

University of Kansas Medical Center
RESEARCH PROTOCOL INVOLVING HUMAN SUBJECTS
TEMPLATE WITH GUIDANCE

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Principal Investigator: Jason Stubbs, M.D.

Study Title: Impact of Rifaximin Therapy on Intestinal Byproducts in Chronic Kidney Disease

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(NOTE: not all sections of this template will apply to all projects. "N/A" is an acceptable response.)

I. Purpose, Background and Rationale

A. Aim and Hypotheses

1. Begin with a brief introduction to describe the origin and importance of the study.

Trimethylamine-N-oxide (TMAO) is a circulating organic compound produced by the metabolism of dietary L-carnitine and choline. TMAO was recently identified to directly induce atherosclerosis in rodents and is strongly associated with the incidence of cardiovascular events in humans. The proposed investigation is a prospective pilot study to assess the impact of alterations in the intestinal flora by short-term antibiotic suppression (with Rifaximin) and to measure its effect on serum TMAO levels in patients with advanced-stage (stage IV-V) chronic kidney disease.

2. Clearly state the aim(s) and hypothesis(es), listing them by number if there is more than one.

Hypothesis: Treatment of CKD patients with Rifaximin will suppress the bacterial flora that are responsible for the generation of trimethylamine, a TMAO precursor, and subsequently reduce serum TMAO concentrations.

Primary Aim:

1. The primary outcome of interest will be the change in serum TMAO concentrations (post-therapy minus pre-therapy TMAO) following Rifaximin administration for 10 days.

Secondary Aims:

1. To measure the change in urine TMAO
2. To measure the change in serum endotoxin, IL-6, IL-8, TNF-alpha levels
3. To measure the alteration of bowel microbiota
4. To assess the above changes in steady state, 2 weeks after completion of therapy

B. Background and Significance

1. Study Significance: what the proposed research is intended to accomplish and the importance of the results

The proposed investigation is a prospective pilot study to assess the impact of alterations in the intestinal flora by short-term antibiotic suppression (with Rifaximin) and to measure its effect on serum TMAO levels in patients with advanced-stage (stage IV-V) chronic kidney disease. Results may lead to future investigations to better understand how alterations in TMAO metabolism may impact cardiovascular outcomes in patients with chronic kidney disease.

2. Describe the facts, events, and thought processes leading to the currently proposed research project.

We previously postulated that TMAO levels would be substantially elevated in patients with CKD, and to test this hypothesis we performed a cross-sectional analysis of serum TMAO concentrations in a cohort of patients with varying levels of CKD and normal healthy controls. In this study, we observed serum TMAO concentrations progressively rise in CKD. We seek to determine if circulating concentrations of TMAO can be reduced by alterations to the gut flora.

3. Literature Review: Summarize any pertinent studies supporting this proposed project. Human studies are preferred; include animal studies only if human data are lacking.

Wang Z., et al. Gut Flora Metabolism of Phosphatidylcholine and Cardiovascular Risk. *Nature* 2011.

- Dietary supplementation of mice with choline, TMAO or betaine promoted up-regulation of multiple macrophage scavenger receptors linked to atherosclerosis, and supplementation of mice with choline or TMAO promoted atherosclerosis.
- Suppression of enteric microflora in atherosclerosis-prone mice inhibited dietary choline enhanced atherosclerosis.
- Prognostic value for the risk of CVD was determined in humans by measuring fasting levels of TMAO and determining its association with prevalent vascular events, including peripheral vascular disease, coronary artery disease and myocardial infarction.
- In atherosclerosis prone mice supplementation with choline was shown to increase aortic atherosclerosis when compared to atherosclerosis prone mice on a normal chow diet.

Koeth RA, et al. Intestinal Microbiota Metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nature Medicine* 2013

- They revealed that subjects with elevated L-carnitine, if also found to have elevated TMAO, had increased prevalence of cardiovascular disease and higher incidence of major adverse cardiovascular events (MI, stroke or death).
- In mice they found that chronic supplementation with L-carnitine resulted in alteration of cecal microbial composition, enhanced synthesis of TMAO, and increased atherosclerosis but not when intestinal microbiota were suppressed.

Tang WH, et al. Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk. *New England Journal of Medicine* 2014.

- Plasma and urinary levels of TMAO and plasma choline and betaine levels were measured by liquid chromatography and online tandem mass spectrometry after they administered a phosphatidylcholine challenge in 40 healthy participants. There were time dependent increases in serum TMAO levels and its D9 labelled isotopologue as well as other choline metabolites after the phosphatidylcholine challenge. The levels were also assessed before and after suppression of bowel flora by use of oral broad spectrum antibiotics (metronidazole 500 mg BID plus Ciprofloxacin 500 mg daily for 1 week) in 6 of the participants. Plasma levels were suppressed after administration of antibiotics but returned after withdrawal of antibiotics.
- They examined the relationship between fasting serum TMAO level and the incidence of major adverse cardiovascular events (death, MI, or stroke) during 3 years of follow up in 4007 patients who underwent elective coronary angiography. Elevated serum TMAO level predicted increased risk of a major adverse cardiovascular outcome after adjusting for traditional risk factors.

Stubbs, Jason, et al. Manuscript currently under consideration

- In order to assess TMAO levels in CKD a cross-sectional study was undertaken in a group of patients with variable degrees of chronic kidney disease ranging from normal to ESRD (n=104). We observed a graded rise in serum TMAO that corresponded to increasing CKD severity. The median concentrations in dialysis-dependent patients was approximately 30 times higher than in control patients (94.4 μ M in ESRD compared to 3.3 μ M in Controls, $P < 0.001$).
- In a second cross-sectional investigation we evaluated TMAO levels compared with prevalent coronary artery atherosclerosis in a subset of subjects with chronic kidney disease undergoing coronary angiography (n=220). We noted a significant correlation between serum TMAO and coronary atherosclerosis burden quantified by modified Gensini scoring ($r = 0.15$, $P = 0.03$ by Spearman correlation). After multivariable adjustment for traditional cardiovascular risk factors the correlation remained significant ($P = 0.048$).

