COVER PAGE:
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TITLE:
Incorporation of patient reported outcomes data in the care of US veterans with rheumatoid arthritis

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ABSTRACT:
The overall goal of this proposal is to address barriers to the use of patient reported outcome (PRO) data in the Dept. of Veterans Affairs (VA) health care system. A preliminary survey of rheumatologists at the Malcom Randal VAMC confirmed that there is currently no use of PRO data. This survey identified two barriers to the use of PRO data: (1) rheumatologists were not convinced that the use of these data makes a difference in patient's outcomes, and (2) limited access to these data. Both issues are addressed in this proposal. The question addressed by this proposal is whether PRO data change patient's outcomes. The hypothesis is that the availability of these data in the form of the patient-completed MDHAQ/RAPID3 questionnaire will change patient-centric outcomes such as patient reported well-being, patient satisfaction and medication compliance. The targeted population is US veterans with rheumatoid arthritis who receive medical care within the North Florida/South Georgia Veterans Integrated Service Network (NF/SG VISN). The intervention is a single-blinded, randomized controlled trial to provide (or not provide) PRO data to the treating physicians. The second component of this study is implementation of an electronic version of the PRO that provides VA physicians with a graphical version of these data. Outcome measures used to evaluate the results of this study include a comparison between intervention and control subjects for patient-derived instruments of patient satisfaction, patient-reported disease outcome data, medication compliance, and physician/lab-derived instruments of clinical efficacy as measured by DAS28 change and DAS28 remission.

A. Overall Goal & Objectives

The overall goal of this study is to address barriers to the use of patient reported outcome (PRO) data for the treatment of rheumatoid arthritis (RA) in the Dept. of Veterans Affairs (VA) health care system. Why are PRO data not utilized? As a component of quality improvement efforts at the Malcom Randal VAMC, a questionnaire addressed to faculty revealed two barriers. The first barrier is the impression that PRO data do not matter, i.e., do not influence outcome. The second barrier is that PRO data are not readily available in the clinical setting at the VA health care system.

The two specific objectives of this proposal coincide with these two barriers. Objective 1 is to test the hypothesis that addition of PRO data, coupled with education regarding significance of these data and treat-to-target (T2T) strategies in RA, will result in better reported outcome measurements. In particular, those measurements that reflect patient – centric outcomes, such as patient satisfaction, patient global health, and compliance are anticipated to be most affected. Physician-derived outcome data, such as disease activity measurements and remission rates, will be affected, but less so. The rationale for this hypothesis is the expectation that when physicians are educated regarding the implications of PRO data and their relationship to disease activity, therapy will be more closely linked to the patient's perception of overall health, pain and function. High PRO scores will motivate a transition to closer follow up and therapy that reflects the patient's priorities. Correspondingly, a lesser effect might be expected on physician-derived outcome measurements because PRO data are not perfectly correlated with these physician ratings. Objective 1 will be met with a single blind, randomized, controlled study that measures the benefit of providing PRO data to VA rheumatologists.

Objective 2 will address the availability of PRO data to VA providers. A digital version of the Multidimensional Health Assessment Questionnaire/Routine Assessment of Patient Index Data (MDHAQ/RAPID3) form will be completed by patients using computer tablets just prior to their appointment with treating rheumatologists. Questionnaires will be completed under supervision of the research staff and the data will be imported into the VA electronic medical record (EMR). The VA EMR software is named the Computerized Patient Record System or CPRS, and the data will be available to the physicians treating the patient at the time of the visit in graphical form. The outcome of objective 2 will be to overcome the barrier to access to PRO data.

