UNIVERSITY OF WASHINGTON
CONSENT FORM

- Randomized Trial of Glutamine in Chronic Kidney Disease - (T-Glute)

Researchers:
The Kidney Research Institute at UW Medicine Nephrology / Nephrology
(Business hours 8 to 4:30, or leave message) **– (206) 616-8574**

Principal Investigator:

Jonathan Himmelfarb, MD	Professor	(206) 616-4717

Study Contact:

Laura Curtin, BA	Research Coordinator	(206) 221-3938

24-hour Emergency Numbers
UW Hospital Operator 206-598-6190 (ask for nephrologist on call)
Dr. Roshanravan (Study Doctor) pager 206-540-8416

Researchers' statement

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to be in the study or not. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions, you can decide if you want to be in the study or not. This process is called "informed consent." We will give you a copy of this form for your records.

PURPOSE OF THE STUDY

Kidney disease is the inability of the kidney to process waste properly, which can lead to heart disease and limited mobility. Glutamine can help build proteins in your body which promote good health. In this study, we want to find out if glutamine is helpful in improving metabolism and in turn, leads to healthier muscle and blood vessels that can slow the progression of kidney disease.

We will analyze "biomarkers" found in the blood by imaging and blood tests. Biomarkers are components in the blood which may help to identify health related issues. In this study, we will look at how glutamine affects biomarkers of oxidative stress (an imbalance in fighting the effects of bad oxygen, which can damage proteins). Glutamine may help prevent health problems in kidney disease patients. We will also use Magnetic Resonance Spectroscopy and Optical Spectroscopy to check the health status of your muscle and blood vessels.

This study will include about 20 subjects. These subjects will come from the participants enrolled in the Muscle Mitochondrial Energetics and Dysfunction (MEND) study.

STUDY PROCEDURES

If you decide to be a part of this study, your participation will last about 2 months.

You will be randomly assigned, like flipping a coin, to start with either glutamine or sugar powder.

When you take glutamine powder or the placebo (maltodextrin, a type of sugar), you will dissolve it in water or juice prior to taking it. If you are diabetic, you will need to dissolve the powder in water or a low sugar beverage such as Crystal Lite or diet soda. If you are not diabetic, you can dissolve the powder in water, juice, or other beverage as you prefer. You should not take any protein containing foods for 30 minutes after drinking the powder mixed with juice. You should take this three times daily. You should take it about the same time each day.

We will also ask you whether you have any signs or symptoms that could be related to the treatment. We will look at your medical records for anything that may be related to the treatment.

We will ask you to come to each study visit fasting except for the screening visit. This means nothing to eat or drink except medications and water for 8 hours before the visit.

The study visits take place at the Kidney Research Institute, either at UW Medical Center, Harborview Medical Center, or the Haviland Unit at the Northwest Kidney Centers. Then you will go to the UW Diagnostic Imaging Center for special scans. You can arrange the scans for a different day if you need to, but it has to be within a week of the rest of the visit.

If you join this study, you will continue to see your usual doctor for your on-going health care.

Details of the Visits:

Screening Visit (about 1 hour)

If you decide you would like to participate in this study, the study staff will complete the following procedures during a screening period to determine if you can take part in this study. In some cases, this visit may be done over the phone or in combination with Visit 1, if that's more convenient.

- You will sign the informed consent form, prior to any study procedures being performed.
- You will be asked about medications that you are currently taking, including over-the-counter medications and supplements.
- You will have a brief physical examination (this may be done at Visit 1).
- You will be asked about your previous medical history.

Visit 1 – Start Phase I Treatment (about 1 hour) - Fasting required

You already had Magnetic Resonance Spectroscopy (MRS) and Optical Spectroscopy (OS) imaging, and a Muscle Fatigue test as a part of the MEND study. The results of those tests will be used as the "baseline" tests for this study.

We may ask you to repeat the MRS, OS, and Muscle Fatigues tests at Visit 1 if more than 180 days has passed since your MEND visit, or if you've had a change in health status since then.

