Study Protocol

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SToRytelling to Improve DiseasE outcomes in GOut: The STRIDE-GO 2 study

Introduction

Gout is the most common inflammatory arthritis that affects 4% of U.S. adults (1) and 5% of Veterans.(2) Gout is more common in African-Americans(1) who have worse outcomes compared to Caucasians.(3) Medication adherence of >80% to urate-lowering therapy (ULT), the cornerstone of gout treatment, in the first year is only 37%.(4) This medication adherence for gout was the lowest as compared to medication adherence of 55-72% in six other chronic disease, including hypertension, hypothyroidism, type 2 diabetes, seizure disorders, hypercholesterolemia and osteoporosis.(4). We recently found that the total charges for admissions for gout as primary or secondary diagnosis for hospital admission increased from $14.3 billion/year in 2009 to $18 billion/year in the U.S. in 2012 based on national inpatient sample, a U.S. representative study (6). Gout is common in Veterans, affecting up to 5% of all Veterans.(2) Thus, gout-related healthcare utilization and cost, especially emergency department and inpatient costs, constitute a huge burden for the VA. A recent study found that 89% of gout hospitalizations were preventable, many related to poor medication adherence (5). This indicates that a significant proportion of this health care costs and patient suffering due to gout is likely preventable.

Compared to Caucasians, AAs have lower rates of ULT prescription (42% vs. 80%) and 1.86-times odds of inadequate ULT adherence (<0.80, 64% vs. 77%).(7, 8) Optimal ULT adherence is key to gout management, since it improves the ability to achieve the target serum urate <6 mg/dl, and is associated with lower medical care costs and risk of gout flares.(11-13) This treatment goal is also recommended by gout treatment guidelines.(9, 10) A patient-centered intervention is highly appropriate in gout, since a lack of knowledge and misconceptions regarding ULT use are common among patients,(14-16) similar to other chronic conditions.(17, 18) Thus, gout is a very useful test case for chronic symptomatic diseases.

With VA HSR&D pilot funding (PPO 14-111), we have completed the development of the storytelling intervention. The purpose of developing the Storytelling Intervention Video in the pilot study was to test it with our subsequent study, which is this fully funded HSR&D merit review. The veterans participating in the intervention video signed the HIPAA Authorization and consent for use of picture and voice. These documents stated that the video recordings will be “analyzed for effectiveness”(as stated in the video recording consent document). The proposed study is to analyze the effectiveness of the intervention video that will “disseminated to other gout patients” (as stated in both HIPAA and Video recording consent documents- **Appendix 1**- highlighted). We will determine the effectiveness of the intervention compared to usual care by conducting a 12-month multicenter randomized controlled trial (RCT) among 150 AA Veterans with gout with a ULT adherence of <0.80 at Birmingham VAMC (total 300 AA Veterans at the 3 proposed VA sites- Birmingham, St. Louis, and Philadelphia VA Medical Centers)**.**

Our objective is to test the effectiveness of a patient-centered, culturally relevant narrative intervention, or “storytelling,” based on the solid conceptual foundation of the narrative communication theory(19) and the constructs of the Health Belief Model,(20) (HBM) to improve medication adherence and outcomes in chronic diseases among African-Americans (AA), using gout as an example. Gout is a chronic disease associated with chronic symptoms and disability interrupted by intermittent acute flares, similar to Chronic Obstructive Pulmonary Disease (COPD) and Congestive Heart Failure (CHF) that leads to joint destruction if not treated appropriately. Due to the intermittently symptomatic nature of chronic conditions patients, often don’t perceive disease severity and susceptibility to disease complications, and, therefore, may not balance the barriers and benefits to medication adherence.(21) Storytelling in the patients’ own voice has the power to directly and more effectively confront a patient’s barriers to medication adherence, reinforce the benefits and provide useful cues to action.(22) Storytelling promotes patient engagement when the patient identifies with the storyteller and can lead to a patient’s recognition of the need to treat the condition and improve health outcomes, as

