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Rationale and Design of the Randomized Evaluation of an Ambulatory Care Pharmacist-Led Intervention to Optimize Urate Lowering Pathways (RAM-P-UP) Study

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Abstract

Background—Despite the availability of effective therapies, most gout patients achieve suboptimal treatment outcomes. Current best practices suggest gradual dose-escalation of urate lowering therapy and serial serum urate (sUA) measurement to achieve sUA < 6.0 mg/dl. However, this strategy is not routinely used. Here we present the study design rationale and development for a pharmacist-led intervention to promote sUA goal attainment.

Methods—To overcome barriers in achieving optimal outcomes, we planned and implemented the Randomized Evaluation of an Ambulatory Care Pharmacist-Led Intervention to Optimize Urate Lowering Pathways (RAM-P-UP) study. This is a large pragmatic cluster-randomized trial designed to assess a highly automated, pharmacist-led intervention to optimize allopurinol treatment in gout. Ambulatory clinics (n=101) from a large health system were randomized to deliver either the pharmacist-led intervention or usual care to gout patients over the age of 18 years newly initiating allopurinol. All participants received educational materials and could opt-out of

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Authors Contributions: All authors were involved in the design of the RAM-P-UP study and have participated in its conduct to date. Investigators from Kaiser Permanente Southern California are responsible for the day-to-day study operations as detailed above. All data analyses and outcome assessments will be performed independently by analysts at the University of Alabama at Birmingham coordinating center.

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the study. For intervention sites, pharmacists conducted outreach primarily via an automated telephone interactive voice recognition system. The outreach, guided by a gout care algorithm developed for this study, systematically promoted adherence assessment, facilitated sUA testing, provided education, and adjusted allopurinol dosing. The primary study outcomes are achievement of sUA < 6.0 mg/dl and treatment adherence determined after one year. With follow-up ongoing, study results will be reported subsequently.

Conclusion—Ambulatory care pharmacists and automated calling technology represent potentially important, underutilized resources for improving health outcomes for gout patients.

Keywords

gout; allopurinol; serum urate; quality of care; pharmacist; randomized trial; pragmatic trial; adherence; Dose Titration

1. Background

For over a decade, evidence has accumulated that gout patients are not achieving optimal outcomes due, in part, to suboptimal provider and patient behaviors.¹⁻⁶ Clinical inertia, defined as the failure to either initiate or appropriately intensify an indicated therapy,⁷ appears to be commonplace among health care providers prescribing urate lowering therapy (ULT) for gout.¹⁻³ In 2012, the American College of Rheumatology published gout management guidelines suggesting that patients receiving allopurinol, the most commonly prescribed first-line ULT,^{2,8} receive gradual dose titration guided by serial serum urate (sUA) measurement.⁹ Yet, only one in four patients have sUA assessments within 6 months of ULT initiation and less than one-third undergo ULT dose escalation.¹ Additionally, nonadherence to ULT has been well-documented among gout patients further limiting achievable outcomes.^{1,4} For chronic diseases, suboptimal patient and provider medication prescribing and usage patterns may be interdependent suggesting that addressing either in isolation may have a limited impact.¹⁰ Despite the widespread nature of these barriers,¹⁻⁶ scalable interventions addressing both patient and provider behaviors have yet to be developed in gout.

Good outcomes are eminently attainable for most gout patients. Gout has a well-defined pathogenesis, and available treatments are highly efficacious, low-cost and generally well-tolerated by the vast majority of patients.¹¹ Achieving and maintaining a sUA of < 6.0 mg/dL, a practice endorsed in management guidelines, strongly reduces the chance a patient will experience a flare after 1 year of treatment.^{9,12} If the aforementioned barriers are overcome and ULT is taken consistently at doses adequate to reach sUA goal, it can prove efficacious to the point that some consider it a cure.¹³

Preliminary reports suggest that clinical inertia in allopurinol dose escalation can be overcome using interventions led by health professionals other than primary care providers. As part of a proof-of-concept, single-center, observational study, a predominantly nurse-led intensive intervention resulted in 9 out of every 10 gout patients achieving sUA goal after one year of ULT.¹⁴ For other medical conditions, the use of technology has broadened the impact similar interventions. For instance, a pharmacist-managed anticoagulation clinic used

a centralized telephone system to engage patients directly and reduce anticoagulation therapy-related complications by nearly 40% relative to usual care.¹⁵ There is an opportunity in gout to broaden the population achieving optimal outcomes through the use similar low-cost approaches.

The Randomized Evaluation of an Ambulatory Care Pharmacist-Led Intervention to Optimize Urate Lowering Pathways (RAmP-UP) study aims to develop a scalable, semi-automated, pharmacist-led intervention to optimize allopurinol use and related outcomes in gout. A major product of our design effort was the development of a gout care algorithm intended to promote optimal gout outcomes including sUA goal attainment. The algorithm and intervention were designed to supplement, rather than replace, usual gout care with patient education, promotion of medication adherence, and facilitation of allopurinol dose escalation guided by periodic sUA assessments. The intervention was assessed using a pragmatic cluster-randomized design with comparison against usual care. The development, rationale, protocol and components of the intervention are described herein.