C. Rationale

1. Explain how the background information from the literature supports the current proposed hypothesis(es).

It is a known phenomenon that patients diagnosed with chronic kidney disease (CKD) exhibit a high prevalence of cardiovascular disease which largely accounts for the remarkably high mortality in this group. The average 5-year survival for patients receiving chronic dialysis therapy is approximately 35%, with >50% of this mortality resulting directly from cardiovascular causes (1). It is apparent that patients with chronic kidney disease experience an increased burden of atherosclerosis compared to matched individuals with normal kidney function. The presence of traditional risk factors for the development of atherosclerosis, such as diabetes, smoking and hypertension, do not fully account for the accelerated atherosclerosis observed in CKD patients. From this observation it appears that patients with altered renal function possess unique risk factors that contribute to the disease pathophysiology in this setting.

One potential, yet unproven, risk factor for the development of atherosclerosis in patients with chronic kidney disease is trimethylamine-N-oxide (TMAO). TMAO is a circulating organic compound produced by enteric microbial metabolism of dietary L-carnitine and choline (2,3) which results in formation of trimethylamine (TMA), a metabolite that is absorbed from the intestine and subsequently oxidized by hepatic flavin monooxygenase enzymes to form TMAO (6). TMAO has been observed to directly induce atherosclerosis

in rodents and was found to be strongly associated with the incidence of cardiovascular events in humans (2-5). In normal physiologic conditions, circulating TMAO is rapidly removed from circulation primarily by excretion into the urine (7). We previously postulated that TMAO levels would be substantially elevated in patients with CKD, and to test this hypothesis we performed a cross-sectional analysis of serum TMAO concentrations in a cohort of patients with varying levels of CKD and normal healthy controls. In this study, we observed serum TMAO concentrations become markedly elevated in the advanced stages of CKD, with end-stage renal disease (ESRD) patients exhibiting mean levels 30-fold higher than healthy controls.

If TMAO contributes to atherosclerosis formation in CKD patients, therapeutic interventions to reduce TMAO production may represent a method to reduce cardiovascular morbidity and mortality in this population. Prior studies suggest that short-term suppression of gut flora with antibiotics dramatically decreased TMAO levels in patients with normal kidney function (5); however, this approach has not yet been tested in patients with CKD that exhibit much higher serum levels of TMAO.

Rifaximin is a novel antibiotic that is currently approved for treatment of hepatic encephalopathy in patients with end-stage liver disease. Rifaximin demonstrates little systemic absorption, with 97% of the parent drug being excreted unchanged in the feces (9). Its primary use is to target pathogenic intestinal bacteria in various disease states, including cirrhosis and traveler's diarrhea. In this study we seek to evaluate whether Rifaximin will decrease levels of TMAO in patients with advanced kidney disease and to study the effects of Rifaximin on the intestinal microbiome of patients with CKD.

2. Explain how the performance of this proposed project will advance our knowledge in this field, and/or improve our understanding of the disease or physiological condition being studied.

This study will determine if elevated levels of TMAO in CKD are at least partially dependent on the presence of certain intestinal flora and if serum TMAO levels are modifiable by therapy with Rifaximin.

3. Explain how this study might improve the diagnosis or treatment of the disease being studied (if applicable), or advance knowledge in the field.

This will provide preliminary evidence to support the intestinal flora as a target for reducing TMAO levels in CKD patients.

II. Research Plan and Design

- A. Study Objectives:** List the broad research goal and specific aims of the project in a clear, concise manner using lay language. List primary and secondary; include statement of purpose. (NOTE: the Department of Biostatistics is available to assist with study design, sample size calculation, and statistical analysis matters. Contact 588-4795 or see Consulting and Collaboration at [Department of Biostatistics](#))

Primary objectives: To determine if administration of Rifaximin for the period of 10 days reduces serum TMAO levels.

Secondary Objectives: To determine if Rifaximin additionally alters urine TMAO, serum endotoxin, IL-6, IL-8, TNF-alpha, and the composition of the intestinal flora and the composition of the intestinal flora as compared to placebo.

- B. Study Type and Design:** Indicate type of study (e.g. cross-sectional vs. longitudinal; multicenter, controlled, cross-over, randomized, chart review, case cohort, non-interventional, etc) and describe how the study is to be conducted to accomplish specific aims of the project.

This is a prospective, randomized, placebo-controlled, double-blinded interventional pilot study.

C. Sample size, statistical methods, and power calculation

1. Describe the analytic and statistical methods to be used, including the method of randomization and randomization ratio (1:1; 3:1; etc) if randomization is used.

We seek to enroll a total of 30 patients for this investigation, 15 participants will receive Rifaximin and 15 control patients will receive placebo with a 1:1 randomization ratio. No prior data are available on the impact of rifaximin on serum TMAO levels in CKD patients; therefore, our sample size determination is based on a conservative estimate of the predicted change in TMAO and the expected response variability between study participants. Based on an expected true mean change in serum TMAO concentrations in matched pairs of -30% with a standard deviation of -30% change, we will need to study 13 subjects to be able to reject the null hypothesis that this response difference is zero with 90% power and type I error probability of 0.05. We plan to enroll 15 subjects in our intervention group in case the observed variability in this response is greater than our initial prediction.

2. If blinding (masking) is involved, describe the procedures, indicate who has the code to the blind, and the circumstances and procedures for breaking the code.

Blinding will be involved in this study. The primary investigator, study participants, and team members involved in serum/urine end point analyses will be blinded to treatment arm. The investigational pharmacy is responsible for study group assignment and is not blinded. The study team member involved in the fecal bacterial genome analysis will not be blinded, as knowledge of treatment arm will be necessary for the accurate assessment of changes in fecal microbiome composition among study participants.

3. State the maximum number of subjects to be enrolled in each group. Include power calculations to explain what can be studied with the proposed sample size and specify the statistical tests that will be used to test **each** hypothesis. If the research project needs to be pilot tested, state how many subjects will be enrolled in the pilot test and how the procedures for the pilot test will differ from those used in the research protocol.

There will be a total of 30 subjects enrolled; 15 participants will receive Rifaximin and 15 will receive placebo.

- D. Subject Criteria (See Vulnerable Populations appendix, if applicable):** Include age range, gender, disease, and stage of treatment. Justify excluding subjects based on race or

gender (including child-bearing potential for women), age (children), or non-English speakers.

1. Inclusion criteria: State the criteria for inclusion in the study in a specific and detailed manner.

- Patients 18 years of age or older
- Stage IV-V chronic kidney disease (eGFR \leq 39 ml/min/1.73m²)

2. Exclusion criteria: State the criteria for excluding potential subjects from the study in a specific and detailed manner.