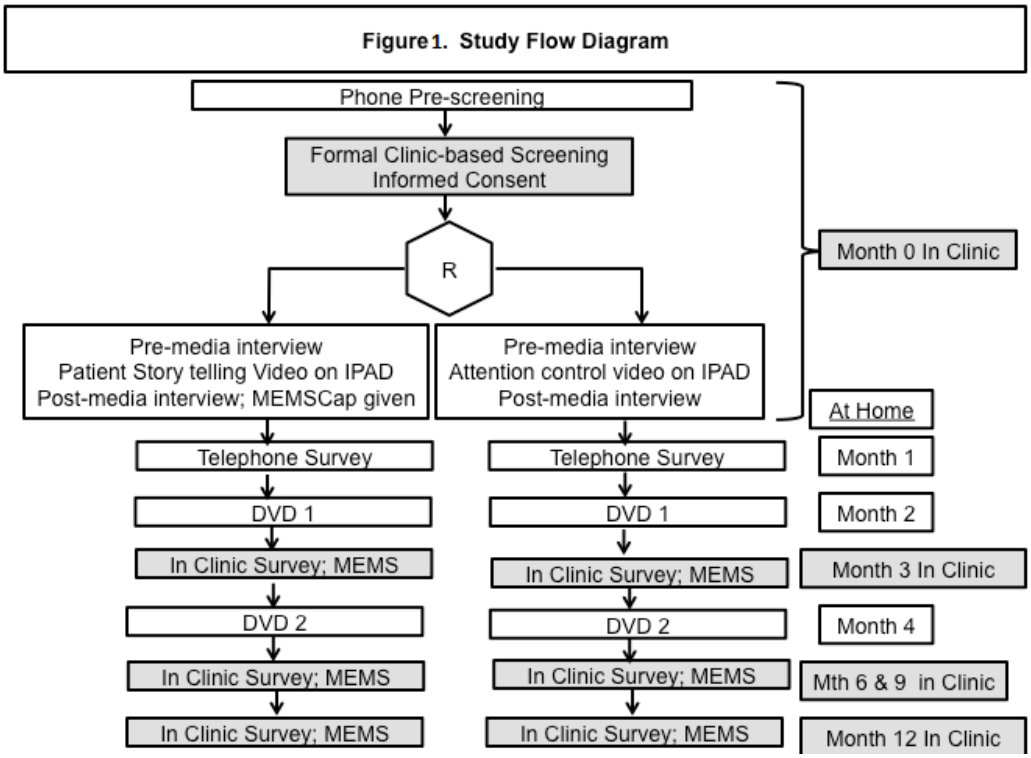
shown by a meaningful improvement in blood pressure in a recent clinical trial in AA with hypertension.(23) The success of this project, combined with other published data, will represent a major step toward demonstrating the effectiveness of storytelling to improve medication adherence in chronic diseases and will address **two VA research priority areas, i.e., health care disparities and health care delivery.**

Our **Specific Aims (SAs)** are to assess the effectiveness of a storytelling intervention in African-American Veterans with gout for:

SA1: Improving ULT adherence, directly measured by using MEMS (Medication Event Monitoring System) Caps at 3, 6 and 9 months (assess intervention's effect) and 12 months (assess durability of effect),

SA2: Improving Gout flare rate, patient satisfaction and target serum urate (sUA) <6 mg/dl achievement, as indirect measures of better ULT adherence and important gout outcomes. We will also explore the effect of storytelling on health-related quality of life (HRQOL), self-reported ULT adherence, alcohol ingestion, body mass index (BMI) and gout-related inpatient and emergency room utilization.