2. Methods

2.1. Trial Development and Logistics

2.1.1. Overview and Timeline—RAmP-UP is an ongoing two-year cluster-randomized, parallel group, usual care-controlled trial evaluating the impact of a novel pharmacist-led, protocol-driven intervention focused on facilitating sUA goal attainment among gout patients initiating allopurinol in the Kaiser Permanente Southern California health system (Figure 1). The intervention uses system redesign and direct patient engagement to optimize gout care. The aim of the study is to develop and test a pharmacist-led intervention to improve patients' treatment adherence and increase the proportion achieving sUA goal < 6.0 mg/dl, the two primary study outcomes. The intervention has been led by an ambulatory care pharmacist and delivered, in part, using an automated calling system to encourage appropriate laboratory testing, allopurinol dose titration as needed, and medication adherence. The intervention has been designed to supplement usual care in a highly scalable manner that would be generalizable to many healthcare systems.

Figure 2 provides an overview of the study timeline for this investigation including protocol development steps, system-level communication efforts, patient enrollment, and outcome assessment. During 2013, an expert consensus panel meeting, site randomization and 10-week pilot study were completed. Additionally, stakeholder involvement began in early 2013 and continued throughout the study. In May 2014, patient enrollment began and continued until July 2015 when the study enrollment goal was achieved. In May 2015, IVRS messages to prompt blood draws for the primary outcome assessments began to be sent to the first study enrollees from intervention and usual care sites. Study follow up is scheduled to be completed in July 2017.

2.1.2. Study Setting—Kaiser Permanente Southern California (KPSC), the setting for this study, is an integrated healthcare delivery system with over 4 million members. The system is comprised of 14 major medical centers that include over 200 medical offices. Of these offices, we identified 116 ambulatory clinics that prescribed allopurinol during a recent one-

year period. Few primary care providers or pharmacists practice at multiple clinics and each site typically has its own dedicated outpatient pharmacy. KPSC membership reflects the demographics of the region, accounting for 15% of the area's population.¹⁶ Based on a preliminary study in this population, we estimate that 78% of study patients will be men and participants will have a mean $\pm$ SD age of 60 ± 14 years and BMI of 31.5 ± 6.6 kg/m².¹ Further, we estimate that approximately 40% will be white/non-Hispanic, 16% will be black/African American, 20% will be Hispanic and 23% will be Asian/Pacific Islander.¹ Finally, we expect that approximately 40% will have chronic kidney disease (CKD) stage III/IV while the remainder will have kidney function of mild CKD (Stage II) or better.¹ Membership in KPSC can be obtained through individual or family plans, Medicaid/Medical, Medicare or employers.¹⁶

2.1.3. Participants—The target population for this study was English-speaking patients, 18 years of age or older with at least one *International Classification of Disease* (ICD-9) code for gout (274.XX) and receiving a fill for an incident allopurinol prescription. To be considered an incident allopurinol prescription, patients were required to have at least 12 months of observation prior to the allopurinol fill with KPSC membership, medication eligibility, and no allopurinol prescriptions filled. These criteria were designed to limit the patient population to incident allopurinol users for whom a streamlined and generalizable intervention could be developed. Patients were excluded if they had CKD stage 5 (i.e. end-stage renal disease) for which there exists little consensus for gout treatment based on the systematic literature review and expert consensus panel (see Section 2.1.5). Pre-intervention provider and/or patient opt-out were the final exclusion criteria. Consistent with the CONSORT extension for pragmatic trials, these criteria were designed to maximize generalizability.¹⁷

2.1.4. Stakeholder Engagement—Stakeholder engagement in system redesign efforts is critical for successful implementation.¹⁸ For the RAMP-UP Study, stakeholders were involved early in project development and then continually informed of progress to ensure that the protocol aligned with health system priorities. Thus, the study coordinating committee included study investigators in addition to local rheumatologists, a quality of care representative, and ambulatory care pharmacists. Consultations with three KPSC provider groups (Family Practice, Internal Medicine, and Rheumatology) and the directors of all the major medical specialties from the health system were completed prior to study initiation. Family medicine and internal medicine provider groups, whose providers prescribe over 95% of first-time allopurinol prescriptions,¹ were informed of study progress at least yearly throughout the duration of the study (Figure 2).

2.1.5. Expert Consensus Panel—Optimization of system redesign for quality improvement requires combining evidence synthesis with an institution-appropriate workflow.¹⁸ We convened an expert panel of rheumatologists and used a modified RAND/UCLA Appropriateness Method to design the supplemental gout care algorithm that would guide our pharmacist-led intervention. In order to emphasize development of intervention components that would translate to other health care systems, we strategically sought out expertise from multiple large U.S. health systems. The expert panel consisted of 8

rheumatologists: 5 with academic / university-based appointments (2 with dual Veterans Affairs appointments); 2 from Kaiser Permanente; and 1 from Geisinger Health System.

As a first step, we updated a literature review conducted initially for the ACR gout management guidelines to develop scenarios to guide input from the expert panel.^{9,19} Based on the systematic review and guidelines, 12 scenarios of potential supplemental care actions were developed (Table 1). Many scenarios had multiple permutations leading to a total of 23 total assessments. A panel of 8 experts voted on the scenarios in January 2013. The appropriateness of each scenario was scored on a scale from 1 representing “inappropriate” to 9 representing “appropriate.” Median scores of 1 to 3 were considered “inappropriate”, 4 to 6 were considered “less appropriate” and 7 to 9 were considered “appropriate.” Additionally, the expert panel provided free response feedback. Each scenario score was considered by the study coordinating committee in the context of free response feedback as well as safety and logistical challenges. Table 1 outlines the 12 scenarios, the expert panel response and the final decision of the study coordinating committee. The evidence- and consensus-based gout care algorithm was subsequently designed based on this expert input.

