UNIVERSITY of MARYLAND
THE FOUNDING CAMPUS

RESEARCH CONSENT FORM

Protocol Title: TAME-PKD: Trial of Administration of Metformin - Polycystic Kidney Disease

Study No.: HP-00064971

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Sub-Investigator: Stephen Seliger, MD MS 410-328-5720

Sponsor: Department of Defense

Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to allow the research team to discuss your potential enrollment for this study. All data collected from this study is for research purposes only. Your participation is voluntary which means you can choose whether or not to participate. There will be no loss of benefits to which you are otherwise entitled if you decide not to participate. The research team is going to talk with you about the study and give you this consent document to read. Before you make a decision on whether or not to participate, you may take this consent document home and share it with your friends, your doctor, and your family.

PURPOSE OF STUDY

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease. This disease affects roughly 500,000 patients in the US alone and is the fourth leading cause of end stage renal disease..

This study will investigate the use of Metformin, a widely used generic drug, which is FDA-approved for the treatment of diabetes mellitus. In experiments with animals with polycystic kidney disease, metformin was found to reduce the development of new cysts in the kidneys. This may be due to the effects of metformin on how cells in the kidney generate energy (known as "metabolism"); however, the effect of metformin in humans with ADPKD is unknown. Metformin is not approved by the FDA for the treatment of ADPKD. However, the FDA has permitted the use of metformin for the purposes of studying its effects in this research study.

This study will test to see if metformin is safe and tolerated in adult ADPKD patients with beginning stages of chronic kidney disease. We will also measure its effect on progression of kidney disease as reflected in the kidney volume (size of the kidneys) and the kidney function, along with its effect on kidney pain and quality of life. Using urine collected from participants, we will also examine the effect of metformin on markers of metabolism. Participants will be treated either with metformin or a matching dummy pill ("placebo"). If Metformin - when compared to placebo - is found to be safe and tolerable in ADPKD patients, then a larger, definitive study will be planned to determine whether it is effective at slowing progression of ADPKD.

You will be one of approximately 53 participants at the University of Maryland School of Medicine, and one of approximately 106 participants nationally.

PROCEDURES

Your total participation in this study will last for approximately 26 months and will include 12 in-person visits to the University of Maryland with study team members, along with additional blood draws and telephone communications with study team members, as described below:

1. **Screening Visit:** Your first study visit is called a "screening" visit which includes procedures to determine if you are eligible to take part in this research study. We will discuss with you the purpose, procedures, and potential risks involved with this study, and we will answer any questions you might have. If you agree to participate, you will be asked to sign this consent document. We will perform some tests and ask questions (as described below) to determine if you qualify for the study. This screening visit will take approximately 2 1/2 hours and will be performed in the General Clinical Research Center (GCRC) at the University of Maryland Medical Center (UMMC).

   During this screening visit, the following information will be collected and procedures will be performed:
   - Your personal medical history will be obtained by reviewing your medical records and asking you questions about your medical history
   - We will ask you about the medications you are taking
   - You will receive a physical exam by one of the study doctors
   - We will draw blood from your vein to measure your kidney and liver function, blood sugar, blood cell counts, and levels of vitamin B12.You will be asked to fast at least 8 hours prior to this visit. You should not eat and only drink water during this time. A total of 5.5 teaspoons of blood will be collected.
   - We will perform an electrocardiogram (electrical recording of your heart).
   - Your height, weight and blood pressure will be measured.
   - If you are a woman with the potential of becoming pregnant, a urine test for pregnancy will be obtained.

2. **Baseline Visit:** If you are determined to be eligible for participation based on the information collected at the screening visit, you will be asked to return for a baseline visit within 8 weeks. This visit will take approximately 2 hours to complete.

   During this baseline visit, the following information will be collected and procedures will be performed:
   - You will be asked about any changes in your health status that may have occurred.
   - We will review your family medical history, liver history and life style history.
   - Your blood pressure will be measured.
   - Blood (4 teaspoons) will be collected from your vein for measurement of kidney and liver function, lactic acid (a type of acid that can very rarely build up in the blood of patients taking metformin), blood sugar, and blood cholesterol. You will be asked to fast at least 8 hours prior to this visit. You should not eat and only drink water during time.
   - Urine will also be collected for pregnancy testing (if you are a woman with the potential to become pregnant),
   - You will be asked to complete three questionnaires related to pain, quality of life, and stomach and intestinal problems.
   - Urine will be collected for measurement of protein and markers of energy metabolism for shipment to the laboratory of Dr. Kenneth Hallows at the University of Southern California.

