A. Cover Page

1. TITLE: TREAT TO TARGET (T2T) IN RHEUMATOID ARTHRITIS (RA) WITHIN THE CONSORTIUM OF RHEUMATOLOGY RESEARCHERS OF NORTH AMERICA (CORRONA) NETWORK

Grant ID 20882063

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2. ABSTRACT

Evidence-based guidelines recommend that rheumatoid arthritis (RA) treatment should achieve clinical remission or low disease activity, a goal that has been called 'treat to target' (T2T). Despite available therapeutics, data from the Consortium of Rheumatology Researchers of North America (CORRONA) show that <50% of patients with moderate/high disease activity receive guideline recommended treatment escalation. Working with patients and rheumatologists, we will assess their barriers to achieving T2T, and based on their perspectives, we will develop a 2-component educational intervention (one for patients, the other for physicians) to improve T2T adherence. Barriers will be identified through nominal groups with patients and physicians, their prevalence estimated through patient surveys, and the interventions will be designed using Adult Learning Theory and Bandura's Social Cognitive Theory. Based on our preliminary findings, we anticipate that the physician-directed intervention will incorporate the results of the qualitative research with patients and will coach rheumatologists in effective strategies to guide and empower their patients to achieve T2T treatment goals. The patient-directed intervention will include education about the rationale for T2T, use of patient reported outcomes (PROs) to assess health status, differences between disease activity markers and symptoms, and the experiences of other patients who achieved T2T goals. We will pilot-test the interventions in eight rheumatology practices and 200 patients within the CORRONA network using a web/mobile interface, and we will evaluate its effectiveness in improving patient willingness to adopt T2T and achieving remission or low disease activity. This project builds on well-established collaborations between the University of Alabama at Birmingham (UAB), Northwestern University, CORRONA, and Medscape, including experts in rheumatology, epidemiology, risk communication, decision-making, and adult education.

C. Reviewer Comments. Thank you for the opportunity to resubmit our proposal "Treat to Target (T2T) in Rheumatoid Arthritis (RA) within the Consortium of Rheumatology Researchers of North America (CORRONA) Network", Grant ID 20882063. Below we address the reviewers' concerns.

1. Expand description on linkage between the needs, intervention, and assessment plan. We detail these linkages on pages 6-7. Briefly, our preliminary data suggest that physicians need more information about T2T and communication skills to optimize shared decision-making, and patients need more information about their disease, its natural progression, and the risks and benefits of available treatments. We will gain a deeper understanding of these needs through objective 1, by conducting nominal groups with physicians and patients. These barriers will shape the design of the educational interventions, one for physicians and the other for patients, as part of objective 2. The effectiveness of this education program will be assessed in objective 3 by comparing pre and post intervention scores on patient willingness to change treatment and improved disease activity. Patient willingness to escalate treatment should result in treatment modification, and then lower disease activity. The assessments are selected to assess willingness to change treatment, process changes that should lead to greater willingness (e.g., patient activation), treatment changes and disease activity. See Figure 1 for project scheme.

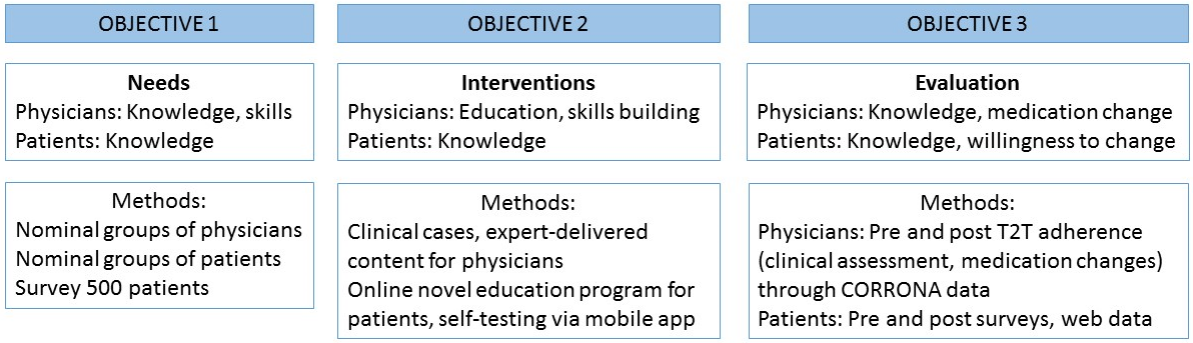

Figure 1. Schematic of the project linking the needs assessment, interventions, and evaluation.

2. Provide more information about the educational needs in this target audience. As detailed on page 6, the educational needs of the target audience are emerging from a recently concluded CORRONA trial of a T2T protocol-driven intervention. This negative trial found substantial educational barriers to T2T that may have contributed to the study's negative findings. Eleven in-depth interviews with intervention arm participants revealed that patients have little understanding of the T2T approach, they prioritized symptom relief over achieving T2T goals, and there was low provider awareness of patient barriers to T2T. Our proposal addresses all three of these findings. We apologize for the lack of clarity in describing these interviews; a sample of 109 participants was approached for interviews until saturation was reached, which occurred after 11 subjects.

3. Include a detailed recruitment plan. Please see detailed plans on pages 9-10, 13-14.

4. Provide more information about your evaluation plan and statistical analysis plan. The evaluation plans are detailed on pages 15-17. The statistical analysis of data generated from carrying out objective 3 is provided on pages 17-18.

D. Main Section of the proposal

1. OVERALL GOALS & OBJECTIVES**:** This collaboration between the University of Alabama at Birmingham (UAB), Northwestern University (NU), the Consortium of Rheumatology Researchers of North America (CORRONA) network, and Medscape has the overall goal to identify and overcome barriers to achieving low disease activity or remission as recommended by the International Task Force convened by American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 'treat-to-target' (T2T) strategy in rheumatoid arthritis (RA).[1] A recent trial of an intervention intended to improve T2T did not succeed, and preliminary data suggest that a better understanding of barriers to achieving the T2T goal is needed. We will therefore conduct a qualitative needs assessment of physician and patient reported barriers that will guide the development of a theory-driven, multifaceted, 2-component patient and provider intervention designed to optimize communication, facilitate shared decision-making, and overcome barriers to adhering to T2T. The patient-directed intervention will be designed to educate patients about the rationale for the T2T treatment strategy and address their barriers to adopting this paradigm, including patient vignettes and symptom self-monitoring using web/mobile technology. In parallel, the physician-directed intervention will be designed to enhance physicians' communication skills with the goal of facilitating shared decision-making to develop a realistic personalized T2T treatment plan.

