ORGANIZATIONAL DETAIL

If funded, this project will be conducted at Northwestern University Feinberg School of Medicine and its affiliated rheumatology clinical practice. It will be co-led by Drs. Eric Ruderman and David Cella. Dr. Ruderman is Professor of Medicine and practice director for the rheumatology clinical practice. Dr. Cella is Professor and Chair of the Department of Medical Social Sciences and Principal Investigator of the PROMIS Statistical Center. Both have published extensively in the area of rheumatology outcomes, Dr. Ruderman from a clinical perspective, and Dr. Cella from a patient-centered and patient-reported outcomes research perspective. Together, they will comprise a compelling team to advance the practical and effective use of tools to enable and advance T2T approach to RA treatment.

Northwestern University is one of the country's leading private research universities, with an annual budget of $1.6 billion and sponsored research in excess of $500 million. Located on two lakeshore campuses - one in Chicago and one in Evanston, Northwestern enrolls about 17,000 students and has some 2,500 full-time faculty. The University has a long history of leadership in interdisciplinary research programs and centers. More than 90 school-based centers and 26 University centers support interdisciplinary research that spans a wide spectrum of areas, including neuroscience, nanotechnology, biotechnology, and outcomes research. The Feinberg School of Medicine (FSM) is one of 11 colleges and schools at Northwestern University. Feinberg is a research-intensive medical school that is part of a highly-ranked academic medical center. Located adjacent to Chicago's Magnificent Mile, Feinberg has built a national reputation for excellence through a strong history of collaborative, interdisciplinary medical education and research, and along with Northwestern Memorial Hospital and Northwestern Medical Faculty Foundation is part of the premier academic medical center known as Northwestern Medicine. Through its affiliates, it provides patient care to thousands of individuals every year, and plays an integral part in the communities it serves. Feinberg is a top 20 medical school where nationally renowned researchers collaborate with skilled clinicians to improve human health.

Research is conducted in all Feinberg departments, institutes, and centers, and is supported by the Northwestern University Office for Sponsored Research and more than 30 research core facilities. Within this infrastructure, the Rheumatology Section in the Department of Medicine has a national reputation for excellence in clinical care and cutting-edge research. The Department of Medical Social Sciences is a research-intensive group that focuses on bringing the patient voice into clinical care and research. The Departments of Medicine and Medical Social Sciences convene regularly through the Institute for Public Health and Medicine (IPHAM), a nexus for public health activities at FSM. IPHAM accelerates innovation at the interface of medicine and public health to achieve measurable improvements in health for patients and populations. IPHAM Centers, including the Center for Patient Centered Outcomes, provide a rich resource base for this proposed work. In fact, this work has the advantage of building on a successful prior effort to integrate patient-reported outcomes into clinical practice in the area of supportive oncology for women with gynecologic malignancies. This effort, a collaboration of Medical Social Sciences, the Robert H. Lurie Comprehensive Cancer Center of Northwestern, Hematology/Oncology (Medicine) and Gynecological Oncology (Ob-Gyn), was so successful as a demonstration project, integrating PROMIS with the Epic EHR to drive supportive care, that it has been institutionalized as an active clinical program with all new patients. It has also served as a model for IPHAM to propose, and have approved, a similar project in Orthopedics (joint replacement program), to begin in FY 2014. These local milestones demonstrate our ability to successfully and meaningfully integrate the patient's voice into clinical workflow, care planning and disease management. We look forward to moving in this direction in the management of RA.

A. Cover Page

Standardizing and Personalizing Patient-Centered Rheumatoid Arthritis Treatment Targets

Grant ID: 10179243

Main Collaborators:

David Cella, PhD (Co-PI)
Eric Ruderman, MD (Co-PI)
Art Mandelin, MD, PhD
Karen Kaiser, PhD
Jennifer Beaumont, MA

Goals: To evaluate the added value of the Patient Reported Outcomes Measurement Information System (PROMIS) to an existing treat to target (T2T) rheumatoid arthritis (RA) treatment program, to use PROMIS to standardize the patient-centered targets of pain, fatigue, depression and physical function, and to individualize (personalize) these treatment targets. **Target population:** Adults with a documented RA diagnosis. We will enroll two groups of patients: those with low disease activity (CDAI < 10), and those with moderate to high disease activity (CDAI $\geq$ 10). **Intervention:** Patients meeting inclusion criteria will be enrolled and assessed at baseline and every 3 months for 12 months, for a total of 5 assessments. Patients will receive our modified T2T approach, which adds PROMIS measures of pain, fatigue, depression, physical function and social function, to our standard CDAI and RAPID3 assessments. In a baseline interview, patients will identify their most important (target) domains, and then select up to five (5) specific questions for that domain. These individualized questions will be added to all CAT assessments and tracked for progress. **Evaluation:** We will evaluate the degree of adoption of a web-based patient portal linked to our (Epic) electronic health record (EHR), assessing scoring and reporting PRO scores on both RAPID3 and PROMIS; Northwestern rheumatologists' attitudes toward the use of PROs in clinical practice; patient satisfaction at the conclusion of their one-year participation in the program, improvement in all 5 PROMIS domains; and comparison of outcomes in this cohort to those from our CORRONA T2T study.