B. Technical Approach –

1. Current Assessment of Need in Target Area

As summarized in the RFP for the current proposal, there is excellent evidence of the validity of PRO data with good correlations (with caveats discussed later) to clinical remission and physician estimates of disease activity. There are also substantial data that incorporation of PRO data into a treat-to-target treatment (T2T) algorithm with an aggressive management protocol improves outcome (Castrejon *et al*., 2013), suggesting that PRO data are as effective as physician-derived data. Given the very low percentage of RA patients who meet eligibility criteria to participate in therapeutic trials (5 to 30%; Zink *et al*., 2006), it was important to show

that the results for T2T could be achieved in routine clinical practice, as documented in the Dutch DREAM registry (Vermeer *et al*., 2011). Overall, the data suggest that PRO data are sufficient in implementing a T2T strategy. However, the necessity of PRO data is unproven. That is, does the use of PRO, in itself, improve on a physician's ability to achieve T2T goals, either as improvement in the patient's reported symptoms, the achievement of remission or the reduction of disease activity? Pincus *et al*., 2012 concludes, "It is suggested that all rheumatologists should consider having each patient complete an MDHAQ/RAPID3 at each visit in the infrastructure of usual care." The argument is logically developed, but what is the evidence? Surprisingly, there is little or no evidence that the availability of PRO measurements by themselves, improve patient care.

Rheumatologists at the Malcom Randal VAMC within the NF/SG VISN were surveyed in July 2013 regarding their use of PRO data. The physician response rate of three is small but represents 100% of RA patient care by rheumatology at this VAMC. Conclusions from the survey indicated (1) that there is no use of PRO data, (2) that all the physicians were aware of the international task force T2T recommendations (Smolen *et* al., 2010), and (3) that remission rates for RA patients were unknown. An open ended question about barriers to use of PRO data revealed that all respondents noted lack of accessibility attributed to the paperless EMR, CPRS, which made it difficult to incorporate any patient-derived questionnaire into the medical record. Also, a universal response was that while the data would be welcome, there was the consistent impression that these data were unnecessary for implementing a T2T strategy. That is, the physicians were not convinced that PRO data would result in any meaningful improvement in patient outcomes.

The results of this survey were broadened to the national level. Participants in the Veterans Affairs Rheumatoid Arthritis (VARA) registry were contacted and asked the same questions as at the local level. Even at institutions that participate in the VARA registry, PRO remain a research tool and there is no ready access to PRO to practicing clinicians caring for VA patients. The use of a nearly paperless EMR system within the VHA represents a formidable barrier to adoption of PRO unless a specific effort is made to address this issue. The question of availability of PRO was again asked at the October 28, 2013 meeting of the Veterans Affairs Rheumatology Study Group with the answer that there is no expected incorporation of PRO data into the VA EMR in the foreseeable future.

In real world situations, specifically at the NF/SG VISN, rheumatologists are managing patients without the benefit of PRO data. The preliminary questionnaire revealed that these rheumatologists agree philosophically with the concept of T2T, however they are unconvinced that PRO data will assist in this endeavor. The implication being that these physicians believe they can estimate disease activity sufficiently well based on history and exam to implement T2T without additional information that correlates with disease activity. Without questioning the validity of PRO data, this skepticism is well placed. Importantly, both older and very recent data suggest that as therapy is advanced with application of a T2T algorithm, and remission is approached, PRO data and activity data may diverge. This was confirmed experimentally in a study that evaluated the attenuation in RA severity with addition of biologic therapy, but did not see the same attenuation in a PRO measurement (Welsing et al., 2005). Physicians are understandably reluctant to treat more aggressively when they believe disease activity is low in spite of patient-based somatic complaints, thinking that there is little potential for

improvement yet high risk of harm. Thus in clinical practice, a high PRO score may not reflexively trigger change to more aggressive therapy. More recently this same divergence was detected, noting that in patients with a good response to a biologic, T2T could improve activity score without a meaningful improvement in PRO, but the conclusion was quite different. Emphasizing the relative importance of PRO, these data were suggested to imply that strict adherence to activity measurements may not meet patients needs (Curtis et al., 2013). This is particularly relevant to the VA RA population, with a high incidence of PTSD, anxiety and depression, which have been shown to affect PRO data (Mikuls et al., 2013).

