Title: Examining the Individual Response to a Restricted Sodium Diet in Hypertensive Patients

NCT#: NCT04764253

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Form CT
UTHSA Clinical Trial Description

This form is not mandatory. Other documents are acceptable if equivalent information is provided.

UTHSCSA Tracking Number *(internal use only)*	HSC20200504H	**1. Original Version Date**	1.0
		1.1. Revision Date(s) *add rows as needed*	

Study Title: Examining the individual response to a restricted sodium diet in hypertensive patients

2. Background

Briefly discuss the important literature relevant to the trial and that provides background for the trial. Include the importance of the trial and any relevant treatment issues or controversies.

Excessive dietary sodium intake is an independent risk factor of hypertension and cardiovascular disease. A vast array of efforts have tried to reduce sodium consumption based on evidence indicating a public health benefit. Yet this benefit has been questioned, mainly based on studies showing variability in individual responses to a sodium-restricted diet (SRD).

The original Sodium Watchers Program (R01NR012967) was developed and implemented by Dr. Misook Chung (University of Kentucky). In this pilot study, the modified Sodium Watchers Program will propose improving adherence to an SRD through education and digital self-monitoring for gradual reduction to low salt foods.

This variability may result from a range of factors, from genetics and lifestyle to various environmental parameters. The response of BP regulation to dietary interventions has been investigated through a metabolomics approach in several studies where different dietary patterns were adopted, including the Dietary Approaches to Stop Hypertension (DASH), Optimal Macronutrient Intake Trial for Heart Health Diets, and use of the Mediterranean Diet. BP was significantly associated with 6-10 urinary metabolites reflecting dietary intake. These results demonstrate, in a trial setting, changes in metabolite profile from manipulation of dietary macronutrient content to lower BP levels. However, the metabolite profile in relation to micronutrients such as dietary sodium intake remains unknown.

The study aims are (1) to examine the associations of urine metabolites with urinary sodium levels and BP control; (2a) to determine the feasibility and preliminary efficacy of delivering an SRD intervention focused on changes in metabolomic profiling and reduction of urinary sodium level and BP; (2b) to estimate the effect size of the SRD intervention on metabolomic profiling, urinary sodium level, and BP metrics and (3) to examine the association of the SS candidate gene with urine metabolites, sodium excretion, and BP control.

The study results will increase knowledge regarding how the SRD alters the urinary metabolome in pre-hypertensive patients, investigating associations of salt sensitivity and within- and between-person variations in the SRD intervention, and exploring how these alterations may improve BP control and cardiovascular health. Also, it will provide foundational information for future work on developing personalized nutrition interventions to reduce dietary sodium intake through identified mechanisms.

3. Objectives and Endpoints *All data points collected in the study should support an objective or have a regulatory purpose. Complete the table – add rows as needed.*

3.1. Objective(s) *Clearly and concisely define the primary and secondary outcomes.*	**3.2. Endpoint** *Clearly define the endpoints. (endpoints are the basis for concluding that the objective has been met).*	**3.3. Justification for Endpoint** *Briefly explain why the endpoint(s) were chosen.*
• To examine the associations of urine metabolites with urinary sodium levels and BP control.	• The metabolite profiles identified in this study will provide insight into the mechanisms underlying changes in sodium intake and BP levels in hypertension.	• Previous studies in our team found some novel metabolites which are reflecting dietary sodium intake using targeted urinary metabolites.
• To determine the feasibility, preliminary efficacy, and estimate of the effect size of sodium-	• Findings of the study will help develop effective interventions to improve sodium restricted	• Numerous studies have shown that low-sodium diet can reduce blood pressure and improve cardiovascular outcomes.

restricted diet intervention on changes in metabolomics profiling and BP reduction among 40 pre-hypertensive patients.	diet adherence and cardiovascular outcomes.	
• To examine the association of the salt sensitivity candidate genes with urine metabolites, sodium excretion, and BP control.	• Findings of the study will explain how the salt sensitivity moderates the relationships among urine metabolites, sodium excretion, and BP control.	• Previous studies found some genetic variants which are relevant to the salt sensitivity, and these genetic variants are highly associated with hypertension.

4. Rationale

Briefly state the reason for conducting the clinical trial.

