Randomized evaluation of an Ambulatory Care Pharmacist-Led Intervention to Optimize Urate Lowering Pathways (RAmP-UP) Study

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1 Contents

2 Summary

Title: Randomized evaluation of an Ambulatory Care Pharmacist-Led Intervention to Optimize Urate Lowering Pathways (RAmP-UP) Study
Study Site(s): Kaiser Permanente Southern California Medical Centers (14 medical centers; 116 ambulatory offices)
Approximate number of participants: 1400
Investigators: Jeff Curtis, MD, MPH (University of Alabama at Birmingham, UAB); David Redden, PhD (UAB),Kenneth G. Saag MD, MSc (UAB); Brian Coburn, MD, PhD (University of Nebraska Medical Center, UNMC); Ted Mikuls, MD (UNMC) Craig Cheetham, PharmD (KPSC); Naz Rashid, PharmD (KPSC); Gerald Levy, MD (KPSC)
Methodology: Open-label two-year cluster-randomized, parallel group, protocol-driven large pragmatic multicenter usual care-controlled trial designed to assess a highly automated, scalable, pharmacist-led intervention to optimize allopurinol treatment in gout.

3 Background

Gout is the most common form of inflammatory arthritis, affecting up to 8 million individuals in the US [1]. Characterized by painful episodes of arthritis, gout results in substantial morbidity, physical disability, and reduced survival [2-5]. Contrary to other forms of arthritis, gout pathogenesis is well understood, with signs and symptoms resulting from inflammatory responses triggered by monosodium urate crystal deposition in joints or surrounding soft tissues. Under normal physiologic conditions, this occurs when serum urate (SU) concentrations exceed 6.8 mg/dl [6].

Recognizing the role of hyperuricemia as the primary pathophysiologic culprit urate-lowering therapy (ULT) represents a cornerstone in gout management [6]. Allopurinol the most frequently prescribed first-line ULT is both efficacious and well tolerated in most patients. Despite this, allopurinol use is frequently accompanied by suboptimal patient outcomes that stem, in part, from inadequate prescribing practices and poor adherence [7-13]. For gout patients initiating allopurinol, management guidelines endorse gradual dose escalation to achieve a target SU goal [14,15]. These recommendations are based on evidence that achieving and maintaining SU concentrations below 6.0 mg/dl greatly reduces the long-term risk of gout flares [14,16]. Contrary to best practices promoted by these guidelines, the vast majority of patients initiating allopurinol in “real world” healthcare settings fail to undergo requisite SU assessment following initiation and only a small minority ever receive dose increases [10,17,18]. In previous reports, only one in three gout patients initiating allopurinol ever received a dose increase and only a small fraction of these (~10%) ever received a daily dose exceeding 300 mg, dosing typically required to achieve desired SU concentrations and control of gout symptoms [10,19].

To address and potentially overcome barriers in achieving outcomes with allopurinol treatment, we completed the Randomized Evaluation of an Ambulatory Care Pharmacist-Led Intervention to Optimize Urate Lowering Pathways (RAmP-UP) study. RAmP-UP is a large pragmatic site-randomized trial designed to assess a highly automated, scalable, pharmacist-led intervention to optimize allopurinol treatment in gout.

4 Rationale for the Study

This project fits the UAB CORT in Gout and Hyperuricemia theme of “from bench to bedside, bedside into the community, and back again,” by proposing a novel Type 2 translational research project that addresses a currently unanswered question in gout, namely, how to effectively implement evidence into clinical populations.

4.1 Burden of Gout

Gout is a chronic and progressive form of arthritis occurring as a result of monosodium urate deposition in the joints and surrounding tissues. Chronic hyperuricemia is a necessary, although not sufficient, precursor of gout. It is estimated that gouty arthritis affects > 8 million people in the US alone,[20] now recognized as the most common form of inflammatory arthritis. Accompanying increased rates of disease risk factors including hypertension, renal insufficiency, and increased use of predisposing medications, gout incidence has risen two-fold in recent decades.[21,22] Approximately two-thirds of gout patients will experience progressive disease and declines in physical function over time if left untreated.[23,24] Recent studies show that gout is associated with work absenteeism and losses in work productivity.[4] With an aging population, the burden posed by gout

will only continue to grow. Despite its extremely well known pathogenesis and the availability of highly efficacious therapies, gout continues to lead to considerable morbidity and mortality due to poor management and limited therapeutic adherence. Our translational research study will address this deficit in evidence implementation.

4.2 Urate Lowering Therapy (ULT) as the Cornerstone of Treating Chronic Gout

The treatment of chronic gout is based primarily on the use of ULT to reduce the frequency of, and eventually eliminate, acute flares in addition to reducing the risk of progressive joint destruction.[23] There are currently four ULT agents approved for the treatment of gout in the US including probenecid (a uricosuric), pegloticase (a biologic therapy approved for treatment-refractory gout), allopurinol, and febuxostat. Allopurinol and febuxostat work through the inhibition of xanthine oxidase, the rate limiting enzyme in endogenous urate production. A well-accepted goal of ULT administration in gout is to lower and maintain serum urate concentrations below 6.0 mg/dl, a concentration at which urate is more soluble and far less likely to form monosodium urate crystals that serve as a nidus for gouty inflammation. Achieving a serum urate of < 6.0 mg/dl with ULT leads to several clinical benefits in gout including decreased flare rates and dissolution of tophi.[25-27] The target serum urate threshold of < 6.0 mg/dl has been adopted as a primary outcome in recent randomized controlled trials comparing febuxostat with allopurinol[25,27,28] and has been endorsed as a goal of ULT administration in recently published international gout treatment guidelines.[29]