- Patients with normal renal function or those with less advanced kidney disease
- Inability or unwillingness to provide consent
- Patients undergoing hemodialysis or peritoneal dialysis therapy or those who have undergone organ transplant
- Patients who may be pregnant
- Hemodynamically unstable patients
- Patients with liver failure, pancreatic insufficiency, or inflammatory bowel disease
- Patients with ongoing or recent infection and those with history of C-diff infection
- Patients with abnormal bowel structure secondary to surgical or anatomic variations
- Patients on certain medications including immunosuppressants, antidiarrheal agents, and current or recent (within the last 2 months) use of antibiotics

3. Withdrawal/Termination criteria: Include the specific circumstances in which the subject's participation will be terminated by the investigator. Include any necessary safety precautions to be applied to those who withdraw (tapering drug doses, evaluative x-ray, etc.)

Participation may be terminated if subject is found to not meet the inclusion or exclusion criteria. Participants may withdraw at any time.

4. Clarify whether a study subject may participate in another research study while participating in this research study.

Patients should not participate in another research study while taking the study medication but exceptions may be made dependent on the nature of the other research study.

E. Specific methods and techniques used throughout the study

1. **Laboratory tests:** Methods for collecting specimens and data. Indicate purpose, amount and timing of tests performed (e.g., blood tests, urine tests, CSF tests, EKGs, etc.). Include specific test components and estimated volume and type of specimens needed for each test.

Serum and urine samples (30ml each) will be collected at the baseline and post-therapy visits (day 0, day 11, and day 25) for measurement of TMAO, endotoxin, IL-6, IL-8, and TNF α levels. Fecal specimens will be collected at these same time points in order to assess changes in the intestinal microbiome after administration of Rifaximin.

2. **Study Procedures:** Describe each procedure to be used in the study, including the instruments used, time required for each procedure, cognitive assessments, etc.

Blood, urine and stool samples will be collected for analysis. Aside from venipuncture there will be no other procedures.

3. Clearly indicate which procedures, tests, visits, etc., are parts of usual standard therapy and which are performed solely for research purposes. Make it clear which tests are routinely performed for clinical care but are providing data for the research (and are billable to insurance companies), and which tests are only performed for research purposes (not billable to insurance companies).

Any samples collected during the specified research appointments will be used for research purposes only and will not be billed.

4. Describe the fate of any body component (blood, CSF, bone marrow, etc.) used in the study, emphasizing confidentiality of labeling of the sample and the sample's destruction or storage.

Blood, urine and stool samples will be labeled with study information and by the subjects' unique study ID. They will be analyzed in the lab of Dr. Jason Stubbs and the lab of Dr. Tom Nolin at the University of Pittsburgh Medical Center. Additional serum and urine samples will be stored in a -80°C freezer in Dr. Stubbs' lab for those patients consenting for sample storage.

5. **Timeline:** Consider attaching a study flow chart illustrating subject visits and tests or procedures to be performed at each visit **and/or** include a chart or graph format that reflects the project activities and anticipated time frame of completion.

Day 0 (baseline visit): Consented participants will have an initial appointment dedicated to the collection of baseline samples and study medication will be dispensed at this visit. Complete review of the patient's history and physical examination will be recorded. All study participants will continue receive standard of care treatment for their chronic kidney disease. Study participants will be provided with a 10-day course of Rifaximin. A medical history will be obtained, including current medications, comorbid conditions, lifestyle indicators (such as tobacco and alcohol use), review of recent laboratory studies (such as BMP, CBC, and lipids); this information will be recorded and stored on all study participants. Serum, urine and fecal samples will be collected at this

visit. On Day 1, study participants will begin Rifaximin 550mg PO BID or placebo for a total of ten days duration.

Day 11 (post-therapy follow-up visit): Study participants will provide stool samples within 24 hours of their last dose of Rifaximin or placebo. Serum and urine samples will be drawn at this study visit. Vital signs will be checked and a brief interview will be conducted to assess for any potential adverse reactions to the study medication. Follow up visits can be arranged at the patient's request if needed.

Day 25 (steady state follow-up visit): Study participants will provide stool samples. Serum and urine samples will be drawn at this study visit. Vital signs will be checked and a brief interview will be conducted to assess any recent health changes.

F. Risk/benefit assessment: As appropriate, address the following parameters as each relates to the individual subject in the study. Be sure to include consideration of study assignment (Arm A, Arm B, placebo, active substance, etc):

1. Physical risk: Rifaximin has known potential side effects. Since this medication has primarily been studied in patients with advanced liver disease, it is unclear which of these side effects are unique to this population of patients. The most common side effects reported in patients with liver disease included peripheral edema, ascites, nausea, dizziness, fatigue, headache, muscle spasms, pruritus, abdominal pain, and rash. Most common side effects in patients without liver disease are believed to be gastrointestinal in nature; mainly including nausea, abdominal pain/bloating, and diarrhea. Serious reactions have been reported by the manufacturer with this therapy, including superinfection with clostridium difficile, hypersensitivity reaction, angioedema, anaphylaxis, and exfoliative dermatitis. The risks associated with venipuncture in order to obtain blood samples carries a small risk of excessive bleeding, vasovagal syncope, hematoma/infection at the site of vein puncture, and potentially multiple punctures in order to locate veins.
2. Psychological risk: No anticipated risk.
3. Social risk: No anticipated risk.
4. Economic risk: Low anticipated risk. The patient will have no cost associated with the study. In the instance of an adverse event, normal medical treatment should be sought and insurance billed as is standard.
5. Potential benefit of participating in the study:
 - a. To the individual subject and/or parent if any: Individuals are not expected to benefit directly from participation in this study.
 - b. To the population from which the subject is drawn: This study may provide critical insight into understanding the altered metabolism of TMAO in CKD and provide preliminary evidence to support the development of future large-scale studies.
 - c. To science, society, and humanity in general: This may lead to development of interventions which could decrease the burden of cardiovascular disease in patients with chronic kidney disease, ultimately reducing health care costs and outcomes for patients with these conditions.

G. Location where study will be performed: Indicate where all portions of the study will take place and where the research subject's records will be kept.

This study will be conducted at the University of Kansas Hospital with patients being recruited from the outpatient nephrology clinics. Records will be kept on secure spreadsheets that can only be accessed by the study team.

H. Collaboration (with another institution, if applicable): If this is a collaborative effort with another institution, explain the collaboration and attach a copy of their current IRB protocol, consent form and approval.

