

**Dietary Approaches to Stop Hypertension
(DASH) Diet Effects on Serum Uric Acid (SUA)
in Adults With Hyperuricemia and Gout at Johns
Hopkins University**

Short Title: The Diet Gout (DIGO) Trial

PROTOCOL Version 1.4

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SUMMARY OF PROTOCOL VERSIONS AND CHANGES

Version 1.0

- Original version submitted to the Johns Hopkins Institutional Review Board on February 5th, 2018.

Version 1.1

- Changes to consent, recruitment, protocol on May 4th, 2018.

Version 1.2

- Changes to recruitment strategy on August 6th, 2018.

Version 1.3

- Changes to recruitment strategy on January 26th, 2019.

Version 1.4

- Submission of protocol and final statistical analysis plan to the IRB on June 11th, 2019.

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LIST OF ABBREVIATIONS / GLOSSARY

BMI	Body mass index
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
DD	Dietitian-directed DASH diet (experimental group)
DIGO	The Diet Gout Trial
FP	Follow-up Period Visit
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
NHANES	National Health and Nutrition Examination Survey
OH	Orthostatic hypotension
PCP	Primary care provider
PS	Pre-Screen contact
RZ	Randomization visit
SD	Self-directed assignment (reference group)
SPB	Systolic blood pressure
SUA	Serum uric acid
SV	Screening Visit
TUG	Timed Up and Go
ULD	Urate lowering drugs

1. ABSTRACT

The conceptual framework of the proposed trial is grounded in our prior experience in the conduct of dietitian-directed dietary interventions with the provisions of food. In this randomized controlled trial (RCT), the Diet-Gout trial or DIGO, we will randomized at least 40 adults with gout and with hyperuricemia (serum uric acid [SUA] $\geq 7\text{mg/dL}$) who are not actively taking urate-lowering drugs (ULDs) to a grocery intervention designed to reflect the previously published Dietary Approaches to Stop Hypertension (DASH) diet. This trial has been funded by the Rheumatology Research Foundation. Following a crossover design, all 40 adults will undergo 4 weeks of a self-directed feeding period (reference) and a DASH grocery intervention (value \$105 per week). The primary outcome is serum uric acid. Our approach is adapted from the framework of the recently completed “Five Plus Nuts and Beans Trial.” Groceries will be purchased from an online grocery store (AmazonFresh) in serving proportions that reflect the DASH diet – a diet high in fruits, vegetables, low-fat dairy and lean meats and low in fat and saturated fat. This, as a corollary, will reduce consumption of a pro-gout dietary pattern: an unhealthy dietary consumption pattern that is due in parts to excesses (e.g., red meat and sugary soda) and deficiencies (e.g., vegetable protein and low-fat dairy) in typical American diets.

2. SPECIFIC AIMS

Primary Aim

Aim 1. To determine the effect on the DASH Diet on uric acid among adults with selfreported gout and hyperuricemia. In this randomized controlled trial (RCT) of 40 patients with hyperuricemia (SUA level $\geq 7\text{mg/dL}$) or gout, who are not taking ULDs and have a uric acid $\geq 7\text{mg/dL}$, we will compare the effects of 4 weeks of DASH groceries compared to typical grocery purchases on SUA levels.

Hypothesis 1. The DASH diet will show a clinically meaningful improvement in lowering SUA levels as compared to the control diet.

Other aims: To estimate the effects of the DASH diet on the following outcomes:

- A. Clinic blood pressure
- B. Orthostatic hypotension
- C. Timed up and Go
- D. Body mass index
- E. Urinary sodium, potassium, and creatinine excretion
- F. Self-reported fruit, vegetable, and fat consumption
- G. Gout severity
- H. Global physical function
- I. Joint pain
- J. Fasted LDL cholesterol
- K. Fasting blood sugar
- L. Urine pH and uric acid level

3. BACKGROUND

Substantial and Increasing Disease Burden of Gout – The Modern Gout Epidemic.