2.1.6. Ethical Considerations—The study was IRB approved and has been conducted in accordance with the Declaration of Helsinki and the guidelines for Good Clinical Practice. Because the study was deemed to be a quality improvement project, a waiver of written informed consent was granted by the IRB allowing an opt-out study design.

2.2. Trial Intervention

2.2.1. Study Technology—Pharmacist-patient interactions in this study were facilitated by an interactive voice response system (IVRS). IVRS has been used in health care to facilitate clinical care, aid patient self-management of disease, and improve health outcomes.²⁰ IVRS is a relatively low-cost automated calling system that allows a health system to send patient reminders and collect patient-assessed health measures. Using scripted dialogue and a keypad response system, IVRS is a consistent and efficient method for tailoring communication to each patient. IVRS allows simultaneous calls, patient identity validation, convenient time-of-day calling and the ability for patients to repeat or save messages for a later date. IVRS was used in this study to assess medication adherence, alert patients about laboratory appointments or prescription updates, and provide encouragement.

2.2.2. Gout Care Algorithm and IVRS Messages—The primary goals of the gout care algorithm were to: 1) promote patient engagement in gout self-management especially through medication adherence and 2) overcome clinical inertia related to allopurinol dose titration and sUA measurement. We included IVRS messages in the algorithm to efficiently accomplish certain tasks while using live telephone calls by the pharmacist to provide more in-depth assistance or follow-up. Importantly, the algorithm was meant as a guide for the pharmacist leading the intervention; the pharmacist was allowed to deviate from the algorithm as circumstances dictated. A KPSC expert rheumatologist (GL) was available to the study pharmacists for ad hoc consultation throughout the trial.

IVRS messages used in the algorithm were divided into 5 categories: 1) participation reminder, 2) allopurinol adherence survey, 3) sUA lab order, 4) allopurinol prescription/dose

adjustment, and 5) sUA goal achievement (Appendix A). The participation reminder was designed to encourage return mailing of the baseline health survey. The allopurinol adherence message was designed to solicit self-reported adherence where a report of 5 daily doses taken in the past 7 days was considered adherent. The sUA lab order messages informed or reminded patients that they were due for a blood draw. The allopurinol prescription and dose adjustment messages informed patients of changes to their prescriptions as initiated by the study pharmacist. Finally, the sUA goal achievement message was designed to celebrate a “good outcome” and remind patients to continue allopurinol unless otherwise instructed. The number of IVRS calls made and successful contacts were tracked and documented by the study pharmacist and research associate.

The algorithm was tailored to accommodate the slightly differing risk profiles of patients with normal kidney function or CKD stage I/II (Figure 3a) and stage III/IV (Figure 3b). In particular, the initial suggested dose increment of 50 mg/d represented the likelihood for CKD stage III/IV patients to start with 50 mg/d of allopurinol and escalate more slowly in order to reduce risks related to allopurinol hypersensitivity.²¹ For the same reason, the algorithm suggests that all dose escalation for CKD III/IV patients be done according to sUA measurements whereas those with stage II or better kidney function could be dose escalated to 300 mg/d without sUA measurements. This allowed the study pharmacist to reduce patient burden related to blood draws recognizing that at least 50% of patients are likely to need at least 300 mg/d of allopurinol to achieve sUA < 6.0 mg/dl.²² Beyond these differences, the algorithm has a similar design for all levels of kidney function.

After receiving an incident allopurinol fill, the study packet and IVRS reminders, all patients in the intervention received an adherence assessment IVRS message. If classified as nonadherent (took allopurinol as indicated on < 5 day over the past week), the patient received a phone call with encouragement from the pharmacist followed by a repeat assessment. If the patient was adherent, they would receive an IVRS message notifying them that a blood draw was due. Following sUA measurement, patients with a sUA < 6.0 mg/dl would receive the sUA goal achieved IVRS message while patients ≥ 6.0 mg/dl would receive allopurinol dose escalation and the corresponding IVRS dose adjustment message. An adherence assessment IVRS message would follow 2-4 weeks later. The sequence of dose escalation, adherence assessment and blood draw IVRS messages would continue until the patient achieved a sUA < 6.0 mg/dl. While not implemented in this study, the algorithm can accommodate long-term follow-up every 6-12 months to ensure that patients remain adherent and have the allopurinol dose required to maintain sUA < 6.0 mg/dl (Figure 3, dashed lines and boxes).

2.2.3. Pilot Study and Feasibility Assessment—A pilot study was conducted from November 2013 to December 2013 at a single KPSC clinic site randomized to the intervention group. Table 2 summarizes feasibility assessments and refinements resulting from the pilot study. Patients enrolled in the pilot study were not included in the RAmP-UP Study. Over a 10-week period, 69 patients were enrolled in the pilot study, all satisfying the aforementioned eligibility criteria. The original study design used an opt-in strategy requiring that patients complete a mailed questionnaire to participate further. Based on a low response rate (<15%), the study was amended to an opt-out design with approval from the

Institutional Review Board. The new design allowed patients in either usual care or the intervention to opt-out of the study following receipt of the same opt-out letter. A workflow analysis conducted after the pilot study supported the feasibility of up to 15 patients being enrolled each week per study arm. Pilot study results confirmed the validity of the proposed eligibility criteria and led to minor refinements in the IVRS messages (Table 2).