Hypertension is a major public health concern. However, the effects of a sodium-restricted diet (SRD) on blood pressure vary, and adherence to an SRD is not optimal. In addition, few studies have examined individuals' metabolic responses to the SRD. In a secondary analysis, we further will examine genetic variants associated with salt sensitivity and whether such a genetic component is associated with sodium excretion and BP control.

5. Study Design

5.1. Number of Groups/Arms	2	**Group name(s)**	Group 1: Modified Sodium Watcher Program + Digital self-monitoring Group 2: Usual care + Digital self-monitoring

5.2. Overall Design

Select all applicable

☒	**Randomization**	☒	**Cluster Randomized**
☐	**Group-Sequential**	☐	**Adaptive Design**
☐	**Parallel Design**	☐	**Placebo-Controlled**
☐	**Superiority**	☐	**Equivalence** ☐ **Non-inferiority**
Device ☐	Pilot	☐	Pivotal ☐ Post-Approval
Drug/Biologic ☐	Phase 1 ☐ Phase 1/2 ☐ Phase 2 ☐ Phase 2/3 ☐ Phase 3 ☐ Phase 4		
☐	**Dose escalation**	*If yes, details →*	
☐	**Dose ranging**	*If yes, details →*	
☐	**Sub-studies**	*If yes, details →*	

5.3. Other Design Details: This will be an 8-week randomized controlled trial. The study will start after the IRB approval from UT Health San Antonio. Subjects recruitment will be performed in the communities and utilized EHR (Electronic Health Record) and data collection will be conducted at UT Health San Antonio School of Nursing. Bio-specimen (blood sample) will be transported to and processed in the laboratories of Center for Renal Precision Medicine and School of Nursing at UTHSCSA.

6. Study Population

6.1. Study Population(s) Label/Name	6.2. Identify the criteria for inclusion	6.3. Identify the criteria for exclusion
To add more populations – select a row, copy & paste	*The criteria that every potential participant must satisfy, to qualify for study entry.* All individuals in this study population must meet all of the inclusion criteria in order to be eligible to participate in the study	*The characteristics that make an individual ineligible for study participation.* All individuals in this study population meeting any of the exclusion criteria at baseline will be excluded from study participation.
• 40 Pre-hypertensive patients	• Aged 40 or older. • Systolic blood pressure of 120-159 mmHg or diastolic blood pressure of 80-99 mmHg, whether or not taking blood pressure medications.	• Participating in another related research study • Cardiovascular disease event (e.g. stroke, myocardial infarction) in prior 6 months

	• Smartphone with a data plan • Valid email address • Willing and able to participate in online study videoconferencing visits (Zoom) • Reads and writes in English	• Active cancer • Recent hospitalization due to psychiatric condition or event • Pregnancy or breastfeeding - current or planned during the study period • Documented dementia • Prisoners • Diabetes Diagnosis • Heart Failure Diagnosis

6.4. Will screen failures be allowed to <u>re-screen</u> at a later date?	☒	**No**	☐	**Yes**	*If yes, describe criteria below ↓*

7. Study Intervention(s) being tested or evaluated

This can include prevention, diagnostic or therapeutic interventions (e.g., drug or device) or educational, health services or basic science interventions (e.g., educational program, health care delivery model, or examining basic physiology)

- Modified Sodium Watchers Intervention Group (IG): The modified Sodium Watchers Program intervention consists of 8 weeks of education sessions (45 minutes) for gradual reduction to low salt foods that will be held at the subjects' preferred time delivered to their homes using Zoom which is a video conferencing program through the subject's personal computer or smartphone. In addition, goal setting for SRD and digital self-monitoring using Fitbit and its companion app, and wireless BP monitor will be used over 8 weeks.
  - Understanding hypertension
  - Low sodium diet in hypertension
  - Keeping a food diary
  - Taking a blood pressure
  - Identify barriers in following low sodium diet
  - Strategies to overcome barriers

- Usual Care Control Group (CG): The 20 subjects will receive their routine medical and nursing care for pre-hypertension that consists of a recommendation to follow SRD and take medications as prescribed. Usual care consists of recommendations to follow an SRD, but without explicit skills training including instructions on gradual adaptation to sodium restricted diet, follow-up of progress or provision of monitoring. In addition, digital self-monitoring using Fitbit and its companion app, and wireless BP monitor will be used over 8 weeks.