Serum samples will be sent for analysis to Dr. Tom Nolin at the University of Pittsburgh Medical Center for measurement of serum TMAO levels.

I. Personnel who will conduct the study, including:

1. Indicate, by title, who will be present during study procedure(s):

Investigators: Jason Stubbs, MD., Cassandra Kimber, DO., or Kerri McGreal, MD

Study Coordinators: Cathy Creed, Debbie Griffin, Judy Vun, Michelle Hansen

2. Primary responsibility for the following activities, for example:

- a. Determining eligibility: Jason Stubbs, MD, Cassandra Kimber, DO, Imran Gani, MBBS or Kerri McGreal, MD.
- b. Obtaining informed consent: Jason Stubbs, MD, Cassandra Kimber, DO, Imran Gani, MBBS or Kerri McGreal, MD.
- c. Providing on-going information to the study sponsor and the IRB:
Investigators: Jason Stubbs, MD., Cassandra Kimber, DO., Imran Gani, MBBS, or Kerri McGreal, MD.
Study Coordinators: Cathy Creed, Debbie Griffin, Judy Vun, Michelle Hansen
- d. Maintaining participant's research records:
Investigators: Jason Stubbs, MD., Cassandra Kimber, DO., Imran Gani, MBBS, or Kerri McGreal, MD.
Study Coordinators: Cathy Creed, Debbie Griffin, Judy Vun, Michelle Hansen
- e. Completing physical examination:
Investigators: Jason Stubbs, MD., Cassandra Kimber, DO., Imran Gani, MBBS or Kerri McGreal, MD.
- f. Taking vital signs, height, weight:
Investigators: Jason Stubbs, MD., Cassandra Kimber, DO., Imran Gani, MBBS, or Kerri McGreal, MD.
Study Coordinators: Cathy Creed, Debbie Griffin, Judy Vun, Michelle Hansen
- g. Drawing / collecting laboratory specimens:

Study Coordinators: Cathy Creed, Debbie Griffin, Judy Vun, Michelle Hansen

Investigators: Jason Stubbs, MD., Cassandra Kimber, DO., Imran Gani, MBBS, or Kerri McGreal, MD

- h. Performing / conducting tests, procedures, interventions, questionnaires:

Investigators: Jason Stubbs, MD., Cassandra Kimber, DO., Imran Gani, MBBS, or Kerri McGreal, MD

Study coordinators: Cathy Creed, Debbie Griffin, Judy Vun, Michelle Hansen

- i. Completing study data forms:

Study coordinators: Cathy Creed, Debbie Griffin, Judy Vun, Michelle Hansen

Investigators: Jason Stubbs, MD., Cassandra Kimber, DO., Imran Gani, MBBS, or Kerri McGreal, MD

- j. Managing study database:

Investigators: Jason Stubbs, MD., Cassandra Kimber, DO., Imran Gani, MBBS, or Kerri McGreal, MD

Study coordinator: Judy Vun, Michelle Hansen

J. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan

1. Please note that any study proposal with more than minimal risk must include a data and safety monitoring plan. Elements of the plan include:
 - a. Persons/groups who will review the data (study team; independent safety monitor, data monitoring committee or formal DSMB)
The study team
 - b. Data/events that will be reviewed
Adverse reactions, early discontinuation, tolerance and side effects.
 - c. Frequency of review
After ten days of therapy and PRN.
 - d. Types of analyses to be performed
Patient interview
 - e. Safety-related triggers that would cause the PI to stop or alter the study
Multiple adverse reactions may lead the team to reconsider the dose or the chosen agent.
2. Describe how adverse events and unanticipated problems will be ascertained and handled. Explain exactly which type of problems will be considered serious and reported to the IRB. The reporting timeframe should also be detailed.

Participants will be given contact information for KU nephrology on-call numbers. There have been rare serious adverse medication reactions with Rifaximin, including intestinal

superinfection, C-diff associated diarrhea, angioedema, or exfoliative dermatitis. In these instances a patient will be instructed to seek emergency medical attention.

3. Explain exactly what will happen if a patient experiences an adverse event or other problem (for example, will discontinue study participation).

Patients will be asked to report any adverse reaction. They will be given the contact information for the nephrology nursing line who can contact a member of the study team. This is a short study lasting 25 days and patients will have 3 total study visits, on day 0, day 11, and day 25.

III. Subject Participation

A. Recruitment:

1. Describe locations from which the subjects will be recruited and what arrangements have been made with other institutions (if applicable).

The initial contact will occur at KU nephrology clinic. There will not be outside institutions involved.

2. Describe by whom and how the recruitment is conducted.

A subject's primary treatment team will be the initial contact to gauge interest in learning about the study. From there a member of the study team will discuss the study in further detail.

3. Attach a copy of advertisements and/or flyers and state where they will be placed.

There will not be advertisements or flyers.

4. Attach a copy of the recruitment letter or introductory statement and describe planned use or distribution of the document.

There will not be a recruitment letter.

- #### **B. Screening Interview/questionnaire:** If an interview or questionnaire will be used for screening, attach a copy and indicate where, how, and who will conduct the interviews and their qualifications. Address how consent to participate in the screening process will be obtained.

Clinic patients will be screened for inclusion and exclusion criteria. If they are appropriate for inclusion in the study they will be approached by their clinical nephrology team members who will assess their interest and willingness to participate in the study. If they are interested in participation a member of the study team will discuss the study in further detail.

C. Informed consent process and timing of obtaining of consent

1. Indicate who will give subjects detailed and comprehensive information about the study and obtain their written consent.

A member of the study team as outlined above.

- 2 Indicate how the consenting process will be structured to ensure independent and thoughtful decision-making, and what steps will be taken to avoid coercion and guarantee confidentiality.

Clinic patients will be screened in advance for inclusion and exclusion criteria. During their clinic visit with their clinical nephrologist, their doctor will ask if they are interested in participating in the study. If the patient expresses interest, a member of the study team will discuss the project with the patient. The consent may be obtained at that clinical visit if time permits for full explanation and patient is agreeable. Alternatively they may take the consent form home for review and a study visit will be arranged at a separate time and location.

- 3 Indicate how, and by whom, it will be determined whether the subject is able to give informed consent, or whether their legal guardian will give informed consent. For subjects whose ability to give informed consent may be compromised by cognitive and/or decisional impairment (examples may include individuals with a psychiatric disorder, an organic impairment, a developmental disorder, or those suffering from a terminal illness, degenerative disease, severe physical handicap or dependence on drugs or alcohol), complete Appendix I.

