A. Cover Page

Title:
A Novel Mobile App & Population Management System to Manage Rheumatoid Arthritis Flares

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ABSTRACT

Although most rheumatoid arthritis (RA) patients experience at least one flare over a six-month period, the majority of these flares are not reported to health care providers (HCPs). This disconnect between patient experience and HCP awareness impairs effective disease management. The *goal* of this study is to implement a smartphone application (app) + population management system to monitor RA disease activity between scheduled HCP visits. We plan to accomplish this objective by pursuing two specific aims: 1) to determine the impact of the smartphone app + population management system on patient satisfaction with treatment and perception of the patient-HCP interaction, and 2) to assess the effect of the smartphone app + population management system on RA disease activity. The *proposed project* will be a randomized controlled trial, with participants randomized to the smartphone app + population management system vs. a waitlist control. The *target audience* includes 190 RA patients with moderate-severe disease activity who are taking disease-modifying antirheumatic drugs. The primary outcomes will be scores on the Treatment Satisfaction Questionnaire for Medication, the Patient-Physician Interactions Questionnaire, and the Clinical Disease Activity Index at six months. The *evaluation* of treatment effects (mean differences in outcomes between groups at six months) will be estimated with mixed models. The results are expected to have an important positive impact by enabling patients to document self-reported disease activity on a real-time basis, securely transferring data to HCP offices via a web-based dashboard, and consolidating and communicating concerning trends to HCPs via a population manager.

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C. MAIN SECTION

C1. Overall Goal and Objectives

The majority of rheumatoid arthritis (RA) patients experience at least one flare in a six-month period (1). RA patients describe these increases in disease activity as emotionally distressing and physically disabling (2). It is assumed that prompt reporting of flares to rheumatology healthcare providers (HCPs) will lead to faster resolution of symptoms and greater control of overall disease activity (2). In practice, however, many RA patients do not notify their HCPs of flares between scheduled appointments, and, instead, try to manage flares on their own (3). There is an *urgent need* to improve the real-time assessment and management of flares in RA. The *overall objective* of this proposal is to implement a smartphone application (app) + population management system to monitor RA disease activity between scheduled HCP visits. The population management system includes: 1) a web-based dashboard that consolidates incoming patient-reported data using pre-programmed algorithms to identify increases in disease activity, and 2) the population manager, a trained individual who monitors the web-based dashboard and connects patients with their HCPs. Our *central hypothesis* is that the combined smartphone app + population management system will improve patient satisfaction and management of RA disease activity. The *rationale* is that the smartphone app will increase patient involvement in disease assessment, while the population management system will support the integration of patient-reported data into the workflow of a busy clinical practice. We plan to test our central hypothesis and accomplish the objective of this proposal by pursuing the following two *specific aims*:

1. ***To identify the impact of the smartphone app + population management system on patient satisfaction with treatment and perception of the patient-HCP interaction***. The population will include 190 RA patients, randomized 1:1 to a smartphone app + population management system vs. a waitlist control. RA patients will complete components of the validated Patient Activity Scale II (PAS-II) on a daily basis. A population manager will monitor incoming data and alert each patient's rheumatology HCP of sustained (e.g., ≥ one week) increases in patient-reported disease activity. We expect scores on the validated Treatment Satisfaction Questionnaire for Medication (TSQM) and the Perceived Efficacy in Patient-Physician Interactions Questionnaire (PEPPI) to be higher among patients randomized to the smartphone app + population management system, compared to patients on the wait-list.
2. ***To determine the effect of the smartphone app + population management system on RA disease activity.*** We expect patients randomized to the smartphone app + population management system to have lower disease activity, measured by the Clinical Disease Activity Index (CDAI), at the end of the six month intervention.

The proposed project is innovative because it implements advanced smartphone technology to monitor RA disease activity, *within the context of a population management system*. Our resesarch team is perfectly positioned to conduct this project because we have: 1) access to a population of nearly 3,000 RA patients who receive care in our Arthritis Center, 2) experience in training project managers and patient navigators, and 3) expertise in the development and implementation of smartphone apps for monitoring RA disease activity.

C2. Technical Approach

Our proposal builds upon pilot work involving: 1) the frequency and management of RA flares, 2) the development of smartphone apps, and 3) HCP surveys on the use of mobile technology.

C2a. Current Assessment of Need in Target Area

C2a.1 Quantitative Baseline Data Summary.

Frequency of RA Flares. In 2011-2012, Dr. Solomon (Co-Investigator) performed a comprehensive study of flares among RA patients enrolled in the Brigham and Women's Hospital (BWH) Rheumatoid Arthritis Sequential Study (BRASS) (1). BRASS is a longitudinal cohort of 1,105 established RA patients who receive their usual rheumatologic care from HCPs at BWH. Of the 744 participants with at least three years of follow-up, 738 (99.2%) reported at least one flare, and 736 (98.9%) reported more than one flare during the course of follow-up. Flares were frequent, with 74% of participants reporting at least one flare in the six months before study entry (the period when the least participants were on effective disease-modifying antirheumatic drug (DMARD) treatment), and 54-59% reporting flares in each of the subsequent six-month intervals. Among individuals who reported at least one flare, 47% never achieved inflammatory disease remission, and only 12% achieved sustained remission over the three-year study. *These data indicate that flares are common among patients treated at this institution, and these flares have a significant impact on long-term disease activity*.

Flares between scheduled visits vs. disease activity at visits. In the BRASS study, the majority of flares (65%) occurred between study visits (1). Flares that happen between scheduled visits may be overlooked when assessing disease activity at visits, leading to discrepancies between flare reporting and disease activity assessment. Close assessment of BRASS patients in remission showed that 30% had flares in the past six months, indicating that these patients were not maintaining remission between visits. *These data highlight the importance of assessing flares between scheduled appointments*, *but in practice, this assessment may be difficult because the majority of flares (71% in this study) last less than two weeks.*

Management of flares between scheduled visits. Patients are often reluctant to seek medical help between regularly scheduled appointments. In BRASS, 18% of RA patients reported using non-pharmacologic techniques (e.g., resting, applying heat or cold, using a splint or brace) as their primary means of management for RA flares, and 27% reported no treatment for their flares (1). In a focus group, one patient stated, "It's always the last port of call coming to see the rheumatologist. I go through absolutely everything at home before I come and see them" (3). *This reluctance may hamper the effective treatment of RA flares.*

Studies examining efficacy of smartphone apps. Although the use of smartphone apps for health monitoring is rapidly proliferating, HCP involvement in app content and development is low (4). Few studies have examined the clinical effectiveness of smartphone apps as interventions for chronic disease management (5, 6). The majority of existing studies have focused on diabetes, depression and cancer (7). These studies suggest that real-time assessment of patient reported outcomes via mobile operating systems improves reporting accuracy, enhances patient reflection and improves patient-HCP communication (8, 9). To our knowledge, no randomized, controlled studies have examined the use of smartphone apps to

improve the management of RA.