Program Objectives: We propose the following 3 specific objectives:

1) Identify physician- and patient-reported barriers to achieving T2T goals. We will first conduct nominal groups with CORRONA physicians and, separately, patients, and then confirm and prioritize these barriers based on survey responses of 500 CORRONA patients.

2) In partnership with patients and physicians and based on the results of objective 1 activities, design a 2-component educational intervention for i) patients, and ii) physicians. The interventions will be guided by Adult Learning Theory[2] and Bandura's Social Cognitive Theory,[3] and will be designed to overcome barriers and enhance shared decision-making about T2T. The patient education component will include a patient-friendly synthesis of clinical evidence underlying the T2T strategy in RA, illustrating the use of PROs and emphasizing the difference between physiologic disease activity markers and symptomatology. It will incorporate vignettes of patients sharing their strategies for overcoming barriers, and will encourage empowerment through symptom self-monitoring using novel web and smartphone technology. The physician education program will educate physicians about patient-reported barriers, and build skills in how to help patients to overcome these barriers and facilitate shared decision-making.

3) Pilot test the 2 interventions in 8 CORRONA rheumatology practices and evaluate their effectiveness in i) improving patient willingness to escalate treatment and ii) achieving clinical remission or low disease activity consistent with evidence-based T2T guidelines. Secondary outcomes will include the quality of physician communication and shared decision-making.

Study Overview: This proposal relies upon our collective expertise in 1) provider and patient education; 2) quality improvement interventions; 3) and longitudinal data collection and outcomes research. We leverage the established infrastructure of the CORRONA network and the ability to support data-driven interventions with rigorous evaluation. This proposal builds directly on previous Pfizer IGLC grants awarded to both UAB and NU around PRO data collection by extending this work to a defined and highly relevant domain in RA care: T2T. It

also builds on a recent Pfizer-sponsored negative trial within the CORRONA network of an intervention designed to assess the real-world implementation of T2T approach in clinical practice which revealed that a better understanding of patient and physician barriers to achieving T2T was needed. Based upon the findings of objective 1, we will create a 2-component educational intervention directed at i) patients, and ii) physicians guided by Adult Learning Theory and Bandura's Social Cognitive Theory.[3] The patient-directed education intervention will be designed to empower patients to be receptive to T2T by learning of the real gains in quality of life achieved through T2T by patients with a similar degree of disease activity. It will integrate practical suggestions offered by patients themselves on how to overcome commonly cited barriers elucidated in objective 1 and will also encourage engagement through self-monitoring using a web/mobile platform. The physician-directed education intervention will use scripted behavior modeling via multiple video vignettes interspersed with expert commentary to portray realistic physician-patient communication scenarios and sequential interactions. It will be designed to facilitate effective discussions about T2T, offering realistic solutions to barriers reported by both patients and physicians, and guiding clinicians in the use of patient-collected data (through web and mobile apps) to promote shared decision-making with the goal of optimizing RA treatment (Figure 1).

2. TECHNICAL APPROACH:

a. Current assessment of need in target area. To attain remission or, at a minimum, low disease activity in RA, systematic quantitative assessments of disease activity and timely medication adjustments are recommended by national and international professional societies. This paradigm has been called 'treat-to-target', or T2T. Despite the development of RA management guidelines and their broad dissemination as well as the existence of RA quality indicators, there is a gap between guideline-recommended care and real-world rheumatology practice.[1] For example, using data from the CORRONA RA registry, a 2012 study found that <50% of RA patients with active disease did not escalate treatment consistent with American College of Rheumatology (ACR) guidelines.[4] In addition, of 495 rheumatologists, 18% eschewed T2T, 44% practiced in a manner concordant with the T2T guidelines, and 38% recently initiated a T2T approach.[5] These results may over-estimate adherence to T2T because more than one third of those who said that their practice was concordant with T2T were not performing routine quantitative assessments for their RA patients, an essential part of T2T. On the patient side, patients often decline escalation of guideline-recommended care because they fear worsening symptoms with switching therapies, a fear that outweighed their optimism for improvement with therapy escalation.[6] Patient's risk aversion may contribute to under-treatment, a finding substantiated within CORRONA.[7]

Baseline Data Summary. The CORRONA research network recently completed a cluster-randomized trial of a T2T protocol-driven intervention among 28 practices and 536 patients. Practices were randomized to provide either T2T or usual care for patients who met the 2010 revised ACR criteria for the diagnosis of RA and had moderate to high disease activity as measured by the clinical disease activity index (CDAI).[8] Specific medication choices were left to the treating physician and patient. The CORRONA T2T clinical trial was powered to show a 20% difference between trial arms in the proportion of patients achieving low disease activity or remission. Intervention practices were instructed to measure disease activity for their RA

patients at every visit and respond with treatment escalation and monthly follow-up visits until low disease activity or remission was attained. Preliminary results suggest that although a higher proportion of intervention arm participants achieved lower disease activity or remission compared to control patients, these differences were not statistically significant, and treatment acceleration occurred in < 50% of visits where there was elevated disease activity. The most common reason cited for non-acceleration was patient preference.