Figure 1 below shows the anticipated study flow diagram for this project. The primary aims are to study the effectiveness of novel storytelling on ULT adherence and patient outcomes in gout. In **Aims 1 and 2,** we will conduct a multicenter, parallel 2-arm, 12-month **RCT** comparing the storytelling intervention to usual care in African-American Veterans with gout. Patients in the storytelling intervention group will view the designed storytelling video and the usual care group will view a presentation on stress management for the same time duration (attention control), on an iPAD in the clinic during the baseline visit. Mailed DVDs to the enrolled patients at 2- and 4-months with additional storytelling clips will reinforce messages for behavioral change received during the baseline visit through storytelling videos; mailed DVDs to the attention control group will provide more information on stress management. MEMSCap (Aprex Corp., Fremont, California), a medication bottle cap with a microprocessor that records the occurrence and date and time whenever a patient opens a vial using integrated microcircuits, will be used as a measure of primary outcome of ULT adherence.(24) It will be dispensed at baseline visit and data downloaded at 6- and 12-month in-person visit. Patients will receive the first 90-day supply in special bottles with MEMSCap and be trained at the initial visit regarding the importance of MEMSCap and not to discard it but bring it to the 3-, 6-, 9- and 12-month clinic visits.



Methods

Study Population.

This is a prospective randomized study of AA Veterans with gout and low adherence to urate-lowering therapy (ULT), the cornerstone of gout treatment. The intervention being tested is a series of three videos shown at baseline, 2, and 4-months post-enrollment with follow up assessments completed at 3, 6, 9, and 12 months. We anticipate 150 Veterans to be enrolled from rheumatology and primary care clinics within the Birmingham VA Medical Center and its affiliated community-based outpatient clinics (CBOCs). Detailed patient recruitment plan is provided in **Appendix 2, a flow chart (Appendix 3) and related details in Appendix 4**. Data sources include administratively collected data from the electronic health record and the Corporate Data Warehouse (CDW) and inpatient/outpatient SAS files assessed through the VA informatics and Computing Infrastructure (VINCI) patient interviews, medication usage from MEMSCap, and a usual care blood draw to assess serum urate.

The storytelling intervention has been developed to be generalizable to all gout patients and thus we plan to recruit a representative sample at the Birmingham VA. Gout patients seen at referral clinics such as rheumatology are often selected for worse or more advanced disease and thus not representative of general patients with gout. Patients in primary care clinics are more representative and therefore, we plan to recruit across all Birmingham VA primary care clinics and rheumatology clinics.

Study Run-in period:

We have learnt that medication adherence estmates based on the medication possesson rato (MPR) calculated from prescription refill data are imperfect, and vary substantially when based on 6, 9, or 12 month data. We will therefore have a study run-in period of 4, 8, or 12 weeks by patient choice during which we will determine medication adherence using the MEMScap device on patients who have been determined to have low gout medication adherence (<80%) calculated from pharmacy refill data. Only patients meeting the MPR <80% calculated using MEMScap data will be enrolled in the study and randomized. We will re-consider patients who fail the run-in for future enrollment in the study, when their medication possession ration decreases again.

The study run-in period also allows for a more time for the veterans to review the informed consent and to ask more questions, since veterans would have had from 1-3 months to review the consent form after having signed it, before entering the study.

Intervention.
The intervention being tested is a series of three videos shown at baseline, 2, and 4 months post-enrollment. The baseline video will be shown at the Birmingham VA using VA-approved iPADs and the follow up videos will be distributed to patients as DVDs via mail. We chose the platform of touchscreen computer (e.g., iPAD) for the baseline video for two reasons: (1) the patients will be in the clinic for the baseline visit, and this would ensure that every patient gets the complete intervention in both groups at baseline; and (2) patients will be interacting with the touchscreen technology, which is the proposed platform for the future implementation. To ensure data security, the iPADs will be set up by the Office of Information Technology and will be encrypted prior to use by the study team personnel (FIPS 140-2).

Throughout the study, each video will either have the gout storytelling intervention with patient narrated stories and “Learn More” gout material in a patient’s own voice or the stress management video. The duration of the videos is the same (15-20 minutes based on previous experience). DVDs will have new stories from our storytelling stars but will be similar to those presented at the baseline visit.