There are no prior studies that directly address the value of PRO data. Interestingly, in the published study that most closely parallels the current proposal, provision of activity measurements (DAS28) to providers in 2004 resulted in little measurable improvement in any outcome measures (van Hulst *et al*., 2010), suggesting that the current proposal to assess the value of providing PRO data addresses a very reasonable question. Are PRO data unnecessary? Why might the results of the 2004 study with provision of quantitative information in the form of a DAS28 score different from the currently proposed study? As above, PRO and physician-derived activity data may diverge. DAS28 data may correlate so well with a physician's perception that the actual information may add little. PRO data, however, offers a different perspective, that of the patient, and perhaps the uniqueness of PRO data may make it more valuable. In fact, when considering the factors that matter most to a patient that can be summarized in the broad context of quality of life, there is evidence that PRO, particularly the subjective patient global assessment better reflects what is important to a patient than do other objective, physician-derived or laboratory results (Linde *et al*., 2013). There are other potential reasons that could lead to a different conclusion with the current study – there was no educational component in the 2004 study and there is more general acceptance of T2T than in 2004; also biologic availability and use was lower with less perceived ability to influence outcome in 2004.

In summary, the need in the target area is absolute, as there is currently no use of PRO data locally within the NF/SG VISN. The primary audience targeted with this project are rheumatology providers within the NF/SG VISN. If the PRO software is adopted nationally, then rheumatology providers throughout the nationwide VA health care system could potentially benefit.

2. Intervention Design and Methods

The intervention design is a single blind, randomized controlled trial. The intervention is to provide PRO data to rheumatologists treating patients who have RA. PRO data will not be provided to physicians for control subjects. The population studied will be patients in the NF/SG VISN with RA. Baseline inclusion criteria will include patients older than 18 who have had rheumatoid arthritis according to the 1987 ACR revised criteria for RA for fewer than 5 years, but have been seen at least one time previously with diagnosis of RA. Enrolled subjects will have at least moderately active disease, defined by a disease activity score (DAS28-CRP) of more than 3.2. The primary outcome will be a change in RAPID3 score. Secondary outcomes will include patient satisfaction, percent with minimal clinically important improvement (MCII)

in patient global, medication compliance, DAS28, and frequency of achievement of remission criteria (DAS28-CRP<2.3). The study duration (length of active follow up) is 12 months.

The trial design also includes physician education: a series of six lectures that will be delivered to the Malcom Randal VAMC faculty and the faculty of the local academic affiliate, as well as community rheumatologists: (1) Measures of remission & disease activity in RA; (2) Validity assessment for PRO measures and the implications of discordance with disease activity; (3) A review of T2T strategies; (4) Description of a study evaluating the utility of incorporating PRO data at the VA supported by Pfizer Independent Grants for Learning & Change; (5) Implementation of PRO in clinical practice - lessons from the VA health care system; (6) Future needs in management of RA. The lectures will be refined/updated and recycled in the second year of the study, and then published on-line for the benefit of the VA rheumatology community and other interested providers. CME credit will be provided.

It is important to emphasize at the outset that this study is unique relative to any other study in the current literature. This is not a trial of T2T efficacy or strategies. This study will seek evidence to support the hypothesis that there are measurable benefits from adding patient reported outcomes to the routine management of RA patients in the setting where physicians are aware of T2T strategies. In fact, those physicians will be provided education about the available data concerning T2T, and will be explicitly encouraged to T2T. However, they will receive PRO information to guide treatment only for subjects that are in the intervention arm.