Smartphone apps in RA. To ensure that we do not duplicate other programs and materials that have been developed, we searched PubMed, the National Institutes of Health Research Portfolio Online Reporting Tool (NIH RePORTER), Google and the iPhone App Store. Although several apps exist to educate patients and/or HCPs about RA, few enable patients to monitor disease activity on a daily basis. The five apps that assess patient-reported outcomes in RA are: "Track and React," "RheumaMonitor," "MyRA," an app developed by Ginger.io and available through the Arthritis Internet Registry (AIR), and an app developed by researchers at Kyoto University (10, 11). Only the apps developed by Ginger.io and Kyoto University include validated outcomes assessment measures (PAS-II, the Health Assessment Questionnaire and self-assessed measures of swollen and tender joint count).

App Selection: We met with three mobile app companies with existing platforms that could be adapted for this study. We chose the Ginger.io platform because:

1) Ginger.io has an existing platform that can be modified (see Section Cb.2) to include all the functionalities required for this study. The Ginger.io smartphone app has already been piloted in 189 individuals in AIR (12). It has been used to collect over 7,700 daily surveys, including components of the PAS-II (the primary self-reported measure of disease activity in this study), as well as over 2,200 weekly surveys, which have included the complete PAS-II (12).

2) The Ginger.io platform includes a secure, encrypted, web-based dashboard that can be used to directly transmit patient-entered data to study staff/HCPs on a real-time basis. This dashboard was not included as a component of the original AIR study, and none of the other available apps have this functionality. Because 62% of patients in the AIR study thought that sharing data with their HCP would improve management of their arthritis (12), we believe this element will be critical to the integration of smartphone apps into routine clinical care.

3) Ginger.io has established a master contract with BWH, which governs all research collaborations between BWH and Ginger.io. This master contract paves the way for timely study initiation because much of the negotiation and paperwork has already been completed. Completed elements include templates for institutional review board (IRB) protocols, a business associates agreement to protect patient health information, as well as agreements regarding the use and ownership of study data.

HCP attitudes towards smartphone apps. In preparation for this project, Dr. Yvonne Lee (Principal Investigator) surveyed 12 full-time BWH rheumatologists about their attitudes regarding smartphone technology for monitoring RA symptoms. Two-thirds felt that this intervention would be helpful, particularly in improving communication and understanding between patients and HCPs.

C2a.2 Primary Audience. The target audience for this proposal includes 190 RA patients with moderate-severe disease activity who are taking DMARDs.

Sample Size Rationale: *2,920 RA patients were seen at the BWH Arthritis Center between April 30, 2013 and May 1, 2014. Of these patients, 1,980 were prescribed at least one DMARD between April 30, 2013 and May 1, 2014. Based on data from BRASS, approximately 60% (N = 1,188) have moderate to high disease activity. From the 2013 Pew Internet Tracking Survey (13), we estimate that 50% of these patients (N = 594) own smartphones. Of these 594 individuals, we expect 80% to meet the remainder of the inclusion criteria (≥ 18 years old, English-speaking), and 40% to agree to participate for a total enrollment of 190 individuals. See Section C2c.6 "Statistical Approach" for the relationship between this sample size, the expected effect size and the power to detect this effect.*

The specific selection criteria will be:

- *Inclusion criteria*: 1) Meet the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 classification criteria for RA (14), 2) Taking a DMARD (sulfasalazine, methotrexate, leflunomide, azathioprine, cyclosporine, adalimumab, etanercept, infliximab, golimumab, abatacept, tocilizumab, anakinra, tofacitinib, rituximab), 3) Have moderate to high disease activity, defined by a Clinical Disease Activity index (CDAI) score > 10 (15), 4) Own a smartphone with either an Android or iPhone operating system, 5) Be at least 18 years old, 6) Be English-speaking.

- *Exclusion criterion*: Patients who do not plan on receiving follow-up care at the BWH Arthritis Center.

Design Consideration: *We chose to focus on RA patients with moderate-severe disease activity because this group is most likely to experience frequent flares (1). We did not further restrict the population to include only RA patients starting DMARDs because this would limit the generalizability of our results. The majority of patients at our institution (as well as other institutions) are established RA patients who have been exposed to DMARDs, and our preliminary data show that, even among those treated with DMARDs, flares are common (1). Also for generalizability reasons, we did not restrict the population to only RA patients being treated according to a treat-to-target strategy. Although we believe that real-time monitoring of RA flares would certainly improve outcomes of the treat-to-target strategy, we do not feel the benefits of this system are limited to patients treated with the treat-to-target paradigm. To investigate whether the smartphone app + population management system is different depending on whether HCPs practice according to the treat-to-target strategy, we will include an interaction term in the multivariable models to assess effect modification.*

C2a.3 Benefits. We expect the project to directly benefit patients by providing them the tools to easily track and record their disease trajectories. In return for entering data on a daily basis, patients will gain the knowledge that their data will be directly and securely transmitted to the population manager and, if concerning trends in disease activity are noted, to their primary rheumatology HCP. If successful, this system will reduce the reliance on patients to independently determine when to contact their HCP regarding flares. We also expect this system to benefit rheumatology HCPs by providing them with a more complete picture of their patients, beyond the snapshots they currently see during scheduled clinic visits. This increased

reservoir of information may then serve as a catalyst for more effective patient-HCP communication. If successful, pilot data from this study will be used to advocate for the dissemination of the smartphone app + population management system to all 2,920 RA patients seen at the BWH Arthritis Center.

C3a.4 Alignment with the RFP. This proposal aligns with the focus of the RFP because it: 1) uses validated outcome measures to assess RA disease activity at a granular level, between routinely scheduled visits to HCPs, 2) takes advantage of novel smartphone technology to engage patients in monitoring their condition, and 3) facilitates communication between patients and HCPs through a population management system.