Ongoing work led by Dr. Harrold, a member of the project team and co-investigator in the CORRONA T2T clinical trial, is evaluating the factors related to why care was not escalated in the T2T arm per the clinical trial protocol as part of her project optimizing management of RA flares. Specifically , she has so far conducted in depth interviews with 12 (out of 109 invited) participants in the T2T trial to aid in the development of a toolkit for patients and providers to use at the time of the clinical encounter to facilitate better flare management and disease control. From the patient perspective, they were unaware of the goals of the T2T strategy, prioritized symptom relief and ensuring function and less reducing disease activity or preventing disease progression. Patient lack of participation in the T2T approach focused on concerns regarding side effects, long-term effects and out-of-pocket costs related to the medication, as well as trust that their provider is making the best recommendations for them. The interviews also explored the sources of information accessed by patients while making health care related decisions such as whether to escalate therapy, and these included patient support groups, websites, and blogs rather than discussions with their health care provider. The majority of patients voiced interest in the ability to track their symptoms using a patient-driven mobile/ web system, which they viewed as a resource for guidance on how to manage inter-visit symptoms and on the circumstances when they should contact their rheumatologists. In contrast to this application, neither Dr. Harrold's study on flare management nor the T2T trial itself were designed to systematically evaluate patient barriers to a T2T strategy. Furthermore, their work confirms that we need patient-centered tools to encourage uptake of T2T with patient-friendly syntheses of clinical evidence underlying the T2T strategy given that theT2T trial was a negative study. **We will address these key gaps in patient education in objectives 1 and 2 of this study.**

In terms of the challenges faced by rheumatologists in implementing the T2T protocol, Dr. Harrold's interviews with 6 providers assigned to the T2T arm revealed that many liked having a formal disease activity metric to guide therapy, but the frequent visit schedule was challenging for patients and their clinical schedules. Perhaps the most salient challenge from providers' perspective was that they had no access to patient educational materials on the T2T approach and few resources or training to enable their patients to overcome barriers to the T2T strategy. **We will address this critical need for building communication skills in empowering patients in objectives 1 and 2 of this study.**

Data source and methods. This timely study is a natural extension of prior work and addresses the need to educate patients on the T2T goals, the need to better engage patients through self-monitoring, and the need to provide communication skills to physicians. The CORRONA T2T study recruited sites that agreed to provide T2T care if randomized to the T2T arm and therefore focused on motivated physician populations. This proposal will use the lessons learned to gather additional information from a more diverse population of patients and providers to create a product that reaches a general audience. Moreover, this proposal is in

alignment with one of the top 100 Institute of Medicine (IOM) comparative effectiveness research priorities, which reflects the need to increase health professionals' compliance with evidence-based guidelines and patients' adherence to guideline-based regimens for chronic conditions.[9] This proposal is strengthened by our ability to build on the results of the qualitative work associated with the CORRONA T2T clinical trial in order to develop a patient-centered intervention, with patient and provider components, specifically designed for national scale-up.

To develop the proposed 2-component patient- and physician- intervention, we will first conduct nominal groups with 30 physicians and, separately, 30 patients to identify key barriers to achieving T2T outcomes from both the physician and the patient perspectives.[10] Physician and patient nominal group participants will be recruited from the CORRONA network from practices that did not participate in the above mentioned T2T trial. We will not include individuals previously enrolled in the CORRONA T2T trial in order to complement Dr. Harrold's previous qualitative work in this area and because providers who participated in the CORRONA T2T trial are likely the early adopters of T2T recommendations. Our selection of nominal group technique as the method for identifying challenges to T2T rests on the strengths of nominal groups in efficiently providing prioritized, unique ideas and the balanced participation of group members compared with traditional focus groups.

Using the results of the physician nominal groups, in collaboration with Medscape, we will design a text- and video-based physician-directed educational intervention aiming to coach physicians in shared decision-making strategies around T2T goals. We will integrate solutions to physician-reported barriers elucidated in the nominal groups, using peer modeling in the intervention. We will also guide physicians to encourage patients to use the novel web-based or mobile app self-monitoring system and provide guidance on how to use these self-monitoring results to promote shared decision-making.

Similarly, informed by the results of the patient nominal groups, we will create a web-based patient-directed educational program to assist patients in understanding the rationale, disease activity metrics, and outcomes associated with T2T strategy in RA. We will include vignettes of patients to contrast the outcomes of T2T-driven RA care with the risks of under-treatment of RA, as well as peer-modeling of how patients overcame barriers to achieving T2T goals. The patient-directed intervention will detail the role of PROs in monitoring health status and encourage web/mobile patient symptom self-monitoring using validated instruments that are part of the NIH's Patient Reported Outcomes Measurement Information System (PROMIS) as well as other measures (e.g., PROMIS pain interference, fatigue, depression, Routine Assessment of Patient Index Data 3 [RAPID3], RA Disease Activity Index [RADAI], Health Assessment Questionnaire [HAQ], work productivity). [11] Collaborator Dr. Cella heads the NIH PROMIS Statistical Center, and the NU CORRONA site will be a participating site for objective 3. Web/mobile patient-collected data, which can identify disease impact beyond that which is ascertained via standard, objective disease activity metrics, will be made available at the time of the encounter to both patients and their physician to facilitate treatment decisions, improve physician-patient communication, and optimize shared decision-making about the T2T goals.

Primary audience and expected beneficiaries of the intervention. Informed by the negative results of the recently concluded T2T trial, we will first conduct a pilot test of the 2-component physician and patient educational intervention through at 8 CORRONA research network sites. If the pilot shows promise, we anticipate national deployment within CORRONA, and eventually

nationwide. The CORRONA research network was founded in 2000 and currently includes more than 300 physicians at 104 sites (83 private practices) across 42 US states. As of April 30, 2015, data have been collected on more than 40,813 patients with rheumatologist-diagnosed RA representing more than 110,000 patient-years of data and the largest RA registry in the US. Previous work from our collaborators, Drs. Curtis and Harrold showed that while Medicare enrollees participating in the CORRONA registry were somewhat more likely to be managed aggressively with traditional and biologic disease-modifying antirheumatic drugs (DMARDs) than nonparticipants, the demographics and comorbidity profiles of CORRONA participants with RA were similar to older U.S. RA patients not in CORRONA, confirming the generalizability of the cohort's enrollment.[12] We will disseminate the physician-directed component of the intervention to rheumatologists through diverse venues including i) presentations at local, regional and national meetings; ii) journal publications; iii) CORONNA's quarterly newsletter; and iv) making the intervention available online on Medscape's website. The collaboration with Medscape will allow UAB to offer CME credits for completion of the educational intervention online as well as invite Medscape members to complete the educational activity. We will disseminate the patient-directed component of the intervention to RA patients through UAB's ongoing collaboration with Creaky Joints, the largest online patient community with arthritis. We will use social media associated with Creaky Joints, as well as making the intervention available on the Creaky Joints web portal at www.creakyjoints.com.