A member of the study team will determine if a subject is able to consent for the study. This study will not involve patients under the age of 18, pregnant patients, or those who are unable to provide consent.

D. Alternatives to Participation: A statement of alternatives to participation in this research study, if any.

Subjects may choose not to participate in the study. This will not affect their ability to receive care at KU.

E. Costs to Subjects: Indicate what will happen if the subject's insurance company refuses to pay for costs of clinical care when those tests are also used for research purposes. Indicate what will happen if the study subject does not have insurance.

Patients will not incur costs associated with this study.

F. How new information will be conveyed to the study subject and how it will be documented: Articulation of how new information will be conveyed to the study subject and how it will be documented.

Patients will be informed at the time new information is recognized. This will likely be conveyed during a research appointment but if urgent a phone call will be initiated.

G. Payment, including a prorated plan for payment: Indicate how much subjects will receive for each portion of the study and the reimbursement schedule to be used if the subject withdraws or is withdrawn during the study. Indicate if travel costs be reimbursed.

Subjects will not receive payment for participation.

H. Payment for a research-related injury: Information regarding payment for a research-related injury.

Patients will be directed to standard medical care in the event of an adverse reaction and their insurance will be billed accordingly.

IV. Data Collection and Protection

A. Data Management and Security: Describe how data will be collected and protected

1. State the persons/groups who will have access to study data.

Only members of the study team will have identifying information. Information will be de-identified before analysis.

2. Discuss procedures for maintaining subject confidentiality, any special data security requirements, and record retention per the university policy.

All records relative to the research will be treated in confidence, with hard copies of consent forms stored in a locked office in the Kidney Institute. Study spreadsheets will be maintained on secure drives that can only be accessed by study members and agents of the University or federal government who oversee research involving human subjects.

3. State whether human subjects will be identifiable directly or through coded information.

Subjects will be assigned a unique study ID.

4. If data will be coded, state who will maintain and have access to the key to the code.

Only Members of the study team will have access to identifiable study information.

5. State how the data will be linked to the subjects during the study.

By means of a unique study ID. Master sheet linking patients with their ID's will be stored on secure drive as noted above and maintained by the lead study coordinator.

6. State how and where the data will be stored, and how it will be protected.

All records relative to the research will be treated in confidence and stored in the Kidney Institute. Electronically stored information will be maintained on a secure server.

7. Discuss any use of mobile devices for data collection or storage.

Mobile devices will not be used for study collection or storage.

8. Discuss security measures if identifiable data are sent outside KUMC.

Only de-identified information will be sent outside KUMC.

- B. Sample / Specimen Collection:** Describe how samples will be collected at each site. Include how they will be stored, protected, and shared, as applicable. Include length of storage.

Serum and urine samples will be collected on day 0 (prior to antibiotic administration), day 11 and day 25. Patients will be asked to provide a stool sample for future microbiome analysis prior to their baseline visit and within 24 hours of each study visit. The specimens will be labeled with the study ID. Unless consent for long-term blood and urine storage has been obtained, the samples will be destroyed after testing. A separate consent form will be provided for optional blood and urine storage for future testing. Samples will be stored in a -80°C freezer in Dr. Stubbs' lab for those patients consenting for sample storage.

- C. Tissue Banking Considerations:** If samples will be banked for future use, describe the purposes of the future use, how samples will be labeled and with whom they will be shared. Seek further guidance from the IRB if you are creating a repository.

Samples will be labeled with the study information and the participants unique study identification. Samples may be used in further studies involving chronic kidney disease.

- D. Procedures to protect subject confidentiality:** Identify any part of the study that may place subject confidentiality at risk. Describe study procedures to protect subject confidentiality.

The researchers will only use and share information that is needed for the study. Identifying information collected may include such information as name, address, phone, date of birth, or other identifiers. Participants health information will be reviewed at KUMC by Dr. Jason Stubbs, members of the research team, The University of Kansas Hospital Medical Record Department, the KUMC Research Institute and officials at KUMC who oversee research, including members of the KUMC Human Subjects Committee and other committees and offices that review and monitor research studies. Data will be de-identified prior to analysis and prior to outside involvement in the study.

E. Quality Assurance / Monitoring

1. Describe steps to be taken to assure that the data collected are accurate, consistent, complete and reliable. (source data verification, audits or self – assessment)

Self-assessment.

2. Describe whether there are plans to have ongoing third party monitoring.

There is no plan for third party monitoring.

V. Data Analysis and Reporting

A. Statistical and Data Analysis: A description of the statistical methods to be employed in data analysis, including timing of any planned interim analysis

The study will be considered complete when the necessary power is obtained. A paired, two-sided Student's t-test will be used to compare differences in pre-antibiotic and post-antibiotic TMAO levels.

B. Outcome: Describe what results are expected, the criteria for success or failure and the end point of the study.

We expect that our intervention will lead to significant short-term reductions in serum TMAO levels.

C. Study results to participants: List any study results to be given to subjects and indicate how, when and why they will be given.

Study findings may be discussed at the conclusion of the study by participant request.

D. Publication Plan: Describe plans for publication of research results.

Results may be published in abstract form or as part of a peer-reviewed original research manuscript.

VI. Bibliography / References / Literature Cited (choose the applicable title and list citations according to APA or other accepted style in your discipline)

1. US Renal Data System: USRDS 2013 Annual Report, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.
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4. Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, Wu Y, Hazen SL: Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med* 368: 1575-84, 2013.
5. Wang Z, Tang WH, Buffa JA, Fu X, Britt EB, Koeth RA, Levison BS, Fan Y, Wu Y, Hazen SL: Prognostic value of choline and betaine depends on intestinal microbiota-generated metabolite trimethylamine-N-oxide. *Eur Heart J* 35: 904-10, 2014.
6. Lang DH, Yeung CK, Peter RM, Ibarra C, Gasser R, Itagaki K, Philpot RM, Rettie AE: Isoform specificity of trimethylamine N-oxygenation by human flavin-containing monooxygenase (FMO) and P450 enzymes: selective catalysis by FMO3. *Biochem Pharmacol* 56: 1005-12, 1998.
7. Al-Waiz M, Mitchell SC, Idle JR, Smith RL: The metabolism of 14C-labelled trimethylamine and its N-oxide in man. *Xenobiotica* 17: 551-8, 1987.
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9. Xifaxan (rifaximin) [prescribing information]. Raleigh, NC: Salix Pharmaceuticals Inc; March 2014.