Outcomes.
- Primary outcome: Adherence to ULT as assessed directly with MEMSCap
- Secondary outcomes: Adherence to ULT as assessed indirectly by the following improved outcomes. These secondary outcomes will be assessed from patient surveys and by using the VA laboratory and

other relevant data collected by the CDW and inpatient/outpatient SAS files assessed through the (VINCI) database.

a. Frequency of gout flares requiring treatment
b. Patient satisfaction with treatment
c. Achieving target serum urate (sUA) <6 mg/dl

- Exploratory outcomes will be assessed with surveys (HRQOL, self-reported ULT adherence, alcohol use) or from the VA database (BMI, healthcare utilization). Additional exploratory outcomes will focus on taking advantage of the detailed MEMS Caps data to examine the temporal relationships between medication adherence and specific research study events, e.g., the initial study visit, telephone survey, each DVD mailing, the 6 month research visit, and clinical events (e.g., an acute gout exacerbation or hospitalization).

Table 1: Summary of Primary and Secondary Outcomes and Outcome Measures to achieve SA1 and SA2

Outcome	Assessments	Description	Clinically Meaningful Change
ULT adherence measured using MEMS*	3, 6, 9 and 12	Medication adherence to ULT measured using MEMSCap[79]	Absolute difference of 6% between groups representing a medium effect size of 0.40 (A smaller difference is unlikely to be meaningful)
Secondary outcomes (SA2)			
Number of Gout flares needing treatment	0, 1, 3, 6, 9 and 12	4-item patient-reported assessment of gout flare[59]	20% fewer patients with gout flares needing treatment
Patient Satisfaction with Medications Questionnaire (SATMED-Q)	0, 6 and 12	17-item patient-reported with six dimensions;[80]	Total score is between 5.9 and 13.4 and for SATMED-Q domain scores from 5.9 to 20.6, with most estimates close to 10.[81]
Serum urate <6 mg/dl	0 and 12	Serum urate standard biochemical assay[78]	20% more patients achieving target serum urate <6 mg/dl

*Analyses of 12-month MEMS and secondary outcomes will indicate sustenance of treatment effects noted at 6-month

Inclusion/Exclusion Criteria.

Inclusion criteria are:

(1) AA Veterans (self-identified race will be the gold standard; bi- and multi-racial included) aged 18 years or above (19 years or older in Alabama) with a diagnosis of gout (1 inpatient or ≥2 outpatient International Classification of Diseases, ninth revision, clinical modification [ICD-9-CM] codes 274.x or 274.xx)(2),
(2) Meet the American College of Rheumatology (ACR) classification criteria for gout,(25)
(3) Currently prescribed and filled oral ULT medication prescription (allopurinol or febuxostat) for at least 6-months,
(4) ULT MPR <0.80 during the run-in period; and
(5) Able to provide informed consent.

Exclusion criteria are ULT MPR ≥0.80, current enrollment in another research study and patients who must redistribute daily pill into pillbox.

Study advertisement and recruitment.

The study will be advertised via IRB-approved flyers at various VA bulletin boards for research studies at BVAMC and in the primary care clinic patient waiting rooms. We will also advertise through emails to the primary care physicians at regular intervals. Since we are recruiting gout patients with low medication adherence only from minority population and patients with low medication adherence have low recruitment and retention rates, we will have a three-pronged study recruitment approach for a period of 3 years.

Mailed Letter with Opt-out (**Appendix 5** shows the Standard operating Procedure [SOP]). An IRB-approved invitation letter will be sent to all BVAMC and affiliated CBOC patients with a diagnosis of gout found with the help of Automated Data Package Application Coordinator (ADPAC) at BVAMC (**Appendix 6)**. Eligible patients will be identified using an automated VINCI pharmacy query for all AA Veterans with lgout. On a weekly basis, the research assistant will receive a list of Veterans at BVAMC who filled a ULT prescription along with the dates of ULT refills in the last 6-9 months. This list will be accessible to the research assistant within VISTA. From this weekly list of potential participants, the research assistant will identify AAs with gout. Race will be preliminarily ascertained from the patient's inpatient and outpatient CPRS medical record. Letters will be mailed on a weekly or less frequent basis (based on the number of new eligible patients) and tracked using Microsoft Excel to avoid re-contacting patients.