4.3 Allopurinol: the Most Commonly Administered ULT in Gout

Available for more than 40 years, allopurinol remains the most frequently prescribed ULT, accounting for ~99% of all ULT prescriptions (Section C.1.1)). In contrast to probenecid, allopurinol can be dosed once daily (vs. twice to three times daily for probenecid), is effective in patients who overproduce and in patients who under-excrete uric acid (whereas probenecid is effective only in under-excretors), and may be effective in the context of significant renal insufficiency (whereas probenecid is not).[30-32] Febuxostat, a novel non-purine inhibitor of xanthine oxidase, also appears to have potent urate lowering effects at approved doses and may represent an important alternative in patients intolerant to allopurinol.[25,27,28] While adverse events occur with allopurinol administration, these events appear to be uncommon with less than 5% of patients intolerant to the drug.[33] At present, febuxostat prescriptions represent only a small proportion of total ULT prescriptions in gout. With daily drug costs 20- to 40-fold higher than allopurinol (www.drugstore.com, accessed June 16, 2011), the precise role that febuxostat will play in cost-effective gout management remains unknown.

4.4 Gout Outcomes with Allopurinol Use

Many early studies confirmed the robust urate lowering effect of allopurinol, a treatment also yielding ample improvements in long-term outcomes including a reduction in gouty flares.[25-28,31,34-37] A recent 28-week randomized trial examining fixed dose daily allopurinol revealed a 34% reduction in serum urate concentrations vs. a decrease of 3-4% for those receiving placebo.[25,27,28] In a separate study, allopurinol in a fixed daily dose of 300mg was associated with a significant 50% reduction in tophus area.[25] Recent trials of allopurinol with more limited study durations (range of 4 to 12 months) have shown no significant declines in flare rates compared to the pre-trial period,[25,27] a beneficial effect that appears to require up to 2 years of effective ULT.[25] To date, published studies examining the long-term impact of ULT on health-related quality of life, physical functioning, pain, and other patient reported outcomes are scarce, a knowledge deficit that will be addressed in Aim 1 of the current proposal. In addition to decreasing uric acid concentration, reducing tophus size and deposition, and reducing or eliminating acute flares, allopurinol use may be associated with other health benefits. Hyperuricemia is independently associated with cardiovascular morbidity and mortality.[38-41] In a placebo-controlled study of pediatric essential hypertension *led by our collaborator (Daniel Feig, MD, PhD,)*, allopurinol use resulted in significant, albeit modest, declines in blood pressure.[42] Xanthine oxidase inhibition via allopurinol has been shown to improve endothelial function, improving measures of both local and systemic blood flow[43] and been associated with improvements in renal function, [44,45] physiological effects that will be the focus of Project 2 of this CORT application. In a retrospective study of over 9,000 US veterans with hyperuricemia, allopurinol administration was associated with a significant 22% reduction in all-cause mortality, that the authors speculated relates to protective cardiovascular effects.[46]

4.5 Barriers to Optimal Allopurinol Use

Although approved at daily doses as high as 800 mg, allopurinol is rarely given at daily doses exceeding 300 mg. In one study, 97% of gout patients treated with allopurinol received doses of 300 mg/d or less (Figure 1).[47] It is well established that only a minority of patients achieve a target serum urate < 6.0 mg/dl with 'standard' dose allopurinol. Using a target serum urate threshold of < 5.0 mg/dl, investigators have shown that one-fourth of gout patients achieve this goal with 300 mg of daily allopurinol, a proportion that increases to 78% with a daily dose of 600 mg [48]. The limitation of 'standard' dose allopurinol has been borne out in recent clinical trials that have compared fixed daily doses of 300 mg to febuxostat. In those studies, ~40% of allopurinol treated gout patients achieved a final study urate level of < 6.0 mg/dl.[25,27] Factors contributing to suboptimal allopurinol administration likely include, but are not limited to: 1) failure of prescribers to appropriately titrate allopurinol dose to achieve optimal serum urate target levels; 2) poor long term patient adherence to therapy; 3) drug intolerance, recognizing that this affects only a small proportion of patients;[33] 4) limited data regarding the effectiveness of doses exceeding 300 mg/day; and 5) concerns regarding increased toxicity with higher doses, particularly in the context of chronic kidney disease (CKD). It is important to note that despite common misconceptions, allopurinol administration has never been associated with deterioration in renal function in patients with renal impairment. Indeed, at least one small study has shown that allopurinol use may actually retard the progression of CKD.[45] In addition to unfounded concerns over potential deleterious effects on kidney function, results from a single case series of 78 patients suggested that 'higher dose' allopurinol may increase the risk of allopurinol hypersensitivity syndrome (AHS), an uncommon (0.1% to 0.4%) but serious drug related adverse event that appeared to be heightened in the context of CKD. These results led directly to the generation and promulgation of non-evidence based dosing guidelines that were founded on the relationship of renal function with observed oxypurinol concentrations (an allopurinol metabolite).[49] It is important to note that the 'effectiveness' of these guidelines in preventing AHS has not been demonstrated.[50] Indeed, many patients with CKD have developed AHS even with 'appropriately' dosed allopurinol.[51,52] In their review of 120 gout patients receiving allopurinol, more than half (57%) required daily doses above the 'renal threshold' recommended by Hande to achieve target urate goals. In this study, only 1 patient developed AHS, a patient with normal renal function receiving 300 mg per day.[53] In a recent study of 90 gout patients, Stamp and colleagues found that increasing the dose of allopurinol above the thresholds proposed by Hande led to significant reductions in serum urate without increased toxicity.[54] Independent guidelines from both the European League Against Rheumatism (EULAR) and the British Society for Rheumatology have recommended that allopurinol dosing should be gradually increased to doses as high as 800 to 900 mg/day with a goal of achieving and maintaining serum urate concentrations below either 6.0 mg/dl or 5.0 mg/dl, respectively, recognizing the need for initial dose adjustments in the context of renal insufficiency.[29,55] Current practice that adheres strictly to the Hande dosing guidelines[49] contrasts starkly with expert recommendations of judicious dose escalation accompanied by appropriate surveillance to achieve a target serum urate goal of < 6.0 mg/dl.[50]