APPENDIX I: VULNERABLE POPULATIONS

- I.** If the recruitment plan includes any of the groups noted below, explain how they will be protected and how consent will be obtained. In general, regulations allow subjects identified as part of vulnerable populations to be included if the research cannot be accomplished without their involvement.

This study will not involve vulnerable populations.

- II. Cognitively or decisionally impaired individuals:** These populations include those with a psychiatric disorder, an organic impairment, a developmental disorder, and those with a terminal illness, degenerative disease, severe physical handicap or dependence on drugs or alcohol. The protocol should explain how the appropriate surrogate decision-maker will be identified, in accordance with Kansas state law. Recruitment procedures and materials, and consenting procedures and documents must be submitted.

This study will not involve subjects who are unable to consent for themselves including cognitively impaired subjects.

- III. Children:** Consenting procedures, assent and consent forms must be submitted. Recruitment procedures and materials are also required. Consideration and procedures for re-consent will be required if the minor will attain age 18 years while in the study.

This study will not include anyone under the age of 18.

- IV. Pregnant women:** Federal regulations require that inclusion of pregnant women must be justified by scientific rationale and based upon animal studies when applicable. Please refer to the IRB website for a fact sheet about including pregnant women and fetuses in research. This study will not include pregnant subjects.

- V. Prisoners:** Research involving prisoners requires specific justification and also requires review by an IRB that includes a prisoner representative. Please consult with the IRB office prior to proposing a prisoner population for your research.

This study will not involve incarcerated individuals.

- VI. Students and/or Employees:** to reduce potential coercion or interference with normal job duties, if students or employees are to be recruited as subjects of human research:

- A.** For research involving KUMC students, include a letter of support from the Dean of the School.

Students will not be sought for inclusion in this study.

- B.** For research that specifically targets KUMC employees, explain [see SOP 9]

Employees will not specifically be sought for inclusion in this study.

- C.** If students from a public or private school system are to be recruited, the method of identification of and contact with the students must be explained. It will be necessary to obtain permission from the school's officials to conduct the research at a specific site (school).

This study will not include anyone under the age of 18 including school aged children.

CONSENT FORM

Impact of Rifaximin Therapy on Intestinal Byproducts in Chronic Kidney Disease

Sponsor: The University of Kansas Division of Nephrology and Hypertension

You are being asked to take part in a clinical research study. You qualify to take part in this study because you have chronic kidney disease.

You do not have to participate in this research study. Your participation is strictly voluntary. Participating in research is different from getting standard medical care. The main purpose of research is to create new knowledge for the benefit of future patients and society in general. Research studies may or may not benefit the people who participate.

You may change your mind about the research at any time. There will be no penalty to you if you decide not to participate, or if you start the study and decide to leave the study protocol early. Either way, you can still get medical care and services at the University of Kansas Medical Center (KUMC).

This consent form explains what you have to do if you are in the study. It also describes the possible risks and benefits. Please read the form carefully and ask as many questions as you need to before deciding about this research.

You can ask questions now or anytime during the course of the study which is expected to last 25 days. The researchers (nurses, doctors) will tell you if they receive any information that might cause you to change your mind about participating.

This study will take place at the University of Kansas Medical Center (KUMC). The study will require participation of 30 people.

BACKGROUND

Patients with chronic kidney disease are at increased risk for cardiovascular disease (heart disease and blood vessel disease) and are suspected of having unique risk factors for cardiovascular disease. One such risk factor may be produced by intestinal bacteria which breakdown substances in our diet to form trimethylamine (TMA). TMA is absorbed into the bloodstream and converted by the liver to form trimethylamine-N-oxide (TMAO). TMAO has been shown in studies to be associated with an increased risk for cholesterol plaque formation in blood vessels and cardiovascular disease.

In a study performed here at KUMC, we observed that patients with chronic kidney disease have higher blood levels of TMAO compared to healthy subjects with normal kidney function. Prior studies suggest that short-term antibiotic therapy can lower the blood levels of TMAO in patients with normal kidney function; however, this approach has not yet been tested in patients with kidney disease who generally have much higher blood levels of TMAO.



We are investigating the use of Rifaximin, an antibiotic that kills susceptible bacteria, in patients with chronic kidney disease to measure the change in fecal bacteria and the effect on TMAO blood levels. Rifaximin is an antibiotic that currently is FDA approved for hepatic encephalopathy, a form of mental confusion that occurs in patients with advanced liver disease and is also approved for traveler's diarrhea, a form of infectious diarrhea. This antibiotic is unique in that 97% of the drug passes unchanged into the feces rather than being absorbed. For this reason side effects are believed to be lower for Rifaximin than for other traditional antibiotics; however, this medication has not been studied in chronic kidney disease and is therefore experimental for this use.

In this study we seek to evaluate how treatment with Rifaximin will alter the bacteria that live in the intestine and if this will lead to a decrease in blood levels of TMAO in patients with kidney disease.

PURPOSE

The purpose of this study is to determine if Rifaximin decreases blood and urine TMAO levels in patients with chronic kidney disease and to evaluate changes in the bacterial content of the stool from these individuals. This study may lead to future investigations of the long-term effects of Rifaximin therapy on TMAO levels and to evaluate for a cardiovascular benefit in patients with chronic kidney disease.

PROCEDURES

During a baseline visit we will determine if you qualify to be in the study, perform a brief exam, and answer your questions. If you consent for study participation, you will be provided with a 10-day course of Rifaximin or placebo.

You will be randomly assigned (like flipping a coin) to one of 2 groups. A computer will decide which group you are in.

- Group 1: Rifaximin (550 mg twice daily)
- Group 2: Placebo, (no dosage, twice daily)

You will have a 1 in 2 chance (50%) of receiving Rifaximin or placebo. A placebo has no active ingredients but is made to look like the study drug. Neither you nor the investigator will know which treatment you are receiving. In the event of an emergency, the investigator will be able to find out what treatment you are receiving. From this point forward, Rifaximin and placebo will both be referred to as "study drug."

On your initial visit your medical history will be obtained, including current medications, comorbid conditions, lifestyle indicators (such as tobacco and alcohol use). We will review your medical record including your past medical conditions, current medications and your recent laboratory studies (including blood work that measures your kidney function, electrolytes and lipids including cholesterol). This medical information will be coded to protect your privacy and stored on all study participants.