Perpetuated by the “Western” lifestyle and resulting obesity epidemic, the prevalence of gout has increased over the past few decades to **3.9% of US adults (8.3 million individuals)**.¹ This prevalence increases with age to 9.3% of US adults over 60 years (4.7 million). The disease burden of gout has been similarly rising worldwide for decades.² **Compelling Lack of Dietary Intervention Trials in Gout.**

Despite substantial epidemiologic evidence for the potential extrapolation of certain dietary and lifestyle factors as therapeutic strategies in gout care, there are no dietary intervention trials for high-strength evidence, as clearly recognized by the latest ACR guidelines and the 2015

Agency for Healthcare Research and Quality (AHRQ) review for the American College of Physicians (ACP),³ constituting a critical gap in the field of gout care.

The Need for the Current Trial

As mentioned above, a compelling research gap exists in dietary intervention studies for gout. The current trial will be significant for the following reasons: (1) Halting or reducing the remarkable and rising disease burden of gout (an excruciatingly painful arthropathy) has important public health implications; (2) Reducing both gout risk and simultaneously the major cardiovascular-metabolic comorbidities and sequelae associated with hyperuricemia and gout, which could lead to improved survival; (3) The DASH diet is particularly appealing, as 74% of US gout patients have hypertension,⁴ which contributes to the rising prevalence of gout in the US; (4) Other key elements of effective anti-gout lifestyle approaches have reasonable palatability, sustainability, and practical simplicity (for patients and practitioners alike), which are not provided by the current low purine diet approach. To these effects, our proposal to evaluate the potential anti-gout effects of a well-established, sustainable dietary approach is highly promising; and (5) Ultimately, the approach that lowers SUA levels among gout patients with proven added cardiovascular-metabolic benefits would have a significant positive impact among millions of gout patients in the US and beyond.

Urate-Lowering Effect of the DASH Diet in Hyperuricemic Non-Gouty Individuals

Our recent ancillary analysis (N = 103) of an original DASH diet trial has found that the DASH diet lowers SUA levels as compared to a typical American diet (i.e., control diet), particularly among those with hyperuricemia (i.e., by 0.8 mg/dL in those with a baseline SUA level of 6-7 mg/dL, and by 1.3 mg/dL in those with a baseline SUA \geq 7 mg/dL).⁵ While this trial did not specifically target a gout population, these findings suggest that the DASH diet could have considerable urate-lowering benefits among those with hyperuricemia or gout.

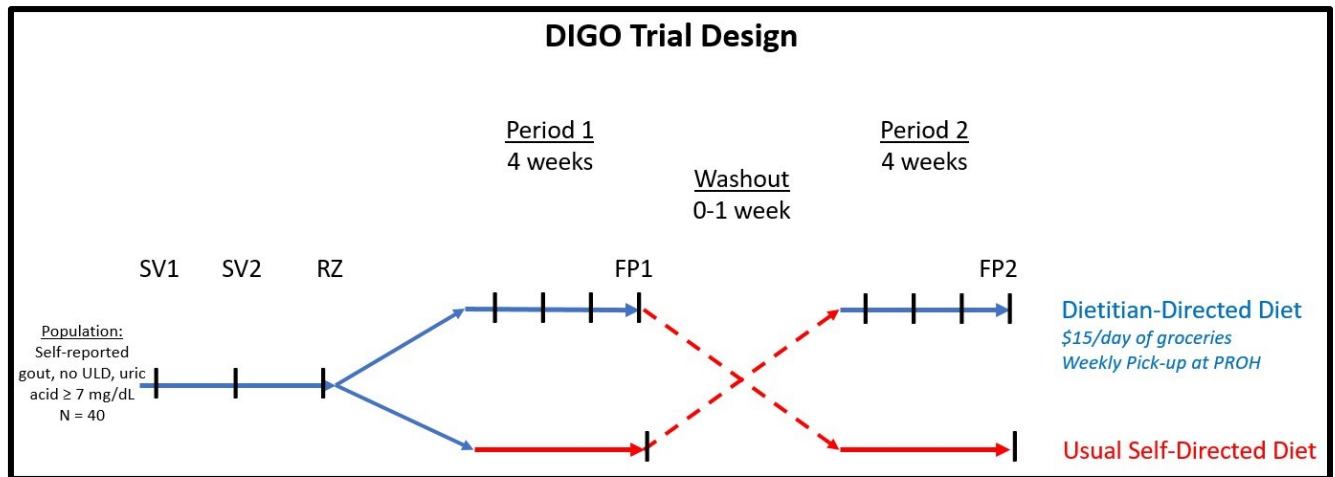
All DASH trials (published in *NEJM* and *JAMA*)^{6,7} found that the DASH diet substantially reduced both systolic and diastolic blood pressure among hypertensive as well as normotensive adults. For example, the original DASH trial found that among subjects with hypertension, the DASH diet reduced systolic and diastolic blood pressure by 11.4 and 5.5 mmHg more, respectively, than the control diet.