2.2.4. Patient interactions—Initial allopurinol dosing was at the discretion of the primary gout provider. All patients meeting eligibility criteria and randomized into either study arm were mailed a study packet including an opt-out letter, baseline health survey and gout educational material. The opt-out letter notified patients of the quality improvement program, and asked them to return a pre-addressed, postage-paid notification if they wished to opt-out of participation. Patient opt-out was uncommon (6.5% from intervention sites and 4.1% from usual care sites). The baseline health survey recorded the presence and number of gout attacks in the past 3 months, patients' gout-specific health as measured on a 21-point visual analog scale and the 12-question Short Form Health Survey (SF-12). The same health survey was originally planned for follow-up mailing at the end of years 1 and 2, but was dropped from the study design due to low response rates for the baseline survey (approximately 20%). The gout educational material included in the mailing was produced by the Arthritis Foundation and covers a variety of topics including: gout as a chronic disease, typical treatment options used, and important lifestyle changes for self-management.²³ After the mailing, all patients were entered into the IVRS system to receive weekly IVRS reminders (maximum of 3) to return baseline questionnaires. The usual care patients received no further contact after these IVRS messages until the blood draw IVRS for the 1 year and 2 year outcomes. Intervention patients, by contrast, continued into the gout care algorithm with the adherence assessment IVRS message.

The study pharmacist intervened further when the IVRS proved insufficient at any task for intervention patients. There were three primary indications that IVRS was insufficient: 1) if the patient was unresponsive to IVRS calls or failed to show up for ordered labs or prescription fill pick-up; 2) a patient self-reported allopurinol nonadherence via IVRS; or 3) a patient called the pharmacist using a contact phone number provided in initial study communications. Direct telephone communications were categorized into four broad categories: 1) introduction of IVRS and its purpose with the intent to improve use among unresponsive or confused participants, 2) gout education, 3) adherence reassessment and encouragement, and 4) dose adjustments. For gout education, a guide to frequently asked questions (FAQ) was created (Appendix B). Adherence reassessment and encouragement was designed to determine the extent of nonadherence, identify reasons for nonadherence and provide encouragement for improved adherence as appropriate. Finally, dose adjustments were facilitated by the study pharmacist using live telephone calls if not accomplished by IVRS.

2.2.5. Provider Interactions—Two sets of broadcast emails were sent to providers: a pre-study email and an end-of-study email one year after the first patient was enrolled. Providers at usual care sites were informed that a federally-funded study to facilitate gout management was being initiated and their patients may receive questionnaires and a request to have blood

drawn for laboratory testing, but that their patients would continue under their care without any study intervention. By contrast, providers at intervention sites were informed that patients newly initiated on allopurinol would have a pharmacist assist in patients' care by monitoring sUA levels and escalating the allopurinol dose until a sUA < 6.0 mg/dL was met. The email stated that these actions were only intended to supplement care while other medications related to gout such as anti-inflammatory medications or colchicine would not be impacted by the study and may still be required. Study personnel were available for questions and providers were given the opportunity to opt their patients out of the study. Provider opt-out was uncommon with only one KPSC provider choosing not to have their patients participate in the study. Direct interactions between patients and the study pharmacist were documented in the electronic health record where they were accessible to all providers.

2.3. Study Outcomes

2.3.1. Primary Outcome Measures—The two primary outcomes for this study were allopurinol adherence during the first year of therapy and achievement of sUA goal at one year, defined as a sUA < 6.0 mg/dl at any time between 243 and 395 days after the patient's first allopurinol prescription. This period reflects the variability of follow-up times in practice and minimizes study burden for patients related to blood draw frequency. To encourage blood draws for the primary sUA outcome, each month patients who started allopurinol during the same month one year earlier were identified. If the patient had a sUA evaluated any time in the previous 3 months, they were not contacted. If no sUA was available, a single IVRS was initiated to inform the patient that a blood draw was due. Our 395 day maximum ensures that all patients had at least 30 days to complete the blood draw. If multiple sUA values were available during this period, we used the value nearest 365 days after the incident allopurinol date.

Allopurinol adherence was assessed using pharmacy refill data to generate the proportion of days covered (PDC). The PDC was defined as the number of days a patient has medicine available out of the total days of observation (days with medication available/days of observation), adjusting for early refills and truncating at the end of observation to avoid over counting days of supply. Consistent with recent gout literature, adherence to allopurinol was defined as a PDC ≥ 0.8.¹

2.3.2. Secondary Outcome Measures—Secondary outcomes included: 1) the proportion of patients with sUA < 6.0 mg/dl at 2 years to assess durability of the intervention; 2) the change in sUA from baseline to years 1 and 2; 3) the proportion of patients adherent to allopurinol during year 2; 4) total healthcare utilization; and 5) changes in renal function, measured using estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) equation.²⁴

2.3.3. Adverse Effects—Serious adverse events (SAEs) and other general adverse events (AEs) were captured by either self-report or through electronic health records review and classified in accordance with Good Clinical Practice (GCP) guidelines. SAEs and AEs captured in medical records will be ascertained and compiled retrospectively at the end of

years 1 and 2 of follow-up. SAEs include any event or illness leading to death or hospitalization during observation. SAEs of special interest captured and reviewed in the electronic health records as part of the patient's normal care include any hypersensitivity or cutaneous drug reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute renal failure, or major acute coronary event (MACE). Recognizing that acute gout flares are a common complication of ULT, gout flares occurring during the first year of observation will be considered as a potential SAE if leading to hospitalization and an AE if leading to an emergency room visit. Less severe AEs will include all other drug-related events captured using diagnostic outpatient claims data during observation.