On Day 1 (the day after your first study visit), participants will begin the study drug to take orally twice daily for a total of ten days. Blood and urine samples will be collected on day 0 (prior to antibiotic administration), day 11, and day 25. Participants will be asked to provide a stool sample for analysis prior to or at their baseline visit and again within 24 hours of each the remaining two study visits. The samples will be analyzed for TMAO and other markers of inflammation. Additional serum and urine samples left over from this initial investigation will be stored in a freezer in Dr. Stubbs' lab for those patients consenting for additional sample storage or destroyed if consent was not obtained. We will record any adverse reactions and a follow up visit can be arranged at the participant's request. If during the course of your antibiotics you are concerned you are having a reaction or adverse event you should call our treatment team immediately.

Initial Visit (Baseline) – Day 0:

- Your medical history and current medications will be reviewed
- If you have not been seen by your physician in the last 3 months, you will have a brief physical exam by the investigator
- Your vital signs will be measured and recorded (blood pressure, heart rate, weight and temperature)
- Approximately 2 tablespoons of blood will be drawn and urine sample collected
- Patient will bring stool sample to visit
- You will be supplied with a 10 day supply of the study drug.

Post-treatment Visit – Day 11:

- Approximately 2 tablespoons of blood will be drawn for labs
- Urine and stool samples will be collected
- Your medication dosage and frequency will be reviewed, and you will be asked about any adverse events that may have occurred since the last visit

Post-treatment Visit – Day 25:

- Approximately 2 tablespoons of blood will be drawn for labs
- Urine and stool samples will be collected
- Your medication dosage and frequency will be reviewed, and you will be asked about any adverse events that may have occurred since the last visit

The study visits and blood tests will take place at a designated clinical research examination room (2085 Delp) at the University of Kansas Hospital. Unless consent for long-term blood and urine storage has been obtained, the left-over samples will be destroyed after testing. At the end of this consent form you will indicate whether you are willing to allow use of your remaining samples for future research studies.



RISKS

Rifaximin has primarily been studied in patients with advanced liver disease. It is unclear which of these side effects are unique to patients with liver disease.

- In patients with **liver disease** the most common side effects were:
 - Peripheral Edema (15%)
 - Nausea (14%)
 - Dizziness (13%)
 - Fatigue (12%)
 - Ascites (11%)

- **Common:** Most common side effects in patients without liver disease are believed to be gastrointestinal in nature. When given for traveler's diarrhea the following side effects were noted (please note that the dose and frequency of Rifaximin varies when given for traveler's diarrhea - 200 mg three times a day):
 - Gas 11% (vs 20% of those taking placebo)
 - Headache 10% (vs 9% of those taking placebo)
 - Abdominal pain 7% (10% reported in those taking placebo)
 - Rectal pain with sensation of a need to have a bowel movement 7% (9% reported in those taking placebo)
 - Urgency to have a bowel movement 6% (9% reported in those taking placebo)
 - Nausea 5% (8% reported in those taking placebo)
 - Constipation 4% (4% reported in those taking placebo)
 - Fever 3% (4% reported in those taking placebo)

- **Serious Reactions** (estimates of frequency cannot be made due to voluntary reporting) have been reported:
 - Diarrhea related to infection with a bacteria called clostridium difficile (a bacteria that is not susceptible to most antibiotics and which would require treatment with a different antibiotic if diagnosed)
 - Severe allergic reactions leading to rashes including a severe rash called exfoliative dermatitis, facial and tongue swelling, itching, flushing or anaphylaxis (severe allergic reaction). While these types of reactions are not common, facial swelling or breathing issues are life-threatening reactions and emergency medical attention should be sought.
 - Allergic Reaction Risks: Sometimes, people have serious allergic reactions to drugs. A severe allergic reaction could be life-threatening and may result in death. Symptoms of allergic reactions include:
 - Swelling of the mouth, throat or eyes
 - Rash
 - Difficulty Breathing
 - Coughing
 - Wheezing
 - Sudden drop of blood pressure
 - Seizures
 - Flushing



- A fast pulse
 - Sweating
- You should call 911 if you think you are having a severe allergic reaction. Please also contact the study team if you have any of these or other side effects during the study.

The risks of drawing blood include:

- temporary discomfort from the needle being inserted into your arm
- bruising
- fainting
- swelling at the injection site
- In rare cases, infection or blood clot at the injection site.

Those receiving Placebo will not be taking active medication. We do not anticipate any effect on your chronic kidney disease for either those taking placebo or those taking Rifaximin.

NEW INFORMATION

You will be told about anything new that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS

You may or may not benefit from this study. Researchers hope that the information from this research study may be useful in the treatment of other patients with kidney disease and may lead to future treatments to decrease heart and artery disease for these patients.

ALTERNATIVES

You can choose not to be in this study.

COSTS

Cost of the study drug (Rifaximin or Placebo), lab measurements for this study, and blood draw supplies will be covered by the investigators using research funds. There will be no cost to the patient for participation in this study. This study will not impact your standard of care treatments. Your usual clinic visits, laboratory costs, and medications will be billed to you or your insurance as is normal.

FINANCIAL DISCLOSURE

The Investigators are not receiving payments for this study.

PAYMENT TO SUBJECTS

There is no payment for being in this study.

IN THE EVENT OF INJURY

If you have a serious side effect or other problem during this study, you should immediately contact Jason Stubbs, MD, at 913-588-6074. If it is after 5:00 p.m., a holiday or a weekend, you should call 913-588-5000 and ask the operator to page the nephrologist on call. A member of the research team will decide what type of treatment,



if any, is best for you at that time.

If you have a bodily injury as a result of participating in this study, treatment will be provided for you at the usual charge. Treatment may include first aid, emergency care and follow-up care, as needed. Claims will be submitted to your health insurance policy, your government program, or other third party, but you will be billed for the costs that are not covered by the insurance. You do not give up any legal rights by signing this form.

INSTITUTIONAL DISCLAIMER

If you think you have been harmed as a result of participating in research at the University of Kansas Medical Center (KUMC), you should contact the Director, Human Research Protection Program, Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160. Under certain conditions, Kansas state law or the Kansas Tort Claims Act may allow for payment to persons who are injured in research at KUMC.