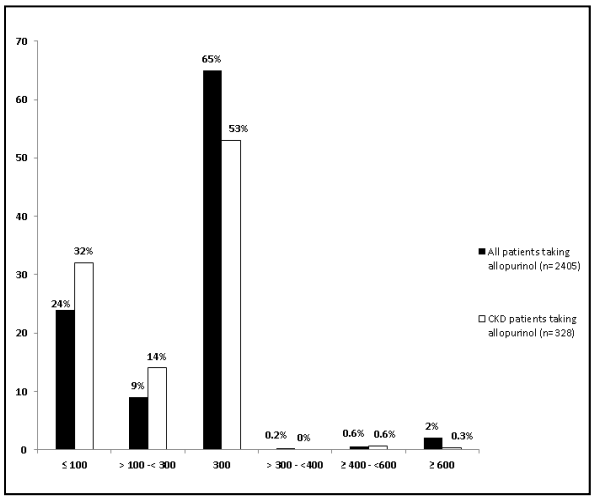


Figure 1: Daily allopurinol dose use among patients with gout prescribed allopurinol; 97% with daily doses of ≤ 300 mg (Sarawate CA et al. Mayo Clin Proc 2006)

Without implementation of evidence into practice, the public health benefits of basic and clinical research cannot be realized. Yet, evidence has been notoriously difficult to implement across virtually all medical conditions, including gout. Discovering novel methods to implement evidence and conducting scientifically rigorous trials to test these methods has become an important area of research featured in this proposal. The Institute of Medicine (IOM) defines Type 2 (T2) translational (evidence implementation) research as research moving discovery from the bedside to community practice.[56] In gout, perhaps more than other musculoskeletal conditions, disease pathogenesis (including the central role of hyperuricemia) is well understood and highly effective therapies exist. The IOM has defined deficiencies in medical care as the "quality chasm",[57] and we have highlighted that a gout quality chasm also exists.[47,58-60] The existence of this quality chasm in gout

management underscores the urgent need for quality T2 translational research in gout. The proposed study represents the largest systematic T2 translational research study to date ever conducted in gout patients, examining the use of a highly novel intervention with the goal of improving not only processes of care but also patient outcomes. The implementation of evidence through transportable and innovative data-collection and chronic disease-management technologies holds the promise of improving care for a larger number of gout patients than is either practical or feasible with more 'traditional' approaches.

5 Research Strategy

5.1 Study Design

RAmP-UP is a 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(Fig. 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 b6.0mg/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. Fig. 2 provides an overview of the study timeline 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 will continue throughout the study.