B. Table of Contents

C. Main Proposal

C1. Overall Goal and Objectives

Goal: To evaluate the added value of the Patient Reported Outcomes Measurement Information System (PROMIS; www.nihpromis.org) to an existing treat to target (T2T) rheumatoid arthritis (RA) treatment program, to use PROMIS to standardize the patient-centered targets of pain, fatigue, depression, physical function, and social function, and to individualize (personalize) these treatment targets in patient-centered language that retains valid and responsive measurement. By personalizing T2T patient-reported endpoints, we maintain adherence to patient values; by using PROMIS to do so, we enable use of a common measurement framework and standard score for tracking and reporting.

Objectives: To meet these goals, we propose the following five (5) objectives:

1) To add PROMIS assessments to the existing electronic health record (EHR) for our RA patients in such a way that enables individualized patient goal-setting;
2) To evaluate the impact of a T2T approach as measured by the Clinical Disease Activity Index (CDAI), Routine Assessment of Patient Index Data-3 (RAPID3), and PROMIS pain, fatigue, depression, physical function, and social function;
3) To individualize patient targets by helping patients identify the PROMIS domain, including item content within that domain, that is most important to them, and modifying treatment targets based on their unique preferences;
4) To evaluate patient satisfaction with the individualized T2T system, and the effectiveness of RA treatment with regard to CDAI, RAPID3 and PROMIS targets, individually and in combination, after one year of participation in the program; and
5) To evaluate clinician satisfaction with the individualized T2T system in terms of feasibility and usefulness for achieving the goals they perceive as important for patients after one year of participation in the program.

PROMIS is a 10-year NIH Common Fund initiative that developed patient-reported outcome measures for use across chronic conditions. PROMIS instruments assess outcomes relevant in RA including pain interference, physical function (mobility; upper extremity function), social function, fatigue, and depression. PROMIS instruments were developed utilizing a rigorous, mixed (qualitative and quantitative) methodology,[1] and they have been validated in RA.[2] PROMIS instruments have demonstrated reliability and validity.[3,4] Specifically, the PROMIS Physical Function instruments have demonstrated responsiveness and measurement precision across a range of RA patients that was superior to the Health Assessment Questionnaire (HAQ) and SF-36 PF-10. Furthermore, PROMIS scores can be linked to scores on existing PRO measures such as the HAQ Disability Index and SF-36 PF-10 (see www.prosettastone.org). The use of PROMIS instruments in this study offers three advantages: 1) improved psychometric performance in RA; 2) efficient and precise measurement; and 3) ability to link scores with other commonly utilized PROs. With PROMIS item bank measures, regardless of what combination of items is administered, scores utilize the same metric. For example, a patient stating she is having some difficulty walking a short distance would be administered a follow-up

item about ambulating for a shorter distance. Items about jogging or engaging in other vigorous activities would be skipped. In this way, the assessment is tailored to the individual thus reducing the number of items needed, while maintaining a high level of measurement precision. This increased test efficiency makes collection of PROs more feasible in busy clinical settings and enables completion of multiple domains to provide a broader understanding of a patient's wellbeing. Another advantage of item banks over conventional patient-reported assessments is the fact that all items are calibrated to the same underlying scale. This enables us to select items that are particularly meaningful to individual patients (i.e., different items for different patients), and still express everyone's score on the same common metric. Thus, we can envision, and propose, a patient-centered, individualized, T2T approach, using PROMIS item content selectively by patient and expressing all patient scores on the common PROMIS metric.

C2. Technical Approach

There is no existing tool that enables RA clinicians to include, in an objective manner, "the patient's perspective in setting goals and monitoring response to therapy." Indeed, development and validation of such a tool is the main goal of this RFP. Our group has considerable experience in this area and is well-positioned to develop and test a truly patient-centered approach to treatment goal-setting. We propose to do this by adding a standardized and validated patient reported outcome assessment, PROMIS, to the existing core set of treatment targets already available, and to do it in such a way that individualizes treatment goals while retaining standardized scoring and reporting metrics.