C3a.5 Innovation. This project is innovative because it: 1) takes advantage of smartphone technology to empower patients in the assessment of disease activity, using a validated tool, the PAS-II (16), 2) incorporates a population manager in the routine care of RA patients, and 3) scientifically tests the utility of the combined smartphone app + population management system in a randomized, controlled trial. Although several smartphone apps exist to monitor symptoms of chronic disease (6, 10), none have been rigorously tested in RA, and none have incorporated the use of a population management system, including a web-based dashboard, automated alerts and a trained population manager, to collate incoming data for HCPs.

C2b Project Design and Methods

C2b.1 Overview.

The project includes three critical components: 1) the smartphone app to enable RA patients to record disease activity on a real-time basis, 2) the web-based dashboard to transmit summary information to the population manager and provide notifications of increases in disease activity, and 3) the population manager who will monitor the web-based dashboard and serve as a liaison between the patient and his/her rheumatology HCP.

The smartphone app and web-based dashboard will be provided by Ginger.io, a healthcare technology company that helps HCPs and hospitals manage patient populations using smartphone technology. Ginger.io has partnered with researchers at several leading academic institutions (University of California at San Francisco, University of California at Davis, University of Pennsylvania, Duke University Medical Center, Cincinnati Children's Hospital, etc.) to develop apps to monitor individuals with chronic diseases, including depression, diabetes and arthritis. Ginger.io has an existing platform with a robust architecture, including: 1) a patient smartphone app that is compatible with the Android and iPhone operating systems, and 2) a provider dashboard that allows the population manager and HCPs to access their patients' data (Figure 1). All data collection complies with HIPAA regulations. Patient-reported data are transferred to Ginger.io secure Linode web servers, using SSL over an encrypted secure connection. All personal data are encrypted.

In the following sections, we will describe the currently existing app and web-based dashboard, as well as planned modifications to this app and dashboard. In particular, we will highlight how this project builds upon prior work by establishing systems to integrate data from the app and dashboard into the work flow of a high volume arthritis center.

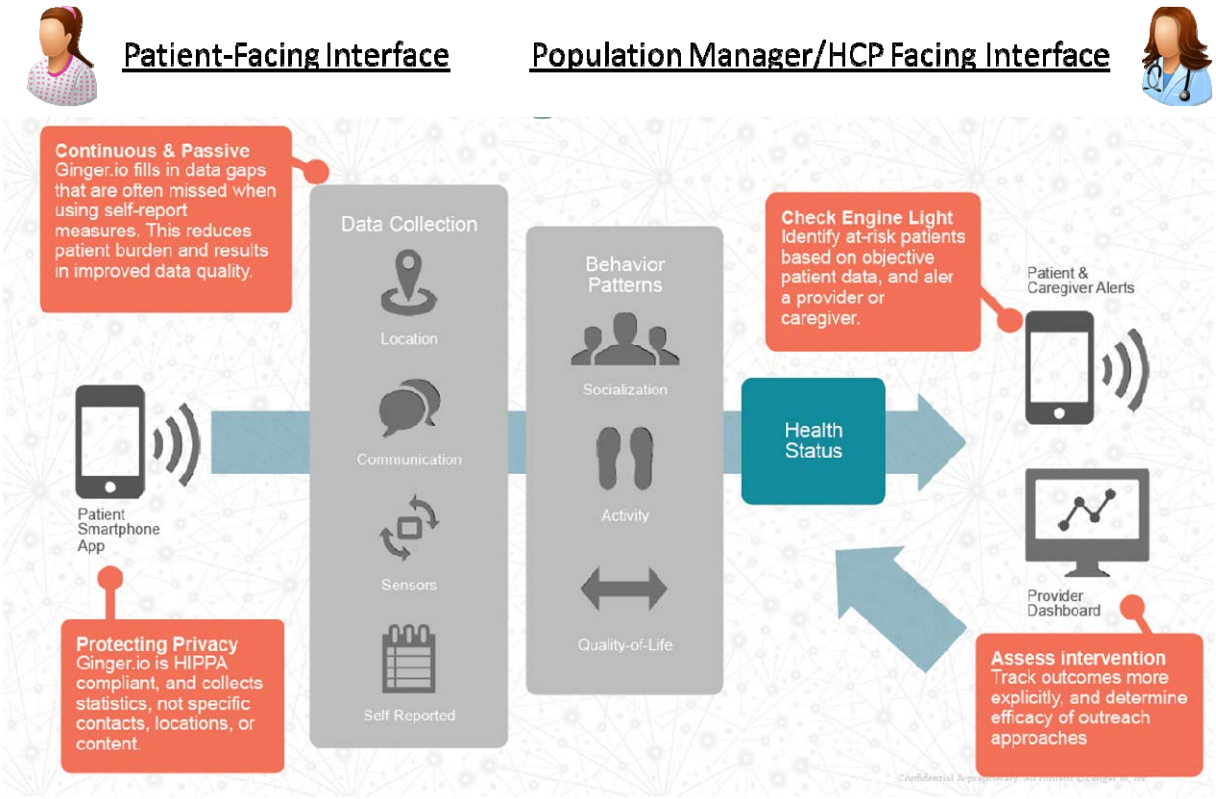


Figure 1. The Ginger.io platform collects self-reported data, as well as passive data about location, movement and communication patterns. It is HIPPA compliant, and data are summarized to providers through a provider dashboard.

C2b.2 Smartphone App.

Through a collaboration with the Arthritis Internet Registry, Ginger.io has developed a smartphone app to monitor patient-reported disease activity in RA using the PAS-II (Figure 2) (12). This app has real-time notifications to remind participants to complete the survey questions at pre-specified times of day. The daily surveys expire after 16 hours, so participants are not able to retrospectively complete surveys, minimizing the risk for recall bias. To supplement this data, the app is also able to collect passive patient data, including information regarding physical activity, using motion sensors.

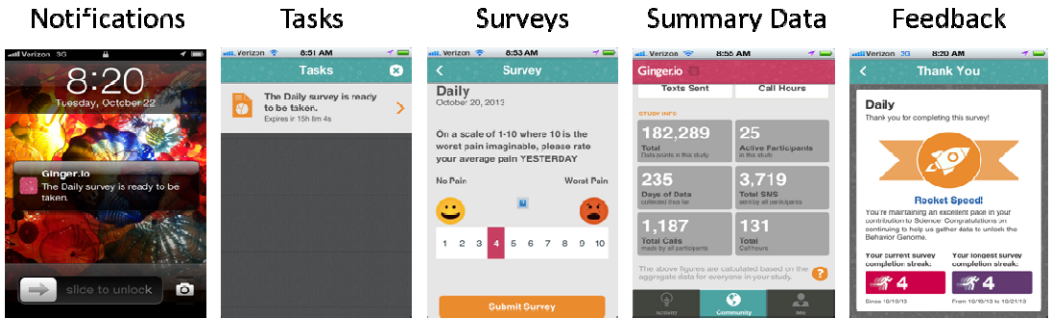


Figure 2. Screenshots of the existing Ginger.io platform.