In the mailed letter, patients will be provided with an opt-out card (**Appendix 7)** indicating that they do not wish to be contacted for the study participation. Patients who send back the opt-out card will not be contacted. The PI/study coordinator will call (**Appendix 8-10**) eligible patients not returning the opt-out card after 14 days and complete the study screening form over the phone (confirmation of age, race/ethnicity, gout diagnosis, current adherence to gout medications, etc.) (**Appendix 10**). Patients meeting eligibility criteria will be invited to participate. The step-by-step logistics of mailing Recruitment Letters are described in **Appendix 5**. Details of how we will maintain records of patients screened and recruited are shown in **Appendix 11-12.**

Clinic Recruitment from Primary Care and Rheumatology Clinics. As a second form of recruitment, their providers will tell patients in primary care and rheumatology clinics about the study. Eligible patients will be identified from a second VISTA query of AA Veterans with low adherence to ULT who have primary care clinic visits scheduled for that week. The research associate will inform VA physicians of potentially eligible gout patients. On days when a potential research subject is scheduled for their clinic visit, the research assistant will be available. The primary care providers will inform potential research subjects of the study and ask them if they would like to participate. Those potential research subjects interested in the study will either be given a card to contact Dr. Singh or his study coordinator or speak with the research associate if available when the patient is at the BVAMC. Subjects will be screened in the clinic by filling the screening form provided by the research associate and enrolled in the study if eligible at the time of the primary care clinic visit.

Flyer Assisted Recruitment. This will be done by placing IRB-approved study flyers in the VA primary care clinics and CBOCs with the contact information for Dr. Singh/study coordinator (**Appendix 13**). Veterans interested in the study will contact the study coordinator and will be screened for eligibility either on phone or at their next visit to BVAMC. Eligible Veterans will be enrolled immediately after screening (if screened in person) or at their next visit to BVAMC (if screened on phone).

Using the 3 methods of recruitment, we have created a Study Recruitment Diagram (**Appendix 3).**

Enrollment.

Veterans screened on the phone will be enrolled in the study at their next clinic visit. Patients recruited in clinic will be enrolled in the study following their clinic visit. Every patient will first complete the study run-in visits, as detailed above. To enroll, patients will meet with the research associate at their regular clinic location and, once their scheduled clinical visit ends, walk to a private area for more detailed screening and enrollment. Alternatively, the patient will meet the research associate at the study clinic if they we screened on the phone and are coming for the study visit only that were scheduled with the research associate on the phone at the time of screening.

The setting for the consent process will be in a clinic room (rheumatology or primary care) or conference room 7204 in the Birmingham VA Medical Center. This room (7204) has been reserved for this activity. During the consent, we will avoid language and attitudes that could imply coercion or undue influence. Dr. Singh or a member of the research team approved to consent patients will tell interested patients about the study. Prior to beginning the informed consent process, they will confirm with the patient that they are interested in hearing more about the study. If so, then the PI and/ or a member of the research team will proceed with the informed consent process, reading through the IRB-approved consent form with the patient. After each section, they will pause to ask the patient if they have any questions. Once completed, the participant will be asked to sign the

informed consent and HIPAA documents. During the consent process, we will avoid language and attitudes that could imply coercion or undue influence. The entire consent process will be conducted in a private office behind a closed door to ensure privacy. Patients will be given up to 60 minutes to read the informed consent, discuss any question they may have with the study staff, and sign the consent. After informed consent documents are signed, copies will be immediately taken to the Research Compliance Officer at the BVAMC. The original documents will be stored in a locked file cabinet in Dr. Gaffo's office at the BVAMC. We expect all our patients to be fluent in English and no need to have the consent translated to other languages.