DASH Dietary Pattern and a Lower Risk of Incident Gout - The Nurses' Health Study

In our recent NIH-funded project to investigate several cardiovascular-metabolic dietary approaches for the outcome of incident gout (the clinical end-point of hyperuricemia), the DASH diet was associated with a lower risk of gout, whereas the Western dietary pattern was associated with an increased risk of gout, which would explain the rising prevalence of gout.⁸

In our extended analyses (N = 3,075 incident cases of gout), the top quintile most reflective of the DASH diet was found to be associated with a 32% lower risk for incident gout compared to the bottom quintile least reflective of the DASH diet. In contrast, the Western dietary pattern score was associated with an increased risk for gout. These observational data with the clinical endpoint of gout further support the DASH diet as an attractive dietary approach for gout.⁸

4. OVERVIEW OF DESIGN



This study will be an individual level, crossover RCT with 2 periods (**Figure**). The participants will be 40 adults with gout and hyperuricemia (≥ 18 years) who have SUA ≥ 7 mg/dL, who are not currently taking ULD. After informed consent, screening, and run-in, participants will be randomly assigned to each of two groups in random order: 1) Self-Directed (SD) vs. 2) DietitianDirected DASH Tailored (DD) with the provision of food. The primary outcome variable is SUA.

The duration of the intervention will be 4 weeks. Two screening visits will be used to determine interest and eligibility. The rationale for this timeline is that it is of sufficient duration to allow a complete effect of the intervention on uric acid to occur. Because it is not a prolonged period of intervention, the risk of non-compliance will be reduced, allowing for a better determination of the efficacy of the intervention. The DASH diet effects on SUA occur within 4 weeks and on blood pressure occur within 2 weeks, and are sustained from 2 weeks forward. As such, the 4 weeks will also provide sufficient time to see maximum diet effects on SUA and blood pressure and reduce the time period where recidivism is likely to occur.

Protocol visits for in-person data collection will occur during the screening period, at randomization, at week 4 after follow-up period 1 and follow-up period 2. At all protocol visits, our blinded data collectors will collect blood pressure and study questionnaires from participants in both arms of the study. Blood collection will be performed by phlebotomists blinded to the intervention arm.

5. STUDY POPULATION AND ELIGIBILITY

Eligibility criteria are summarized below. This trial focuses on gout in the setting of no active ULD use. Given potential potassium overloading from the DASH diet, we will exclude patients with hyperkalemia or CKD stage 4 or higher, similar to previous DASH trials, although the DASH diet is even expected to slow the progression of CKD.