Randomization will be in blocks of 6 allocated to each provider. The general purposes of block design are to (1) assure an equal number of subjects in each group, to (2) avoid confounding due to calendar time and (3) avoid confounding due to differences between study sites (the individual physician's clinic) . In this case, the number of subjects is large enough that (1) is not a significant concern. There is no specific reason to be concerned about confounding due to calendar time, although it is always a plausible limitation, for example, if a new very effective therapy is approved during the course of the study, then ideally patients would be equally randomized to control and intervention both before and after the date the therapy is approved. Confounding due to study site (in this case each provider's clinic) is the most serious concern in the current proposal. It is clearly plausible that some physicians will achieve greater patient satisfaction, be more responsive to pain management issues or achieve better compliance, which are all outcomes for which we hypothesize to see an impact of the intervention. To avoid confounding based on who is the treating physician, rather than detection of differences based on the presence of the intervention, it is important that each physician be assigned patients in blocks. The block design does raise concerns about allocation concealment, but in this case the PI will be obtaining informed consent and enrolling patients without any specific knowledge of prior allocations, which will be handled by the study coordinator.

All patients will complete the questionnaires in a blinded fashion. Subjects will be randomized in a 1:1 ratio with results of the MDHAQ/RAPID3 made available in a convenient graphical format, including prior accumulated data, to the health care provider for the study subjects who are in the intervention arm at the time of the initial and each subsequent visit. A decision was made to perform the study as a single blind intervention, so that the patient is unaware of whether the physician will or will not have access to PRO data. As a limitation to

this design, a patient could ask the physician about the results of the MDHAQ/RAPID3 even if patient is randomized to the group for which the physician does not receive this information, and this would effectively unblind the subject. However, based on experience with the questionnaire, patients very rarely if ever ask the physician about the results of this questionnaire. Similarly, the patient may observe the physician looking at MDHAQ/RAPID3 data. However, the information will be in the EMR, which the patient rarely sees in the VAMC. Overall, a decision was made that if the trial was single blinded it could eliminate a significant placebo effect based on completion of the form, and this advantage was more important than the theoretical limitations. Also, a test of blinding has been added at the conclusion of the trial to determine the efficacy of the blinding procedure. To this end, at the conclusion of the study, subjects in both arms of the study will be asked whether they believe they were in the intervention or control arm.

Ethical considerations and recruitment: "Routine collection of these quantitiative data…rather than simple notation of gestalt impressions by the physician, would appear to be an intellectual and ethical responsibility…" (Pincus; J. Rheumatolog 2013:40, 1469-74). This statement explicitly raises ethical concerns. While some would consider the use of PRO data to be standard-of-care, this clearly is not the attitude among VA rheumatologists, who currently do not make use of these instruments. Moreover, as addressed throughout this application, a serious question exists as to whether these data are necessary and/or result in improved outcomes. Thus the denial of access to PRO data to physicians caring for subjects in the one arm of the study in which PRO data is not used, will constitute "usual care" for those subjects. The informed consent will need to make potential subjects aware of these issues, but individual subjects should not be denied the opportunity to participate if they desire to do so. Recruitment will be from three ½ day outpatient rheumatology clinics at the Malcom Randal VAMC. Attendings in those clinics will be reminded to discuss the study with their patients, and interested patients will be encouraged to speak further with Drs. Bubb or Chauffe about enrollment, a HIPPA authorization will be completed, and we will then discuss the study. No external advertising is planned.

3. Evaluation Design

Outcome measures were chosen to enhance the ability to detect differences between the intervention and control arms. A major concern is whether the effect size is sufficient to produce a positive outcome, particularly since the study of DAS28 as an intervention showed only a trend in improvement in several parameters, but did not achieve significance (van Hulst *et al*., 2010). In the proposed study, the barrier to achieving statistical significance is high. The study is designed to show a benefit only if the benefit is due to the addition of PRO data without the additional intervention of a change in protocolized treatment (as would be the case in the typical T2T trial). To this end, an attempt was made to eliminate any placebo effect from questionnaire completion. Also the subjects will not be randomized by provider, in which case specific T2T instructions would be given only to providers who see subjects who receive the intervention. As mentioned above, this would have introduce a confounding variable because different physicians may get different subjective responses from their patients, but more

importantly, it is important in this study that all subjects see physicians that have the same T2T education. If education alone is sufficient to achieve the desired result, then the MDHAQ/RAPID3 component is unnecessary.