2.4. Statistics

2.4.1. Randomization and Sample Size Considerations—Clinic site served as the first level of randomization. As noted, coverage at multiple clinics by primary care providers and pharmacists is uncommon at KPSC making clinics an ideal unit of randomization to limit cross contamination between intervention and usual care sites. However, more than one clinic or pharmacy could reside in the same or nearby building. To further minimize the risk of contamination, 24 close-proximity clinics were combined into 9 units for randomization, resulting in 101 unique locations. Demographic characteristics (age, gender and race/ethnicity) and size of clinic membership reviewed prior to randomization indicated that randomization by clinic would likely balance these important factors. Randomization of the 101 clinic locations to intervention or usual care then proceeded at an approximate 1:1 ratio. Randomization produced 51 intervention clinic locations and 50 usual care clinic locations.

Results from pilot testing suggested that the number of eligible patients could potentially outnumber the capacity of the single study pharmacist (either AK or KL) assisted by a research associate (JMC), estimated to be 15 intervention and 15 usual care patients each week. The study pharmacist had 10 hours each week dedicated to administering the study intervention. Therefore, a second level of randomization was used. Each week, central research office personnel generated two randomized lists (intervention and usual care) of eligible gout patients who received incident allopurinol during the prior 7 days. The study research associate (JMC), would then identify the top 15 patients on each list to be mailed the study packet.

Sample size estimates were based on an assumption that 30% of gout patients given allopurinol from usual care clinics would achieve a sUA below 6.0 mg/dL.¹ To be conservative, we assumed a worst-case scenario intra-class correlation coefficient of 0.1 by study site. Based on these assumptions, an alpha of 0.05 and 51 intervention sites, 11 patients per site (or 561 total patients from intervention sites) would provide 80% power to detect a 10% absolute improvement in sUA goal achievement (i.e. 40% success rate)²⁵. Finally, we estimated that after opt-out up to 20% of patients would drop-out or otherwise be nonresponsive to the study. We thus inflated the sample size estimate using a standard equation of the estimated sample size divided by 1 minus the estimated drop out proportion. Our target enrollment using this equation was over 702 per study arm.

2.4.2. Analytic Plan—Here we present the planned analyses. We will initially examine the distribution of patient characteristics overall and according to randomization arm. Generalized estimating equations (GEE) will be used to analyze both primary outcomes, accounting for correlation among patients nested within a given clinic location. Dichotomous outcomes (one year sUA < 6.0 mg/dl and PDC ≥ 0.8) will be regressed on the intervention assignment using a logit link and accounting for random clinic location effects. Intent-to-treat analyses according to intervention status at randomization will be used for the primary analyses. The proportion of randomized patients completing sUA follow-up by group will be noted. Multiple imputation techniques will be used for any missing sUA.²⁶ A completer analysis of sUA goal attainment for only those with the primary sUA outcomes recorded will be conducted as a secondary analysis. The same approach will be used for medication adherence. If patients drop out of the study (e.g. due to death or lapse in medication eligibility) before the end of year one, medication adherence values will be set to missing and multiple imputation methods will be used. A completer analysis of medication adherence will be used as in secondary analysis. Analysis of secondary outcomes including sUA < 6.0 mg/dl at 2 years and PDC ≥ 0.8 during year 2 will be conducted using the same approach. Mixed effects linear regression will be used to analyze sUA change and change in renal function from baseline at years 1 and 2 with intervention assignment as a fixed effect and clinic as a random effect.

3. Discussion

Inadequate dose escalation and low adherence to ULT among gout patients are significant barriers to achievable outcomes in gout. To our knowledge, the RAMP-UP study is the first to rigorously test a pharmacist-led intervention as a means of improving quality of care and outcomes for a large population of gout sufferers. The RAMP-UP study tests a semi-automated, pharmacist-led intervention to optimize allopurinol adherence and dosing strategies following treatment initiation. By using a relatively low-cost, scalable approach to provide care for nearly all gout patients initiating allopurinol across a health system or health plan, the intervention is designed to be highly generalizable. If successful, we expect this innovation to improve care for the growing population of gout patients at health systems with onsite ambulatory care pharmacists and access to automated calling systems.

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Competing Interests: The RAMP-UP trial was supported by a program project grant from the National Institutes of Health (NIH) / National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), 1P50AR060772, titled “Gout and hyperuricemia: from bench to bedside to backyard” (Co-PIs KGS and SLB; Project PIs TRM, JRC). The trial was designed and has been conducted collaboratively by an interdisciplinary team of clinical-translational research scientists from the Division of Clinical Immunology and Rheumatology at the University of Alabama at Birmingham (Birmingham, AL), the Division of Rheumatology at the University of Nebraska Medical Center (Omaha, NE), Drug Information Services at Kaiser Permanente Southern California (Downey, CA), and the Department of Research and Evaluation at Kaiser Permanente Southern California (Pasadena, CA).