Inclusion criteria:

- Age 18-100 years
- Self-reported gout diagnosis
- Serum Uric Acid ≥ 7 mg/dL

Exclusion criteria:

- Unstable or Stable ULD use or plans to initiate ULD
- Patients with hyperkalemia (>5 mmol/L)
- Consumption of more than 14 alcoholic drinks per week or more than 6 alcoholic drinks in one occasion
- Chronic kidney disease (GFR < 30 cc/min), active dialysis, or history of kidney transplant
- Inability to give informed consent
- Chronic steroid use, warfarin use, insulin use
- Unstable lipid, diabetes, and hypertension medication use (2 month period)
- Active heart attack, heart failure, angina, coronary bypass, COPD
- Active cancer or cancer treatment
- Active inflammatory bowel disease, malabsorption, history of major gastrointestinal surgery involving bowel resection
- Pregnant, plan to become pregnant, or breast feeding
- Plans to leave geographic area in the next 3 months
- Active participation in another clinical trial
- Significant food allergies, preferences, or intolerances
- Unable to give informed consent
- Unable to pick up foods at the research clinic during the DASH intervention phase
- Unable to transport or store food properly, lack of a cooking facility at home □ Terminal or mental illness

6. RECRUITMENT

Field centers

The trial will be conducted at a well-established field center in Central Maryland, namely, the ProHealth clinical research unit in West Baltimore, Maryland.

The ProHealth Clinical Research Unit is a dedicated research facility that has been the site for numerous NIH-sponsored trials. This participant-friendly clinical research facility is 15,000 ft² located in the Woodlawn suburb of Baltimore and is convenient to participants from Baltimore City, Baltimore County, Anne Arundel County, and Howard County. ProHealth has 9 exam rooms and 2 phlebotomy stations and space for up to 50 staff.

Recruitment strategies

We will implement a variety of strategies to achieve our recruitment target, i.e. ~40 participants. Our experience is that multiple strategies work synergistically to promote study name-brand recognition to enhance recruitment. We will employ the following approaches:

- (1) EPIC patient portal messages to patients of Johns Hopkins Hospital with an active patient portal. The Johns Hopkins University Core for Clinical Research Data Acquisition will develop a dynamic query of Hopkins patient's with a gout ICD-9 or ICD-10 code, age>18 years, and in zip codes surrounding the ProHealth Clinical Research Center. Those with an active patient portal will receive a portal message with a link to our website and other contact information. Those with an inactive patient portal will receive a mail invitational letter.
- (2) Community-based recruitment will be performed using a mailed brochure with a stamped, self-addressed reply card. Addresses will be purchased from local vendors.
- (3) Periodical advertisements: We will place a banner ad in local newspapers surrounding our clinical research center.
- (4) Billboards, radio, and bus advertisements will be considered targeting our immediate geography.
- (5) Facebook advertisements (including Instagram): These will target users with an interest in gout in the region surrounding our clinical research center. Advertisements will direct interested adults to our trial website.
- (6) Clinic contact: Study brochures will be placed in the rheumatology clinic waiting areas.

Recruitment of women and minorities

Given the demographic characteristics of individuals residing in central Maryland with gout, we anticipate that ~80% of participants will be men and ~40% will be African-American.

7. DATA COLLECTION AND MEASUREMENTS

Data collection contact schedule

Eligibility, baseline, and follow-up data will be collected by phone, through mailings, and at in-person visits. In-person data collection visits will primarily be conducted at the ProHealth Clinical Research Unit in Woodlawn, MD. In general, we try to be as flexible as possible to meet the needs of our participants. For example, we might divide or bundle data collection across visits. See Table below for an overview of proposed data collection items by visit. Some items might be dropped based upon participant burden, scientific considerations, available resources, and the results of field testing. The primary data collection points for participant-level data are as follows:

Pre-Screen Contact (PS) – A brief questionnaire will be administered by phone to identify potentially eligible participants quickly and efficiently.

Screening Visit 1 (SV1) – This in-person visit will include written informed consent for screening, questions about medical history, medications, and eligibility; serum collection for uric acid screening and urine specimen collection.

Screening Visit 2 (SV2) – This in-person visit will include further questions about demographic characteristics, baseline diet, physical activity, gout, and global pain. We will also measure height and weight and perform seated and standing blood pressure assessments (BP and OH), and a “Timed Up and Go” (TUG) test.

Randomization Visit (RZ) – This in-person visit will include additional questionnaires on physical activity, a repeat weight assessment, measurement of BP and OH. Participants will be provided an opaque envelop to learn the intervention sequence. They will subsequently be provided instructions on the next phase of the study.