Our prior work and experience in this area make this a low-risk/high-reward proposal. We have conducted similar research advancing the use of PROs in clinical care. For example, in oncology, we have established PROMIS standards for minimally important differences and thresholds for clinical action triggered by PROMIS assessments.[5] We have also successfully implemented a supportive oncology screening and intervention program, analogous to a T2T model that identifies treatment thresholds for pain, fatigue, anxiety, depression and physical function, using PROMIS assessments that are integrated into our electronic health record, Epic.[6] In RA, recognizing the need to identify targets, and track performance towards these targets, our institution has added tools to the patients' Epic chart. This allows clinicians to easily monitor standard disease activity measurements, including the HAQ, the CDAI, and the DAS28 (when acute phase reactants are available). To further ensure success, we will draw lessons from related work ongoing at Johns Hopkins and McGill medical centers, by including in this proposal two consultant advisors (Drs. Clifton Bingham and Susan Bartlett). Their work, recently presented at the International Society for Quality of Life Research,[7] demonstrates proof of concept regarding the useful integration of PROMIS into RA care. Thus, we have already made considerable progress toward the goal of advancing a useful, exportable T2T system that includes PROs. This initiative will assess the feasibility and utility of incorporating patient reported measures into the shared treatment decision process.

2a. Current assessment of need in target area

i. Baseline data summary

The T2T recommendations for the management of RA were published by an international task force in 2010.[8] This publication laid out 4 overarching principles and 10 specific recommendations for treating RA to target. At the time, there was little published evidence to support these recommendations; most were based on expert opinion. Subsequently, a number of studies have demonstrated the value of treating to target in RA, as well as the superiority of this approach when compared to usual care.[9] Most of these studies, though, have assessed the use of the T2T approach in a clinical trial setting rather than in clinical practice. While the Dutch DREAM registry looked at the outcomes and feasibility of employing a T2T strategy in routine clinical practice,[10,11] there are no published data that prospectively evaluate the T2T approach in U.S. rheumatology practices.

In making the T2T recommendations, the task force identified the importance of patient involvement in the process, and included a patient version of the recommendations.[12] Despite this, the success of the T2T strategy in clinical trials has been assessed using clinical disease activity outcomes, primarily remission. Patient concerns regarding the value and costs of their therapy and patient centered outcomes, such as work ability, have not typically been considered when implementing T2T strategies in clinical care.[13,14] Also, patients and physicians consider different aspects of disease when making treatment decisions.[15,16] At Northwestern, we use both the CDAI and the RAPID3 to guide treatment goal-setting. We often decide not to advance treatment despite failure to reach the identified target, or, conversely, we elect to advance therapy despite achieving a "desired" target. We have learned from this experience that a targeted treatment approach using RAPID3 or CDAI data, despite their validity, ease of use, and simplicity, lacks patient-specificity or individualization. As a result, we have often been unable to fully engage patients in their participation in the T2T process. We propose that the addition of PROMIS measures and a process by which RA providers and patients seek to individualize treatment goal setting, will close that gap between current practice and a patient-centered T2T approach.

ii. Primary population targeted for this program

The primary population will be adults with a documented RA diagnosis by their treating rheumatologist. To provide a reference group for comparison, and to evaluate whether patients believed to be in remission or "at target" actually agree they have achieved their individual treatment goals, we will enroll 60 patients with low disease activity, defined as a CDAI score less than 10. We will also enroll 60 patients with moderate to high disease activity, defined as a CDAI score of 10 or higher. In the former group, who will have been judged to achieve their treatment target of remission or low disease activity, we seek to determine whether there are patients who believe, from their perspective, that they have not reached their <u>personalized</u> goal of disease control. This would identify a population in which there is disconnect between the patient and the physician in the shared decision making process. In the latter group, we seek to determine whether addition of the PROMIS assessments will facilitate achievement of a shared treatment target and allow for improved integration of the patients' perspective into the steps required to achieve that goal.

All patients must meet the following inclusion and exclusion criteria:

Inclusion criteria:

- Physician-confirmed diagnosis of RA
- Age ≥ 18
- Able to understand and voluntarily sign an IRB-approved consent form prior to study enrollment
- English speaking
- Current CDAI score available at the time of study enrollment
- If CDAI ≥10, patient is an appropriate candidate for treatment acceleration, in the opinion of the investigator, and would be willing to escalate therapy if indicated.

Exclusion criteria:

- Cognitive impairment that would interfere with completing a face-to-face interview
- Primary rheumatologic diagnosis other than RA
- Current and uncontrolled thyroid disease, diabetes, depression, heart, renal, gastrointestinal, hepatic, lymphatic, metabolic or lung disease
- Documented diagnosis of fibromyalgia or other pain conditions, other than RA, that are likely to interfere with assessments of RA disease activity
- Women who are pregnant, breastfeeding or planning to become pregnant during the study period.
- Functional class IV as defined by the ACR classification of functional status
- History of positive tuberculin skin test or equivalent that have not received documented treatment for latent tuberculosis (or are not willing to start such treatment prior to receiving biologic therapy)
- Known history of HIV, HCV, or chronic, active HBV infection
- History of serious infection within the last 6 months, or *recurrent* serious infection (≥ 2 in the last 12 months), defined as an infection requiring inpatient hospitalization and/or treatment with parenteral antibiotics