A main requirement for the successful implementation of a smartphone app is the ability to sustain patient engagement. To maintain the interest of participants, this app includes modules that provide up-to-date information on study progress, as well as feedback on each participant's involvement in the study. For example, the "Community Insight" module supplies general study information (e.g., number of active participants, number of surveys completed by participants, number of days in the study) and summary data on aggregate behavioral patterns of the study population (e.g., number of miles traveled, number of calls and texts sent). Based on 430,000 hours of data from 181 subjects in studies of the Ginger.io smartphone app, 83% reported that the app was easy to use, and 87% reported that the daily self-reported surveys required little effort. User retention rates at 90 days were double those of other medical, health and wellness apps.

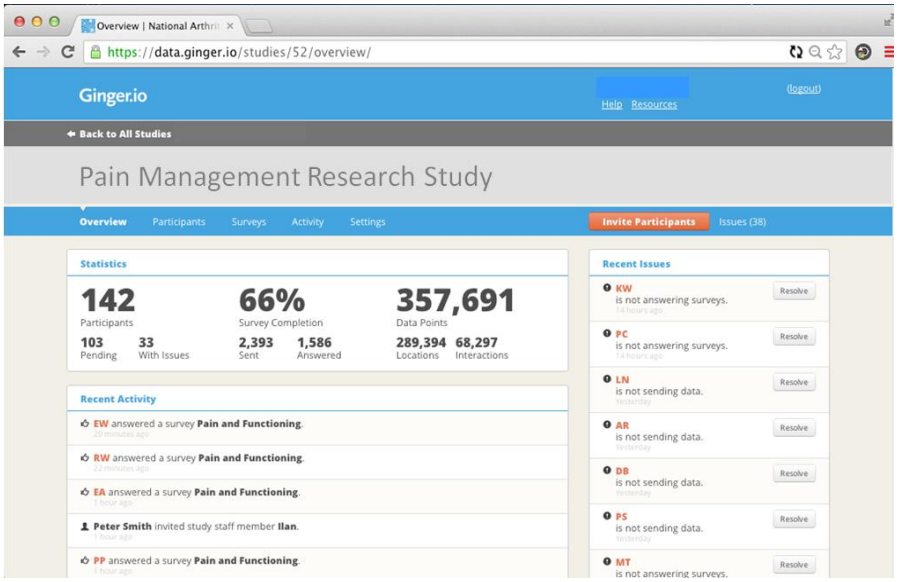
To further improve the utility of the existing app to participants, we will also include two new *enhancements*. Specifically, the app will be modified to provide patients with graphical summaries of their symptoms over time, so that they receive up-to-date feedback on their disease activity. In addition, we are working with Ginger.io to develop a module that allows participants to record treatment strategies for coping with flares. This module will ask participants if they started any new medications for RA and/or increased the dose of any medications for RA. They will also be queried about the use of non-pharmacologic treatments for flare (see Appendix B). Participants will be instructed to complete this module once a week.

C2b.3 Web-Based Dashboard

Data entered by participants will be available to study staff through a web-based dashboard that enables study staff to view summary data for each subject in real-time (Figure 3). This dashboard is currently available via the Ginger.io platform, but it has not been tested in an integrated system involving a population manager (see Section C2b.4). Data entered during the first two weeks will be used to establish each patient's baseline disease activity. After the first two weeks, the system will be programmed to alert the population manager of concerning trends in disease activity. Example alerts include an increase of 30% in components of the PAS-II for ≥ one week.

Design Consideration: Because there is no consensus regarding the definition of an RA flare, we considered a range of thresholds for triggering an alert notification. The decision on the length of flare (≥ one week) was based on our preliminary study showing that increases in the use of corticosteroids and DMARDs occurred more frequently among individuals with ≥ one week of symptoms (1). The threshold of a 30% increase in PAS-II was determined by surveying board-certified rheumatologists in the BWH Arthritis Center about the magnitude of increase they considered clinically significant. Although the web-based dashboard will be programmed with this default setting, we recognize that the published literature contains little guidance for defining flares. In the future, rheumatologists will be able to change the threshold for notifications to suit their own practice patterns. If there is variability in the definition of a clinically significant flare, these data will enable us to explore associations between different definitions of flares and outcomes.

Figure 3. Screen shots of the existing physician dashboard. Physicians can log on and view summary data for study patients.



C2b.4 Population Management System.

A population manager, trained by Drs. Lee and Solomon, will monitor the dashboard. If a participant is flagged as having a significant increase in symptoms, the population manager will contact the patient to inquire about DMARD adherence and other clinical factors (e.g., depression, sleep problems) that may be associated with increases in pain and worsening of functional status. This contact will occur via an encrypted e-mail or via a phone call, depending on patient preference (see Design Consideration).

Design Consideration: In response to our LOI, a panelist expressed concern that participants may want to communicate with the population manager using methods (e.g., phone calls, e-mails) other than the smartphone app. At study entry, all participants will be asked to state their preferred method of communication (phone call, e-mail, chats through the smartphone app). All participants will also be provided the phone number and e-mail address of the population manager. All messages regarding enhanced RA disease activity will be relayed to the participants' primary rheumatology HCP on the same day the message is received.

It is our hope that the smartphone app/web-based dashboard will streamline communication between patients and HCPs by making it "automatic." The electronic platform (smartphone and web-based dashboard) will identify concerning increases in RA disease activity and automatically send a notification to the population manager, who will reach out to the participant's primary rheumatology HCP on the participant's behalf. This process eliminates the need for the patient to initiate a phone/e-mail with his/her HCP.

The population manager will subsequently contact the subject's primary rheumatology HCP and provide him/her with a summary of the subject's disease activity from study baseline until the time of notification, as well as information regarding DMARD adherence and other related clinical factors. In addition, all subjects randomized to the smartphone app + population management system will receive monthly encrypted e-mails showing graphical summaries of

their disease activity patterns. Hard copies of these summaries will also be provided to rheumatologists at the time of the patients' regular clinic visits. The study will not prescribe any specific responses to notifications of increases in disease activity. Any changes in treatment will be at the discretion of the treating rheumatologist.