Feeding Period 1 Visit (FP1) – This in-person visit includes diet screening, a medication questionnaire, physical activity questionnaires, pain assessments, and questions about adverse effects from diet, compliance, and palatability. In addition, we will perform phlebotomy, urine assessments, and physical examinations including weight, BP, OH, and the TUG test. Participants will also receive instructions for their next feeding assignment.

Feeding Period 2 Visit (FP2) – This in-person visit includes diet screening, a medication questionnaire, a physical activity questionnaire, a pain assessment, a questionnaire about adverse effects from diet, compliance, and palatability. In addition, we will perform phlebotomy, urine assessments, and physical examinations including weight, BP, OH, and the TUG test. We will also provide participants with some close-out materials including a certificate of appreciation.

Table. Data Collection Schedule

	Pre-	Screening/Baseline/Randomization			Feeding Periods Period	
	screen PSV	SV1	SV2	RZ	FP1	FP2/Close-out
Pre-screen questionnaire	✓					
Study description/instructions	✓	✓		✓		
Informed consent		✓				
Randomization assignment				✓		
Eligibility checklist		✓	✓			
Medication list questionnaire		✓	✓	✓	✓	✓
Medical history		✓				
Demographic questionnaire			✓			
Physical activity questionnaire (for Calorie estimator)			✓	✓	✓	✓
Gout questionnaire			✓			
Global pain and function questionnaire			✓		✓	✓
Diet compliance					✓	✓
Diet palatability/Symptom/diet tolerance questionnaire (<i>DD intervention only</i>)					✓	✓
Interim event			✓	✓	✓	✓
Diet screener (fruit/vegetables/fat)			✓		✓	✓
Serum collection		✓			✓	✓
Urine collection		✓			✓	✓
Seated blood pressure			✓	✓	✓	✓
Orthostatic hypotension			✓	✓	✓	✓
Height			✓			
Weight			✓	✓	✓	✓

TUG test			✓		✓	✓
Close-out survey with certificate						✓

Note: During the DASH intervention, participants will complete weekly food ordering calls with the study dietitian. Grocery orders will be documented.

Measurements

Primary outcome variable.

Uric acid. Fasting blood will be collected during SV1, FP1, and FP2 for SUA, blood glucose, total cholesterol (TC), HDL cholesterol (HDL-C), and triglycerides. LDL-C will be estimated by the equation ($LDL = TC - HDL - \text{triglyceride}/5$).

Clinical Blood Pressure. Clinical blood pressure (BP) will be determined by the OMRON 907XL. This device records BP using an oscillometric technique. The OMRON device has been validated against the mercury random zero. BP is obtained by trained and certified data collectors according to a standard protocol, adapted from the protocol used in the Omni-Heart trial. Three measurements (each separated by 30 seconds) are obtained at each visit on the right arm of participants after they rest quietly in the seated position for at least 5 minutes. A cuff of appropriate size is identified at the initial visit and used thereafter at all subsequent visits. Heart rate is also recorded by the OMRON device. We will repeat this assessment immediately after standing to assess BP regulation (orthostatic hypotension). BP will be measured at SV2, RZ, and both FPs. The average BP of SV2 and RZ will be used to estimate baseline BP. The average BPs measured after each 4-week period will be used to determine intervention effects on BP.

Secondary outcome variables.

