and can discuss with patients biologics, non-biologic DMARDs, steroids, and even NSAIDs and coxibs. The navigator will never make treatment suggestions but can best reinforce rheumatologist recommendations if s/he is knowledgeable regarding these agents. The training will review the names, dosing, administration, mechanisms, side effects and monitoring of these agents. Since side effect concerns and symptoms are a major reason for non-adherence,(1) this will be a focus of the training. We will educate the navigator on how to recognize side effects, the prevalence of them, and simple strategies for managing them.

iii. *Component 3 – Medication adherence counseling*: While there are no proven strategies for how to best counsel patients to remain adherent with medications, several counseling strategies have been widely used. Among these, Cognitive Behavioral Therapy (CBT) and Motivational Interviewing have many useful aspects. The CBT counseling strategy addresses how patient think about a behavior (cognitions) and focuses on strategies to help patients change behavior.(28, 29) The latter, Motivational Interviewing, focuses on facilitating behavior change through self-discovery and relies on the patient to determine the best strategies for behavioral change based on their current readiness for change.(24, 30) In this proposal, we incorporate the cognitive elements (HBM, self-efficacy) with Motivational Interviewing techniques. We believe the combination of these constructs will provide the most inclusive counseling approach for a diverse sample of patients. Dr. Iversen has combined these strategies in another ongoing navigator program in orthopedic surgery.

iv. Component 4 – Pharmacy benefits/drug assistance programs: The cost of medications is a major concern for many patients. Since BWH is in Massachusetts with universal health care insurance coverage since 2006, most patients who will be enrolled in the proposed program will have some form of health insurance. However, most programs include a co-payment or deductible requiring patients to be financially responsible for a portion of the drug cost. We anticipate that this may present as a barrier to adherence for some patients. The DMARD Adherence Navigator will be trained in drug payment issues including state- and federal-assistance programs, drug-company sponsored assistance programs, and some BWH assistance programs.

c. Training Program Structure: After fully developing the training program during months 1 and 2, the DMARD Adherence Navigator will be trained during the third month of the program (see **Detailed Workplan and Deliverables Section** below). Each week will be devoted to one of the four Components listed above and approximately 8 hours per week will be spent on training. The training will occur face to face in a small group setting, using focused reading material to

supplement the discussions. Furthermore, the DMARD Adherence Navigator will attend Rheumatology clinic sessions with Drs. Solomon and Feldman to observe how the DMARD discussions typically occur between rheumatologist and patient.

d. Key Aspects of the Intervention: Once patients are referred to the navigator and verbal consent is obtained, the navigator will conduct a needs assessment. This may take place by telephone or in person at the time of the patient's next appointment with his/her provider. The needs assessment will include a semi-structured interview that will address the patient's understanding of RA and DMARDs, his/her perception of the benefits and harms of the medication, barriers to adherence, and likelihood to adhere. As described below (see **Secondary Outcomes** Section), the navigator will administer the RA Disease Activity Score Survey, the Arthritis Knowledge Questionnaire, the Arthritis Self-Efficacy Scale, and the Beliefs about Medicine Questionnaire. Based on the results of the interview and the surveys, the navigator will engage in the following activities:

i. Patient education about RA and about the prescribed DMARD

ii. Counseling and Motivational Interviewing based on assessed level of need

iii. Activities to reduce health system barriers for the patient (financial services, patient assistance programs, transportation arrangements for treatment monitoring appointments)

iv. Determination of patient-specific cues to action including text message, phone calls, or emails, to remind patients about medication use, refills, blood tests and follow-up appointments.

C2b4. Subject Recruitment: We have changed the subject selection methods from what was stated in the Letter of Intent. All individuals starting an oral DMARD at BWH main campus will be invited to be part of the program. Identification of potential subjects and their recruitment is described in **Figure 2.**