8. Protocol-Directed procedures, items, services or tests

List all procedures directed by the study plan - including items or services provided as part of routine or conventional care and those needed to diagnosis or treat research related complications.

Important Note – The protocol directed procedures listed must match those in the Schedule of Activities (attachment)

8.1. Drugs *(trade and generic, dosage, route of administration)*

N/A

8.2. Devices

All health devices, including fitness tracker and wireless BP monitor will be provided to each participant by the study team.

8.3. Biologics

N/A

8.4. Laboratory Tests

<u>Blood test:</u>

A total 4.0ml of peripheral blood will be drawn into two EDTA tube during pre-test. The EDTA tube will be centrifuged at 4,000 rpm +4^{o}C for 10 minutes, then serum will be transferred into an Eppendorf tube and stored at -80^{o}C. The Illumina Infinium system will be used for high-throughput genotyping of single nucleotide polymorphisms (SNPs) using microarrays. Genotyping will be conducted by Biobanking and Genome Analysis Core Laboratory Center.

<u>Urine test:</u>

Each participant will be asked to complete two 24-hour urine collections at baseline and 8-week and the containers and instructions for 24-hour urine collection will be given to participants at the baseline visit. The PI will visit the participant's home to pick up the urine sample at their convenience by following general precautions such as wearing a face mask and social distancing.

Dr. Sharma's Center for Renal Precision Medicine lab specializes in metabolomics analysis and will use the targeted capillary electrophoresis/mass spectrometry (CE/MS) method for 48 amino metabolites using the 24-hour urinary sample.

Sodium, 24-hour urine with creatinine will be assessed using the 10 mL urine aliquot. The urinary sample will be sent to Quest Diagnostics.

8.5. Imaging Procedures

N/A

8.6. Other Research Procedures *(e.g., other safety and efficacy assessments.)*

Digital self-monitoring for diet and in-home monitoring of BP will be recorded automatically via wearable fitness tracker and wireless BP monitor over 8 weeks. The following data will be collected by self-reported questionnaire or relevant health equipment. Informed consent will be obtained either at pre-study visit (Day -1) or baseline visit (Day 1).

- Individual characteristics (baseline): We will collect demographic information such as age and gender.
- Physical Assessment (baseline and 8-week): Height, weight, and blood pressure will be measured at baseline and 8-week.

8.7 Attach a Schedule of Activities (SOA) Excel File [Download the Template here: *Schedule of Activities]*	*Check to indicate that the SOA Excel File is attached →* ☒

9.	**Preparation/Handling/ Storage/Accountability of Investigational Drug, Biologic, or Device**
☒	*N/A - This study does not include any investigational products (e.g. drugs, devices or biologics)*
☒	*N/A - An Investigator Brochure is attached*
☒	*N/A - A Drug/Device Manual is attached*

9.1. Acquisition and accountability

State how the study intervention and control product will be provided to the investigator. Describe plans about how and by whom the study intervention will be distributed, including participation of a drug repository or pharmacy, and plans for disposal of expired or return of unused product.

N/A

9.2. Formulation, Appearance, Packaging, and Labeling

Describe the formulation, appearance, packaging, and labeling of the study intervention and control product, as supplied. Information in this section can usually be obtained from the IB or the package insert, or device labeling. This section should include the name of the manufacturer of the study intervention and control product.

N/A

9.3. Product Storage and Stability

Describe storage and stability requirements (e.g., protection from light, temperature, humidity) for the study intervention and control product. For studies in which multi-dose vials are utilized, provide additional information regarding stability and expiration time after initial use (e.g., the seal is broken).

N/A

9.4. Preparation

Describe the preparation of the study intervention and control product, including any preparation required by study staff and/or study participants. Include thawing, diluting, mixing, and reconstitution/preparation instructions in this section. For devices, include any relevant assembly or use instructions.