- a. Urinary sodium and potassium and creatinine excretion. Spot urine collections, urinary sodium (Na), potassium (K), and creatinine excretion will be used to estimate group compliance with dietary aspects of the intervention (i.e., sodium excretion for salt intake and potassium excretion for fruit and vegetable intake). We will also measure urine pH and uric acid to explore the effects of the diets on urine excretion of uric acid as a potential mechanism for serum urate reduction.
- b. Other serum measures. While no specimens will be banked, we will measure serum sodium, potassium, chloride, bicarbonate, and transaminase levels as part of an extended metabolic panel used to determine uric acid levels.
- c. Questionnaires. The trial will collect questionnaire data from participants. These data will be used for a variety of purposes—baseline data to describe participants, outcome data to assess the effects of the trial interventions, and mediating variables to assess potential causal pathways. The Demographic Questionnaire is a self-reported assessment of basic patient characteristics. It assesses ethnicity, tobacco use, alcohol use, health insurance status, income, employment, marital status, and education level. The Medical History Questionnaire and Prescreening Questionnaire includes details related to gout history, kidney disease, diabetes, hypertension, cardiovascular disease, gastrointestinal conditions, cancer, pregnancy, and menopause. The Medication Use Questionnaire will be collected at baseline and during follow-up. The Fat/Fruit/Vegetable Screener, developed by the National Cancer Institute is a brief self-reported assessment of percent energy intake from fat, fruit, and vegetables. It queries respondents regarding consumption of a variety of food products that are high in fat over the past month. The Gout Assessment Form asks detailed question about gout history. The Pain Assessment Form asks about pain performing common tasks. Both the Gout Assessment Form and the Pain Assessment form use elements from other commonly used scales including the GAQ2.0, the SF36, and the WOMAC pain survey on global joint pain.⁹⁻

8. QUALITY ASSURANCE AND QUALITY CONTROL

The investigative team understands the critical importance of collecting complete, high-quality data and developing procedures to accomplish this important objective. Core activities include:

- Standardization - maintaining common study documents (protocol, MOP, case report forms) with special efforts to minimize version control issues.
- Training – developing training procedures led by experienced investigators and senior staff, developing and implementing certification procedures and performance metrics, and conducting annual training.
- Robust data systems – implementing a web-based data entry system with duplicate data entry; using off-site data storage with automated back-up systems; programming data queries to check logic and consistency of data between forms over time; implementing replicate programming for major papers.
- Site visits – conducting site visits has an important role in promoting best practices, identifying operational problems not evident in trial reports, and maintaining a culture that promotes high quality.
- Performance monitoring with feedback – tracking enrollment and follow-up (observed/expected, overall and by key subgroups); monitoring missed visits, data completeness, protocol deviations, and data entry errors; distributing feedback through routine trial monitoring reports. These reports, together with constructive feedback, have an important role in identifying and resolving issues expeditiously.

9. RANDOMIZATION AND MASKING

Randomization

A variable 2, 4, or 6 block randomization scheme will be generated the Johns Hopkins University Institute of Clinical and Translational Research. The scheme will entail two orders AB or BA consistent with our crossover design. Details of the block sizes will be concealed from study staff and investigators and generated prior to the study and placed in opaque, sealed envelopes. A designated staff member will open the envelope with the participant during the randomization visit after confirmation of eligibility and informed consent. This will be performed in a private location away from other staff. Once assigned order is revealed, this information will be shared with the study dietitian, who will provide instructions pertinent for each intervention phase. Order of intervention will not be shared with research technicians performing data assessments or with study investigators. Study personnel and investigators will not be unmasked until follow-up and all data collection are completed.

10. INTERVENTIONS

Distribution and adherence

Overview: The intervention groups are summarized below. Participants will complete each of the study periods in random order. Participants will be asked not to start diuretics or ULD during the trial period (i.e., 10-12 weeks from SV1 to FP2).

Self-Directed (SD): The SD group was asked to continue their typical routine for grocery shopping and meal preparation.

Dietitian-Directed Tailored DASH diet (DD) Group: The DD intervention will consist of a one-on-one session with a dietitian at baseline, followed by weekly calls and assistance with food purchases. After the initial one hour visit, the dietitian will meet with the participant by phone every week to order next week's groceries. Participants will be allotted a stipend of \$105/week for the purchase of food (i.e. \$15/day). We will work with AmazonFresh to order and deliver foods to the ProHealth research center for weekly pick-up. Food will be ordered in fixed proportions reflecting the DASH diet:⁶ 4 servings/day of fruit, 3-4 servings/day of vegetables, 1-2 servings/day of lean meat (poultry/fish), 1-2 servings/day of low fat dairy, and 1-2 servings/day of high fiber foods (nuts, beans). During the intervention period participants will be asked to restrict alcohol, sugary beverages (no soda, no juice), red meat, shellfish, organ meats, and sweets. Food orders will be selected to be low fat, low saturated fat, and low cholesterol with a sodium target of <2300 mg per day. Little education will be provided during the DASH grocery intervention to minimize carryover effects. Rather, education will be focused on how to consume diet per the trial protocol.