b. Project Design and Methods: Theoretical framework for the intervention. According to the Chronic Care Model proposed almost 2 decades ago, optimal functional and clinical outcomes for patients with chronic conditions are realized through productive interactions between informed, activated patients and prepared, proactive practice teams.[13] The T2T strategy for RA care supports the Chronic Care Model through its inclusion of systematic assessments and focus on evidence-based treatment guidelines. Thus, the Chronic Care Model is a suitable framework for interventions designed to meet the complex needs of RA patients, but there are several challenges that need to be overcome around risk communication, adherence to medications, patient self-efficacy, and shared-decision making which are affected by health beliefs. According to Bandura's Social Cognitive Theory, a personal sense of control facilitates a change of health behavior.[3] The intervention we propose to develop in collaboration with CORRONA patients and physicians addresses both elements of the patient-provider dyad by i) creating patient-centric educational materials focused on the barriers identified by patients as limiting their ability to follow at T2T approach to RA care; and ii) improving the communication skills of the physicians and their ability to empower their patients, resulting in shared decision-making intended to attain the T2T goals. Our intervention focuses on increasing the RA patients' confidence and skills so they can be the ultimate manager of their illness, as they should be.[14] The personal sense of control is enhanced by encouraging patients to self-monitor, using an information system established as part of a previous Pfizer grant to UAB that tracks validated PRO measures that matter to patients (e.g. functional status, fatigue, pain). We will evaluate our educational intervention within the Ottawa Decision Support Framework (ODSF) which was developed to guide patients in making health-related decisions.[15] The ODSF defines a high quality decision as informed, consistent with personal values, and acted upon, and in which decision makers are satisfied with the

decision-making process and the decision. Improving the quality of decision-making may positively impact outcomes such as adherence to the decision, health-related quality of life, reduced distress from consequences, and long term satisfaction with care. We will use Adult Learning Theory to guide the development of the intervention, providing practical information that is relevant to both patients and physicians, and respecting their values and preferences.[2]

Objective 1a: Identify physician-reported barriers to achieving T2T goals in RA

Overview: We will conduct up to three online nominal groups, each including 10 CORRONA research network physicians to identify barriers to achieving T2T goals in real-world practice from their perspective. The online nominal groups will be conducted by Dr. O'Beirne, Director of the UAB Division of Continuing Medical Education, which has extensive experience in in facilitating nominal groups in diverse environments and in conducting qualitative research.[16-21] The physician-reported barriers will directly inform the design of the physician-directed intervention (objective 2) that will then be evaluated as part of objective 3.

Physician sample and recruitment: We will conduct up to 3 online nominal groups using a proprietary software system developed at the UAB Division of Continuing Medical Education, each including 10 CORRONA rheumatologists who manage patients with RA. Clinicians will be selected from the CORRONA research network from sites that did NOT participate in CORRONA's recent T2T clinical trial, and who manage at least 25 eligible RA patients with high or moderate disease activity (estimated sampling frame n=200). Because providers who participated in the CORRONA T2T trial are likely the early adopters of T2T recommendations, we will be specifically focusing on providers who may be less experienced in adopting the T2T goals and approach, enhancing the generalizability of our study. Based on our previous experience in conducting nominal groups, we anticipate that we will achieve content saturation for the major barriers by convening 3 nominal groups as we propose. However, in the event that content saturation is not achieved, we are prepared to conduct additional nominal groups.

Potential participants in physician nominal groups will be identified using the eligibility criteria noted above. They will be invited to participate in a 1 hour nominal group through email, fax, or telephone by Dr. Danila. The protocol will be approved by the UAB Institutional Review Board (IRB) and informed consent will be obtained. Rheumatologists completing the nominal groups will be offered a $200 gift card for their participation.

Conduct of the nominal groups: The nominal group technique is a semi-quantitative, structured group process designed to elicit a prioritized list of ideas in response to a carefully designed question. We will provide a brief overview of the T2T strategy, and then ask participants to consider the question "what are some of the challenges *you* face in achieving T2T goals in *your* practice?" Participants generate and share ideas in a round-robin fashion until no new ideas emerge. Subsequently, participants prioritize the ideas that were generated through voting on those 5 items that represent their greatest challenges, resulting in a rank-order list. The prioritized items will be emphasized in the intervention directed at physicians.

Objective 1b: Identify patient- reported barriers to achieving T2T goals in RA

Overview: We will conduct 3 nominal groups with 10 CORRONA patients each to identify barriers to adhering to T2T treatment strategy in RA, from their perspective. Similar to the physician nominal groups, the patient online nominal groups will be conducted by Dr. O'Beirne. The patients' perspectives will directly inform the design of the patient-directed intervention

(objective 2) that will be evaluated as part of objective 3. We will also conduct a survey of 500 CORRONA RA patients using the results of the nominal groups to ascertain the importance of the elicited prioritized barriers. The survey results will inform the intervention development, integrating those barriers most highly rated for importance by survey respondents.

Patient sample and recruitment for nominal groups: Patients will be previously enrolled in the CORRONA research network patient registry and will have indicated that they agree to be contacted for research purposes. To conduct the nominal groups, we will use the same software system described under *Physician Sample Recruitment*. Potential participants will be identified from the CORRONA network registry and they will be invited via email or mail to participate in a 1 hour nominal group. An introductory letter/email will explain the purpose of the nominal groups and explain the procedure with contact information of the principal investigator and research coordinator so that potential participants can ask questions. The study protocol will be reviewed by the UAB IRB and informed consent will be obtained. RA patients participating in nominal groups will be offered a $50 gift card for their participation. As for the physician groups, we anticipate reaching saturation with 3 groups of 10 patients, but we are prepared to conduct additional groups until saturation is reached.

Content of the nominal groups: Similar to the physician nominal groups, patients will be briefed on the rationale for the T2T strategy and protocol, and then they will be asked to respond to the question "what would make it challenging for *you* to follow this protocol, from *your* perspective?" They will then list their barriers in round-robin fashion until no new items are elicited. They will then rank their 5 top barriers from the generated list.