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Appendix A: Gout Treatment: Frequently Asked Questions AmP-UP Trial

Why Allopurinol is Used

- Used to treat gout and sometimes to treat certain kinds of kidney stones
- Lowers uric acid production in the body; uric acid is the substance that causes gout
- Used to prevent gout but NOT to treat acute gout attacks once they occur
- Generally does not cause any symptoms (good or bad) – so no one feels better on it, but that doesn't mean that it's not working
- Should continue to be taken even if people are feeling well, and even if their uric acid level is at goal to maintain that goal

Acute Gout Flares Related to Allopurinol Use

- A relatively common consequence of lowering uric acid levels – often takes months to achieve the full benefit of allopurinol use
- Usually not a reason to hold or stop allopurinol
- Gout flares that occur during allopurinol treatment may need to be treated with antiinflammatory medications (NSAIDs, steroids, or colchicine)
- Gout flares related to allopurinol use can be prevented with the use of preventive antiinflammatory drugs, often used in low dose (daily NSAIDs or colchicine are most commonly used for this purpose)
- Starting lower doses of allopurinol such as 100 mg per day or less is another strategy to reduce gout flares that may occur more commonly with higher starting doses

Role of Diet in Gout Management

- General importance of weight management and healthy diet for many health conditions (e.g. hypertension, heart disease, diabetes, others)
- Diet typically has modest uric acid lowering effect – usually not an adequate substitute for allopurinol or other uric acid lowering drugs because dietary changes alone won't decrease uric acid levels enough for most people. The average reduction in serum urate levels as a consequence of dietary change is a decrease of usually less than 1 unit (mg/dl).
- Foods that may lower uric acid levels and help in gout management:
 - Low fat dairy products (e.g. skim milk, low fat yogurt)
 - Citrus fruits high in vitamin C (e.g. oranges)

- Cherries also appear to lower uric acid and may also have some antiinflammatory effects – although the role of cherry extracts in gout treatment are still being studied
- Foods that may raise uric acid levels and worsen gout:
 - Red meats and seafood, especially organ meats (eg. Liver) and shellfish
 - Foods or beverages high in fructose (e.g. soft drinks)
 - Alcoholic beverages, especially beer

Rash Related to Allopurinol Use

- May require stopping allopurinol and seeing a provider, especially if accompanied by other symptoms such as fever or mouth sores

Forgetting a Dose of Allopurinol

- Take the dose as soon as you remember it, but if it is almost time for the next dose, skip the missed dose and continue with regular schedule
- Do NOT take a double dose to make up for a missed one

Side Effects That Might Occur with Allopurinol

- Skin rash (as above)
- Upset stomach and diarrhea
- Drowsiness
- Swelling of the lips or mouth
- Fever, sore throat, or signs of infection
- Loss of appetite and weight loss
- Itching

Instructions for Taking Allopurinol

- Follow the instructions given by your physician
- Take with a glass of water
- Typically no need to split the doses; all of the dose can be taken at one time; your physician may instruct you though to take this twice daily
- Same time of day; often best if taken after a meal
- Usually started in low doses and then gradually increased
- Obtaining the full benefit of allopurinol in gout treatment often takes several months

- Should not stop allopurinol without discussing this with your physician
- Important to keep appointments with your doctor prescribing the medicine, including scheduled lab tests necessary to monitor the drug
- Stopping allopurinol (e.g. voluntarily or not, like peri-operatively) can precipitate a gout flare, so do this only if directed to by a healthcare provider

Precautions

- Allergies to allopurinol with prior use
- Should not be used in pregnancy
- Possible drug interactions
 - Amoxicillin or Ampicillin
 - Warfarin (Coumadin) – may require close monitoring of INR
 - Azathioprine (Imuran) or 6-MP also called mercaptopurine
 - Chlorpropamide (sometimes used to treat diabetes)
 - Theophylline or Aminophylline (sometimes used to treat asthma)

Appendix B: Interactive Voice Response System Messages RAMP-UP Trial

1. Participation reminder

“Hi, this is Kaiser Permanente calling Mr/Ms _____ on behalf of the Gout Improvement Program. Our records indicate that you may qualify to participate in this program. We recently sent you a letter about this program with a survey. If you would like to participate, please return the survey at your earliest convenience.

Thank you.”

2. Allopurinol adherence survey

“Hi, this is Kaiser Permanente calling on behalf of the Gout Improvement Program. Our records show that you are due to have gout related lab tests done, but before we do that, we'd like to know if you are taking your allopurinol.

Question: Using the touch pad on your phone, press how many days in the last week you have taken your allopurinol for gout.

Once in the past week	Press '1'
Two times in the past week	Press '2'
Three times in the past week	Press '3'

Four times in the past week	Press '4'
Five times in the past week	Press '5'
Six times in the past week	Press '6'
Everyday	Press '7'
Not Sure	Press '8'

Thank you for your response and your participation in this program.”

3a. sUA lab ordered

“Hi, this is Kaiser Permanente on behalf of the Gout Improvement Program. Regardless of whether you have had recent lab tests done, a uric acid lab test has been scheduled for you. Please go to the lab department, and complete your lab test.

Thank you.”

3b. sUA lab and others ordered

“Hi, this is Kaiser Permanente on behalf of the Gout Improvement Program. Regardless of whether you have had recent lab tests done, a uric acid and other necessary lab tests have been scheduled for you. Please go to the lab department, and complete your lab tests.

Thank you.”

4a. Prescription waiting for pick up

“Hi, this is Kaiser Permanente on behalf of the Gout Improvement Program. Your Allopurinol prescription is awaiting your pick up at your pharmacy. Please pick up at your earliest convenience.

Thank you.”

4b. Prescription with new tablet strength waiting for pick-up

“Hi, this is Kaiser Permanente on behalf of the Gout Improvement Program. Your Allopurinol prescription is awaiting your pick up at your pharmacy. Note that the strength has changed to 300 mg tablets rather than the previous 100 mg tablets you have been receiving. Please pick up this prescription at your earliest convenience.

Thank you.”