2b. Intervention design and methods

Protocol Design: One hundred twenty (120) eligible patients who sign informed consent will be enrolled and assessed at baseline and every 3 months for 12 months, for a total of 5 assessments. Patients will receive our modified T2T approach, which will add PROMIS measures of pain, fatigue, depression, physical function and social function to our standard CDAI and RAPID3 assessments. PROMIS measures will be administered on tablet computers in the clinic using our web-based Assessment Center.™ Assessment Center is an online data collection software that enables a user (clinician or researcher) to create a study-specific URL for the administration of patient-reported outcome and proctor-administered instruments. It includes a library of instruments from the PROMIS, Neurological Quality of Life Measurement System (Neuro-QoL), and NIH Toolbox initiatives. Instruments include fixed length short forms, computer adaptive tests (CATs), and proctor-administered performance tests. Multiple features

are included to address clinical research needs such as enabling multiple study arms, multiple time points, item and instrument randomization, clinician-completed instruments, and separation of protected health information from other assessment data.[17]

The PROMIS item banks provide approximately 300 content areas (individual items) across pain (45), fatigue (95), depression (28) physical function (126), and ability to participate in social roles and activities (35). Because of their superior precision in individual assessment, we will utilize PROMIS CATs. However, in addition to the CAT assessment, we will ask participants to select the domain that is most important to them and choose up to five questions within that domain in their initial individualizing treatment target interview, adding up to 5 additional questions. PROMIS CATs each ask an average of 6 questions, resulting in one minute assessments per domain.[7] Thus, for five domains, the average assessment time expected to be added by PROMIS is 5 minutes.

To address the need for patient involvement in RA care, patients will complete a semi-structured interview at enrollment. Interviews will be conducted by a trained, experienced research coordinator using a semi-structured interview guide. The interview will identify patient satisfaction with care and the goals and life activities most important to each patient. First, patients will provide brief sociodemographic information. Next, patients will complete the Functional Assessment of Chronic Illness Therapy - Treatment Satisfaction - Patient Satisfaction (FACIT-TS-PS).[18] The FACIT-TS-PS is a validated measure of patient satisfaction with physician, staff, and nurse communication; satisfaction with doctor and staff competence; confidence and trust in providers; and overall satisfaction with care. The instrument includes an item to assess patient satisfaction with the doctor's understanding of what is important to him/her: "Did your doctor(s) seem to understand what was important to you?" Following the FACIT-TS-PS, patients will be asked to briefly describe the impact of RA on their quality of life: "Please consider anything and everything that relates to your quality of life as you live with RA. What do you think is important in terms of your quality of life?" Next, patients will be asked to rank the importance of each of these concerns using a 0-10 scale where 0=Not at all important and 10=Extremely important. Importance will be defined as the symptoms or function they would most like to improve or maintain. Following open elicitation of patient concerns, the interviewer will then provide each patient with five cards. Each card will represent a PROMIS domain (physical function, social function, fatigue, pain, and depression) and include a definition of the domain and example items from each domain. Patients will be asked to sort the cards in order of importance. Using the tablet computer, the study coordinator will show patients item content bins for the domain they ranked as most important. After selecting a bin, actual item content (patient-reported questions) from that selected bin will be shown to the patient who will select up to five specific items per domain and indicate which item represents their most important concern. These will be regarded as individualized, patient-nominated treatment targets (first priority domain and selected items within that domain). The most important patient-nominated PROMIS domain and their five selected items (with the most important item indicated) will be shared with the treating physician via the EMR. The nominated questions will be loaded into that patient's individualized assessment along with the standardized CAT assessment for the same domain, plus the other four domains. Importantly,

even though patients will select different valued experiences (symptoms) and activities, thereby personalizing their treatment target, the scoring of the source PROMIS bank remains reproducible and standardized.

At the end of the one-year study period, patients and clinicians will complete a brief exit interview. We will develop a structured exit interview guide for the patients and a structured exit survey for the physicians during year 1 of the project. The patient exit interview will assess patient's satisfaction with the modified T2T approach using brief open-ended questions and the FACIT-TS-PS. To assess the patient's perceived improvements on their valued outcomes, they will complete a Global Rating of Change (GRC) question for each of their five individualized PROMIS items: "Thinking about your (content from item ranked as important), please use the scale below to indicate whether there has been any change since the first time you completed questionnaires for this project." Patients will mark their response on a 7-point scale from +3 = "very much better" to -3 = "very much worse." We have used similar GRC items in several studies to estimate patient overall impression of improvement or worsening. We find them to be not only valid, but also highly-intuitive for patients and providers. In addition to evaluating change on their five personal items, they will also evaluate change on five additional items randomly picked, one from each of the PROMIS domains. These items will serve as contract/comparison items in relation to the patient-identified target items, with the expectation that patient-identified items will show more benefit than the randomly-selected items. The clinician exit survey will evaluate their satisfaction with the individualized T2T system in terms of feasibility and usefulness for achieving the goals they perceive as important for patients after one year of participation in the program. Clinicians will be asked to evaluate the ease of integrating individualized targets into care, the extent to which individualized targets were incorporated into care, and barriers to successfully incorporating individualized targets. The survey will also address clinicians' attitudes towards the use of PROs in practice and perceived changes in attitudes over the course of the study.