- We will measure your blood pressure, pulse, respiration rate. We will take 3 readings, spaced about 5 minutes apart. We will check your height and weight.
- A small sample of your blood (about 2 tablespoons) will be collected.
- We will give you supplies and instructions for your first 24 hour urine collection.
- If you are a woman who could become pregnant, a urine pregnancy test will be performed. You cannot be in this study if you are pregnant.
- At this visit you will randomly be given either the placebo powder or glutamine powder. Study staff will instruct you on how to take the powder.

You will take the powder until you come for the next MRS/OS visit. You will take the last dose the morning of that visit 30 minutes to 1 hour before your scheduled time. We will give you enough powder to last for the 14 day treatment periods, plus some extra to give up to 4 days flexibility in scheduling the MRS/OS visit.

Phase I –up to 18 days of taking Placebo or Glutamine

- Study coordinator will phone you halfway through this phase to check in. We will want to know if you're having any trouble taking the study agent and to check on how you are doing.
- We will remind you to phone us if you have any concerns or questions.
- We will remind you of your next study visit.

Visit 2 – End Phase I Treatment (about 3 hours) –Fasting required

- You will take the last dose of study powder in the morning 30 minutes to 1 hour before your scheduled visit. You will return any unused powder. We will check to make sure you've been taking the powder as instructed. If the doctor feels you are having any side effects or you are not taking the powder as prescribed, you could be discontinued from the study.
- You will be asked about any medications changes in the past month.
- We will ask you about any side effects you may have experienced.
- We will measure your blood pressure, pulse, respiration rate. We will take 3 readings, spaced about 5 minutes apart. We will check your height and weight.
- A small sample of your blood (about 2 tablespoons) will be collected.
- You will bring your 24 hour urine collection. We will give you supplies and instructions for your second 24 hour urine collection.
- Magnetic Resonance Spectroscopy (MRS) and Optical Spectroscopy (OS) imaging. These use a magnetic field and radiofrequency to collect information about oxygen and

energy storage in your muscles.
- Muscle Fatigue test
- At this visit you will be given either the placebo powder or glutamine powder, depending on what you took in Phase 1. Study staff will instruct you on how to take these agents. You will begin taking it on Day 38 (after the Washout).

Washout - At Visit 2 you will be instructed to stop taking the study powder and wait 21 (±4) days before you start taking the study agent for Phase II. We call this a "washout" period.

Phase II Treatment –No visit required

- You will start taking the study agent for Phase II. We will call you to check in and remind you to begin.

You will take the powder until you come for the next MRS/OS visit. You will take the last dose the morning of that visit 30 minutes to 1 hour before your scheduled time. We will give you enough powder to last for the 14 day treatment periods, plus some extra to give up to 4 days flexibility in scheduling the MRS/OS visit.

Phase II –up to 18 days of taking Placebo or Glutamine

- Study coordinator will phone you halfway through this phase to check in. We will want to know if you're having any trouble taking the study agent and to check on how you are doing.
- We will remind you to phone us if you have any concerns or questions.
- We will remind you of your next study visit.

Visit 3 – Post Phase II Treatment (about 3 hours) –Fasting required – **Final Visit**

- You will take the last dose of study powder in the morning 30 minutes to 1 hour before your scheduled visit. You will return any unused powder. We will check to make sure you've been taking the powder as instructed.
- You will be asked about any medications changes in the past month.
- We will ask you about any side effects that you may have experienced.
- We will measure your blood pressure, pulse, respiration rate. We will take 3 readings, spaced about 5 minutes apart. We will check your height and weight.
- A small sample of your blood (about 2 tablespoons) will be collected.
- You will bring your 24 hour urine collection.
- MRS/OS will be performed.
- Muscle Fatigue test

Details of the procedures:

24-hour Urine Collection: We ask you to give two 24-hour urine samples. Each time, we will give you a urine collection jug, along with written instructions for collecting a 24-hour urine sample. Women may also like a 'hat', which covers the toilet seat to make collection easier. You will start at any time of day that is best for you. You will urinate until you can't go

anymore. You will flush and not collect any of this, but this marks your start time. You will write down this exact date and time on the label on the jug. After this, every time you urinate, you'll do it in the jug (or in the hat, if this is easier, then pour it into the jug). You will be asked to keep the jug in the refrigerator or on ice. It must be kept cold. At the end of 24 hours, you will collect the urine one more time. This is the end date and time, and you will write this time on the label. If you can't collect for the full 24 hours, then do it for as long as you are able, and still keep the times. You will then bring the samples to visits 2 and 3.