5.2 Study Setting

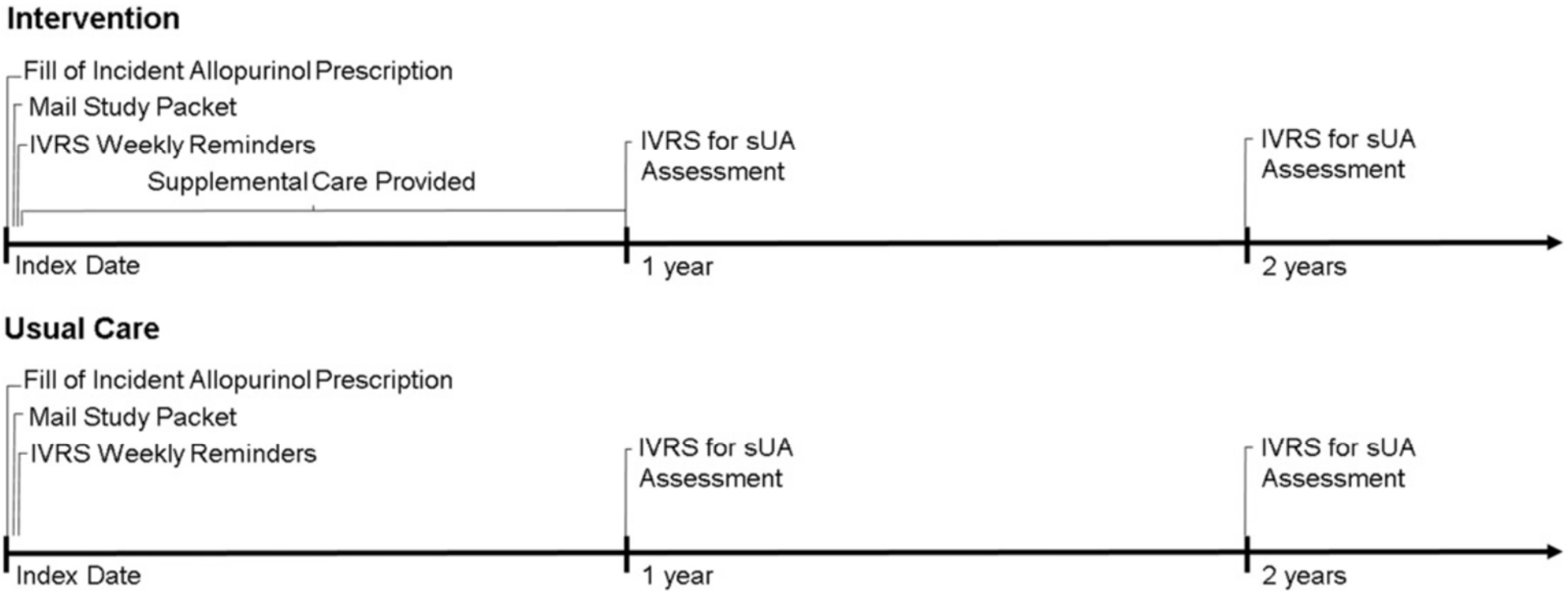
Kaiser Permanente Southern California (KPSC), the setting for this study, is an integrated healthcare delivery system with over 4 million members. The system is comprised of 14 major medical centers that include over 200medical offices. Of these offices, we identified 116 ambulatory clinics that prescribed 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.[61]. Based on a preliminary study in this population, we estimate that 78% of study patients will be men and participants will have a mean ± SD age of 60 ± 14 years nd BMI of 31.5 ± 6.6 kg/m$_2$.[62] 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. [61] 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. [62] Membership in KPSC can be obtained through individual or family plans, Medicaid/Medi-Cal, Medicare or employers.[61]

6 Outcomes

6.1 Primary Outcome

Co-primary outcomes are allopurinol adherence during the first year of treatment and achievement of a target SU (<6.0 mg/dl) at one year. Adherence will be assessed using pharmacy dispensing data to calculate the proportion of days covered (PDC) with adherence defined as a PDC ≥0.8. The PDC has been endorsed as the preferred method for assessing medication adherence using pharmacy claims data. When multiple sUA values are available, we will use the value that is at least 7 days post-index and that is most proximate to one-year of follow-up. The proportion achieving sUA <6.0 mg/dl at one year will be examined in an additional subgroup analysis limited to adherent patients (PDC ≥0.8). The effect of treatment assignment on primary outcomes will be evaluated in a separate subgroup analysis of "completers", defined as intervention patients responding to at least one IVR-administered survey.

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.



6.2 Secondary Outcomes

- sUA goal achievement at year two
- Allopurinol adherence during the second year of treatment
- Absolute change in sUA over follow-up and the difference in PDC at one year
- Gout flares during the second year of observation
- Adverse events (Adverse events will be reported as safety outcomes)

Adverse events will be captured through electronic health record review and compiled retrospectively at year 2 with a special emphasis on diagnostic codes corresponding to severe cutaneous reactions (e.g. drug reaction with eosinophilia and systemic symptoms [DRESS], erythema multiform, Stevens-Johnson syndrome, or toxic epidermal necrolysis [TEN]).

7 Patient Population

7.1 Inclusion Criteria

- English-speaking patients
- ≥18 years of age or older
- Minimum of one International Classification of Disease, 9th edition (ICD9) diagnosis code of gout (274.xx) and receiving an incident prescription for allopurinol*

7.2 Exclusion Criteria

- In the absence of consensus surrounding optimal gout management, patients with advanced chronic kidney disease (CKD state V) were excluded.
- Pre-intervention provider and/or patient opt-out

*Incident prescription was defined by at least 12 months of previous membership in the absence of such a prescription.

8 Informed Consent (IC) Procedures

The study has been approved by the University of Alabama at Birmingham Institutional Review Board and will be 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 for the opt-out study design.

9 Study Procedures, Intervention, and Assessments

All study visits and procedures will be performed in facilities in the Kaiser Permanente Southern California Network.

Following initial allopurinol receipt (index date), prescribed and dosed at the discretion of the primary provider, pharmacist management will be provided to patients from intervention sites. Following a gout management algorithm that was produced through expert consensus [63], we developed the intervention to supplement usual care (UC). The algorithm incorporates a treat-to-target approach with the intervention delivered primarily through an interactive voice response system (IVR) [64] IVR messaging will be used to assess whether intervention patients continued to take prescribed ULT, alert patients regarding pending SU laboratory orders or prescription updates, and to provide encouragement. IVR messaging will supplemented in select cases with telephone calls from the study pharmacist to provide more in-depth assistance (i.e. when patients report that they are not taking allopurinol) or respond to patient queries. Patients at non-intervention sites will receive only UC with the exception that patients without an sUA assessment in the previous 3 months (at both intervention and UC sites) will receive IVR reminders at baseline and after one- and two-years of follow-up to undergo laboratory testing.