Design Consideration: We considered prescribing a specific algorithm for HCPs to follow to address RA flares, but we ultimately decided to allow each rheumatology HCP to respond to the notifications according to his/her own practice patterns. Our decision was based on three considerations: 1) there are no internationally or nationally accepted guidelines regarding the treatment of RA flares, 2) surveys with BWH rheumatologists indicated that physician participation would be negatively impacted by a rigid paradigm, and 3) we believe the smartphone app + population management system will have broad applicability, independent of the specific management paradigm.

C2c Evaluation Design

C2c.1 Study design. This is a randomized, controlled trial of a smartphone app + population management system to inform HCPs of RA flares that occur between scheduled clinic visits. Study visits will occur at baseline, three months and six months. Each study visit will include: 1) a focused physical examination to assess swelling and tenderness in 28 joints, 2) a review of demographic factors, medications and comorbid conditions, and 3) validated questionnaires to assess patient satisfaction with treatment and self-reported measures of RA disease activity.

C2c.2 Screening. Potential participants will be identified by searching for ICD-9 diagnosis codes for RA (714.x) in the Brigham Integrated Computing System (BICS) scheduling database. Every week, study staff will generate lists of potential participants and pre-screen patients via medical record review (Figure 4). Study staff will provide weekly lists to clinicians for their approval to contact the patients. Study staff will also be present in clinic during the busiest clinic sessions to remind HCPs of potential participants and to facilitate referrals. The primary rheumatology HCP will introduce the study in person or via a recruitment letter signed by both the primary rheumatologist and the principal investigator. Patients who are sent a letter and do not opt out will be contacted by study staff via telephone. To maximize the chance for contact while minimizing annoyance, study staff will try to reach patients a maximum of three times at different times of day. If they are unable to contact the patient after three attempts, the patient will be logged as "unreachable" in the tracking database, and no further attempts will be made. All study staff will complete training in HIPAA and Ethics in Human Subjects Research.

Figure 4. Recruitment Process.

C2c.3 Randomization. Participants will be randomized, using a blocked randomization strategy with eight participants per block and a 1:1 allocation ratio, to receive the smartphone app or to a waitlist control. To ensure an equal distribution of patients with moderate vs. severe disease activity in the two groups, randomization will be stratified by disease activity.

C2c.4 Study Visits. Study visits will occur at baseline, three and six months. These visits will coincide with the participants' scheduled clinic appointments with their primary rheumatology HCP. On the day of the first study visit, study staff will explain the study in a private room. All of the participants' questions will be answered. The informed consent document will be explained, and if the patient is willing to participate, the document will be signed. Study staff will download the app onto the participant's smartphone and train them on the use of the app. Participants will be informed that participation is voluntary, and they have the ability to withdraw at any time by contacting study staff and deleting the app from their smartphones.

At each visit, subjects will undergo a physical examination, including swollen and tender joint count, by trained study staff. Subjects will also complete validated questionnaires about patient satisfaction, perceived efficacy of the patient-physician interaction and RA disease activity

C2c.5 Data Collection. Data collection will occur via three methods: 1) All RA patients will complete validated, self-reported questionnaires at study visits using paper forms, 2) RA patients in the smartphone app + population management arm will also provide data daily through the disease activity monitoring app on their smartphones, 3) Rheumatology HCPs will complete surveys documenting their responses to disease activity notifications (one survey per enrolled patient, completed at each study visit), as well as a separate survey about the HCPs' overall impressions of the smartphone app + population management system (one survey per HCP at the conclusion of the study in September 2016).

Data collected from *RA patients at study visits* (paper forms) will include:

1. Baseline demographics
2. Treatment Satisfaction Questionnaire for Medication (TSQM), a validated 14-item survey to assess patient satisfaction with medications (17).
3. Perceived Efficacy in Patient-Physician Interactions Questionnaire (PEPPI), a validated, 10-item questionnaire to evaluate patients' self-efficacy in interacting with physicians.
4. Patient global assessment of disease activity: Participants will be asked, "Considering all the ways in which illness and health conditions may affect you at this time, please rate how you are doing on a scale of 0-100 with 0 being very well and 100 being very poorly."
5. BRASS flare questions: Participants will be asked "During the past three months, have you had a flare in your RA?" If a participant answers yes, the participant will be queried about flare frequency, resolution and how he/she treated the flare(s) in regards to medications or nonpharmacologic treatments, such as modification of activity, splints/braces, heat/ice and physical therapy or no treatment. These questions were previously used in the BRASS study of RA flares, which provided the preliminary data for this study (1).
6. Flare Assessment in Rheumatoid Arthritis (FLARE) questionnaire: This 13-item questionnaire was developed through a Delphi exercise to detect RA flares between medical visits (18).

Data collected from *RA patients daily, between study visits* (smartphone app) will include:

1. Patient Activity Scale II (PAS-II). The PAS-II is a validated index that assesses three ACR Core Data Set patient-reported outcomes – physical function, pain and global health (16). Physical function is measured by the 10-item Health Assessment Questionnaire (HAQ-II) (19), while pain and global health are evaluated using visual analog scales (VAS). Participants randomized to the smartphone intervention will also complete the PAS-II throughout the study period via their smartphones. To minimize user fatigue, only the VAS pain and global health scales will be assessed daily. The HAQ-II will be assessed weekly.
2. Treatment Strategies Module. This module is based on questions asked in the BRASS preliminary study of flares in RA (1). Specifically, this module will ask participants whether they had an RA flare in the last week and whether they treated this flare with either pharmacologic or non-pharmacologic methods. See Appendix B for a draft of this module.

Data collected from *rheumatology HCPs at study visits* (paper forms) will include:

1. Physician global assessment of disease activity: The participant's rheumatology HCPs will be asked the question, "Please rate your patient's disease activity on a scale of 0-100 with 0 being very good and 100 being very bad."
2. Assessment of response to notifications. Rheumatology HCPs will be provided a form to document their responses to the notifications, as well as any changes in treatment. This form will focus on the two most recent notifications in each three-month period. Based on preliminary data (1), we expect this to cover 80% of all flares.

See Appendix C for a draft of this form.