Patient survey: We will develop a survey to quantify priorities on a larger sample of 500 CORRONA patients. We will develop the survey using those items that received any priority votes during the nominal groups, and create a Likert scale to assess the importance of the listed barrier (e.g., "How much of a problem is this for you?" with the anchors "Not a problem at all"/"A minor problem"/"A major problem"). Based on our prior experience, we anticipate the survey will include the 15-20 most highly prioritized challenges elicited during the patient nominal groups. The survey will also include basic sociodemographic information (e.g. age, sex, race, income, education) as well as duration of RA diagnosis and current disease activity. The survey will be pilot tested in a convenience sample of RA patients attending the UAB rheumatology clinic. We will email the survey to 500 CORRONA research network participants who have indicated willingness to be contacted for research purposes. We anticipate 3 waves of the survey to achieve a completion of 60%, based on prior CORRONA research.

Data analysis: One advantage of the nominal group technique is that results are available on completion of the group. We will summarize results across the groups by grouping the prioritized challenges into themes, contrasting the challenges faced by physicians with those faced by patients. These summaries will be included in the interventions to be developed as part of objective 2.The survey will be analyzed separately. We will calculate the response rate guided by the Council of American Survey Research Organization (CASRO) standards.[22] We will report the distribution of responses for each question. We will also conduct correlation analyses of patient characteristics associated with a specific challenge being a greater or a lesser challenge using correlation coefficients as well as logistic regression analyses. All statistical analyses will consider a p-value of 0.05 as the threshold for statistical significance.

Objective 2: In partnership with patients and physicians, design i) patient-directed, and ii) physician-directed educational interventions

i) Patient intervention component. Overview. Based upon the findings of patient nominal groups and the patient survey deployed as part of objective 1, we will create an online, interactive, patient education intervention including innovative text- and video-based educational content. The educational program will include peer testimonials, building on Bandura's Social Cognitive Theory[3] and following principles of Adult Learning Theory[2], with the goal of helping patients to overcome their risk aversion to treatment changes. To ensure that the educational materials address the needs voiced by the patients in objective 1, we will invite 20 patients enrolled in CORRONA network to evaluate the patient-directed intervention materials for comprehensibility, relevance, and acceptability using semi-structure interviews and "think-aloud" procedures. In addition, the patient intervention will also educate the patients about the utilization of PROs (e.g., PROMIS pain interference, fatigue, depression) in monitoring health status over time. We will integrate self-monitoring by teaching patients how to self-monitor using the web-based or mobile app, again using peer modeling through video vignettes of patients sharing their stories on how useful they found self-monitoring to be. Educational effectiveness will be measured across all levels of participation (monthly statistics), satisfaction (evaluation forms), and medical knowledge and/or competence (post-tests).

Instructional design and rationale. Patients have many questions about their health, their chronic conditions, and the treatments they are offered, but current approaches to providing the information they seek fall short. In response to this patient need, as part of a previous funded project, the Patient Activation Learning System (PALS) is being developed at UAB to enhance interactions between patients and physicians and to activate patients to become more involved in their health care. The educational content included in the PALS is based on reusable knowledge objects (RKOs). Patient-focused RKOs use multi-media components that effectively integrate interactive exercises with feedback that engages learners with the material. RKO content is designed to be clear and concise, and to leverage a mix of media to teach the identified concepts. Each RKO will provide education on basic patient concerns such as long-term consequences of RA, role of medications in preventing RA complications, the rationale for the evidence-based T2T strategy for RA treatment, role and use of PROMIS measures and specific data on how much benefit patients can expect to derive from adopting a T2T approach to achieve either remission or low disease activity. Each 1.5–4-minute RKO will focus on a single, discrete learning objective delivered at a patient-appropriate literacy level. This format is well suited to provide practical information to patients/care partners and facilitate understanding of treatment options and consequences of care, and is also amenable to repeat access and review that can reinforce the learning in each self-contained unit.

In addition to basic facts on RA and T2T, patient education content will address the barriers identified in objective 1. We will engage patients in the Creaky Joints online community to relate their stories and strategies for overcoming barriers. We will videotape these vignettes and integrate them into the intervention. We propose that providing easily understood answers to questions prioritized by patients, and by offering practical solutions to their challenges, we will create a solid foundation for shared decision-making, leading to activated patients who are committed to the treatment they select in collaboration with their physician.

Interactivity: In contrast to traditional approaches to patient education, which are typically created by health care professionals, the PALS content addressing the T2T strategy in RA will be patient-driven, based on the questions patients have. This interactive, spaced-repetition patient education system will be designed to be accessed via the web, using a highly innovative approach to education specifically designed to put the patient "in the driver's seat" as an engagement strategy. This approach provides an interactive, spaced-repetition patient education system that enhances patient learning and empowers users to participate in the management of their condition. Content will be searchable, using similar clinical informatics tools as employed by health-related expert systems and knowledge bases (e.g. Dxplain[23]) but will be patient-facing rather than provider-facing. Users will be provided spaced formative assessment to promote recall and understanding[24] and will be encouraged to navigate through content directly using keyword matching, popularity of content with similar users, and physician-recommended content, thus allowing the patient to "drive" through the program.

Self-Monitoring: We will couple the educational content with web/mobile self-monitoring of symptoms selected from the NIH PROMIS system, including pain, fatigue, sleep interference, anxiety, and depression, as described above. Building on a prior Pfizer-sponsored grant, we will customize the display of PROs so that the physician and the patient will be able to review at the point of care a print-out of the patient's self-recorded data. Based on available evidence (e.g., fatigue, work productivity), we will include displays of NIH PROMIS domain improvements attained among those able to achieve T2T disease activity goals.

ii) Physician intervention component. Overview: The physician component of our intervention will be designed by our Medscape collaborators and will use a blended approach which creates an environment of learning that fosters adoption of new practices.[25] Based upon the findings of objective 1, we will create an online education program with multiple video vignettes interspersed with expert commentary to portray realistic physician-patient communication scenarios and sequential interactions. Designed for scripted behavior modeling, this online interactive case-based education will be designed to improve clinicians' ability to efficiently discuss topics with patients, build skills in physician-patient collaboration, educate physicians about patient-reported challenges and how to help overcome them, all designed to promote shared decision-making. The intervention will also educate physicians in the role of PROs in monitoring health status over time, with an emphasizing on how to use the self-monitoring data collected by patients through the web and smartphone-based app to enhance shared decision-making. Educational effectiveness will be measured across all levels of participation (monthly statistics), satisfaction (evaluation forms), and medical knowledge and/or competence (post-tests). The physician educational materials will be reviewed by the UAB and Northwestern research team and CORRONA provider champions at each of the CORRONA sites with the goal to ensure that the intervention addresses the needs of the clinicians identified through the nominal groups completed as part of objective 1. Participants will be invited to complete the CME activity and then to provide feedback on the perceived relevance, comprehensibility, and acceptability of the video- and text-based materials.