MRS/OS: This session will last about 2.5 – 3 hours. It is possible that we will ask you to repeat some tests during an additional session. You may choose not to repeat tests. The testing will take place at the Diagnostic Imaging Sciences Center (DISC) of the University of Washington Radiology Department, located in the University Hospital. The tests and the typical activities for a session are described below.

The tests: We will do 2 types of tests on your muscles during the session. The first is a test called magnetic resonance spectroscopy (MRS). MRS allows us to study the chemicals which supply energy to your muscles. It also allows us to see how much oxygen is in your muscles. The second test is called optical spectroscopy (OS). OS is a different way to look at how much oxygen is in your muscles. Before testing begins we will measure the blood pressure in your arm.

Exercises: During the sessions you will sometimes be asked to do a small amount of exercise with your finger. During the exercise you will press your finger against a bar repeatedly for up to 2 minutes. We will always tell you before you start how long you will exercise. You will know when and how hard to press by hearing beeps and seeing flashing lights or dots. It is possible that we may just ask you to press the bar as often as you can during the exercise time. We will let you practice the exercise before doing it.

Testing sessions: When you come to the laboratory we will measure your blood pressure. You will have to remove loose magnetic items (like watches and cell phones) and magnetic jewelry. You will then place your hand and forearm on a holder and we'll secure your forearm and hand in position. A similar set-up will be used for both the MRS and OS tests.

For the MRS tests a small device will be taped onto your hand. We will place a blood pressure cuff around your upper arm. This will be used to temporarily stop blood flow to your hand during some of the tests. The blood flow will be stopped for 7-15 minutes. You will always be told when the cuff is going to inflate and how long it will stay inflated. After we adjust the devices, you will sit or lie on a padded table and put your arm into a magnet. The magnet is shaped like a long tube, and your arm will go inside the tube with your body remaining outside. You will be asked to hold your arm and body still during all of the tests except when we ask you to exercise your finger. During the tests there may be times when you are at rest with no cuff inflation, at rest with cuff inflation, exercising with no cuff inflation and exercising with cuff inflation. You will always be told ahead of time exactly what you will do. When the tests are finished we will remove you from the magnet and remove the equipment from your hand and arm. If at any time you feel you cannot do the tests or wish to stop for any reason, we will stop.

For the OS test a small device that shines a light will be placed next to your hand touching your skin. We will place a blood pressure cuff around your upper arm. This will be used to temporarily stop blood flow to your hand during the test. During this test you will breathe

through a small mask that fits over your mouth and nose. This will allow us to control the amount of oxygen you are breathing. You will not be asked to breath less oxygen than normal, but you will breath more oxygen than normal for up to 40 minutes. We will inflate the pressure cuff for 10-15 minutes during this time. You will be told before we start when the cuff is going to inflate and how long it will stay inflated. You may be asked to exercise for up to 2 minutes while the cuff is inflated. When the test is finished we will remove the equipment from your hand and arm. If at any time you feel you cannot do the test or wish to stop for any reason, we will stop.

Muscle Fatigue: To test how quickly your muscles tire, we will ask you to do another set of exercises with your finger. You will press your index finger against a disc. We will measure and record the force of each press while you begin to press more quickly. You'll make it more quick each minute. At each minute we will ask you to assess your perceived exertion on a scale of 1-10 until you can no longer maintain the level of pressing.

Two trials will be made (once after the MRS procedure and once after the OS procedure).

Health History: We will ask you at each study visit about any health problems you may have experienced since the last study visit.

Medical Record review: We will also check your medical record for any health events you may have had. We will look at routine labs used for clinical care. We will check your blood pressures taken clinically for each dialysis session while you are in the study. If you have medical records at another facility with medical history that may be important for this study, we may ask you to sign a release for information form for that facility.