N/A

10. Study Intervention Additional Details

10.1. Measures to Minimize Bias: Randomization and Blinding

This section should contain a description of randomization and blinding procedures (if applicable to the study design). It should include a description or a table that describes how study participants will be assigned to study groups, without being so specific that blinding or randomization might be compromised. Plans for the maintenance of trial randomization codes and appropriate blinding for the study should be discussed. The timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unblinding may occur and who may unblind. Provide the criteria for breaking the study blind or participant code. Discuss the circumstances in which the blind would be broken for an individual or for all participants (e.g., for serious adverse evets (SAEs)). Indicate to whom the intentional and unintentional breaking of the blind should be reported.

- Subjects (N=40) will be randomized in a 1:1 ratio into two groups using a computer program that generates random numbers to receive modified Sodium Watchers intervention. Everyone will receive a baseline and end of study visits.

- Subjects randomized to (Group 1) intervention group (IG) will be asked to follow the modified Sodium Watchers Program intervention along with goal setting for low salt foods. Each subject will be registered to assign a unique ID in the Connected Health Platform developed by the Center on Smart and Connected Health Technologies at UT Health Science Center San Antonio (UTHSCSA) and each account from the individuals' wireless and wearable devices (Fitbit and BP monitor) will be connected to his or her unique ID through this platform. Subjects will be instructed to log their activities in real-time, including food intake and in-home BP monitoring using Fitbit and accompanied mobile app and BP monitor. Through the Connected Health Platform, the Fitbit app and BP monitor will transmit the data of the intervention group to the research team. The PI will remotely track user engagement and will call participants if they fail to measure any behavior for 3 days using "Sync function" or subscribing to "Alerts" which will alert us when a user has an inactive or invalid status.

- Subjects randomized to (Group 2) control group (CG) will be asked to follow usual care which is based on their routine medical and nursing care for pre-hypertension that consists of a recommendation to follow SRD and take medications as prescribed. The subjects will receive wireless and wearable devices (Fitbit wristband, BP monitor). Each subject will be registered to assign a unique ID in the Connected Health Platform at the baseline and each account from the individual's wireless and wearable devices (Fitbit and BP monitor) will be connected into their unique ID through this platform. Subjects will be instructed to log their activities in real-time, including food intake and in-home BP monitoring using Fitbit and accompanied mobile app and BP monitor. Through the Connected Health Platform, the Fitbit app and BP monitor will transmit the data of the IG to the research team. The intervention nursing research assistant will remotely track user engagement and will call participants if they fail to measure any behavior for 3 days using "Sync function" or subscribing to "Alerts" which will alert us when a user has an inactive or invalid status.

- Both Group 1 and Group 2 participants will receive information sessions.

10.2. Study Intervention Compliance

Define how adherence to the protocol (e.g., administration of study intervention, use of device,) will be assessed, and verified (if applicable, e.g., plasma assays, electronic monitoring devices, daily diaries).

All research staff involved in this study will be trained to adhere to the study protocol when performing relevant study activities. They will have access to the most current protocol. In addition, mobile health devices will be used in Control group to monitor their compliance with device usages and their dietary intervention adherence. Further, we will take several steps to minimize participant attrition including providing reimbursement and collecting multiple contact information (cell phone, home phone, email addresses) from the participants in order to remind them of the scheduled visits and intervention sessions. We will also provide periodic updates and send thank you note to participants to remind them of the study and the importance of their support. The information gained from the pilot project will inform future SRD interventions to improve SRD adherence and cardiovascular outcomes.

10.3. Permitted Concomitant Therapy

This section should be consistent with the medication restrictions in the inclusion/exclusion criteria previously listed. Describe how allowed concomitant therapy might affect the outcome (e.g., drug-drug interaction, direct effects on the study endpoints).

Participants in both groups won't be restricted from their previous antihypertensive medications. All relevant data, including medication usage and other forms of therapy, will be considered when conducting data analysis wherever necessary to avoid or minimize its effects on study endpoints.

10.4. Rescue Medicine

List all medications, treatments, and/or procedures that may be provided during the study for "rescue therapy" and relevant instructions.

☒ *N/A, no rescue medicine*

11. Study Intervention Discontinuation

11.1. Discontinuation of Study Intervention

Describe the criteria for discontinuing the study intervention (e.g., halting rules), including any monitoring test(s) and associated clinical decision point(s). Include reasons for temporary discontinuation of the study intervention (e.g., type and quantity of adverse events), clearly stating the length of time, if applicable, and describe the data to be collected at the time of study intervention discontinuation and approaches for restarting administration of or re-challenging with study intervention.