Baseline study assessments.
After the patient has been consented and enrolled in the study, they will then complete the baseline patient assessments using VA Research Electronic Data Capture (REDCap) on IPad. Paper surveys will be used as a backup. Asesments will include the folowing:

(1) Demographics: age, gender, income (covariates), marital status;
(2) Baseline frequency of gout flares requiring treatment and baseline patient satisfaction with ULT treatment;
(3) Baseline gout-specific HRQOL assessment using the gout assessment questionnaire (GAQ);
(4) Alcohol use and BMI (covariates; exploratory outcomes since alcohol and higher BMI are associated with higher risk of incident gout, gout flares and higher sUA level (1, 26-28));
(5) Blood draw for baseline sUA;
(6) ULT non-adherence on self-reported questionnaire by Voils et al.;(29) and
(7) Self-reported ULT use from non-VA sites (non-VA ULT use; sensitivity analyses). Patients' usual care serum urate values will be captured at this visit.

Additional information will be obtained including contact information, best time to contact and email address. Veterans will be provided with $25 remuneration (VISA gift card or VA Form 10-7078 - Participant payment voucher) for completing study assessments at the screening and baseline visit. If payment voucher is used, participant will bring this voucher to agent cashier to receive $25 on the same day. VA CDW and inpatient/outpatient SAS files assessed through the VINCI database. Medical records databases will be used to assess comorbidity, demographics (marital status) and baseline health care utilization and ULT medication adherence for the last 6-9 months (see eligibility criteria). Patients without DVD players will be provided with a DVD player to watch the DVDs at home at 2- and 4-months.

The consent process.
The setting for the consent process will be on the conference room 7204 or the clinic room (as preferred by the Veteran). W have reserved 7204 for this activity. We will avoid language and attitudes that could imply coercion or undue influence. Dr. Singh or a member of the research team will tell patients about the study. They will ask the patient if they are willing to participate in the study. Following a description of the study and how the data will be used, the participant will be asked to read and sign the informed consent. All of this will be conducted with the door closed. Patients will be given up to 60 minutes to read the informed consent, discuss any question they may have with the study staff, and sign the consent.

After informed consent documents are signed, those will be immediately stored in the locked study file in Dr. Gaffo's office at the BVAMC. We expect all our patients to be fluent in English and no need to have the consent translated to other languages. All study-related data will be stored in Dr. Gaffo's secure office at BVAMC.

Randomization and allocation to treatment.
Once patients complete all baseline assessments, they will be randomized into one of the two groups (see details below). Randomization will be based upon a permuted variable block design. An online computerized simple randomization scheme will be programmed by Dr. Redden (biostatistician) for BVAMC with redundant systems established to avoid interruption during periods such as server upgrades and maintenance, available through a secure Internet link. Due to the nature of interventions, patients will be aware of the group assignments. The two treatment groups are:
Group 1: Storytelling intervention
Group 2: Usual care (attention control)

The intervention group will receive the delivery of the storytelling video modules at baseline (in-person), study month 2 (by mail), and study month 4 (by mail). Storytelling in African-American Veterans' own voices will focus on improving ULT adherence, along with patient-narrated video segments about gout and its treatment under "Learn More", by adapting a pre-tested power-point slide presentation narrated by a Veteran with gout. Following the baseline assessment and storytelling video modules, Veterans will then complete 6 and 12-month assessments. The intervention group will also get a printed copy of the stories and the power-point presentation in the "Learn More" section at baseline. Each intervention installment will present new stories and "Learn More" gout content. Participants will be introduced to the MEMSCap and trained during their initial visit by research assistants.
The usual care comparison will be identical to the intervention condition, aside from not including the storytelling modules. The usual care group will be attention control with the same length of video segments as in the intervention group on stress management adapted from the Centers for Disease Control narrated by the same Veteran, who narrated the gout power-point presentation.

Patient retention.
Since this is a behavioral intervention study in AA Veterans, patient recruitment and retention are very important. We believe that retention efforts begin at recruitment. Developing rapport with the veteran during the baseline in-person screening/recruitment clinic visit will yield a lasting positive impact on study retention. We will stay connected with the study participants during the follow-up with mailed postcards and phone call reminders. We will mail study newsletters featuring quotes from consenting participants, after appropriate permissions. Study retention rates in the previous studies conducted by the PI that included minorities have exceeded 80%.(30, 31) Our current protocol allows for a dropout of similar magnitude, as the worst-case scenario. However, based on our experience and expertise, we expect the dropout rate to be lower.