Overall, it is plausible that either the intervention has no associated benefit or the effect size of the measured benefit will not achieve significance. If not, then this study will not be able to distinguish between those two possibilities. In order to enhance differences in outcome, the outcome measures were chosen to reflect patient-centric characteristics that are most likely to be influenced by the availability of PRO data. That is, if a physician caring for a subject in the intervention arm adjusts a treatment with the intent to improve the PRO data, then the expectation would be that the PRO data would be the most likely to show a response. Correspondingly, other outcome measures best correlated with PRO data would be the next most likely to be significantly affected. There are some data to support this intuitive conclusion (Khan *et al*., 2012). Therefore the primary outcome measure will be a change in RAPID3 (using range 0–10). For the purposes of power analysis, the minimum clinically important improvement (MCII) for RAPID3 can been estimated to be -1.0 because each component of the RAPID3 has MCII of <10% (Wells *et al*., 2007). Prior observations revealed that clinically important differences for these parameters are asymmetric, with the change associated with meaningful improvement being much less than associated with deterioration, so that the actual MCII may be easier to achieve and be in the range of -0.5 to -1.0 (Wells et al., 1993).

The enrollment criteria that subjects be seen at least once previously with the diagnosis of RA was imposed to create a more homogeneous population; that is, patients starting their first medication for RA would be likely to have the most variable responses, decreasing the precision of the estimate of benefit. Still more homogeneity could have been imposed by requiring stable medical therapy prior to enrollment, but the concept here is to study subjects in the realistic situation of active disease who are still undergoing adjustments in medical therapy. Interestingly, the Hulst *et al*. study that showed insignificant effects when providing physicians with a DAS28 did include newly diagnosed patients, and there was high variability in the range of DAS28 change over 18 months, perhaps partially accounting for the non-significant result.

The estimate of the population size is 800 RA patients seen yearly in the NF/SG VISN with approximately 50% meeting eligibility criteria. In order to detect a change in RAPID 3 score of -1.0 relative to the control subjects, with SD for the sample based on prior studies of 1.8 (Uhlig *et al*., 2009), and with a significance of $p<0.05$ and a power of 95%, 70 patients per arm needed to be analyzed. This implies a reasonable enrollment target of 90 patients per arm. A statistician from the Univ. Florida Clinical & Translational Science Institute (CTSI) was consulted for preliminary evaluation of the study design and confirmation of the power calculation. Formal consultation will be obtained prior to IRB approval.

Secondary end points will include a validated patient satisfaction survey (Leeds Satisfaction Questionnaire; Koksvik et al., 2013), patient global scale, and improvement in DAS28-CRP and % of DAS28 remissions (DAS28-CRP<2.3). A final secondary end point will be compliance as assessed by the medication possession ratio (MPR). The VA Pharmacy Benefits Management (PBM) database provides an opportunity to also collect objective compliance data, and the overwhelming majority of VA patients obtain their prescriptions through the VA pharmacy because of cost savings. The database includes information about the date

dispensed, the number of days' supply and the total number of tablets or liquid vials, and the directions for use. Based on VA pharmacy records, 60% of patients coded with the diagnosis or RA are on methotrexate (MTX). Since most patients are prescribed MTX, compliance to this medication will be used as an estimate of overall medication compliance. The concept of MPR is that a compliant patient will refill a prescription at a predictable date. A delay reflects non-compliance. Generally, if a patient stops a medication such as MTX because of an adverse reaction, this is noted in the EMR and is reported to the VA pharmacy so physician withdrawal of a medication will not be detected as non-compliance. Compliance will be measured for the final course of MTX prior to the study conclusion. The MPR is calculated as the number of days of prescribed MTX divided by the total number of days of a course. For example, if a three month supply is filled after 4 months, the MPR is ¾ or 0.75. This end point can be made a dichotomous variable by classifying MPR < 0.8 as poor adherence and MPR ≥ 0.8 as good adherence (Cannon *et al.*, 2011).