The BWH electronic medical records (EMR) can be searched using an automated program to find new prescriptions. We will use this automated search engine weekly to find new oral DMARD prescriptions. Patients who add an oral DMARD to an existing treatment regiment or start with a new RA treatment regimen will both be eligible. Letters will be sent to these potential subjects letting them know about the program and to expect a call from the DMARD navigator unless s/he opts out. The letter will be signed by the primary rheumatologist, the navigator and Dr. Solomon. This opt-out letter is routinely permitted by the Partners Healthcare IRB. Two weeks after the letter, the navigator will call the individual by telephone to explain the program and ask them to participate. If the navigator is unable to reach them after three attempts at different times of the day, then the navigator will meet them face to face at their next rheumatology appointment. An IRB-approved information sheet will be provided to all patients either in person, via email or via mail, at the time of their first conversation with the navigator describing the intervention and verbal consent will be

obtained. Participation will be voluntary and patients will have the ability to withdraw at any time. We will use the EMR to examine characteristics including demographics, comorbidities and past medical history of patients who agreed to participate compared to those that did not.

Figure 2: Recruitment Process

The EMR is utilized by all BWH Rheumatology sites and new oral DMARD users will be identified at the primary BWH Arthritis Center and at 3 satellite clinics (850 Boylston, Brigham and Women's Faulkner Hospital and Braintree Rehabilitation Hospital). These satellite clinics care for similar patients populations and are staffed by BWH rheumatologists all of whom also see patients at the BWH site. The BWH Arthritis Center will serve as the intervention arm and patients identified through EMR will be contacted using the aforementioned methods. The three satellite clinics will serve as the control arm without a navigator intervention. The primary outcome of 6-month persistence (discussed below in **Primary Outcome Section**) will be compared betweent intervention and control arms using the EMR. The date of the first oral DMARD prescription will be considered the index oral DMARD for the analyses. Second oral DMARD prescriptions during the study period will be considered part of the secondary outcomes.

C2c. Evaluation Design

C2c1. Primary Outcome: Our primary outcome is adherence with oral DMARDs. We will measure adherence using the EMR to calculate the oral DMARD medication possession ratio (MPR), number of days with filled prescriptions x 100 divided by the number of days in the observation period during the 6 months of the intervention.(31) While some studies define adherence using a dichotomized MPR (i.e., MPR>80%), we will consider the MPR as a continuous outcome. The MPR will be compared for patients engaged with the navigator (intervention arm) and for the oral DMARD starters at the Rheumatology satellite practices without the intervention (control arm).

The primary study endpoint will be the MPR at 6 months. We will evaluate the difference in MPR between intervention and control arms.

We anticipate a 12 to 18% absolute greater MPR in the intervention arm versus the control arm (see **Statistical Power Section** below).

C2c2. Secondary Outcomes: In addition to our primary outcome of adherence, we will also evaluate a series of secondary outcomes. Several of these secondary outcomes focus on the patient's experience with her disease and RA medications. These will be available only on the intervention arm subjects and will be measured at baseline and after six months.

a. RA Disease Activity will be measured using the Disease Activity Score (DAS28).(32)

b. Arthritis Knowledge Questionnaire: In keeping with our theoretical framework, we will assess RA-specific knowledge and patient understanding of drug treatments using the Arthritis Knowledge Questionnaire.(33)

c. Arthritis Self-Efficacy Scale will be used to understand patients beliefs in their ability to adhere to DMARDs.(34)

d. Beliefs about Medicine Questionnaire will assess patients' beliefs about the necessity of the prescribed medications to control their disease and concerns about potential adverse effects from the medications.(35, 36)

Information from the baseline surveys will also be used by the navigator to tailor his/her approach to facilitating adherence with each intervention subject.

Other *secondary outcomes* will focus on alternative measures of adherence and will be studied in exploratory analyses. These are described briefly herein:

e. 12-month adherence: Subjects enrolled in the first 6 months of the program (months 4 – 10) will have 12-months of follow-up. We will calculate the MPR for these subjects at both 6 months (primary outcome) and at 12 months (secondary outcome) to compare longer-term adherence in intervention versus control subjects.

f. 6-month persistence: Persistence for the index DMARD will be determined after 6 months. Persistence will be determined based on continued filling of the index oral DMARD through 6 months. Subjects with at least 30 days without active prescriptions will be deemed non-persistent.

g. 12-month persistence with any DMARD: We anticipate that some subjects will become non-adherent with the index oral DMARD but may start or continue other DMARDs. We will assess if patients have an active prescription for any DMARD.