CONFIDENTIALITY AND PRIVACY AUTHORIZATION

The researchers will protect your information, as required by law. Absolute confidentiality cannot be guaranteed because persons outside the study team may need to look at your study records. Your health information is protected by a federal privacy law called HIPAA. By signing this consent form, you are giving permission for KUMC to use and share your health information. If you decide not to sign the form, you cannot be in the study.

The researchers will only use and share information that is needed for the study. To do the study, they will collect health information from the study activities and from medical records maintained by The University of Kansas Hospital. Information such as your past medical conditions, lab results, and medications will be collected. You may be identified by information such as name, address, phone, date of birth, or other identifiers. Your health information will be used at KUMC by Dr. Jason Stubbs, members of the research team, The University of Kansas Hospital Medical Record Department, the KUMC Research Institute and officials at KUMC who oversee research, including members of the KUMC Human Subjects Committee and other committees and offices that review and monitor research studies.

By signing this form, you are giving Dr. Jason Stubbs and the research team permission to share information about you with persons or groups outside KUMC. Your information will be shared with the U.S. agencies that oversee human research (if a study audit is performed). These groups or agencies may make copies of study records for audit purposes. The purpose for using and sharing your information is to make sure the study is done properly. Likewise, you are giving permission to Dr. Stubbs to send your blood and serum samples to the University of Pittsburgh for analysis. All patient samples sent to the University of Pittsburgh will be de-identified and contain none of your personal health information.

The purpose for using and sharing your information is to make sure the study is done properly. Likewise, you are giving permission to Dr. Stubbs to send your blood and serum samples to the University of Pittsburgh for analysis. These samples sent to the University of Pittsburgh will be coded so that the researchers in Pittsburgh do not know



your identity. Because the samples are being analyzed for research rather than standard clinical care, you will not receive the test results.

The HIPAA privacy law may not apply to everyone who receives your health information. Your information might not be protected by HIPAA if persons outside KUMC disclose it. In some cases, there may be other laws that protect your information from improper use.

Your permission to use and share your health information will not expire unless you cancel it. Any research information that is placed in your medical record will be kept indefinitely.

While you are participating in this study, you may see and copy any study information that is placed in your KUMC medical record. However, some study information is kept only by the researcher. The records kept only by the researcher may not be available to you until the end of the study.

The researchers may publish the results of the study. If they do, they will only discuss group results. Your name or other identifiers will not be used in any publication or presentation about the study.

QUESTIONS

Before you sign this form, Dr. Jason Stubbs or other members of the study team should answer all your questions. You can talk to the researchers if you have any more questions, suggestions, concerns or complaints after signing this form. If you have any questions about your rights as a research subject, or if you want to talk with someone who is not involved in the study, you may call the Human Subjects Committee at (913) 588-1240. You may also write the Human Subjects Committee at Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160.

SUBJECT RIGHTS AND WITHDRAWAL FROM THE STUDY

You may stop your involvement in the study at any time. Your decision to stop will not prevent you from getting treatment or services at KUMC.

You have the right to cancel your permission for researchers to use your health information. If you want to cancel your permission, please write to Dr. Jason Stubbs. The mailing address is Dr. Jason Stubbs, University of Kansas Medical Center, 3901 Rainbow Boulevard, Mail Stop 3002, Kansas City, KS 66160. If you cancel permission to use your health information, you will be withdrawn from the study. The researchers will stop collecting any additional information about you unless they need information about a side effect of the study drug. They may use and share information that was gathered before they received your cancellation.

This study might be stopped, without your consent, by the investigator, the sponsor or by the FDA. Your participation also might be stopped by the investigator or by the sponsor if it is in your best interest or if you do not follow the study requirements.

Neither the sponsor, nor the investigator, nor the University of Kansas Medical Center will be obligated to provide you with Rifaximin if the study is stopped early. Your physician will decide about future treatment, if it is needed.



CONSENT

Dr. Jason Stubbs or the research team has given you information about this research study. They have explained what will be done and how long it will take. They explained any inconvenience, discomfort or risks that may be experienced during this study.

By signing this form, you say that you freely and voluntarily consent to participate in this research study. You have read the information and had your questions answered.

You will be given a signed copy of the consent form to keep for your records.

Print Participant's Name

Signature of Participant

Time

Date

Print Name of Person Obtaining Consent

Signature of Person Obtaining Consent

Date



OPTIONAL SAMPLE STORAGE AND FUTURE USE

Purpose: You are being asked to agree to the storage of your blood, urine and fecal samples so that these samples can be used for research in the future. By studying these samples, researchers hope to learn more about chronic kidney disease.

Procedure

In order to do the research with your sample, researchers may need to know some things about you. This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, gender, medical conditions and previous treatments.

Samples will be collected on Day 0 and Day 10 as previously outlined. No additional samples will be collected but after analyzing the data some samples may be left over. These left over samples will be stored to be used for future research.

Privacy

Your samples will be stored in the lab of Dr. Jason Stubbs. They will be labeled with coded with a unique study ID, typically involves the letters of your initials and some numbers. The samples may be stored for up to 10 years. We will maintain a list of the samples and the link to identifying information on a secure database.

You may withdraw your consent to use the remaining samples and associated health information at any time by telling your study doctor. In this case, the sample will be destroyed. Samples or related information that have already been used by researchers cannot be returned or destroyed.

The information about the uses and disclosures of your health information for the main study also applies to this future research.

Reports about research done with your samples will not be given to you or your doctor. These reports will not be put into your medical record. The research will not have an effect on your care. The samples will not be sold and will only be used for research purposes.

If results are published, your name and other personal information will not be given.

Risks

You will not incur additional risks above those outlined for the main study.

The main risk of this study is possible loss of privacy and confidentiality. We will take reasonable precaution to reduce this risk.



Research methods are rapidly changing. In the future, researchers may develop methods that allow your samples to be linked back to you.

If a commercial product is developed from this research, the profits will belong to the study sponsor. There are no plans to provide financial payment to you should this occur.

The choice to share your samples and information is completely voluntary. You can decide not to have your samples used and still participate in the main study. Please mark your choice "Yes" or "No" below. If you have any questions you can talk to the investigator or the study team.

You give permission that your blood, urine, fecal samples, and data may be stored and used for future research.

YES NO

Print Participant's Name

Signature of Participant

Time

Date

Print Name of Person Obtaining Consent

Signature of Person Obtaining Consent

Date

Xifaxan prescribing information, cdn.salix.com/shared/pi/xifaxan550-pi.pdf