Analysis will be performed with an intent-to-treat (ITT) approach, so as to include all patients who complete the enrollment visit. For missing data at the end of treatment related to the RAPID3, the last observation will be carried forward. Other secondary end point data will not be collected except at the enrollment and final visits, so although handled conceptually in the same manner, other data missing at the end of study will be carried forward from the enrollment visit. The independent t-test and Mann–Whitney test will be used to compare differences between groups.

Objective 2, the creation of accessible PRO data in the form of an electronic version of the MDHAQ/RAPID3 is a technical issue that is addressed in the *Detailed Workplan*.

Engagement of target audience: Notice of Lectures will be sent by email to the intended audience, including residents in training and community rheumatologists. A CME planning document will be completed, and the VISN CME Coordinator, Susan Aldridge, has already been contacted to ensure the lecture material is appropriate. An advantage of providing CME for the education portion of the proposal is that this creates a formal mechanism for feedback. Outcome Evaluation strategies will include both post-activity evaluation and a post-activity follow-up survey.

Dissemination: Results of the proposed study will be published in a peer-reviewed journal. Lectures will be disseminated on-line. The MDHAQ/RAPID3 is a copyrighted questionnaire. However, its author has explicitly made it available without restriction for non-profit use. An electronic version compatible with the VA EMR will be made available to other VA medical centers throughout the nation and will be disseminated nationally through the Veterans Affairs Rheumatology Study Group. The Dept. of Veterans Affairs offers a variety of opportunities to take the results of this work to a broader audience. As mentioned in the supporting letters, the Division of Performance Improvement Services has an Organizational Development Program that could be used to implement PRO measurements throughout the country, as they are established with the expresss purpose of helping individual investigators bypass the administrative challenges of dissemination. Also, as can be noted in the attached letter from the Associate Chief of Staff for Education, the VA has considerable expertise in the

development and sharing of training resources such as the proposed lecture series, and the Education Office has offered substantial resources to disseminate the proposed training program.

C. Detailed Workplan and Deliverable Schedule

Objectives 1 and 2 will be implemented simultaneously.

In month 1, Objective 1 will undergo a detailed review by a statistician from the Univ. Florida Clinical & Translational Science Institute (CTSI). An informed consent will be prepared.

In months 1 through 6, the lecture series will be delivered on a monthly schedule. The lecture will take place during the joint Univ. Florida –VAMC rheumatology grand rounds.

In month 2, administrative activities required by the VAMC will be completed. The proposed study will be reviewed by the VA scientific projects committee and the VA safety committee.

In month 3, the protocal and informed consent will be submitted to the IRB, which in this case is operated by the University affiliate, the University of Florida. The PI of this proposal is Dr. Michael Bubb, who as the Director of the VAMC Clinical Research Unit, has a great deal of experience in bringing protocols through both the VA and Univ. Florida administrative requirements. Also of note, the UF CTSI has designated Dr. Bubb as a having achieved Master Certification in the CTSI Academy for Excellence in Clinical Research, and this designation gives his studies priority review at the academic affilliate's IRB.

By the end of month 4, the protocol will have been returned from the affiliate's IRB and final sign-off given by the VA R&D committee, which is the last step before the work can commence.