C2c3. Statistical Analyses and Sample Size Estimation: The statistical analyses will proceed as follows:

a. Comparison of Intervention and Controls: We will examine baseline characteristics of subjects in the intervention versus control arms. Characteristics to compare include age, gender, duration of RA, serologic status, number of comorbid conditions, number of other (non-RA) medications, use of oral glucocorticoids, and the specific index oral DMARD. We will

compare these characteristics using a student's t-test or Wilcoxon rank sum test for continuous measures and a Chi-square test for categorical ones. Among the intervention subjects, we will compare characteristics of subjects who refuse participation with those who consent.

b. Calculation of Subject-level MPR: We will calculate the MPR at 180 days for each participant by dividing the number of available index oral DMARD days into 180 x 100%. This calculation will be made at 365 days as a secondary outcome (as noted above). First, these calculations will be conducted for all subjects in both groups to understand the distribution of values. Then, we will stratify the subjects based on intervention versus control assignment.

c. Comparison of Treatment Arm MPRs: The MPR is a continuous measure and will likely not be normally distributed. The primary analysis will be the comparison of MPRs between intervention and control arms using a Wilcoxon rank sum test under a reasonable assumption that MPR will follow Poisson distribution. As a sensitivity analysis, we will also use a two sample t test even normality assumption is not valid. When sample size is large (e.g. n >100), a two sample t test or linear regression is still valid for non-normal data.(37) Based on the comparison of baseline characteristics in the intervention versus control groups, we will decide whether we should adjust for baseline characteristics. If any of the above variables differ by more than 10%, then we will model the comparison of the MPRs using a Poisson regression or general linear model with that variable included as a covariate. The dependent variable will be MPR and the exposure of interest will be treatment assignment, i.e., intervention versus control.

d. Sample Size/Power Estimation: Based on the comparison of MPRs at 6 months after the start of the index oral DMARD, we calculate the required sample size to attain 80% power. Under a reasonable assumption of Poisson distribution, we calculate the following sample sizes for various plausible differences in the MPR between intervention and control arms and given a two-sided alpha of 0.05 and 80% power using a Wilcoxon rank sum test.(38)

Our preliminary analyses found 69% persistence (see **Current Assessment of Need Section** above). We anticipate enrolling 20 patients per month, or 480 patients over 12-months, in the intervention arm. This is based on a recent chart review of several randomly selected weeks in the BWH Arthritis Center practice. We found an average of 52 new oral DMARD starts per week. We anticipate that about 40% of such patients will agree to participate in the adherence program based on our prior work.(11)

We calculated the sample size required for the anticipated effect sizes based on the preliminary data. As **Table 2** demonstrates, if the MPR is 65% in the control arm, then the sample size required to detect a 18% difference with 80% power will be 393 subjects in each arm. Alternatively, with 480 in each group, we have 80% power to detect differences in the mean MPR between control and intervention arms of 65% to 81% or 70% to 87%.

Table 2: Sample Size Estimation for 80% Power		
Control arm MPR	Intervention arm MPR	Sample size per arm
65%	77%	849
65%	80%	554
65%	83%	393
65%	85%	322
70%	82%	907
70%	85%	592
70%	88%	419
70%	90%	343

C2c4. Alternative Methods Considered:

a. Randomized controlled trial. The current application proposes a non-randomized controlled trial. We decided on this design for several reasons. First, randomization is a better design for an efficacy trial but is often difficult in the setting of a quality improvement trial, such as what we propose. Second, it would have been very difficult to randomize at the patient level (versus the site level), because this intervention will involve many providers and systems of care that would be difficult to keep from contaminating patients in different arms at a single site. Thus, the non-random clustered trial is what we have opted for.

b. Automated reminder intervention. We considered an intervention that would have only included automated reminders via e-mail, text messaging, and/or telephone messages. While some have found that this type of intervention is effective, we strongly believe that it would solve non-adherence for only a small fraction of the non-adherent oral DMARD population. Thus, we have opted for a more novel and holistic counseling approach.

c. Control arm consent. We considered asking control subjects for consent and then offering them some potential quality improvement opportunity (such as an educational seminar or a delay in the intervention). This would allow the subjects in both intervention and control arms to be more similar. However, it would add substantial cost to the control arm for recruitment and consent. We have opted to observe subjects at the control sites and to passively collect their drug adherence data from the EMR.