9.1 Study technology

Pharmacist-patient interactions in this study will be 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. 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.

9.2 Gout care algorithm and IVRS messages

The primary goals of the gout care algorithm are 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 have 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 is meant as a guide for the pharmacist leading the intervention; the pharmacist is allowed to deviate from the algorithms 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 are divided into 5 categories:

1) participation reminder,
2) allopurinol adherence survey
3) sUA lab order
4) allopurinol prescription/dose adjustment
5) sUA goal achievement

The participation reminder is designed to encourage return mailing of the baseline health survey. The allopurinol adherence message is designed to solicit self-reported adherence where a report of $\geq$5 daily doses taken in the past 7 days will be considered adherent. The sUA lab order messages will inform or remind patients that they are due for a blood draw. The allopurinol prescription and dose adjustment messages will inform patients of changes to their prescriptions as initiated by the study pharmacist. Finally, the sUA goal achievement message is designed to celebrate a “good outcome” and remind patients to continue allopurinol unless otherwise instructed.

The number of IVRS calls made and successful contacts will be tracked and documented by the study pharmacist and research associate. The algorithm has been tailored to accommodate the slightly differing risk profiles of patients with normal kidney function or CKD stage I/II (Fig. 2a) and stage III/IV (Fig. 2b). In particular, the initial suggested dose increment of 50 mg/d represents 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. 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 will allow the study pharmacist to reduce patient burden related to blood draws recognizing that at least 50% of patients are likely to need at least 300mg/d of allopurinol to achieve sUA < 6.0 mg/d.

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 will receive an adherence assessment IVRS message. If classified as non-adherent (took allopurinol as indicated on b5 day over the past week), the patient will receive a phone call with encouragement from the pharmacist followed by a repeat assessment. If the patient is adherent, they will receive an IVRS message notifying them that a blood draw is due. Following sUA measurement, patients with a sUA b 6.0 mg/dl will receive the sUA goal achieved IVRS message while patients ≥6.0 mg/dl will receive allopurinol dose escalation and the corresponding IVRS dose adjustment message. An adherence assessment IVRS message will follow 2–4 weeks later. The sequence of dose escalation, adherence assessment and blood draw IVRS messages will continue until the patient achieves a sUA < 6.0 mg/dl.

9.3 Provider interactions

Two sets of broadcast emails will be sent to providers: a pre-study email and an end-of-study email one year after the first patient is enrolled. Providers at usual care sites will be informed that a federally- funded study to facilitate gout management is 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 will be informed that patients newly initiated on allopurinol will have a pharmacist assist in patients' care by monitoring sUA levels and escalating the allopurinol dose until a sUA b 6.0 mg/dl is met. The email will state that these actions are 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 at KPSC will be available for questions and providers will be given the opportunity to opt their patients out of the study.

9.4 Patient interactions

Initial allopurinol dosing will be prescribed at the discretion of the primary gout provider. All patients meeting eligibility criteria will be randomized into either study arm, and mailed a study packet including an opt-out letter, baseline health survey and gout educational material. The opt-out letter will notify patients of the quality improvement program, and ask them to return a pre-addressed, postage-paid notification if they wish to opt-out of participation. The baseline health survey will record 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 will be sent via mail at the end of years 1 and 2. The gout educational material to be included in the mailing is 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.

All patients will be entered into the IVRS system to receive weekly IVRS reminders (maximum of 3) to return baseline questionnaires. The usual care patients will receive no further contact after these IVRS messages until the blood draw IVRS for the 1 year and 2 year outcomes. Intervention patients, by contrast, will continue into the gout care algorithm with the adherence assessment IVRS message. The study pharmacist will intervene further if the IVRS proves insufficient at any task for intervention patients. There were three primary indications where the IVRS may prove insufficient: 1) if the patient is unresponsive to IVRS calls or fails to show up for ordered labs or prescription fill pick-up; 2) a patient self-reports allopurinol non-adherence via IVRS; or 3) a patient calls the pharmacist directly. Direct telephone communications will be 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) will be provided (Appendix A). Adherence reassessment and encouragement is designed to determine the extent of nonadherence, identify reasons for nonadherence and provide encouragement for improved adherence as appropriate. Finally, dose adjustments will be facilitated by the study pharmacist using live telephone calls if not accomplished by IVRS.

10 Data Management and Statistical Analyses

Dr. David Redden of the UAB School of Public Health will oversee all data management and analysis for the proposed study. Dr. Redden and the study team at UAB will ensure that the data collected and analyzed for this study are of the highest quality possible, and updated as needed to guarantee high quality data through quality control and quality assurance. Edit checks will be reviewed by the statisticians, program manager, as well as other team members on an ongoing basis to evaluate whether any checks need to be added or any existing checks need to be modified. All data will be entered into and all analyses will be conducted using Statistical Analysis System (SAS; Cary, NC) Version 9.4 or higher.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to UAB by KPSC and stored on secure servers in the UAB Department of Medicine . This will not include the participant’s contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data will be secured and password protected. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

10.1 Sample Size Justification

Sample size estimates are based on an assumption that 30% of gout patients given allopurinol from usual care clinics will 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) will provide 80% power to detect a 10% absolute improvement in sUA goal achievement (i.e. ≥40% success rate) [25]. Finally, we estimate 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 1minus the estimated drop out proportion. Our target enrollment using this equation was over 702 per study arm; 1404 total.