In months 5 through 12, up to 180 patients will be screened for enrollment and at least 140 of those enrolled as subjects in the current protocol. Study personnel at the clinic will include the PI and coinvestigator, who will both be responsible for obtaining informed consent. The PI or coinvestigator will complete a joint count for calculation of DAS28-CRP. If a CRP is not being drawn as part of usual/standard care, it will be drawn at this time. Once enrolled, a blinded technician will administer or be available for assistance with the digital version of the MDHAQ/RAPID3 questionnaire. No other study personnel will be in contact with the subjects. The project manager will not be blinded, will have no direct patient contact, and will be responsible for ensuring that assignments are correct with respect to intervention and control subjects, with the treating physician getting appropriate data from the questionnaire. Note that over 8 months with 3 clinics a week and 4 weeks a month, on average, just less than 1.5 subjects needs to be enrolled per clinic, which is certainly a reasonable number.

In months 12 through 24, all subjects will reach the final visit in the 12 month trial. Physicians will be asked to plan to have the patient return within plus or minus a 2 week window of the 52 week completion date. There is no plan for interim analysis. At completion, joint counts and lab

work will be completed as was done at the time of enrollment. Subjects will be questioned at completion to determine if blinding was effective. Results will be expressed as the fraction of intervention patient who believed they received intervention compared to control subjects who believed they received the intervention.

Funding will end at month 24, but the PI and coinvestigator will be able to continue with data analysis and publication of results over the next 6 months during this unfunded period as part of the cost sharing provided by the VAMC.

Objective 2 will progress simultaneously with Objective 1, Dr. Bubb and the Chief of Clinical Informatics will meet and designate a VA programmer to work on the project. The VA health care system has a comprehensive electronic patient record called the Computerized Patient Record System (CPRS). The user interface of CPRS allows providers to access individual patient records and supports medical documentation, physician order entry, outpatient pharmacy, imaging, laboratory, and other ancillary test records. CPRS is a paperless medical record used nationwide throughout the Veterans Health Administration (VHA) health care system. In Objective 2, a template will be created for entry of MDHAQ/RAPID3 PRO data into CPRS.

Dr. Theodore Pincus, the developer of the MDHAQ/RAPID3, has agreed to help us implement the electronic version of the questionnaire. A letter from Dr. Pincus is attached to this proposal. Dr. Pincus is currently in the process of developing a tablet version of the questionnaire that he will license to us. He has also agreed to serve as an unpaid consultant, and will make a visit to our facility to help us implement the acquisition of MDHAQ/RAPID3 data. If the timing of his visit is advantageous, he will be asked to participate in the formal education program of Objective 1.

Importing MDHAQ/RAPID3 data from the tablet into with the VA EMR system is not a trivial process. Discussions with the Chief of the Clinical Informatics Service at the VAMC, Dr. Charles Zeilman lead to the development of the plan that is outlined in his letter. In brief, the most desirable solution would provide seamless integration of data into the EMR for review by the clinician. Because there are technical and regulatory issues that cannot be fully explored prior to the actual development of such an instrument, a more simple back up plan will be simultaneously implemented. This alternative plan utilizes a research tool that has been built into CPRS called “health factors”. A wide range of “health factors” are already in use ranging from such parameters as hemoglobin A1c to creatinine clearance. This alternative plan has excellent utility for research purposes, as the values for any “health factor” can be downloaded and analyzed within any traditional database program. The only serious limitation to the alternative plan is that the data would have to be manually loaded into CPRS by a member of the research team support staff.

In month 4 of objective 2, a decision will be made about which alternative will be used for the purposes of the study proposed in objective 1 that will begin in month 5. No matter what decision is made, work will continue on the more desirable alternative for seamless integration of data into the EMR. The development of the alterative process, which will require minimal development time, ensures that the study will begin as soon as IRB and VA R&D have given final approvals. Importantly, Dr. Zeilman does not question the feasibility of implementing seamless data entry into CPRS, but only questions how long it might take to achieve this, with a primary limitation being the regulatory approval process.