Instructional Design and Rationale: Featuring a patient with RA facing a challenge in adhering to T2T goals, an interactive case study will reflect what clinicians may see in their daily clinical practice. The design of this activity with its multimedia approach complements,

reinforces, and extends the reach of educational content via an experience that aligns with the realities of real-world clinical practice. The physician activity will include information on the PROMIS measures and their role and importance in treating patients with RA. The 15-minute case activity will feature a patient who faces one of the top prioritized challenges relating to RA and T2T elicited in objective 1. Video vignettes will demonstrate the role of effective communication, and self-monitoring in helping patients to adhere to T2T goals. Messages will provide practical tips for how to help RA patients overcome their challenges in adhering to T2T. Learners will engage in video simulations that showcase best practices in communication, and use of self-monitoring data, and experience peer validation of responses, and expert observations supported by clinical evidence - all designed to challenge learners to build and apply the skills needed to help engage their patients to escalate therapy when indicated. The case will be viewable from web/mobile browsers. A transcript with embedded images may be downloaded for future offline reference and serve as supplemental learning tools.

Interactivity/Peer-Modeling: Extensive utilization of video vignettes that present scripted behavior modeling will enhance the educational value and impact of educational intervention. Vignettes will illustrate key aspects of communication and are useful for improving techniques that entail explaining complex treatment, or expressing cultural sensitivity. A recognized expert will provide a detailed commentary that will intersperse with key supporting evidence in text and slides, as needed. Finally, the expert will guide learners to associated data available for download, such as guidelines, recommendations, and further reading. This educational approach allows learners to select a "care" tactic, become alert to the potential consequences of suboptimal choices, and experience reinforcement of appropriate decision-making.

Objective 3. Pilot test the interventions in 8 rheumatology practices from the CORRONA network and evaluate their effectiveness in achieving i) willingness to change medications and ii) clinical remission or, at a minimum, low disease activity consistent with T2T guidelines.

Overview: We will conduct a pilot test of the novel 2-component patient and physician intervention in 8 CORRONA rheumatology practices to demonstrate the feasibility of the novel educational approaches developed here in improving adherence to T2T goals. We will leverage the CORRONA infrastructure in order to recruit 25 eligible RA patients who meet the inclusion criteria (see below) per practice. We will recruit patients from practices that were not part of the CORRONA T2T clinical trial because those participating in this recent trial were likely early adopters of the T2T recommendations. The recruited patients and their physicians will complete the educational intervention and the study outcomes will be collected over a 12 month period during which patients will have at least one follow-up visit. Patients will complete baseline and follow-up surveys, and treatment changes will be captured in CORRONA database.

Study setting and population: The interventions will be pilot tested among 8 CORRONA practices not previously participating in the CORRONA recent T2T trial (sampling frame n=134 practices). To be eligible for the study, the clinicians at these practices must manage at least 25 RA patients with high or moderate disease activity.

Inclusion criteria: To be included in the study a patient must 1) have a diagnosis of RA based on the 2010 revised ACR/EULAR diagnosis criteria; 2) be age >18 years; 3) have a CDAI>10; 4) be eligible for treatment acceleration; 5) be able to speak English; 6) be able to understand and participate in the protocol; 7) have ready access internet or a smartphone; 8)

have signed the CORRONA informed consent document allowing for linkage between their in-office CORRONA registry data and data collected at home, over the web, or by smartphone.

Exclusion criteria: 1) RA patient with low disease activity (CDAI≤10); 2) no signed CORRONA informed consent document; 3) no ready access to the internet or a smartphone.

Screening and recruitment: Participants will be recruited through the CORRONA research network based on the inclusion and exclusion criteria detailed above. The decision of the patients and physicians to participate in the proposed study will not impact their participation in the CORRONA network. Based on our preliminary review of recent CORRONA data, the median number of RA patients in CORRONA who have already consented to direct-to-patient outreach and data linkage is 75 per site. The top 30 CORRONA sites have more than 150 such patients and will be prioritized for participation in this study. In prior CORRONA analyses, approximately 50% of individuals have moderate or high disease activity (CDAI > 10) [7] and thus will be eligible for the study. In our past work in CORRONA with this already-consented patient group, we have found a 40% response rate to direct-to-patient add-on research studies like this one.[26] Thus, we expect that there will be no difficulty in recruiting the needed 25 eligible patients at each of 8 CORRONA sites selected from amongst the 30 largest sites.

The UAB research team will work with Dr. Lynn Palmer, Chief Scientific Officer of the CORRONA Research Foundation and study statistician, to pre-identify potential eligible participants at each site based on the inclusion and exclusion criteria. Potential participants will be contacted via email and invited to participate in the study via an attached link. To date, 9,700 RA patients in CORRONA have signed the CORRONA informed consent document, of which ~½ have provided email addresses and agreed to future contact for participation in programs such as the one proposed here. Patients will be asked to review the study objectives and expectations online, including the importance of completing the educational component, self-monitoring, and the baseline and follow up surveys. Those willing to participate will be invited to sign the study informed consent and complete the educational intervention online. Should potential participants have questions the UAB research team will be contacted for clarification. We will track the number of individuals who click on the link as well as those who agree to participate to assess uptake. We will track completion for participants and automatic monthly reminders will be emailed until the educational activity is completed.

Upon agreement to participate, the physicians at the 8 CORRONA sites will be invited to complete the educational intervention designed for physicians and offered CME credits for completing the activity. The intervention will be deployed online and we will track completion rates. Automatic reminders will be provided every month until the educational component is completed. If needed, the principal investigator will contact physicians by telephone and/or email to encourage completion.