C3. DETAILED WORKPLAN AND DELIVERABLES: We describe the milestones and deliverables below in **Table 3**. Each aspect of the workplan is described in detail with deliverables noted in bold. The timeline is aggressive, but the investigators have worked together on many prior projects, all work in the same research group, and the pool of eligible patients is large.

Table 3: Detailed Workplan and Deliverables		
Milestones and Deliverables	Description with Deliverable in Bold	Timeline (months)
IRB protocol	Since we plan on publishing the findings of this quality improvement intervention, we will ask for an **IRB review and approval.**	0 - 1
Structured interviews	RA patients, providers, and pharmacists will be part of structured interviews to discuss barriers to oral DMARD adherence and possible solutions. These interviews will also test the training material developed for the DMARD Adherence Navigator. **The interviews will be summarized.**	1-2
Training curriculum	The training program will be finalized and details fleshed out during months 0-2. The DMARD Adherence Navigator will then be trained during month 3. **The curriculum will be "packaged" so that it can be disseminated.**	1-3
Implement patient search strategy	We have already developed an EMR-based search strategy to develop preliminary data. During the proposed trial, we will refine the search strategy to allow for real-time identification of patients using a weekly automated program. (No deliverable)	1-3
Recruit patients	Using the weekly automated patient search program, we will identify all patients with RA starting an oral DMARD and attempt recruitment. **Patient recruitment reports will be reviewed internally every 2 weeks and shared with the funder ever 3 months.**	4-16
DMARD Adherence Navigator Intervention	Each subject at the intervention site (BWH Rheumatology) will receive follow-up by the navigator for at least 6 months. **Notes on the interactions and intermittent subject assessments will be documented.**	4 – 22
Analyses and reports	We will conduct an evaluation on adherence comparing the intervention site with the concurrent control sites. **Summary data will be presented in Tables and a Manuscript ready for submission.**	22-24

C4. DISSEMINATION: To ensure that the DMARD Adherence Navigator intervention can be disseminated to additional sites after this study, the following steps will be taken:

1) A comprehensive DMARD Adherence Navigator curriculum will be developed with the input of physicians, nurses, pharmacists and patients. To accompany this, a manual will include specific training instructions and suggestions of ways to alter aspects of the curriculum to accommodate variations in baseline knowledge of the navigator and the

clinic site. Specific strategies for implementation of this intervention will also be included in this manual.
2) Patients will be identified in a clear and straightforward way that will be reproducible at other clinic sites with electronic medical records.
3) Reproducible templates to track patients will be created for the navigator.
4) We will use a standard measure of adherence that has been widely used and can easily be recreated in a different setting.
5) To measure secondary outcomes, previously validated surveys with strong internal consistency will be used which will facilitate dissemination of these evaluation tools to other sites
6) All infrastructure and resources necessary for adoption and implementation of the intervention will be closely monitored and carefully recorded.

If this program is successful, we will work closely with the funder to disseminate it through training sessions, educational seminars and production of materials.

C5. INNOVATION: The patient navigator is being utilized increasingly in cancer care and in chronic disease management as a patient-centered, tailored intervention to improve adherence to screening tests and medications and to reduce health care disparities.(3) As discussed, our team is piloting a rheumatology/musculoskeletal disease navigator at a Massachusetts Community Health Center. To accomplish this, we developed rheumatology-specific navigator training materials, and patient and provider surveys. We have learned that there is significant need for this intervention both from the number of provider referrals we received, and from patients who have rarely declined participation. In addition, at our medical center, in primary care, a program was established to identify high-risk chronic disease patients and provide intensive one-on-one management to improve medication adherence and overall disease outcomes.(39) The efficacy of this parallel intervention in primary care demonstrates the applicability and feasibility of this intervention.

The DMARD Adherence Navigator that we propose herein is a novel application of the navigator approach. Since there are few proven interventions to enhance adherence and navigators are becoming more widely accepted with the new health care laws, the proposed program is both innovative and an intervention that has the potential to become widely disseminated. It is also innovative to embed an adherence intervention within a routine practice setting, allowing providers to have input and feeding information back to them through the EMR.

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