Sample Size: We will recruit 120 patients over 12 months. The sample will consist of 60 patients with remission or low disease activity and 60 patients with moderate to high disease activity. Based on prior experience, we anticipate complete data from 110 patients. Our site (with Dr. Ruderman as PI) participates in a study by the Consortium of Rheumatology Researchers of North America (CORRONA) comparing T2T to usual care. This study randomizes by site, and our site was randomized to the T2T arm. We enrolled 31 subjects over a 1 year period with just 3 of our rheumatologists participating. With involvement of the entire practice, comprised of 12 rheumatologists with >1000 RA patients under their care, we do not anticipate difficulty recruiting 60 patients with moderate to severe disease activity and 60 in remission or with low disease activity in one year's time.

Because they are successfully piloting the use of PROMIS CATs in RA practice, we have secured Drs. Bartlett and Bingham as consultants in this proposal. In their recent ISOQOL presentation, Bartlett et al.[7] found that patients in remission or with low disease activity reported a mean PROMIS Physical Functioning (PF) score of 45.9 (SD=8.1, n=74) and patients with moderate to high disease activity reported a mean score of 37.4 (SD=6.2, n=33). The overall pooled standard

deviation of the scores was 7.6. Their data on 107 patients are invaluable for our power calculations.

Based on these recent data, and clinical experience combined with other literature, we hypothesize that PROMIS PF will be worse at baseline among those patients with CDAI≥10 compared to those with CDAI <10. In this study, a total of 120 patients will be enrolled in two equally sized groups: remission or low disease activity (n=60, CDAI 10 or less) and moderate to high disease activity (n=60, CDAI ≥10). Assuming that 55 patients in each group provide complete data, we will have 80% power to detect an effect size (mean difference / pooled standard deviation) of 0.54 using a two group t-test with a 0.05 two-sided significance level. Using the standard deviation reported in Bartlett et al., this corresponds to a difference of 4.1 points on the PROMIS Physical Functioning score. If the true difference between groups is 8.5 points, as observed by Bartlett et al,[7] we will have 99% power to detect this difference. The observed effect sizes for the differences between groups on PROMIS Pain Interference, Fatigue, and Depression ranged from 0.45 to 1.0. Our power to detect differences of these magnitudes in our study ranges from 64-99%.

With regard to power to detect meaningful change, PROMIS investigators have conducted a longitudinal validation study of PROMIS Physical Function in RA.[19,20] These results were analyzed to better estimate likely power for this study. In that PROMIS longitudinal RA study, those who self-identified as changed (improved or worsened) over the previous 6-12 months reported changes in PROMIS Physical Functioning, Fatigue, and Pain Interference scores that ranged from 0.30 to 0.52 standard deviation units in magnitude. With alpha set at .05 and power at 80%, we would require 32 patients per group to detect a change of 0.52 effect size. To detect an effect size for change of 0.30 as significant will require 90 patients. This, we consider this study to be sufficiently-powered to detect effects of a clinically meaningful magnitude.

Innovation: This is a unique proposal. Despite its conceptual appeal and practicality, the only other working example of an individualized patient-reported outcome assessment in RA practice we are aware of is that of Bingham and Bartlett, and they have agreed to collaborate as consultants, so that we might advance this important area harmoniously. Furthermore, this is a PRO application that is both individualized and standardized, something that can only be accomplished with a creative integration of item response theory and qualitative clinical input from patients.

This initiative brings together and builds upon two successful enterprises at Northwestern Medicine: The highly productive rheumatology clinical research group, which is routinely employing the CDAI and RAPID3 in clinical practice today, and the PROMIS research group housed in the Department of Medical Social Sciences. We have an electronic health record (Epic) that has customized fields that allow our clinicians to seamlessly capture and follow standard disease activity measurements, including HAQ, RAPID3, CDAI, and DAS28. Dr. Cella has led the development of the PROMIS instruments to measure patient perspectives on disease outcomes and has collaborated with the rheumatology division on the development and validation of rheumatology specific instruments.