Study procedures at follow-up visits and data collection tools
Follow-up assessments will be done at 1-, 2-, 3-, 4-, 6-, 9-, and 12-months after the baseline visit. The 2- and 4-month visits will be completed via mail, the 3-, 6-, 9-, 12-month visits will be completed in-person lasting 30-60 minutes, and the 1- and 12-month assessments will be completed via phone lasting 15-minutes.

The primary time-point for analyses will be at 6-months. Assessments are kept short considering responder burden and to ensure study retention. Veterans will be provided with $25 remuneration (VISA gift card or VA Form 10-7078 - Participant payment voucher) for completing the screening visit and each study assessment; an additional $25 VISA gift card will be provided as VISA gift card or VA Form 10-7078 (Participant payment voucher) to those who perform both blood draws at baseline and 12-month end-of-study visits. If payment voucher is used, participant will bring this voucher to agent cashier to receive $25 on the same day. 1-month follow-up will be done via a telephone-administered survey at the patient's convenience in their home, given that most assessments are patient-reported. This approach economizes on patient time compared to traditional gout RCTs, where patients are seen in the clinic every 1-3 months with visits lasting 1-3 hours including waiting time (plus travel time). 3-, 6- and 9-month visits will be in-person; MEMSCap data will be downloaded and other outcomes captured. To remind the patient of the follow-up assessments, a post-card (and emails, when applicable) will be mailed 1-week prior and phone call made 2-days prior to the follow-up. To minimize patient responder burden, Veterans are only completing assessments related to primary and select secondary study outcomes (including 4-item gout flare questionnaire at 6- and 12-month follow-up).

The 12-month visit (end-of-study) will be in-person, similar to the baseline visit. The visit will be coordinated with a scheduled VA clinic visit, as much as possible. MEMSCap data will be downloaded and Veterans will complete a questionnaire assessing gout flares since last visit (including those requiring treatment) and patient satisfaction with treatment, as in 3-, 6- and 9-month follow-up. In addition, Veterans will be requested to get a blood draw for end-of-study sUA (secondary outcome)(32) and also complete GAQ as a gout-specific HRQOL measure and self-reported medication adherence questionnaire (exploratory outcomes). GAQ and sUA will be done only at 12-month follow-up (expected to take additional 30-minutes). Veterans unable to come to the study clinic for the 12-month visit will be offered sUA blood draw at their nearest CBOC (routine laboratory test) and the research associate will administer 12-month assessments via the phone interview.

Statistical Analysis.

SA1: Improving ULT adherence, directly measured by using MEMS (Medication Event Monitoring System) Caps at 3, 6, 9 months (assess intervention's effect) and 12 months (assess durability of effect),

SA2: Improving Gout flare rate, patient satisfaction and target serum urate (sUA) <6 mg/dl achievement, as indirect measures of better ULT adherence and important gout outcomes. We will also explore the effect of storytelling on health-related quality of life (HRQOL), self-reported ULT adherence, alcohol ingestion, body mass index (BMI) and gout-related inpatient and emergency room utilization.

For both Aims 1 and 2, descriptive statistics for demographics (age, race, income, marital status, time since diagnosis of gout) and clinical parameters (ULT adherence, # gout flares, satisfaction, serum urate, GAQ) will be examined. Given the two arm study design (storytelling vs. usual care), statistical procedures appropriate for two-group comparisons will be utilized to conduct crude as well as adjusted comparisons based upon the distributional nature of the outcome.

For the primary outcome of ULT adherence, an unadjusted analysis will be conducted using the two-sample t-test to compare ULT adherence across study arms at 3, 6, 9, and 12 months. Adjusted estimates of ULT adherence by study arm controlling for age, gender, income, alcohol, site, and other covariates will be conducted using ordinary least squares regression.