10.2 Randomization

Clinic site will serve as the first level of randomization. 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, close proximity clinics will be combined into units for randomization. Demographic characteristics (age, gender and race/ethnicity) and size of clinic membership will be reviewed prior to randomization to balance these important factors.

10.3 Study Analyses

Baseline characteristics of patients from intervention sites will be compared with those from UC sites using a Chi square test for categorical variables or Student's t-test for continuous variables. General estimating equations will be used to examine group differences in the primary outcomes (sUA <6.0 mg/dl and PDC ≥0.8) in an intent-to-treat analysis, accounting for correlation among patients nested within a clinic site. Factors that are imbalanced by group following randomization (race and calendar year of enrollment) will be included as covariates. Non-responder imputation will be used for models examining sUA goal achievement when follow-up sUA values are missing. A mixed effects linear regression will be used to examine the continuous outcomes of absolute sUA change, differences in PDC, 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. Flare rates will be calculated by treatment assignment for each six-month interval of the two-year follow-up period.

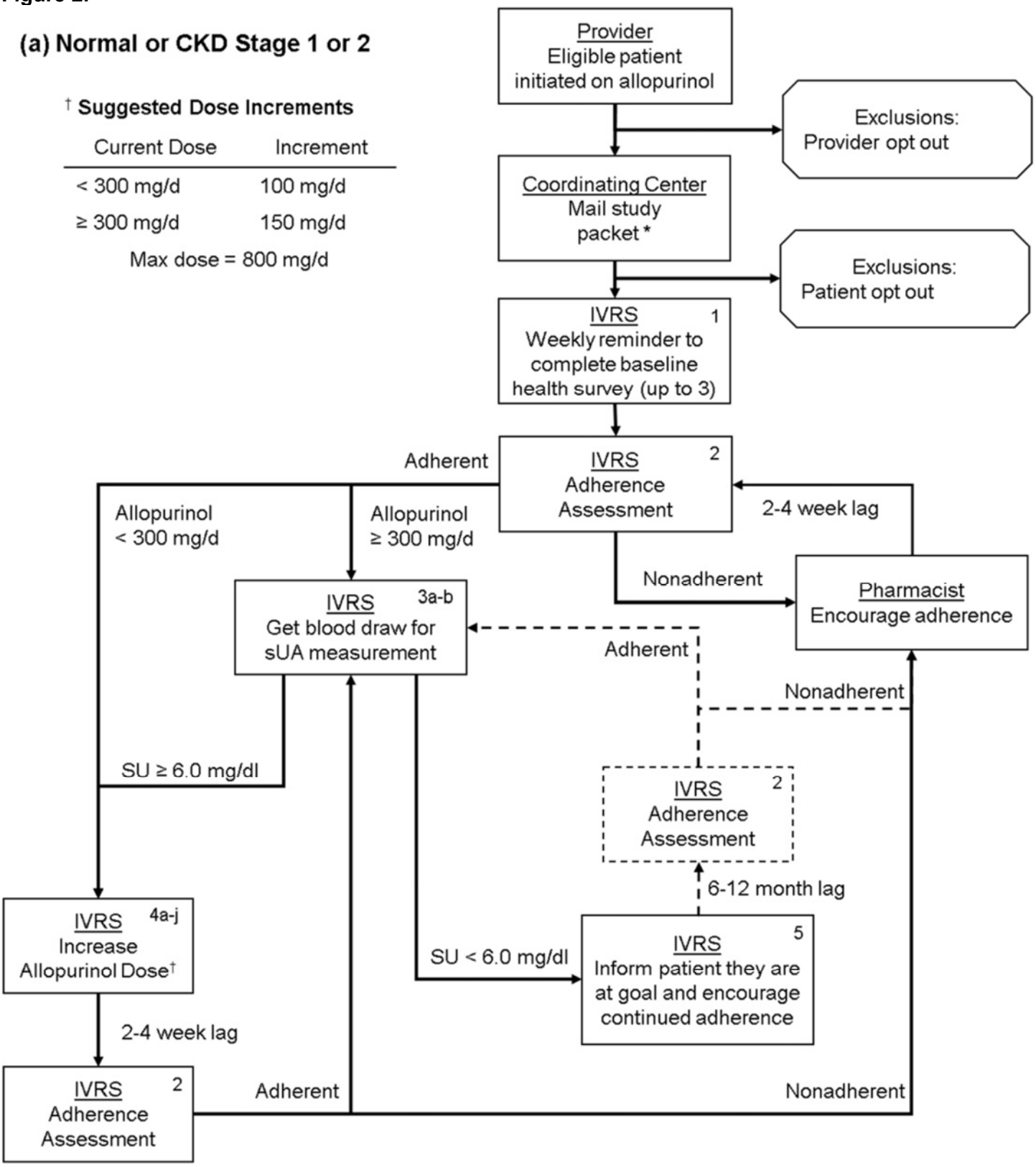
11 Adverse Events (AE)

Definitions below incorporate guidelines provided by the Office of Human Research Protections (OHRP) of the DHHS and describes FDA reporting requirements. All AEs will be collected. An AE is any untoward event whether or not considered related to the use of denosumab or zoledronic acid or alendronate. Any worsening (i.e., any clinically significant adverse change in frequency or intensity) of a preexisting condition which is temporally associated with the use of allopurinol is also considered an AE. Abnormal laboratory values or test results constitute AEs only if they induce documented clinical signs or symptoms or require therapy, and are recorded in the electronic health record. Conditions present at time of enrollment will not be considered adverse events; however, worsening of a preexisting condition may be considered an AE. We will report all AEs according to, the IRB, and the appropriate health authority (e.g., Food and Drug Administration [FDA]).