In month 5 the study proposed in Objective 1 will begin, using one of the two approaches for data entry. For the purposes of this study, the subjects will remain blinded regarding their assignment to intervention or control. To make this possible, a member of the research team support staff will

perform all interactions with the subject. This support staff member will attend all clinics during the course of the study and provide any needed assistance to the subject to ensure accurate and complete data entry into the tablet. The Project Manager will then take responsibility for the data and ensure that information is provided to the rheumatologist (either by manual entry or electronic transfer) consistent with the result of subject randomization. That is, the data will be provided to the rheumatologist only for subjects in the intervention arm of the trial.

Note that in the long term plan to create accessible PRO data, a nurse would provide the patient with a tablet and instructions for data entry, and the data will then be uploaded into CPRS, complete with graphical integration of prior data, and the result will then be accessed by the health care provider. Because CPRS is part of a larger Open Source Electronic Health Record (EHR) Agent project, the MDHAQ/RAPID3 template could be made available throughout the nation within the VHA. In fact, the system is in use world-wide as both a standalone and peer-to-peer EHR, enhancing the ultimate dispersion of the results of this project.

D. Organizational Detail

1. Leadership and Organizational Capability

The grant will be administered by the North Florida Foundation for Research and Education, Inc. (NFFRE) A nonprofit VA research and education foundation, NFFRE, was established in 1997 to administer and facilitate research and educational programs within North Florida/South Georgia (NF/SG) Veterans Integrated Service Networks (VISN) in Gainesville, FL. Researchers at the NF/SG VISN conduct investigator initiated and pharmaceutical-sponsor initiated multi-specialty Phase II–IV trials. The VISN patient population totals 121,346 of whom 67,000 are 65+ years old. Per VA regulation, all non-VA funded research performed within NF/SG is administered by NFFRE. The Human Research Protection Program at VA Research Service is fully accredited. All researchers and staff are subject to annual research training mandates and extensive human research protections program oversight. Research facilities include an Investigational Drug Services unit; laboratories in compliance with OSHA, EPA, NIH and JCAHO standards; computer systems with advanced security and technical support; 24 X 7 on site security, redundant emergency generators and fire protection; and a Clinical Trials Research Center (CTRC). The CTRC is staffed by experienced coordinators assisted by (1) a regulatory specialist team adept at assisting investigators with study start up and regulatory documents submission, IRB and VA protocol approval processes, and adverse event reporting and (2) a recruiting team utilizing VA's electronic medical records system to identify potential subjects. The CTRC supervisor has over 25 years of clinical research experience and has been certified by the Association of Clinical Research Professionals as both a study coordinator and a monitor for 10 years. Contracting for clinical trials is now expedited through the use of the VA Cooperative Research and Development Agreement entered into under the authority of the Federal Technology Transfer Act of 1986, 15 U.S.C. § 3710a, *et seq*. Fourteen major pharmaceutical and device companies now have master agreements with the VA. Or, in the absence of a master agreement, CRADAs for specific studies can be developed by the local site and then utilized by all other VA sites.

Three leadership roles within the NF/SG VISN will assist in meeting the long term objectives of the proposal. First, from Clinical Informatics, the Division Chief Dr. Charles Zeilman, will oversee the effort to create a digital version of the MDHAQ/questionnaire. We have met several times already and have a plan in place to develop the interface with the EMR with the support of personnel from his Division. A letter of support is attached. Second, from an educational standpoint, the Associate Chief of Staff for Education, Dr. Josepha Cheong has provided a letter outlining the several resources that the Education Office has available to put together a comprehensive training program on the use of PRO data. Third, the Chief of the Division of Performance improvement, Wende Dodder, has shown great interest in this proposal, and she also has written a letter of support. Her Division has excellent resources to implement patient care measures as they become standard-of-care. In particular, her staff in the Organizational Development Program have the necessary administrative skills to overcome bureaucrat hurdles that might interfere with implementation of PRO measurements. For example, her office can change the outpatient nursing policy so that staff is available to assist and ensure complete collection of PRO data prior to the visit with the physician.

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