- **Long-term storage of blood and urine:**
  Optional samples of both blood (approximately 2 teaspoons) and urine will be sent to the University of Maryland Biorepository (UMBiobank) for long-term storage for future measurements related to ADPKD research. These tubes containing your blood and urine samples will be coded so that your name cannot be readily identified. However, your identity can be determined by matching the code on the sample with your name in our study file.

  Your samples will be used for research only and will not be sold or used for the production of commercial products. These samples may be shared with other outside collaborators who have agreed to follow the procedures outlined in this consent to protect your confidentiality. You may participate in this study even if you do not agree to long-term storage of these optional blood and urine samples.

  Reports about any research done with your stored blood and urine will be included in your study file and kept confidential. You will not be provided with the results of these tests as these measurements are for research purposes only and are not done as part of medical care nor will you be contacted regarding any additional measurements that may be performed later. You have the opportunity to request that your samples be withdrawn from future use. To do so, please inform Dr. Watnick at 410-328-5720 to request that your samples be destroyed. Measurements already collected from these samples at the time of your request will be maintained, however, and not destroyed.

  Please indicate below whether you agree to long-term storage of your blood and urine samples:

  Initials_____Date_____Yes, my samples can be used for future research testing.

  Initials_____Date_____No, I do not want my blood and urine samples stored for future testing.

- **Storage of genetic material:** With your permission, a portion of your blood (approximately 2 teaspoons) will be separated for the isolation of genetic material (DNA) and stored at the UMBiobank at the University of Maryland School of Medicine. The biorepository meets the broadest needs for banking and storage of biospecimens in a secure and managed environment with an estimated capacity of over 1 million samples. This DNA may be tested for changes in the genes that cause ADPKD, or in other genes that can influence the progression of ADPKD or regulate energy metabolism. The tube of blood containing your DNA will be labeled with a unique study code only, and the UMBiobank will not be able to identify which blood tubeis yours nor know your identity.

  You will not be provided with the results of these genetic tests as they are research related and are not done as part of routine medical care. You will not receive any benefit from this testing. You may participate in this study even if you do not agree to genetic testing. You may agree to storage of this DNA now and later ask that the samples - be destroyed. To do so, please inform Dr. Terry Watnick at 410-328-5720 to request that your samples be destroyed; however the results of testing already completed on your DNA will not be destroyed.

  If you agree to have your DNA stored for future genetic testing, please indicate below:ADPKD.

Initials Date _____Yes, my samples can be used for future genetic testing of genes that may affect.

Initials Date _____No, I do not want my blood samples stored for future genetic testing.

- **Magnetic Resonance Imaging (MRI) Scan –** We will use the MRI scan to measure the size of your kidneys. During this procedure, you will lie on a table in a box-like enclosure while the MRI scanner takes pictures of your abdomen. MRI is a noninvasive technique, usually painless, for visualizing many different body tissues. Unlike x-rays, MRI does not use any radiation. Instead, it uses radio waves, a large magnet, and a computer to create images. This scan will take approximately 30 minutes.

Dispensing of study drug: After completion of the testing described above, you will be placed at random – like the flip of a coin – into either the metformin group or the control (placebo) group. You have an equal chance of being assigned to either group. Neither you nor the study doctor will know which treatment you will be receiving. At the end of your baseline visit, you will be given a set of study pills which will be either metformin (500 milligrams) or placebo (pills that contain no drug) of identical size and appearance. You will be instructed to take one pill once daily initially until the next visit (see below). The capsules should be taken with food or water and should be swallowed whole and not crushed or chewed. On occasion, the capsule may be eliminated in the stool and is no cause for concern.

3. **Laboratory follow-up visits** - at 2 weeks and 6 weeks after your baseline visit, we will ask you to come to the University of Maryland GCRC or – if easier – to go to a Quest laboratory convenient to you - for blood tests to measure blood counts and kidney function (approximately 2 teaspoons of blood will be drawn). The study coordinator will then contact you by telephone to determine how you are tolerating the study drug. After reviewing your laboratory measures and your symptoms, they will instruct you whether to increase, decrease, or remain at the same dose of your study drug . At 8 weeks, 4 months and 5 months after your baseline visit, you will again have blood collected (approximately 2 teaspoons) at the University of Maryland GCRC or a Quest laboratory for measurement of blood counts and kidney function.