Data collected from *rheumatology HCPs at the conclusion of the study* (paper forms) will include an assessment of the smartphone app + population management system. Each rheumatology HCP will be given a survey to assess their perception of the intervention and whether it: a) improved patient-HCP communication, b) led to earlier changes in DMARD therapy, and c) improved the overall management of RA. HCPs will also be asked whether the system increased their workload and whether they would like to continue offering the smartphone app + population management system to their patients. All items will be assessed using Likert scales, and suggestions for improvement will be elicited. See Appendix D for a draft of this form.

C2c.6 Statistical Approach.

Outcomes. The primary outcomes for Aim 1 will be scores on the TSQM (20) and the PEPPI (21) at six months. *Both the TSQM and PEPPI are validated measures* that have been used in studies of patients with arthritis and other chronic inflammatory diseases (22, 23). The primary outcome for Aim 2 will be the Clinical Disease Activity Index (CDAI), a validated measure of patient-reported disease activity (15).

Design Consideration: In response to our LOI, a panelist expressed concern about the use of the CDAI as one of the primary outcomes because it may measure pain from mechanisms other than RA disease activity. As the panelist notes, previous studies have shown that fibromyalgia is associated with inflated estimates of RA disease activity assessed by the CDAI,

as well as other composite measures, including the DAS-28 and RAPID-3 (24, 25). To address the panelist's concern, we will also include "disaggregated assessments," such as the swollen joint count and physician global assessment, which are less affected by fibromyalgia, as secondary outcomes. This approach has been advocated by leading fibromyalgia researchers (25). Because no blood work will be done as part of this study, we will not be able to determine the effects of the intervention on inflammatory biomarkers (e.g., erythrocyte sedimentation rate and C-reactive protein) in the entire study population. However, we expect the majority of participants to get at least one of these measures checked every three months as a part of routine clinical care. We will obtain IRB approval to obtain these values from chart review and examine these relationships in subgroup analyses.

<u>*Statistical Analyses*</u>. The primary outcomes (TSQM score, PEPPI score and CDAI) will be compared between the "treatment group" (randomized to the smartphone app + population management system) vs. the wait list control, using a completer analysis.

Descriptive statistics, including means, medians and standard deviations, will be calculated to summarize baseline characteristics (e.g., age, sex, race, education, disease duration, serologic status, number of comorbid conditions, current DMARD use, past DMARD use) within each arm. Since this is a randomized, controlled trial, we expect that most factors will be controlled for via the randomization scheme and the use of the control group. To evaluate the validity of this assumption, we will assess potential differences between groups using Student's t-tests or Wilcoxon rank sum tests for continuous variables and Chi-square tests for categorical variables.

Treatment effects (mean differences in outcomes between the two groups at three and six months) will be estimated with mixed models. This model includes the interaction of treatment and time (e.g., three months and six months) and allows adjustment for baseline scores. For each outcome measure, we will also adjust for age, sex, race, disease duration and any variables that are statistically different from each other in unadjusted analyses ($P < 0.10$). In addition, the final model will include assessments of interaction and confounding (change in the estimate of at least 20%). The appropriateness of these parametric analyses will be confirmed by visual inspection of the residual plots from the analysis. Model assumptions will be assessed using marginal and conditional studentized external residuals. Cook's d will be used to assess influence on parameter estimates. A two-tailed *P*-value of 0.05 will be considered significant. All analyses will be performed using SAS 9.3. The statistician will be blinded to group allocation.

<u>Additional analyses</u>: In addition to the quantitative analyses described above, we will also take advantage of this rich dataset to explore other important questions:

1) Why do patients flare? Among patients randomized to the smartphone app intervention, we will have access to passive behavioral data derived from the use of mobile devices (e.g., phone activity, number of text messages, number of phone calls, number of screen unlocks). Ginger.io has developed algorithms, showing correlations between these measures and clinical measures of sleep and depression. We will explore whether these patterns predict the onset of RA flares.

2) How do patients self-manage flares? From our preliminary studies, we have established that many RA patients self-manage flares through use of non-pharmacologic treatments (1). Using data obtained from the BRASS flare questions, we will explore: a) whether the frequency of

self-management differs between subjects randomized to the smartphone app + population management system vs. the waitlist control, and b) among subjects in the smartphone app + population management arm, whether specific types of self-management impact the duration and/or severity of the flare.

3) How do HCPs respond to notifications of RA flare? Frequencies of each response (no response, phone call, office visit) will be tabulated, as well as frequencies of changes in treatment (adding/increasing NSAIDs, corticosteroids and/or DMARDs).

Sample Size Calculation. Based on previous studies examining differences in patient satisfaction (26, 27), the *expected difference* between groups is 9.4 (SD 18.4) in TSQM scores. No data exist regarding the expected difference in CDAI scores for this intervention. However, the *minimal clinically important difference* in CDAI scores is 12 (28). Based on attrition rates from previous studies, we expect ≥ 122 out of 190 subjects (61%) to complete the study. Given a sample size of 122 subjects and an alpha level of 0.05, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.80 to 0.99 (Table 1).

Table 1. Power Estimation for Sample Size of 122 Total Participants (N = 61 in each arm)

Aim 1 (TSQM)		Aim 2 (CDAI)	
Detectable Difference	Power	Detectable Difference	Power
8.0	0.66	7.0	0.84
8.5	0.72	8.0	0.92
9.0	0.76	9.0	0.97
9.5	0.81	10.0	0.99
10.0	0.85	11.0	1.00
10.5	0.88	12.0	1.00
11.0	0.91	13.0	1.00

C2c.7 Limitations and Alternative Methods.

Generalizability. In response to our LOI, the panelists questioned whether our study selects individuals who are receptive to smartphone technology and, as a result, may not extrapolate to the entire population. Dr. Michaud, our consultant, has worked closely with Ginger.io, the developer of our smartphone platform, to identify factors affecting smartphone ownership and use in a population of individuals with arthritis. Among 9,183 participants in AIR, older age and lower income were significantly associated with lower rates of smartphone ownership (12). At present, approximately 50% of individuals in the target population (mean 56.3, standard deviation 12.3 years) own a smartphone. According to market predictions based on age, this number is will increase to 70% by 2020 (29). *Thus, although smartphone availability currently limits the applicability of this intervention to half the desired population, we expect this proportion to increase rapidly over the next decade.* We believe it is imperative that this research begins now, so that critical data are available in a few years to identify whether this intervention is effective and, if so, the best methods for implementation.