RISKS, STRESS, OR DISCOMFORT

Study Agent:
Although glutamine is generally well tolerated, there is the potential for side effects such as nausea, vomiting, or confusion, or bleeding. If you experience moderate or severe side effects, the study doctor may tell you to stop taking the study agent, though you can continue to come to study visits. We will report your adverse event to the sponsor.

Pregnancy and Birth Control:
There is not enough medical information to know what the risks might be to an unborn child carried by a woman who takes glutamine. For these reasons, it is important that you do not become pregnant during this study and 1 month after you finish. Therefore, all women who can become pregnant and are sexually active, or their sexual partners, are asked to use birth control measures while in this study. The following birth control measures are acceptable: surgical sterilization, abstinence, sterilized male partner, double-barrier methods. Breast-feeding mothers must stop breast-feeding to take part in this study. Women who can become pregnant must have a pregnancy test before taking part in this study. We will do a urine pregnancy test before the study starts. If the pregnancy test is positive, you will not be able to take part in the study.

If you become pregnant during the study, you must tell the study doctor at once. You will need to stop taking the study product. You can continue to come to study visits. However, because the

MRS/OS procedures involve using the blood pressure cuff to stop blood flow to your arm, you will not take part in these tests.

MRS/OS Study:
Our main concern in the area of safety is to keep any magnetic objects away from you and the magnet. You will be asked about metal objects or implants that could cause problems in the magnetic field. Some people may feel claustrophobic (closed in) when in the magnet.

You may feel uncomfortable while remaining still and holding the same position during the session. This will disappear soon after you get up and walk around at the end of the session. The exercise may feel tiring to your hand. During parts of the exercises you may have a "burning" feeling in the muscle similar to what you may have felt when working the muscles hard. This is a normal reaction of the muscle to exercise and does not indicate that the muscle has been hurt. This feeling will disappear very soon after the test is over. You may feel some mild soreness in your muscle for a day or two after the exercise if you are not used to exercise. This is a normal response that disappears on its own.

You will find it uncomfortable when the blood pressure cuff is inflated. Your arm will feel numb or tingle, and the area under the cuff may ache. Pressure cuff inflation is often used by doctors during surgery. We don't think it will harm your arm, but we don't know. Women who take hormones for birth control and people 40 years of age or older are more likely to form blood clots, usually in their legs. For people who are more likely to develop blood clots in their legs or arms, we do not know if having the pressure cuff inflated for several minutes at a time will further increase the risk of forming a blood clot. You will be given a handout with information about "deep vein thrombosis" (DVT), which is when a blood clot forms in a deep vein of the body. This handout tells you the most common signs and symptoms you would feel if you developed a DVT. If you think you have developed a DVT following these experiments, you should contact your doctor or go to the emergency room. If it turns out that you did develop a DVT, also contact either Dr. Roshanravan at 206-540-8416 or Laura Curtin at 206-221-3938.

There are no known risks to breathing more oxygen than normal for the short periods of time we use in these experiments. You may notice that your breathing speeds up a little when you are breathing more oxygen than usual. This will return to normal when you breathe room air.

Blood Draws:
When we draw your blood, you may have pain at the place where the needle goes in. You may also have bruising, a hematoma (collection of blood underneath the skin), or infection at the needle site.

Confidentiality:
Collection and storage of protected health information will pose some risk to confidentiality. Some risk of breach of privacy.

ALTERNATIVES TO TAKING PART IN THIS STUDY

Being in this study is voluntary. Your alternative to taking part in this study would be to not participate. Whether or not you choose to be in this study will not affect the health care you receive.

BENEFITS OF THE STUDY

There will be no benefits directly to you from your participation in this study. However, the results of this study may help patients with kidney disease in the future.

SOURCE OF FUNDING

The study team and/or the University of Washington is receiving the funding from the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) and through the New York Medical College.

CONFIDENTIALITY OF RESEARCH INFORMATION

All the information you provide will be confidential. Your name and other identifying information will be linked to a unique study ID. Your study ID will not include any information that can identify you. All of the data we collect from you will be coded with your study ID and kept in a locked cabinet, or password protected computer files. The master list linking your identifying information to your study data will be kept in a separate, secure location. Only the study team will have access to the master list. We will keep the link between your identifying information and study data no later than 12-31-2018. By that point, any link to your identity will be destroyed.