4. **Initial in-person follow-up visit:** At 4 weeks after baseline, you will come back to the GCRC for your first in-person follow-up visit. This visit should last approximately one hour.
   At this initial in-person follow-up visit, the following information will be collected and procedures will be performed:
   - The research team will check your blood pressure and review your medications
   - We will ask you about your health status
   - We will collect blood (6 teaspoons) for measurement of kidney and liver function, lactic acid, blood sugar, and blood cholesterol.
   - If you are woman able to get pregnant, urine will also be collected for pregnancy testing
   - Urine will be collected for measurement of protein and markers of energy metabolism for shipment to USC
   - Optional blood and urine samples for the UMBiobank may be collected for long term storage with your consent.
   - You will be asked to complete three questionnaires related to pain, quality of life, and stomach and intestinal problems.
   - The study doctor may perform an updated physical exam.
   - The study team will ask you to return any leftover capsules and will count them to discuss any missed doses.

   The study team will instruct you whether to adjust the dose of your study medications after review of your laboratory tests and symptoms and provide you with enough medication until your next in-person visit in approximately 8 weeks.

Summary of Study Drug adjustment: The study drug will be started at the baseline visit at a dose of one capsule once daily. After 2, 4, and 6 weeks based on your kidney function and how well you are tolerating the study drug, the dose will be increased as follows:

At the beginning of week 3: 1 capsule twice daily
At the beginning of week 5: 2 capsules in the morning, 1 capsule in the evening
At the beginning of week 7: 2 capsules twice daily

We recommend taking the 1st dose in the morning, and the 2nd between 10 and 12 hours later. If your kidney function ("GFR") worsens to a certain extent as determined by your study doctor during follow-up, the dose of the study drug will be decreased to the highest tolerated dose. If you have concerns about tolerating the study drug at any time and for any reason, you can have a conversation with your study doctor about decreasing or stopping your study drug. If your kidney function drops significantly as determined by your study doctor, you will stop taking the study drug or placebo (see "Risks" section below); however, you will continue to participate in the remainder of this study.

6. Follow-up visits: At 3 months, and every 3 months thereafter through 2 years, you will return to the GCRC for an in-person follow-up visit. You will have a total of 8 follow-up visits lasting approximately one hour. During these follow-up visits, the following information will be collected and procedures will be performed:

- Your health status will be reviewed, your blood pressure will be measured, and any symptoms will be discussed with the study doctor, nurse or other study staff.
- You may be examined by one of the study doctors if they are concerned about any reported symptoms or lab results. They will examine only the areas affected or with which you and the study doctor are concerned.
- Blood (6 teaspoons) will be collected from your vein for measurement of kidney and liver function, lactic acid, blood sugar, and blood counts. At the 12- and 24-month visits, levels of vitamin B12 will also be measured. If low B12 is indicated at the 12-month visit, we will continue to monitor your B12 every three (3) months as part of the routine blood screening until an acceptable level is obtained. If you are a woman able to get pregnant, urine will also be collected for pregnancy testing
- Urine will be collected for measurement of protein and markers of energy metabolism and sent to USC.
- You will be asked to complete three questionnaires relating to pain, quality of life, and stomach and intestinal problems.
- The study team will ask you to return any leftover capsules and count them to discuss any missed doses.
- A repeat MRI of your abdomen will be performed at months 6, 12, 18, and 24. If the quality of the MRI are poor at any of these visits or at the Baseline visit, the radiologist may ask that a repeat scan be completed with 30 days of the visit.
- Optional Blood (approximately 2 teaspoons) and urine will be collected for long-term storage at the UMBiobank for future research measurements, if you agreed to such long-term specimen storage.

At the 24 month follow-up visit, you will stop taking study medications but will return within 2 months for a final close-out visit, described below.

7. **Close Out visit** will occur at approximately 26 months after baseline (within 2 months after the last follow-up visit) at the GCRC. At this close out visit, the following information will be collected and procedures will be performed:

- The research team will check your blood pressure and review your medications
- We will ask you about your health status and specific TAME related symptoms
- Blood (6 teaspoons) will be collected from your vein for measurement of blood counts, lactic acid, and kidney and liver function.
- Urine will be collected for protein and measurement of markers of energy metabolism.
- You will be asked to complete three questionnaires relating to pain, quality of life, and stomach and intestinal problems.
- A repeat EKG (electrical recording of the heart) will be performed.
- Optional Blood (approximately 2 teaspoons) and urine will be collected for long-term storage at the UMBiobank for future research measurements, if you agreed to such long-term specimen storage.