Data collection: Patient participants will complete a baseline survey before completing the educational intervention and a follow-up survey after the most proximate CORRONA visit, which occurs every 6 months. The surveys will be operationalized online, allowing for data collection at home through the web or mobile (smartphone) platform. The pre and post patient surveys will assess the following: 1) patient willingness to adopt T2T goals (primary outcome); 2) patient activation (process outcome); 3) decision conflict (secondary outcome); 4) patient knowledge of T2T and its rationale, goals, and benefits, and long term risk of under-treatment (effectiveness of the intervention); 5) patient perception of shared decision making (process

outcome); and 6) whether disease activity measures and T2T goals were discussed at the visit. The baseline survey will also assess computer skill, a potential mediator of the outcomes of interest, using a computer-based tool designed to assess reading literacy and computer skill.[27] The follow-up survey will include items assessing satisfaction with the various intervention components, including content, complexity, and delivery format.

We will leverage the infrastructure of the CORRONA network to capture demographic information (e.g. age, gender, education), disease characteristics (RA duration, comorbid conditions) as these are likely important mediating factors for the intervention. At each visit, CORRONA physicians record disease activity using RAPID3 and CDAI[28] (primary outcome), and changes in DMARDs (secondary outcome). In addition, physicians will be asked to answer the multiple-choice question: "If no medication was changed at the visit, what is the reason behind this decision?" on a case report form. The 1-page case report form will also include a question as to whether disease activity measures and T2T goals were discussed at the visit and a question regarding patient's satisfaction with symptom control, which will be assessed using the patient acceptable symptom state (PASS).[29] We will use the anchoring question "Taking into account all the activities you have during your daily life, your level of pain, and also your functional impairment, do you consider that your current state is satisfactory?" to identify PASS. The response options are "yes" or "no". A "yes" response to this question seems to correspond to a disease activity level within the moderate range in patients with RA.[29] The CORRONA study coordinator will be responsible for collecting this information.

Participant compensation: Patient participants will be compensated $25 for completing the educational intervention and baseline survey, and $25 for completing the follow up survey. Clinician participants will receive CME credit for completing the provider education program.

c. Evaluation Design: Study outcomes (Table 1) will be assessed over a 1 year study period

Table 1: Study outcomes

Activity	Outcomes of Activity	Measure
Physician-focused Activity		
Enduring Materials: Online education	Improved ability to (a) discuss treat-to-target options with patients, (b) handle objections to employing new treatments, and (c) promote shared-decision making	a) Pre- and post-test measures of unit learning objectives b) Survey to evaluate subjective satisfaction levels and medical knowledge of physicians c) Access and completion rates d) User feedback
Pilot of Content Effectiveness	Improved adherence to T2T approach	a) Attainment of low disease activity or remission b) DMARD changes
Patient-focused Activity		
Patient Education Content	Effective, highly innovative communication of T2T strategy aspects important to patients	a) Increased knowledge about T2T strategy aspects important to patients b) Survey to evaluate satisfaction levels c) Access and completion rates d) User feedback
Pilot of Content Effectiveness	Increased willingness to adopt T2T treatment strategies; decreased decision conflict; increased confidence in ability to manage disease	a) Choice predisposition scale b) Decision conflict scale c) Patient activation measure (PAM) d) Shared decision making questionnaire (SDM-Q-9)

to ensure at least one follow-up CORRONA visit. We will use a pre-post design to evaluate the effectiveness of the patient- and physician-directed educational interventions in i) achieving patient willingness to change therapy and ii) achieving disease remission or low activity. CORRONA data (already housed at UAB) will be analyzed by the UAB team and Dr. Lynn Palmer.

The **primary outcomes of objective 3** will be patient willingness to adopt T2T and the attainment of the T2T goals. *Patients' willingness* to adopt T2T goals will be measured using the validated choice predisposition scale that reflects preference for a specific treatment.[15] Patients will be asked "If your doctor recommended that you consider T2T treatment strategy, would you be willing to adopt it?" This item is coded on a 15-point scale anchored by "Not willing at all" and "Extremely willing" with "Unsure" at the midpoint. [30] The choice predisposition scale correlates with values and expectations and is sensitive to change, particularly in the undecided range [6-10].[31] *The attainment of the T2T goals* of disease activity will be measured using validated instruments (CDAI, RAPID3) and utilizing established cut points (i.e. CDAI <10 [0-76 range], RAPID3 <6 [0-30]) for the definition of low disease activity. We will test the hypothesis that within-person change in the disease activity measures during the 1 year study period is significantly different than 0.

Secondary outcomes include changes in the patient's decisional conflict regarding treatment and, and whether DMARDs were changed. *Decisional conflict* will be assessed using the validated 16-item Decisional Conflict Scale (DCS).[32] The DCS captures factors associated with decisional conflict or uncertainty which captures decisional uncertainty, factors that contribute to uncertainty and perceived effective decision. These items are coded on 5-point scales ranging from "Strongly agree" to "Strongly disagree." The DCS is reliable (Cronbach's $\alpha >$ 0.78), discriminates between those who make and delay decisions, and an effect size of 0.3-0.4 is assumed to be a meaningful difference.[32] The total score ranges from 0-100, with 100 indicating extremely high decisional conflict. A total score <25 is associated with decision implementation, while a total score ≥37.5 is associated with decision delay or indecision.[32]

We will use the CORRONA infrastructure to assess whether the patient's *DMARDs were changed* during the 1 year study period compared to the 6 months prior to the deployment of the educational intervention, testing the hypothesis that RA medications are more likely to be changed during the study period rather than immediately prior to it.

As part of the study we will also assess the **processes** of patient activation and shared decision making. *Patient activation* will be measured using the 13-item Patient Activation Measure (PAM), which has been validated in diverse health care settings and diverse patient populations.[33] The PAM assesses an individual's level of knowledge, confidence and skill to manage their health and healthcare needs. Patient activation is classified as: Level 1 (patients tend to be overwhelmed and unprepared to play an active role in their own health); Level 2 (patients lack knowledge and confidence for self-management); Level 3 (patients are beginning to take action, but lack confidence and skill to support some behavior changes); and Level 4 (patients have adopted many of the behaviors to support their health, but may not be able to maintain them in the face of life stressors).

The process of *shared decision making* will be assessed by the perceptions of the patients and clinicians using the 9-item shared Decision Making Questionnaire (SDM-Q-9).[34] Each item is rated on a 6-point scale from 0 (completely disagree) to 5 (completely agree). The SDM-Q-9 has high internal consistency (Cronbach's $\alpha = 0.94$) and has been used in studies investigating the

effectiveness of interventions aimed at the implementation of SDM as quality indicator in health services assessments in chronic diseases.