The blood samples we collect from you will be coded with your study ID and stored in a secure freezer at the Kidney Research Institute to be used for this study. In addition, we will invite you to join a repository maintained by the Kidney Research Institute. You can still be in this study whether or not you join the repository. If you decide to join it, we will ask you to read and sign a separate consent form. Then, if there are any samples left over, they will be kept along with study information for an indefinite period. They may be used to for further studies of kidney disease. If you want to withdraw your samples from use please contact Lori Linke, or any of the study staff listed on page one of this form.

We will not include your name or other identifying information in any presentations or publications.

Government or university sometimes reviews studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm. The U.S. Food and Drug Administration (FDA) reserves the right to review study data that may contain identifying information.

OTHER INFORMATION

You may refuse to participate and you are free to withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled.

The study doctor will stop your participation in this study if he believes it is in your best medical interest. He may take you out of the study if you don't keep up with the study visits or if you don't take the glutamine product correctly. He will also take you out of the study if you show any harmful effects to the glutamine study product, or have an illness or complication even if it is not related to the study. The study doctor may choose to withdraw you from this research study at any time with or without your consent. He will tell you whether or not you can continue to come to study visits even if you've stopped taking the study product.

You will not have to pay anything to be a part of this study. You or your insurer will be responsible for the costs related to your hemodialysis treatment or from routine clinical care.

As a way of helping to reimburse you for your time in taking part in this study, we will give you $25 for Visit 1, $50 each for Visits 2 and 3 (total of $125). We will also reimburse for parking. We will give this reimbursement in the form of a retail gift card. We will give you a card at the end of the study.

For those who complete this study, there are several other studies that you will be eligible to take part in. The information and samples from this study may be used in the other studies. We will let you know if you are eligible for any of them. You don't have to take part in the new studies.

You may ask questions at any time about this study. You should bring any questions to Dr. Himmelfarb at (206) 616-4717 or any member of the study team listed at the top of this form.

COMPENSATION FOR INJURY

If you think you have an injury or illness related to this study, contact the study staff right away. They will treat you or refer you for treatment:

- Jonathan Himmelfarb, MD, (206) 616-4717
- Laura Curtin, (206) 221-3938
- Bob Roshanravan, MD, (206) 540-8416

We will bill you or your insurer for treatment of problems that result from your kidney disease or from standard clinical care.

No money has been set aside to pay for things like lost wages, lost time, or pain. However, you do not waive any rights by signing this consent form.

The UW will pay up to $10,000 to reimburse for treatment of injury or illness resulting from the study.

Printed name of study staff obtaining consent Signature Date

Subject's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, I can ask one of the researchers listed above. If I have questions about my rights as a research subject, I can call the Human Subjects Division at (206) 543-0098. I give permission to the researchers to use my medical records as described in this consent form. I will receive a copy of this consent form.

Printed name of subject Signature of subject Date

Copies to: Researcher, Subject, Subject's Medical Record

Randomized Trial of Glutamine in Chronic Kidney Disease

Treatments/Procedures	Screening	Baseline 1	Treatment Phase 1	Phase I Follow Up	Washout	Baseline 2	Treatment Phase II	Phase II Follow Up
	Day -28	Day -1 (Visit 1)	Day 0 thru Day 14 (±4)	Day 15 (±4) (Visit 2)	Day 16 (±4) thru Day 37	Day 38	Day 39 thru Day 52 (±4)	Day 53 (±4) (Visit 3)
Visit may take this much time:	1 hour	1 hour		3 hours		(phone call)		3 hours
Informed Consent	X		Phone call on Day 7		No study product		Phone call on Day 45	
Inclusion/Exclusion	X							
Medical History	X							
Medication List	X							
Demographics	X							
Brief Physical Exam	X							
Pregnancy test for women		X				Begin Study agent for Phase 2		
Vitals		X		X				X
Fasting Blood Draw		X		X				X
24 hour urine collection				X				X
MRS/OS				X				X
Muscle Fatigue Test				X				X
Study Product Dispensed		X						
Study Product collected				X				X
Study Product Adherence				X				X