4c. Dose adjustment 50 to 100mg

“Hi, this is Kaiser Permanente on behalf of the Gout Improvement Program. Based on your uric acid laboratory test the amount of Allopurinol you are taking needs to be increased from 50 mg (½ tablet daily) to 100 mg (1 tablet daily). Please start this new dosage at your earliest convenience.

Thank you.”

4d. Dose adjustment 100 to 200 mg

“Hi, this is Kaiser Permanente on behalf of the Gout Improvement Program. Based on your uric acid laboratory test the amount of Allopurinol you are taking needs to be increased from 100 mg (1 tablet daily) to 200 mg (2 tablets daily). Please start this new dosage at your earliest convenience.

Thank you.”

4e. Dose adjustment 200 to 300 mg

“Hi, this is Kaiser Permanente on behalf of the Gout Improvement Program. Based on your uric acid laboratory test the amount of Allopurinol you are taking needs to be increased from 200mg (2 tablet daily) to 300mg (3 tablets daily). Please start this new dosage at your earliest convenience.

Thank you.”

4f. Dose adjustment 300 to 400 mg

“Hi, this is Kaiser Permanente on behalf of the Gout Improvement Program. Based on your uric acid laboratory test the amount of Allopurinol you are taking needs to be increased from 300mg (3 tablet daily) to 400mg (4 tablets daily) Please start this new dosage at your earliest convenience.

Thank you.”

4g. Dose adjustment 300 to 450 mg (100 mg tablets previously)

“Hi, this is Kaiser Permanente on behalf of the Gout Improvement Program. Based on your uric acid laboratory test the amount of Allopurinol you are taking needs to be increased from 300mg (3 separate 100 tablets daily) to 450mg (1 ½ 300 mg tablets daily). Please note that the dose strength of each pill will change with this new prescription. You can continue at your current dose until you pick up this new prescription.

Thank you.”

4h. Dose adjustment 300 to 450 mg (300 mg tablets previously)

“Hi, this is Kaiser Permanente on behalf of the Gout Improvement Program. Based on your uric acid laboratory test the amount of Allopurinol you are taking needs to be increased from 300mg (1 tablet daily) to 450mg (1 ½ tablets daily). Please start this new dosage at your earliest convenience.

Thank you.”

4i. Dose adjustment 450 to 600 mg

“Hi, this is Kaiser Permanente on behalf of the Gout Improvement Program. Based on your uric acid laboratory test the amount of Allopurinol you are taking needs to be increased from 450mg (1 ½ tablets daily) to 600mg (2 tablets daily). Please start this new dosage at your earliest convenience.

Thank you.”

4j. Dose adjustment 600 to 750 mg

“Hi, this is Kaiser Permanente on behalf of the Gout Improvement Program. Based on your uric acid laboratory test the amount of Allopurinol you are taking needs to be increased from 600mg (2 tablets daily) to 750mg (2 ½ tablets daily). Please start this new dosage at your earliest convenience.

Thank you.”

5. Achieved serum urate goal

“Hi, this is Kaiser Permanente on behalf of the Gout Improvement Program. Congratulations, you are at goal for your blood uric acid test. Please continue to use your allopurinol as directed unless otherwise instructed by your healthcare provider. Keep up the good work on managing your gout and THRIVE!

Thank you.”

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Abbreviations

ACR	American College of Rheumatology
CKD	Chronic kidney disease

CONSORT	Consolidated Standards of Reporting Trials
ICD-9	International Classification of Diseases - Version 9
IVRS	Interactive voice response system
KPSC	Kaiser Permanente Southern California
PDC	Proportion of days covered
RAmP-UP	Randomized Trial of an Ambulatory Care Pharmacist-Led Intervention to Optimize Urate Lowering Pathways
RAND/UCLA	RAND Corporation/University of California Los Angeles
sUA	Serum urate
ULT	Urate lowering therapy

Figure 1. Parallel Group Design for Intervention and Usual Care Patients

The RAmP-UP Study is an ongoing two-year cluster-randomized, parallel group, usual care-controlled trial evaluating the impact of a novel pharmacist-led, protocol-driven intervention focused on facilitating sUA goal attainment among gout patients initiating allopurinol in the Kaiser Permanente Southern California health system; sUA = serum urate; IVRS = interactive voice response system.

Figure 2. Study Timeline

A study timeline for the RAMP-UP Study is shown, illustrating the timing of trial planning, algorithm development, pilot testing, meetings with stakeholders, patient enrollment, data collection, and outcome assessments.

(a) Normal or CKD Stage 1 or 2**† Suggested Dose Increments**

Current Dose	Increment
< 300 mg/d	100 mg/d
≥ 300 mg/d	150 mg/d
Max dose = 800 mg/d

(b) CKD Stage 3 or 4**† Suggested Dose Increments**

Current Dose	Increment
50 mg/d	50 mg/d
100 or 200 mg/d	100 mg/d
≥ 300 mg/d	150 mg/d
Max dose = 800 mg/d

Figure 3. Gout Care Algorithm for Patients in Intervention Arm

, A supplemental care algorithm was developed through an iterative process that included a systematic review, expert consensus panel, input from study investigators and assessment of safety and logistical limitations; supplemental care algorithm was tailored separately for: (a) patients normal renal function or chronic kidney disease (CKD) I/II and (b) patients with CKD III/IV; sUA = serum urate; IVRS = interactive voice response system.