Educational effectiveness will be measured for both the physician- and patient-directed educational components. We will develop questionnaires to measure patient knowledge of the T2T strategy, long term risk of under-treatment, and understanding of the PRO domains. Medical knowledge and/or competence (post-tests) will be evaluated for clinician participants.

Finally, we will collect **implementation outcome measures**, such as *feasibility* and *acceptability* of the educational interventions**.** To determine the *feasibility of the educational interventions* we will calculate participant (physicians and patients) recruitment and attrition rates, as well as the proportion of participants that completes baseline and follow up surveys (for patients) and completed case report forms (for physicians). To evaluate the *acceptability of the educational interventions* we will ask participants (patient and physicians) to complete an online survey addressing their satisfaction with the content and delivery format of the educational intervention. Engagement of participants in this study will be assessed using feasibility targets (e.g., >50% recruitment, >90% completion of the follow-up survey).

Statistical analysis: Analysis of outcome measures will be summarized using measures of central tendency and dispersion. Pre-post differences for continuous variables will be performed using paired t-test. We will also use general linear models to examine pre/post differences in the outcomes of interest after adjusting for covariates (e.g. age, gender, education, disease activity, etc.). Pre-post differences for categorical variables such as success (or not) of achieving T2T goals will be analyzed using chi-square tests and logistic regression.

Sample size and power considerations: Primary outcomes. A study by Fraenkel et al.[30] found that in subjects who viewed a decision support tool, mean scores in willingness to try a biologic measured on the choice predisposition scale (a 0-10 scale) increased significantly from 6.1 to 7.5 (average standard deviation [SD] of 2.65). Given this study's SDs and similar findings, with 200 patients and even allowing for a 10% dropout rate over the course of the study, we would be able to detect improvements in the mean change in patient's willingness to adopt T2T as small as 0.47, at a 0.05 significance level and 80% power. This mean change is approximately 0.18 SDs. The 200 patients that we estimate are robust to various assumptions about sample size attrition (up to 25%) and across a range of effect sizes, allowing us adequate power to detect any change in this scale less than 1.0 units.

Attainment of T2T goals. Given our inclusion criteria and past data about the likelihood to achieve T2T goals of approximately 50% in patients changing therapies[7], we hypothesize that our intervention will be able to increase the proportion of patients who attain T2T goals by at least 10%. With 200 patients and 10% attrition, we will have 90% power with a 2-sided significance level of 0.05.

Secondary outcomes. Li et al.[35] reported on results of using the DCS in RA patients after using a decision support tool. She found, with 30 patients, a highly significant decrease ($p<0.001$) in decision conflict before and after this intervention with a mean of 49.5 decreasing to 21.83 (average SD equal to 23.65). If our study is at least this effective, we will be able to detect differences of -4.4 with 200 patients, assuming a 1-sided significance level of 0.05 and 80% power, and a dropout rate of no more than 10%. Given 200 patients and assuming a 10% dropout rate, we will be able to detect decreases in patient activation, shared decision making and educational effectiveness over time that are at least 0.19 SD of the mean, given 80% power

and a significance level of 0.05. Finally, with 200 patients, we will be able to declare as significant that the proportion of patients who change DMARDs between their baseline and 6-month follow-up visit differs from the proportion who change DMARDs in their prior 6 months if this increase in proportions is 9.5% or greater, with 80% power and a 0.05 significance level. This assumes a dropout rate of no more than 10%.

Dissemination of the study findings: We will use a multi-dimensional strategy to broadly disseminate the results of our study. We will tailor our dissemination channel to our major stakeholders: patient and physicians. The education materials developed as part of this project will be made available to both the CORRONA physician network and to the 50,000 member Creaky Joints arthritis online patient community, composed largely of RA patients. In addition, patient education materials can also be deployed in the physician offices' waiting rooms through tablets available for patients' use. We will submit the results of this project for presentation to professional and scientific meetings, including the ACR Annual Meeting, as well as manuscript submission to peer-reviewed journals. Importantly, the physician education materials will also be disseminated through Medscape and will be optimized for mobile devices, including tablets .

Limitations and alternative approaches: We chose to first test our interventions in a pilot study in 8 CORRONA sites to assess feasibility and acceptability of the procedures proposed and provide data for a future larger trial and national scale-up. Internal validity is more important than external validity (generalizability) in this proof-of-principle study and the internal validity of CORRONA is supported by the consistency in sampling procedures and survey methods across sites. In addition, because our data collection tools are available only through web/mobile platforms we will include in our pilot study only individuals who have access to the internet or a smartphone. In terms of generalizability, we expect our results to be generalizable to the general US population, because of the majority of Americans use the internet (84% of American adults; ~58% of senior citizens),[36] and ~64% of American adults and ~27% of seniors own a smartphone.[37] Moreover, as noted above, Medicare enrollees participating in the CORRONA registry have considerable similarity with RA patients enrolled in Medicare.[12]

3. WORKPLAN AND DELIVERABLES

SCHEDULE: The project timeline and deliverables are shown in Table 2. The timeline presented below is based on a 32- month (February 2016 to September 2018) performance as outlined in the RFP. The first three months will be focused on study start-up (e.g., IRB approval). In the next 7 months we will conduct nominal groups and develop and deploy patient surveys (**objective 1**). In months 11-16, we will use the results of the nominal groups and patient surveys to develop the intervention (**objective 2**). In months 11-16 we will also recruit the sites and ensure that the administrative requirements are fulfilled so that we can start recruiting patients and deploying the intervention in months 17-28 (**objective 3**). Finally in months 29-32 we will evaluate the outcomes of the intervention, develop manuscripts, disseminate the findings, and plan scale-up of our intervention.

Table 2. Project timeline and deliverables.

Description of Task and Deliverables (months)	1-3	4-10	11-16	17-28	29-32
Obtain IRB Approval, study start-up	x				
Objective 1- Conduct nominal groups		x			
Objective 1- Conduct patient surveys		x			
Objective 2- Analyze the results of Objective 1, develop the interventions, recruit sites			x		
Objective 3- Recruit patients, deploy interventions, collect data				x	
Objective 3- Assess outcomes, develop manuscript, disseminate the findings, plan scale-up					x

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