This is expected to be a minimum risk study with behavioral diet interventions. All participants will be allowed to discontinue the study at any time. In addition, participants' blood pressure will be monitored by mobile device. Should any unusual readings (e.g.

unusual low/high blood pressure), which may threaten participant's health, are identified for a participant, the study team will discontinue the study intervention in this participant.

11.2. Continued Follow-up Discontinuation of Study Intervention

Describe efforts that will be made to continue follow-up of participants who discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Reasonable efforts must be made to undertake protocol-specified safety follow-up procedures to capture adverse events (AE), serious adverse events (SAE), and unanticipated problems involving risks to subjects or others (UPIRSOs).

This is expected to be a minimum risk study with dietary interventions. All participants will be allowed to discontinue the study at any time. Despite study intervention termination, it is optional for participants to continue use mobile devices to monitor their health status.

12. Statistical Considerations

12.1. Statistical Hypotheses

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.

We hypothesize that compared with those in the control group (usual care), the subjects in the intervention group (modified Sodium Watcher Program-Hypertension) will show;
- Hypothesis 1: a trend for reduced urinary sodium excretion
- Hypothesis 2: a trend for improved BP control

12.2. Sample Size Determination

Include number of participants to recruit, screen, and enroll to have adequate power to test the key hypotheses for the study. Provide all information needed to validate your calculations and judge the feasibility of enrolling and following the necessary number of participants.

Given the pilot nature of the study, we will recruit 40 participants and conduct a stratified randomized clinical trial. Specifically, 40 subjects will be recruited, and block randomized to either an intervention or a control group in a 1:1 ratio. Per power analysis, the study will be underpowered; therefore, quantitative outcomes will be interpreted only as feasibility and pilot data. A sample size of 40 subjects will give us adequate sample size to provide meaningful confidence intervals for our estimates of feasibility and preliminary effects. With this overall sample size, we expect to have sufficient diversity of input on the intervention components to plan refinements prior to testing in a larger intervention trial.

12.3. Populations for Analyses

Clearly identify and describe the analysis datasets (e.g., which participants will be included in each).

For data analysis, we will include data from study participants who have completed baseline and follow-up survey, and anthropometric and biomarker measurements.

12.4. Statistical Analyses

Include analysis of primary efficacy endpoints, secondary endpoints, safety analyses, and any planned interim analyses

Data analysis will be performed with SAS (Cary, NC) version 9.4 and R (Vienna, Austria) version and 3.6+. After verifying the normality of distribution of the continuous variables, the mean and standard deviations will be calculated. If data are not normally distributed, log transformation will be conducted. All analyses will also be conducted after controlling for age, gender, and BMI.

Specific Aim 1: Using pre-test data, random forest will be applied to identify associations between 48 amino metabolites, BP phenotypes (including SBP or DBP), and 24-hour urinary excretion to predict the classification of study subjects and will be achieved by R program. For urinary metabolites nominated by the random forest analysis, generalized linear model (GLM) will further be performed to generate p values and false discovery rates (FDR) to correct for testing multiple urinary metabolites using the Benjamini-Hochberg procedure.

Specific Aim 2a: Using both pre and post-test data, feasibility will be assessed by measuring: 1) % subjects who come to the 8-week follow-up; 2) number of education sessions attended online (intervention group); 3) % days that subject log his/her meals using mobile dietary app; and, 4) % days that subject log in-home BP using BP monitor device. The preliminary effect of SRD on the outcome variables will be tested by using a repeated measures analysis of variance (RM-ANOVA) with one between-subjects factor (intervention and control) and one within-subject factor (pre-test and post-test).

Specific Aim 2b: We estimate that 20 participants/group will provide sufficient data for estimating intervention effects on metabolomic profiling and reduction of urinary sodium level and BP. The estimated effect size will be used for sample size justification and power analysis for a future larger study.

Specific Aim 3: Using pre-test data, analysis of targeted genotyping will be conducted by the R program. A moderator analysis will be used to determine whether the relationship between urine metabolites or sodium intake and BP depends on the SS candidate gene (GNAI2 SNPs).

All testing will be two-sided and $p<0.05$ or FDR < 10% will be considered as significant.