2c. Evaluation design

i. Determining if practice gap was addressed

The primary purpose of this project is to more effectively address the patient's perspective in setting goals and monitoring response to RA therapy, and to disseminate successful methods to do so. Current barriers to integrating PROs when treating to target include concern about the validity of patient-reported outcomes, feasibility (ease) of PRO use in clinical practice, and confusion regarding how to interpret, or act upon, discordance between measures incorporating clinician-rated elements, such as the CDAI, and patient-rated information in the RAPID3. Metrics we will assess in a program outcome evaluation will include:

- Degree of (%) adoption of a patient portal linked to the (Epic) electronic health record (EHR), assessing scoring and reporting PRO scores on both RAPID3 and PROMIS
- Northwestern rheumatologists' attitudes toward the use of PROs in clinical practice at the conclusion of the this program
- Improvement in patient satisfaction with, and participation in, care at the conclusion of their one-year participation in the program, compared to satisfaction and participation prior to initiating the program
- Improvement in pain, fatigue, depression, physical function and social function, as measured by PROMIS
- Improvement in the five patient-selected items within their most important PROMIS domain.
- Patient perceived improvement in their most five most important PROMIS items, as measured by Global Rating of Change scores.
- Comparison of outcomes in this cohort to those of the cohort in the CORRONA T2T study. This project is not designed or powered to provide an unbiased comparison between the two groups. However, we will consider our cohort of 31 CORRONA patients as historical controls for selected outcomes. We understand that effects observed in a controlled, single-arm trial are subject to unknown cohort, placebo and Hawthorne effects; nevertheless we believe we will have sufficient basis for our results to inform the design of a future randomized trial evaluating the incorporation of PROMIS into a T2T strategy

ii. Expected change.

Based upon the fact that RAPID3 is already collected routinely in practice, we expect to observe full adoption and high satisfaction with the EHR patient portal. Our target population includes patients and providers. We expect that at least 50% of patients will move from the moderate/high disease activity group to a state of remission or low disease activity over one year. Recalling the above estimate of 32 patients required to show a change of 0.52 effect size, and that patients in remission or with low disease activity differ from those with moderate/high disease activity by more than that amount, we consider the longitudinal component of the study to be sufficiently powered to detect patient-reported benefit among those patients whose CDAI improves over the course of the year they are being followed. We anticipate that utilizing the PROMIS assessments and the proposed T2T management approach will increase the percentage of patients who improve, and that patients will be more satisfied that their own perspectives have been included in the process. We expect to find moderate effect sizes in the

changes observed over one year in patient satisfaction and provider satisfaction, as well as non-priority PROMIS outcome measures.

iii. Evaluating the target population's engagement in the intervention.
In addition to the outcome measures described above, engagement will be assessed by: 1) percent of the sample who completed all assessments; 2) patient satisfaction with the individualized T2T approach as measured by the FACIT-TS-PS; 3) patient satisfaction with the individualized T2T approach as measured by the open-ended exit interview questions (e.g., "You indicated at the start of the study that (name most important PROMIS item) was very important to you. In your opinion, did sharing this information with us improve the care you received? Why/why not?" "How likely would you be to continue in a program like this?" and 4) a questionnaire to assess clinicians' views of the feasibility and utility of the program (page 7).

iv. Dissemination of project outcomes.
Results of the research will be disseminated through local and national scientific presentations and publications. The program guide will be distributed to others upon request, including other academic centers who wish to link Assessment Center program to their EHR. A proper randomized clinical trial to demonstrate the effectiveness of this program is beyond the scope of this proposal; however, we expect to produce sufficient evidence of efficacy to justify a subsequent RCT testing the efficacy suggested by the results, and focusing on the most effective and engaging components of the intervention with regard to the T2T process.

C3. Detailed work plan and deliverables schedule
The project timeline is shown in Table 1. The timeline assumes a start date of January 1, 2014 and a 30-month total study duration.

Table 1. Project Timeline

TASK	2014				2015				2016	
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Obtain IRB approval	X									
Create study in Assessment Center	X									
Create patient and clinician interview guides	X									
Train clinic research coordinator	X									
Enrollment		X	X	X	X					
Data collection		X	X	X	X	X	X	X	X	
Analyze PRO and clinical data									X	X
Final report										X
Develop dissemination materials										X

Study kick off tasks. During months 1-3, we will obtain IRB approval, create the study in Assessment Center, create the interview guides, and train study staff. Dr. Kaiser will work with the study coordinator to obtain IRB approval. Drs. Cella and Kaiser will work with the study

coordinator and a senior developer from the Department of Medical Social Sciences to design the longitudinal study in Assessment Center. PROMIS instruments are already available in Assessment Center. Thus, study design will involve designating instruments for the study, incorporating sociodemographic questions for the initial assessment, and programming Assessment Center to include the five patient-selected items in each assessment. Quality assurance testing will be conducting to identify and address any errors in Assessment Center prior to data collection. Dr. Kaiser, in close collaboration with Drs. Ruderman and Cella, will create the interview guide for the initial patient interview and the end of study patient and clinician exit interviews. Dr. Kaiser will train the clinic research coordinator. Training will include review of the study consent form and recruitment procedures and conducting mock interviews until the coordinator is skilled at administering the study interview.