Orders will target the following weekly servings with an emphasis on fruit/vegetables/dairy if budget constraints:

- i. Grain: 36-49 servings (5-7/d)
- ii. Vegetables: 28 servings (4/d)
- iii. Fruit: 28 servings (4/d)
- iv. Low fat/fat free dairy: 14 servings (2/d)
- v. Lean animal protein: 9-14 servings (1-2/d)
- vi. Nuts/Seeds/Legumes: 2 servings (<0.5/d)
- vii. Fats/oils/spices: not applicable; use over week

Monitoring Adherence

For all participants, adherence to dietary changes will be assessed by the Fruit, Vegetable, and Fat Screener questionnaire: a self-reported and validated measure of daily fruit and vegetable intake.¹² Respondents are asked about how often they ate a variety of fruits and vegetables over the past month. They are also asked to indicate portion size for each fruit or vegetable item that they ate. Objective measures of adherence will be urine potassium and sodium excretion. The brief screeners have been found to be a useful tool for monitoring diet and correlates well ($r=0.6$ to 0.7 , $P<0.0001$) with the Block full length food frequency questionnaire.

11. SAFETY

Safety monitoring

The study will monitor participant safety. One aspect of safety monitoring is to evaluate screenees to determine whether it is safe for them to participate. Key safety related eligibility criteria are the exclusion of persons with baseline hyperkalemia or chronic kidney disease as the DASH diet is a higher potassium diet.

In addition, while risk from the diet is anticipated to be minimal we will be obtaining clinical data, specifically blood pressure and lab values, and it is possible to detect abnormal clinical values unrelated to the study. All labs will be reviewed by a study physician. Any critically abnormal values will be communicated immediately to participants and permission will be obtained to communicate directly with their primary care provider (PCP). Values that are mildly abnormal will be communicated via letter with encouragement to follow-up with their PCP. With regards to blood pressure, if systolic blood pressure is >180 mm Hg or diastolic blood pressure is >110 mm Hg, we will notify the study physician and advise the participant to follow-up with their primary care provider within 7 days. If systolic blood pressure is >160 , but ≤ 180 mm Hg or if diastolic blood pressure is >100 , but ≤ 110 mm Hg we will advise participants to follow up with primary care provider within 1 month.

We will also monitor participants for gout flares (a health condition related to our intervention) and for medical conditions unrelated to our intervention. If a participant develops a medical problem this will be reviewed by the study physician and discussed with the participant's PCP.

Our study will have a designated study clinician who will review medical eligibility criteria, clinical measures, and laboratory reports. This individual will also serve as the primary contact for staff, participants, and their PCPs regarding medical issues.

The study clinician will also be responsible for reviewing and reporting any adverse events for the site. This person or persons will have appropriate back-up during vacations or other absences to provide 24/7 medical safety coverage for the duration of the study.

Potential risks

This study should not involve any major risk to screenees and trial participants. However, there are some potential risks associated with participation in this study, which are as follows:

1. Participants may be uncomfortable with certain questions on the questionnaires.
2. Bruising and a rare chance of local infection from venipuncture to collect blood samples could occur.
3. There might be loss of confidentiality and privacy.
4. Change in uric acid levels could precipitate a gout flare

Adverse event surveillance and reporting procedures

The OHRP defines an adverse event as "Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research."