11.1 Capture of Adverse Events (AE) and Serious AE (SAE)

General adverse events (AEs) and serious adverse events (SAEs) will be 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.

Figure 2.

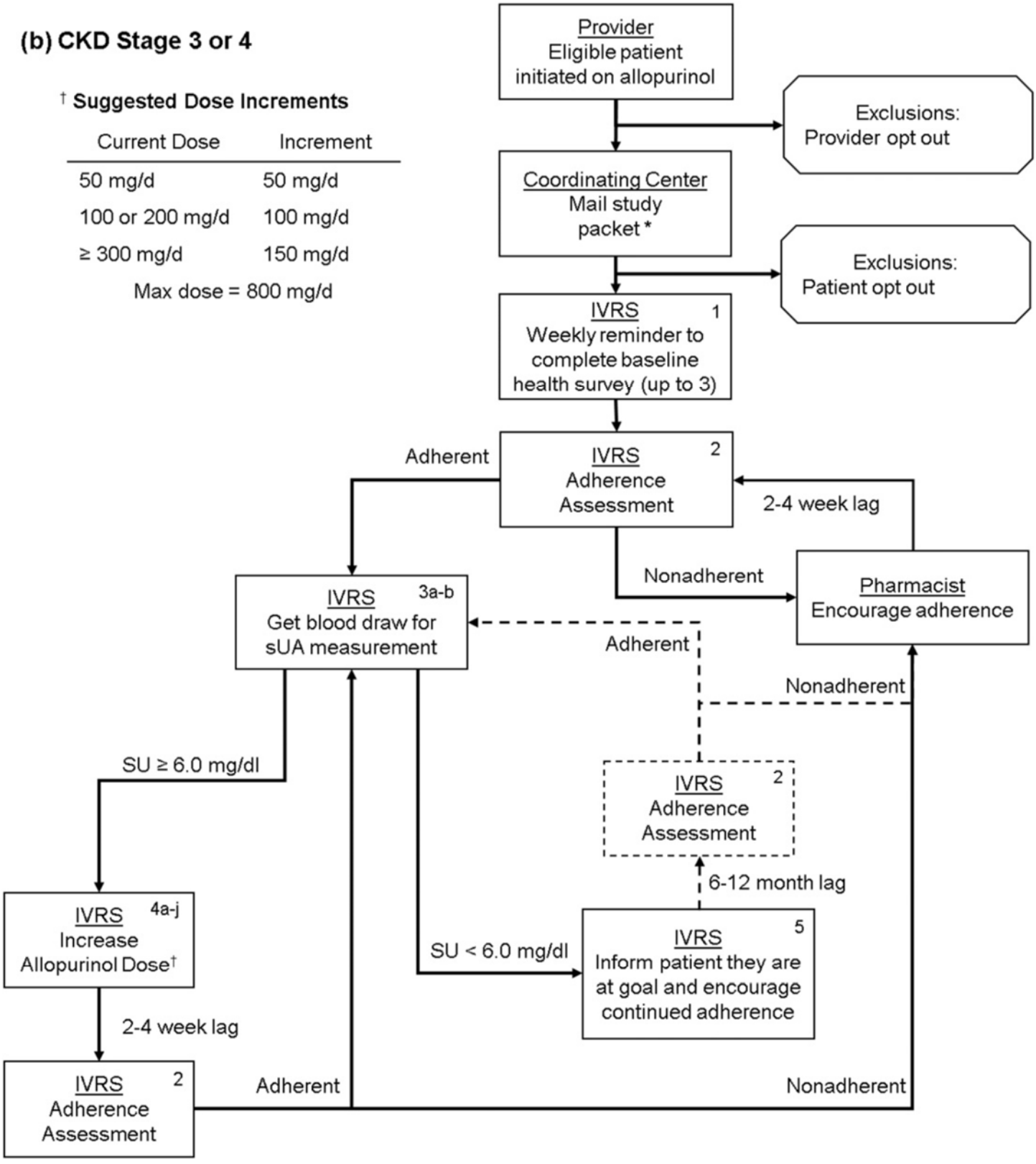

(a) Normal or CKD Stage 1 or 2
† Suggested Dose Increments
Current Dose
Increment
< 300 mg/d
100 mg/d
≥ 300 mg/d
150 mg/d
Max dose = 800 mg/d
Provider
Eligible patient initiated on allopurinol
Exclusions:
Provider opt out
Coordinating Center
Mail study packet *
Exclusions:
Patient opt out
IVRS 1
Weekly reminder to complete baseline health survey (up to 3)
IVRS 2
Adherence Assessment
Adherent
Allopurinol < 300 mg/d
Allopurinol ≥ 300 mg/d
2-4 week lag
Nonadherent
Pharmacist
Encourage adherence
IVRS 3a-b
Get blood draw for sUA measurement
Adherent
Nonadherent
SU ≥ 6.0 mg/dl
IVRS 2
Adherence Assessment
6-12 month lag
IVRS 4a-j
Increase Allopurinol Dose†
SU < 6.0 mg/dl
IVRS 5
Inform patient they are at goal and encourage continued adherence
2-4 week lag
IVRS 2
Adherence Assessment
Adherent
Nonadherent

(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



11.2 Adverse Event (AE) Classifications

11.2.1 Expected AE

The expected adverse effects of allopurinol could be found in the drug Investigator's Brochure. AEs will be collected as described in section 10.1.