Patient enrollment, data collection, analysis, and final report. We anticipate enrolling 120 patients over 12 months, beginning in April of 2014. The clinic research coordinator will identify patients meeting eligibility criteria, approach them in clinic, describe the study, and obtain informed consent from interested patients. Dr. Ruderman will work closely with the coordinator throughout the study to ensure that enrollment remains on target. Data collection will occur over 24 months, to allow for complete data collection from the last patient enrolled. The study coordinator will ensure that data is correctly entered into Assessment Center and that key data components are entered into the electronic medical record. Although data review and management will be ongoing, the main analyses of quantitative and qualitative data and report preparation will occur during the six month period from January 1, 2016 to June 30, 2016.

Develop dissemination materials. Project findings will be disseminated through publications and national meetings. Manuscripts(s) and abstracts will be prepared during data analysis and preparation of the final report.

Table 2. Project Deliverables and Due Dates (assuming January 1, 2014 start)

Deliverables	Expected data of completion	Suggested distribution
Study kickoff (Secure IRB approval, Create study in Assessment Center, Create baseline interview guide, Train clinic research coordinator)	March 15, 2014	$90,000
Enrollment of 50% of patient sample (N=60)	September 1, 2014	$100,000
Enrollment of 100% of patient sample (N=120)	March 1, 2015	$100,000
Completion of data collection (last patient final visit)	February 28, 2016	$30,000
Data analysis and final report	June 30, 2016	$30,000

References

1. DeWalt DA, Rothrock N, Yount S, Stone AA. Evaluation of item candidates: the PROMIS qualitative item review. *Med Care.* May 2007;45(5 Suppl 1):S12-21.
2. Fries JF, Cella D, Rose M, Krishnan E, Bruce B. Progress in Assessing Physical Function in Arthritis: PROMIS Short Forms and Computerized Adaptive Testing. *The Journal of Rheumatology.* September 1, 2009 2009;36(9):2061-2066.
3. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol.* Nov 2010;63(11):1179-1194.
4. Rothrock NE, Hays RD, Spritzer K, Yount SE, Riley W, Cella D. Relative to the general US population, chronic diseases are associated with poorer health-related quality of life as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS). *J Clin Epidemiol.* Nov 2010;63(11):1195-1204.
5. Yost KJ, Eton DT, Garcia SF, Cella D. Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer patients. *Journal of Clinical Epidemiology.* 2011;64(5):507-516.
6. Wagner LI, King K, Kozkowski C, et al. Integrating a Web-Based Assessment to Identify Distress into Routine Cancer Care: Clinical Application of the NIH Patient Reported Outcomes Measurement Information System (PROMIS) Computer Adaptive Test. *American Psychosocial Oncology Society*. Huntington Beach, CA2013.
7. Bartlett SJ, Orbai AM, Duncan T, DeLeon E, Bingham CO. Validity of PROMIS CATs, Short Forms, and Global Health Items in Rheumatoid Arthritis. Paper presented at: International Society for Quality of Life Research; Miami, Fl. 2013.
8. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Annals of the rheumatic diseases.* Apr 2010;69(4):631-637.
9. Jurgens MS, Welsing PM, Jacobs JW. Overview and analysis of treat-to-target trials in rheumatoid arthritis reporting on remission. *Clinical and experimental rheumatology.* Jul-Aug 2012;30(4 Suppl 73):S56-63.
10. Schipper LG, Vermeer M, Kuper HH, et al. A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Annals of the rheumatic diseases.* Jun 2012;71(6):845-850.
11. Vermeer M, Kuper HH, Bernelot Moens HJ, et al. Adherence to a treat-to-target strategy in early rheumatoid arthritis: results of the DREAM remission induction cohort. *Arthritis research & therapy.* Nov 23 2012;14(6):R254.
12. de Wit MP, Smolen JS, Gossec L, van der Heijde DM. Treating rheumatoid arthritis to target: the patient version of the international recommendations. *Annals of the rheumatic diseases.* Jun 2011;70(6):891-895.
13. Almoallim H, Kamil A. Rheumatoid arthritis: should we shift the focus from "Treat to Target" to "Treat to Work?" *Clinical rheumatology.* Mar 2013;32(3):285-287.
14. Pincus T, Castrejon I, Bergman MJ, Yazici Y. Treat-to-target: not as simple as it appears. *Clinical and experimental rheumatology.* Jul-Aug 2012;30(4 Suppl 73):S10-20.
15. Robinson SM, Walker DJ. Negotiating targets with patients: choice of target in relation to occupational state. *Rheumatology (Oxford).* Feb 2012;51(2):293-296.