Similar analyses will be conducted for the secondary outcomes defined in aim 2. When examining sUA level, analyses will also be adjusted for use of other medications that effect serum urate (diuretics, lipid-lowering agents, aspirin and angiotensin receptor blocking drugs etc.), BMI and alcohol use. For frequency of gout flares, analyses will also be adjusted for use of anti-inflammatory prophylaxis during initial ULT treatment. If the normality assumption is violated, nonparametric methods will be used, instead of the parametric tests.

Careful attention will be paid to the distributional assumptions for Poisson regression and methods to adjust for over-dispersion will be employed. Finally, separate logistic regression models will be used to measure treatment differences in the odds of achieving target serum urate <6 mg/dl and odds of healthcare utilization. To analyze the longitudinal data (1-, 3-, 6-, 9- and 12-months), we will use mixed linear models for ULT adherence (continuous outcome) and generalized estimating equations for target serum urate < 6 mg/dl, to analyze temporal relationships between the delivery of the intervention and medication adherence. All analyses will be guided by intent-to-treat analysis principles.

Protocol for Handling Prospective Data Collection Instruments. We will use VA Research Electronic Data Capture (REDCap) within the VA Information Resource Center for all data storage and data collection for the prospective data. An enrollment and tracking system will be developed. The research coordinator and research assistant will be trained on its use. Each site will have its documents maintained on a secure shared folder. The Birmingham research coordinator will maintain a master tracking system to monitor overall study progress with recruitment goals. Preference will be for digital data collection. For in-hospital data collection, iPads with the Citrix application will be used to access the electronic data collection tools. The iPads will be set up by the local Office of Information Technology and will be encrypted prior to use by the study team personnel. We have confirmed that all participating hospitals have WIFI for remote connection. We will assist Veterans navigate through the survey on Ipad if they are not familiar with the use of Ipad technology. For follow-up phone calls, the research coordinator or research assistant will access the forms directly and complete. If REDCap access is unavailable, paper forms will be used. Once paper assessments are complete, data will be entered into an electronic database using double data entry and securely stored. All data will be protected behind VA firewall.

Data management, quality assurance and monitoring.

Data management and quality assurance are particularly important for this study. Data from paper surveys and telephone interviews from baseline and follow-up visits will be entered by a trained and IRB-approved research assistant into the study database. Dr. Redden (WOC appointment, BHM VA), who has extensive experience in the design and management of database systems for large studies, will coordinate data management. Since

personal identifiers will be collected, all database versions will be stored on VA server with password protected electronic files. The survey will be merged with baseline enrollment data collected at BVAMC to create master SAS datasets. We will program logic and range checks in SAS 9.3 (SAS Cary, NC) to ensure timely identification of data fields requiring querying and clarification. A frequent multiple-backup strategy is proposed due to our desire not to lose any study data**.**

Human subjects protection.
All research will be conducted at the Birmingham VA and Birmingham VA Health Services Research & Development Center. We have stringent protection against breach of confidentiality using secured servers and locked office spaces for data entry at the Birmingham HSR&D. All electronic data will be housed on the Birmingham HSR&D secure server, located behind VA firewalls. At the start of the study, all project team members will be trained in practices that ensure participants' confidentiality and privacy. We will work with the local OI&T to create a secure folder, which will be used to receive and share data between study sites. Access will be restricted to only those with appropriate IRB approval and will be monitored by BVAMC OI&T. No data will be transferred off the secure server. All paper records will be stored in a locked cabinet until such time that they are archived off-site. The Birmingham VAMC has a contract with a secure offsite Records storage facility. Records will be transferred in sealed boxes with documentation of chain of custody for transfer to this facility.

All data will be collected ensuring patient privacy and upholding highest standards for information security. Data will only be accessed by the approved study personnel listed in this protocol, who have all the necessary trainings required by the VA to access data. All study personnel who leave the study will be removed from the study. All access to research data will be removed from any study personnel who leave the study. All incidents related to data security will be immediately reported to ISO, Privacy officer, ACOS-research and the Chair of IRB committee. Dr. Singh will use his encrypted VA laptop for electronic communication related to the study. Data will be destroyed as per the VA regulations. The VA currently requires that data to be kept indefinitely as per the VA regulations. We will not use any non-VA devices for this project.

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