In addition to owning a smartphone, Dr. Michaud assessed whether patients would download and use the app. As with smartphone penetration, older age was associated with lower usage of the app (12). To improve the usability of the app for elderly patients with arthritis, we will work with Ginger.io to incorporate large fonts and buttons on the touch screens. We will also

include Help screens that are easy to access (e.g., by pushing down the button in question for two seconds). In addition, subjects who wish to communicate with the population manager via phone or e-mail will be provided with the her contact information. Even without these additions, however, 90% of participants rated the app non-burdensome and easy to use.

Inability to disentangle the effects of daily symptom monitoring vs. the population management system. In response to our LOI, the panelists were concerned that the inclusion of a population manager would contaminate our results since a trained coordinator is a known successful intervention. We agree that the population manager significantly enhances the chance of success. In fact, some studies suggest that health information technologies alone are rarely successful and require more personalized, monitored support (30). This is the exact reason we included the population manager as a critical component of our intervention. We believe the population management system will serve as a model for integrating smartphone technology into the structure of a busy rheumatology clinic. To isolate the effects of the smartphone app from the effects of the population manager, we considered designing the study with an additional intervention group that only receives the smartphone app but is not enrolled in the population management system. However, given budget and time constraints, this study would not be adequately powered. Instead, we will use data from participants enrolled in the wait-list control group who subsequently receive the app (after the first six months) to explore differences between participants who receive just the smartphone app and those who receive the complete intervention. Although the wait-list control group will not undergo study visits after the first six months, they will enter data via the smartphone app. These data will be compared with data from patients randomized to the smartphone app + population management intervention to identify differences in PROs after six months.

Integration with the Electronic Medical Record (EMR). Over this grant's project period, BWH will transition from its own EMR to EpicCare. Given the complexities of this transition, integrating the app with the EMR would significantly delay implementation. Rather than directly linking data from the smartphone app to the EMR, the population manager will provide HCPs with summary data, downloaded from the web-based dashboard, in two formats: 1) PDF files e-mailed securely to HCPs whenever their patients' disease activity exceeds the notification threshold, and 2) hard copies clipped to the patients' billing forms at the time of clinic visits. In addition, if the patient consents to have these data scanned into the EMR, the population manager will provide this service. This presents an extra step, but maintaining this app as an external system is advantageous because it ensures that the app is portable and can be adopted by other institutions with different EMRs. The Ginger.io platform will allow for HL7 interfacing so that, in the future, integration with major EMRs will be possible.

Recruitment. With large eligible subject pools and colleagues who are enthusiastic recruiters, we are well-positioned to recruit adequate numbers of subjects. If needed, additional sources can be accessed, including patients at nearby hospitals (Beth Israel Deaconess Medical Center and Massachusetts General Hospital are both within 5 miles), and patient recruitment sites (Craigslist, local newspapers). These have all been useful sources in prior studies (31-33).

C3. Detailed Workplan and Deliverables Schedule

This project will occur over 30 months. Months 1-3 will focus on: 1) study set up, including IRB approval and 2) smartphone app refinement and programming (see Timeline Considerations box below). Recruitment, screening and baseline visits will occur between months 4 and 18. Three-month visits will occur between months 7 and 21. Six-month visits will occur between months 10 and 24. Data analysis will occur during months 25-27. The final three months will be dedicated to manuscript preparation and optimization of the app for public dissemination.

We describe the milestones and deliverables in Table 2. Each aspect of the work plan is described in detail with deliverables noted in bold italics. Although the timeline is aggressive, the investigators are confident that this project is feasible within the specified time period because: 1) BWH and Ginger.io have an established relationship, formalized through a master contract (see section C2a.1 App Selection box), 2) Ginger.io has already developed and piloted the initial version of the smartphone app, and 3) the investigators have a very productive, established track record of recruiting RA patients for clinical studies.

C4. Dissemination

To ensure that this intervention can be disseminated to other RA patients at BWH and other sites after this study, the following steps have or will be taken:

1. The app will be based on the existing Ginger.io platform, which can be (and has been) used at other academic institutions and private physicians' practices. Support services will be in place, including an established Help Line phone number and e-mail address, to assist patients and HCPs in downloading and using the app.
2. The population manager will be a trained individual with a bachelor's degree and at least one year of experience working with patients in research studies and/or clinical care. We will not require the population manager to have a professional nursing degree. This model has worked well for similar positions (e.g., patient navigators) and is more cost-effective. Drs. Lee and Solomon will develop training materials, which will be available to other practices who wish to establish this model of care management.
3. Meetings will be held every six months between study staff, the BWH Arthritis Center Leadership and members of BWH Information Systems. These forums will be used to update all stakeholders on study progress and the transition to EpicCare. If this intervention is successful, these forums will facilitate the dissemination of this model to other patients who receive care in the BWH Arthritis Center, as well as to other clinics within BWH and the Partners Healthcare System.

In summary, we believe that the smartphone app + population management system has the potential to benefit all RA patients, seen not only at the BWH Arthritis Center, but also at other rheumatology practices around the country. We expect this model to be easily adaptable to other rheumatic conditions, as well as non-rheumatic chronic illnesses. We anticipate that it will have broad applicability in helping patients better understand their disease and symptoms, improving patient-HCP communication and, ultimately, improving disease management.

Table 2. Detailed Work Plan and Deliverables		
Milestones	**Description and Deliverables**	**Dates**
Study Set-Up		
IRB protocol	An IRB protocol will be written and submitted to the Partners Human Research Committee. ***Deliverable: IRB approval.***	Start: 10/1/14 End: 10/31/14
Smartphone App Refinement and Programming		
Refinement of app specifications	The original version of the app will be modified to include a treatment strategies module. The web-based dashboard will be programmed to send alert notifications when a specified increase in disease activity (default: 30%) has been reported over a specified period of time (default: one week) ***Deliverable: Mock-ups of the modified smartphone app; algorithms for the alert notifications.***	Start: 10/1/14 End: 10/31/14
Programming	Ginger.io will complete the development and programming of the modified app and web-based dashboard to maximize usability. ***Deliverable: Final version of the smartphone app and web-based dashboard.***	Start: 11/1/14 End: 11/30/14
Study Staff Training		
Population management training	The population manager will receive didactic and practical training by Drs. Lee and Solomon. This will include at least 10 sessions in the BWH Arthritis Center, interacting with RA patients as they are seen by their rheumatology HCPs. ***Deliverable: Training sign-off by principal investigator.***	Start: 10/1/14 End: 12/31/14
Study staff training on downloading and using the smartphone app	Study staff will receive didactic training from Ginger.io regarding use of the smartphone app. ***Deliverable: Training sign-off by principal investigator.***	Start: 12/1/14 End: 12/31/14
Smartphone App + Population Management Trial		
Recruitment and baseline study visits	Participants will be identified through the schedules of participating rheumatologists, using the BWH Integrated Computing System (BICS). ***Deliverable: Patient recruitment reports will be***	Start: 1/1/15 End:

	reviewed internally every month and shared with the funder every three months.	3/31/16
Follow-up visits	All participants will be followed for six months. Participants will be evaluated every three months for changes in disease activity and study-related outcomes. ***Deliverable: Summary tables will be generated every month to monitor subject retention and completion of data entry.***	Start: 4/1/15 End: 9/30/16
Provide app to waitlist controls	All participants randomized to the waitlist control will receive the smartphone app ***Deliverable: The smartphone app will be downloaded to the phones of all patients in the waitlist control group.***	Start: 7/1/15 End: 3/31/17
Data Analysis and Manuscript Preparation		
Data analysis	We will conduct a completer analysis comparing patient satisfaction with treatment, perception of the patient-HCP interaction and CDAI score among patients enrolled in the smartphone app + population management system compared to patients randomized to the waitlist control. ***Deliverable: Summary data will be presented in tables and shared with all co-investigators and the funder.***	Start: 10/1/16 End: 12/31/16
Manuscript preparation	A manuscript will be prepared, sent to co-investigators for edits and revised. ***Deliverable: Submission of manuscript for publication.***	Start: 1/1/17 End: 3/31/17
Dissemination	An oral presentation will be prepared. In addition, final meetings with BWH Arthritis Center administrators and BWH Information Technology staff will be conducted to discuss steps for disseminating the smartphone app to all RA patients seen at BWH. ***Deliverable: Presentation of final results to the BWH Arthritis Center physicians and administrators. Minutes from meetings with BWH Arthritis Center administrators and BWH Information Technology will be compiled and shared with the funder.***	Start: 1/1/17 End: 3/31/17

APPENDIX A: REFERENCES

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APPENDIX B: TREATMENT STRATEGIES MODULE

1. During the past week, did you have a flare of your rheumatoid arthritis (RA)?
   □ Yes (continue to question #2) □ No (no further questions are asked)

2. If you had a flare in the past week, how did you treat your flare? (Check all that apply)
   □ New medication (continue to question #3)
   □ Increased medication dose (continue to question #4)
   □ Other treatment (continue to question #5)
   □ No treatment (no further questions are asked)

3. If you started a new medication for flare, please check which medication.
   □ Acetaminophen (Tylenol)
   □ NSAID (Advil, Motrin, Aleve, ibuprofen, naproxen, etc)
   □ Opioids (Tramadol, Percocet, Vicodin, oxycodone, etc)
   □ Corticosteroids (prednisone, methylprednisolone, Medrol, etc)
   □ Methotrexate (Rheumatrex, Trexall)
   □ Leflunomide (Arava)
   □ TNF inhibitor (Enbrel, Humira, Remicade, Simponi, Cimzia, etc)
   □ Other biologic DMARDs (Orencia, Rituxan, Actemra, etc)
   □ Tofacitinib (Xeljanz)
   □ Other

4. If you increased a medication dose, please check the medication you increased.
   □ Acetaminophen (Tylenol)
   □ NSAID (Advil, Motrin, Aleve, ibuprofen, naproxen, etc)
   □ Opioids (Tramadol, Percocet, Vicodin, oxycodone, etc)
   □ Corticosteroids (prednisone, methylprednisolone, Medrol, etc)
   □ Methotrexate (Rheumatrex, Trexall)
   □ Leflunomide (Arava)
   □ TNF inhibitor (Enbrel, Humira, Remicade, Simponi, Cimzia, etc)
   □ Other biologic DMARDs (Orencia, Rituxan, Actemra, etc)
   □ Tofacitinib (Xeljanz)
   □ Other

5. If you used other treatments, please check the type of treatment.
   □ Modification of activity
   □ Splints/braces
   □ Heat/ice
   □ Physical therapy
   □ Other

APPENDIX C: PHYSICIAN STUDY VISIT FORM

1. Please rate your patient's disease activity on a scale of 0-100 with 0 being very good and 100 being very bad.

   □
   0 100

2. In the past three months, how many notifications of flares did you receive?
   □ 0
   □ 1
   □ 2
   □ ≥3

If you received any notifications, please continue to the following questions. If you did not receive any notifications, you may stop here.

3. Please check your response to the most recent two notifications:
   a. Notification #1
      □ No response
      □ Phone call
      □ Saw patient in person

   b. Notification #2
      □ No response
      □ Phone call
      □ Saw patient in person
      □ Not applicable (only received one notification)

4. Please check your response to the most recent two notifications:
   a. Notification #1
      □ No change
      □ Added/increased NSAIDs
      □ Added/increased oral corticosteroids
      □ Joint injection(s)
      □ Added/increased DMARD

   b. Notification #2
      □ No change
      □ Added/increased NSAIDs
      □ Added/increased oral corticosteroids
      □ Joint injection(s)
      □ Added/increased DMARD
      □ Not applicable (only received one notification)

APPENDIX D: PHYSICIAN EXIT FORM

Please indicate your level of agreement with the following statements.

1. The smartphone app + population management system improved patient-physician communication.
   □ Strongly disagree
   □ Disagree
   □ Neither agree nor disagree
   □ Agree
   □ Strongly agree

2. The smartphone app + population management system resulted in earlier changes to long-term DMARD therapy.
   □ Strongly disagree
   □ Disagree
   □ Neither agree nor disagree
   □ Agree
   □ Strongly agree

3. The smartphone app + population management system improved overall management of RA disease activity.
   □ Strongly disagree
   □ Disagree
   □ Neither agree nor disagree
   □ Agree
   □ Strongly agree

4. The smartphone app + population management system increased my workload.
   □ Strongly disagree
   □ Disagree
   □ Neither agree nor disagree
   □ Agree
   □ Strongly agree

5. I would like to continue offering this system to my patients.
   □ Strongly disagree
   □ Disagree
   □ Neither agree nor disagree
   □ Agree
   □ Strongly agree

6. If you have any additional comments or suggestions, please provide them here:
   _____
   _____
   _____