16. van Hulst LT, Kievit W, van Bommel R, van Riel PL, Fraenkel L. Rheumatoid arthritis patients and rheumatologists approach the decision to escalate care differently: results of a maximum difference scaling experiment. *Arthritis care & research.* Oct 2011;63(10):1407-1414.
17. Gershon RC, Rothrock N, Hanrahan R, Bass M, Cella D. The Use of PROMIS and Assessment Center to Deliver Patient-Reported Outcome Measures in Clinical Research. *J Appl Meas.* 2010;11(3):304-314.
18. Peipert J, Beaumont J, Bode R, Cella D, Garcia S, Hahn E. Development and validation of the functional assessment of chronic illness therapy treatment satisfaction (FACIT TS) measures. *Quality of Life Research.* 2013/09/24 2013:1-10.
19. Fries J, Krishnan E, Rose M, Lingala B, Bruce B. Improved responsiveness and reduced sample size requirements of PROMIS physical function scales with item response theory. *Arthritis Research & Therapy.* 2011;13(5):R147.
20. Hays RD, Spritzer KL, Fries JF, E K. Responsiveness and minimally important difference for the patient-reported outcomes measurement and information system (PROMIS) 20-item physical functioning short-form in a prospective observational study of rheumatoid arthritis. *Ann Rheum Dis.* In press.

D. Organizational detail

D1. Leadership and Organizational Capability

If funded, this project will be conducted at Northwestern University Feinberg School of Medicine and its affiliated rheumatology clinical practice. It will be co-led by Drs. Eric Ruderman and David Cella. Dr. Ruderman is Professor of Medicine and practice director for the rheumatology clinical practice. Dr. Cella is Professor and Chair of the Department of Medical Social Sciences and Principal Investigator of the PROMIS Statistical Center. Both have published extensively in the area of rheumatology outcomes, Dr. Ruderman from a clinical perspective, and Dr. Cella from a patient-centered and patient-reported outcomes research perspective. Together, they will comprise a compelling team to advance the practical and effective use of tools to enable and advance T2T approach to RA treatment.

Northwestern University is one of the country's leading private research universities, with an annual budget of $1.6 billion and sponsored research in excess of $500 million. The University has a long history of leadership in interdisciplinary research programs and centers. More than 90 school-based centers and 26 University centers support interdisciplinary research that spans a wide spectrum of areas, including neuroscience, nanotechnology, biotechnology, and outcomes research. The Feinberg School of Medicine (FSM) is one of 11 colleges and schools at Northwestern University. Feinberg is a research-intensive medical school that is part of a highly-ranked academic medical center. Located adjacent to Chicago’s Magnificent Mile, Feinberg has built a national reputation for excellence through a strong history of collaborative, interdisciplinary medical education and research, and along with Northwestern Memorial Hospital and Northwestern Medical Faculty Foundation is part of the premier academic medical center known as Northwestern Medicine. Through its affiliates, it provides patient care to thousands of individuals every year, and plays an integral part in the communities it serves. Feinberg is a top 20 medical school where nationally renowned researchers collaborate with skilled clinicians to improve human health.

Research is conducted in all Feinberg departments, institutes, and centers, and is supported by the Northwestern University Office for Sponsored Research and more than 30 research core facilities. Within this infrastructure, the Rheumatology Section in the Department of Medicine has a national reputation for excellence in clinical care and cutting-edge research. The Department of Medical Social Sciences is a research-intensive group that focuses on bringing the patient voice into clinical care and research. The Departments of Medicine and Medical Social Sciences convene regularly through the Institute for Public Health and Medicine (IPHAM), a nexus for public health activities at FSM. IPHAM accelerates innovation at the interface of medicine and public health to achieve measurable improvements in health for patients and populations. IPHAM Centers, including the Center for Patient Centered Outcomes, provide a rich resource base for this proposed work. In fact, this work has the advantage of building on a successful prior effort to integrate patient-reported outcomes into clinical practice in the area of supportive oncology for women with gynecologic malignancies. This effort, a collaboration of Medical Social Sciences, the Robert H. Lurie Comprehensive Cancer Center of Northwestern, Hematology/Oncology (Medicine) and Gynecological Oncology (Ob-Gyn), was so successful as a demonstration project, integrating PROMIS with the Epic EHR to drive supportive care, that it

has been institutionalized as an active clinical program with all new patients. It has also served as a model for IPHAM to propose, and have approved, a similar project in Orthopedics (joint replacement program), to begin in FY 2014. These local milestones demonstrate our ability to successfully and meaningfully integrate the patient's voice into clinical workflow, care planning and disease management. We look forward to moving in this direction in the management of RA.