Table 1
Study Components Assessed by Expert Consensus Panel

Component	No. of Questions	Summary Recommendation (Median score) and Comments	Final Decision Made by Study Coordinating Committee*
Exclusion of patients with CKD V	1	Appropriate (8.5); limited evidence to guide dosing	Patients with CKD V were excluded.
Requirement of serum Cr and CBC before titrating allopurinol or within the 6 months preceding the first allopurinol prescription	1	Appropriate (7.5); some concern about how long ago allopurinol initiation might be; Cr may need to be more recent	Because anti-inflammatory prophylaxis was not included in the study, no CBC was required; serum Cr was not required either, but ordered with earliest sUA.
Mailing gout educational material to the intervention group	1	Appropriate (7.5); tailored information ideal; should contain information about what patients should do in case of an attack after treatment initiation	Educational materials produced by Arthritis Foundation were sent to all patients. ²³
Initial dose increases to 300 mg/d if adherent, sUA > 6.0 mg/dl and [normal kidney function or CKD I/II] before checking sUA again	2	Increasing doses to 300 mg/d was considered appropriate for patients with normal kidney function (8.0) or CKD I/II (8.0) even without follow up sUA	Doses were allowed to be increased to 300 mg/d without follow-up sUA for those with preserved kidney function
Initial dose increase to 300 mg/d if adherent, sUA > 5.0 mg/dl and [normal kidney function or CKD I/II] before checking sUA again	2	Inappropriate (3.0 and 3.0); a 5.0 mg/dl target may be useful in some cases, not essential to majority of patients	Achieving sUA of < 5.0 mg/dl was not included as study outcome
For all patients, dose increments of 50 mg/d for those starting on < 100 mg/d and increments of 100 mg/d for all others [GFR < 60 ml/min or GFR < 90 ml/min]	2	These dose increments were considered appropriate for patients at both levels of kidney function (7.0 and 7.5)	Dose increments of 50 mg/d were used in the algorithm for CKD III/IV patients when starting at 50 mg/d moving to 100 mg/d increments when taking anything else < 300 mg/d; dose increments of 100 mg/d were suggested for normal or CKD I/II when beginning at < 300 mg/d.
Allow [50-100 mg/d or 150 mg/d] dose increments for all patients	2	While 50-100 mg/d dose increases were considered appropriate (8.0), 150 mg/d increases were also considered appropriate for patients requiring higher doses (7.0)	The treatment algorithm used 150 mg/d increments for those increasing above 300 mg/d (could be administered as half of a 300 mg pill)
Max dose of [800 or 900 mg/d]	2	Escalation above 800 mg/d was less appropriate for the intervention (3.5 and 4.0)	Dose of 750 mg/d used in the algorithm (2.5 tabs of 300 mg allopurinol); Maximum dose of 800 mg/d was allowed if directed by the pharmacist; the study did not provide the option of 900 mg/d
Requiring assessment of allopurinol adherence before measuring sUA	1	Appropriate (8.5) because adherence is a known issue for long-term gout therapies	Allopurinol adherence assessed by IVRS using self-report of days adherent during the past 7 days
Providing Naproxen 250 mg/d twice daily and/or colchicine if no contraindications (kidney function, contraindicated concomitant medications, peptic ulcer history, anemia)	4	Prophylactic naproxen 250 mg twice daily was considered less appropriate for patients with a GFR of < 90 ml/min (6.0) or < 60 ml/min (6.0); colchicine was considered appropriate (8.5); dual therapy was considered inappropriate (2.5)	No anti-inflammatory prophylaxis was provided in study; anti-inflammatory prophylaxis was deferred to primary provider.
Automatic discontinuation of anti-inflammatory therapy based on timing (6 or 12 months) or sUA goal attainment	3	Discontinuation of anti-inflammatory prophylaxis at 6 or 12 months was considered less appropriate (3.5 and 4.0); discontinuation at time of sUA goal attainment was only marginally better (6.5)	No anti-inflammatory prophylaxis was provided in study; anti-inflammatory prophylaxis was deferred to primary provider.
Referral to rheumatology directly or requesting the primary provider to make referral for adherent patients intolerant to allopurinol or failing to achieve sUA goal.	2	Direct rheumatology referral as part of intervention was considered appropriate (8.0); considered less appropriate was to require action by the primary provider (5.5)	Direct referrals were allowed on a case-by-case basis as initiated by the study pharmacist.

* Final decisions reflect considerations of both evidence and study-specific concerns. Those wishing to use the algorithm may consider these topics in the context of their own practice.

CBC = complete blood count; CKD = chronic kidney disease, Cr = serum creatinine; GFR = glomerular filtration rate; IVRS = interactive voice response system; sUA = serum urate

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Table 2
Pilot Study Results and Study Design Refinements

Issue	Pilot Study Results	Study Design Refinements
Assess Opt-in Strategy	Response rates between 7% and 10% even after reminder calls; threat to study power	Use an opt-out strategy.
Feasibility of pharmacist follow-up calls (time requirements)	Estimated that a single study pharmacist with 10 hours/week dedicated to the study could assist up 15 new patients per week per study arm while maintaining needed follow-up	A second-level of randomization was added. The choice to use randomization reduced the potential for introducing selection bias.
Validity of inclusion criteria	Of 69 patients, only 3 (4%) were unlikely to have gout including one with knee pain following trauma.	Deemed to be an acceptable level of misclassification.
IVRS messages	One patient was started on 150 mg/d and no IVRS was developed for that starting dose.	A new IVRS message was developed for patients started on 150 mg/d.

A 10-week, 69-patient pilot study provided insights into study design decisions.