We will monitor for adverse and other relevant clinical events associated with study participation during in-person visits. In addition, it is possible participants may report events during grocery ordering calls (phone contact). A study clinician will review completed forms and labels and take appropriate action for any abnormal clinical values or reports of medical conditions. Serious events thought to be secondary to the study intervention will be reviewed by the investigative team of 4 physicians, during our weekly trial meeting.

The trial operation will be organized into teams of investigators and staff. The primary decision making body for the trial operation will be the Oversight Committee, chaired by the PIs (Choi and Miller) and comprised of all investigators and senior staff. This committee will convene monthly, review the progress of all components, and focus on high-level scientific and administrative issues.

12. ANALYSIS

The trial has sufficient resources to enroll 40 participants who will be randomly allocated to 1 of 2 sequences for each the two groups: (1) the SD group followed by the DD group or (2) the DD group followed by the SD group.

Power and sample size

Based on a cross-over trial design, using a variance of 1.71 at an alpha level of 0.05 with a power of 0.8, we estimated that we would need 41 participants to detect a change of -0.75 mg/dL between interventions.¹³ In two prior studies we had observed reductions of -1.3 and -1 mg/dL among subpopulations with a uric acid above 7 mg/dL.^{5,14}

Analysis Plan

This study is a randomized trial that tests the effects of an innovative intervention against a minimal intervention on a selected set of outcomes. The analysis will be conducted under the intent-to-treat principle for both the primary and the secondary endpoints. For the Primary Aim, groups will be compared using within-person differences in SUA levels. The analysis will be carried out with generalized estimating equations to compare 4-week SUA levels from both phases of the study, adjusted for baseline. This will allow us to test the null hypothesis that there is no difference in uric acid between the DASH diet intervention and the self-directed group (reference). Other outcome variables will be analyzed with a similar approach. For continuous outcomes, the distribution of outcome residuals will be assessed for normality and transformed where appropriate. Continuous outcomes will be analyzed via an identity function, while binary variables will be evaluated via a logit function.

Missing data

Based on the existing literature, we will employ recommended strategies to address missing data.⁷¹⁻⁷⁴ However, every effort will be made to collect outcome data on all participants.

13. DATA MANAGEMENT

Data will be collected from three main sources: 1) data collected by trial staff on trial case report forms for later entry into the data management system (DMS); 2) data generated by ancillary facilities, such as Quest laboratories, and sent to the research clinic; and 3) data derived from ESHA software, estimating the nutrient content of the intervention. The DMS will be accessible only via the secure website and only to authorized personnel. Data entered into the DMS will be subject to intra- and inter-item checks, such as range checks, logic checks, and consistency checks. Missing data items will be noted in the database, although certain key values (e.g. uric acid) will not be allowed to be marked 'missing.' Data entry staff will perform data entry as soon as possible after data have been collected.

Data confidentiality and integrity

The investigative team, including staff at all levels of the study will be trained on the importance of data integrity and maintaining participant confidentiality, including HIPAA (Health Insurance Portability and Accountability Act). All data will be stored on secure servers. All study-related computers will be located behind appropriate firewalls and will maintain automated virus update mechanisms. Printed materials will be maintained in locked rooms and file cabinets. All staff will sign statements attesting to their understanding of and willingness to abide by policies regarding confidentiality and data integrity.

Trial-wide data release.

De-identified trial data will be shared with external investigators on an individual basis through contact with the trials' principal investigator.

14. TIMELINE

The trial consists of three main phases: planning and protocol development, implementation (recruitment, intervention and data collection), and data analysis/dissemination. Protocol and intervention development will start in Year 1. Recruitment, randomization, and follow-up will commence in Year 1 and last approximately 15 months, allowing us to meet our recruitment target of 1-2 patients per month. The remaining time will be devoted to data analyses, presentation/publication of findings, and other dissemination activities.

Project Years	1				2			
Calendar Year	7/2017 - 6/2018				7/2018- 6/2019			
Quarters	1	2	3	4	1	2	3	4
Protocol Development								
Intervention Development								
Recruitment, Randomization, Follow-up								
Data Analysis and Publication								

15. REFERENCES

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