11.2.2 Unexpected AE

Any AE, the specificity, frequency, or severity of which is not consistent with either:
The known or foreseeable risk of AEs associated with the procedures involved in the research that are described in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, the current IRB-approved informed consent document, and other relevant sources of information, such as product labeling and package inserts; or the expected natural progression of any underlying disease or condition of the participant(s) experiencing the AE.

11.2.3 Related to the research

An event is related to the research if, in the opinion of the investigators, it was more likely than not to be the result of the interventions and interactions used in the research or the collection of identifiable private information in the research (i.e., there is a reasonable possibility that the event may have been caused by participation in the research).

11.2.4 Unrelated to the research

An AE is unrelated to the research if, in the opinion of the investigators, the AE is not related to the research.

11.2.5 Unanticipated Problems Involving Risks to Participants or Others (Unanticipated Problems)

Problems that are (1) unexpected (in terms of nature, severity or frequency) given the research procedures and the participant population being studied; and (2) suggest that the research places participants or others at a greater risk of harm or discomfort related to the research than was previously known or recognized including physical, psychological, economic or social harm.

11.3 Relationship to allopurinol

The determination of the likelihood that allopurinol caused the AE will be assessed by the study team and reported as follows

11.3.1 Probably Related to Allopurinol

- There is evidence of exposure to the allopurinol
- The temporal sequence of the AE onset relative to administration of the allopurinol is reasonable
- The AE is more likely explained by the allopurinol than by another cause

11.3.2 Possibly Related to Allopurinol

- There is evidence of exposure to allopurinol
- The temporal sequence of the AE onset relative to administration of the allopurinol is reasonable
- The AE could have been due to another equally likely cause

11.3.3 Unlikely Related to Allopurinol

- There is evidence of exposure to the allopurinol
- There is another more likely cause of the AE
- There is no temporal relationship to allopurinol

12 Investigational Study Sites

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 200medical 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.

13 Institutional Review Board (IRB)

The study will be conducted under the auspices of the IRB at University of Alabama at Birmingham. Prior to initiation of the study, the investigator will forward copies of the protocol, Investigator's curriculum vitae (if applicable), study advertisements (if applicable), and all other subject-related documents to be used for the study to the IRB for its review and approval. Before initiating a study, the PI will have written and dated full approval from the responsible IRB for the protocol. The investigators will also promptly report to the IRB all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The study site PI and/or staff will not make any changes in the study or study conduct without IRB approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the PI to obtain an expedited review by the IRB as allowed. As part of the IRB requirements for continuing review of approved studies, the Investigators will be responsible for submitting periodic progress reports to the IRB (based on the Committee's requirements), at intervals appropriate to the degree of subject risk involved but no less than once per year. The study PI will provide a final report to the IRB following study completion.

14 Administrative Procedures

14.1 Protocol Amendments

Any change that affects the conduct of the study or significantly alters the protocol will be made in the form of an amendment. Any change or addition to this protocol requires a written protocol amendment that must be approved by the UAB before implementation. Amendments significantly affecting the safety of participants, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB. Examples of amendments requiring such approval are:

- An increase in drug dosage or duration of participant exposure
- A significant change in the study design (e.g. addition of a new immunosuppressive)
- An increase in the number of study visits and procedures to which participants are exposed

14.2 Compliance with Law, Audit, and Debarment

The study PI will prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules and regulations. Study documentation will be promptly and fully disclosed by the study PI upon request for inspection, copying, review, and audit at reasonable times by any regulatory agencies. The study site PI agrees to promptly take any reasonable steps that are requested by designated representatives as a result of an audit to cure deficiencies in the study documentation. Persons debarred from conducting or working on clinical studies by any court or regulatory agency will NOT be allowed to conduct or work on this studies.

14.3 Compliance with Financial Disclosure Requirements

The study PI will provide accurate financial information to allow submission of complete and accurate certification and disclosure statements as required by US FDA regulations (21 CFR Part 54). This requirement also extends to Sub-Investigators.

14.4 Confidentiality and Privacy

Participant confidentiality and privacy will be strictly held in trust by the participating investigators, their staff, and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. All research activities will be conducted in as private a setting as possible.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in secure servers at the University of Alabama at Birmingham. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases will be archived at UAB.

14.5 Study Reports

Annually, the study team will provide to NIAMS copies of all reports related to the study. These include annual safety reports filed with the IRB.

14.6 Publication of results

It is mandatory that the first publication will be based on data that has been analyzed as stipulated in the protocol. Participating investigators agree not to present data before the full publication, unless formally agreed to by all other investigators.

14.7 Changes in study personnel

If there is a change of any personnel listed on human subjects protocol, a new form reflecting the change will be completed and forwarded to the IRB along with the new staff member's signed curriculum vitae, medical license (if relevant), and signed financial disclosure statement.

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