  After this visit, your participation in this study will be completed and you will no longer receive the study drug or placebo.

Additional Laboratory Study visits: If at any time after the 3-month follow-up visit - your kidney function is lower than 45 mL/min/1.73m^2 (based on your blood test results), you will be asked to go for additional blood tests each month during which you are not already coming for an in-person follow-up visit. These blood tests can be performed at a Quest laboratory convenient to you or at the University of Maryland GCRC.

The total volume of blood to be collected from you during the entire study is approximately 80 teaspoons, including blood for long-term specimen storage and for DNA storage; additional blood collections may be required if your kidney function declines, as described above. All procedures described above are for research purposes only.

WHAT ARE MY RESPONSIBILITIES IF I TAKE PART IN THIS RESEARCH?

If you take part in this research, you will be responsible to take your assigned medication in the prescribed dose and frequency, to attend your in-person and telephone-based study visits, and to notify study staff of any change in your health status or other medications.

POTENTIAL RISKS/DISCOMFORTS:

Risks associated with Metformin: The Food and Drug Administration (FDA) has approved Metformin to treat type II diabetes. Although widely used to treat diabetes, studies have demonstrated that Metformin can be used in non-diabetic adults without significant hypoglycemia (low blood sugar). The most common side effect of Metformin is gastrointestinal distress, a side effect which can be minimized by taking the medication with food, as well as increasing its dosage slowly. The table below describes many potential side effects:

Likely

- Diarrhea,
- Nausea and/or Vomiting
- Flatulence (gas)
- Weakness
- Metallic taste
- Anorexia (Loss of appetite)

Less Likely:

- Chest discomfort, flushing, palpitation (sensation of heart beating or racing)
- Headache, chills, dizziness, lightheadedness
- Rash
- Hypoglycemia (low blood sugar)
- Indigestion, abdominal discomfort, abdominal distention, abnormal stools, constipation, dyspepsia/ heartburn, taste disorder
- Muscle pain
- Shortness of breath, upper respiratory tract infection
- Decreased vitamin B_{12} levels, increased sweating, flu-like symptoms nail disorders

Rare (Limited to important or life-threatening)***:***

- Lactic acidosis (build-up of lactic acid in the body which leads to fatigue, nausea and vomiting, and stomach pain). The risk of this complication is believed to be increased among those with reduced renal function. Other rare risks include leukocytoclastic vasculitis (inflammation of small blood vessels), megaloblastic anemia (low red blood cell counts caused by large immature red blood cells), and inflammation in the lung.

To protect against these risks:

- We will check your vitamin B12 levels at screening visit – if your levels are low, we will recommend to your primary doctor that you be treated for these low levels; such treatment will be part of standard clinical care and not part of this study. You will not be eligible to participate in this study unless your vitamin B12 levels are normal. . If B12 level is low at 12- or 24-month visit, you will be directed to your PCP for B12 replenishment therapy.
- The levels of lactic acid will also be checked regularly in your blood (as described above), and you will be instructed to stop your study drug and seek immediate medical attention if increased levels are found.
- Your blood will also be checked regularly for the presence of low blood sugar. We will explain to you what it would feel like if you have low blood sugar and how to respond if these symptoms occur. Generally the best ways to avoid low blood sugar are to insure that you eat enough calories to compensate for strenuous exercise or when drinking alcohol.
- Some of the risks, especially the risk of excess lactic acid in the body, depend on the level of kidney function ("GFR"). We will be carefully monitoring your kidney function and levels of lactic acid throughout the study, as described above. The dose of metformin will be reduced if your GFR declines to less than 45 cc/min/1.73m^2 and will be stopped if your GFR declines to less than 30 cc/min/1.73m^2.
- Please let your study doctor know if you develop a rash or shortness of breath.
- We ask that you avoid excessive alcohol intake and let your study doctor know immediately if you experience any of the following symptoms: malaise (a general feeling of unwell), muscle pain, bradyarrhythmias (disruption in your heart beat or rhythm), trouble breathing, unusual sleepiness, any pain or discomfort in the abdomen, hypothermia (abnormally low body temperature), low blood pressure, or weakness. If you experience any of these symptoms, your study doctor may take you off the study drug and undergo additional lab tests.
- Your study doctor will slowly increase your dose of study drug based on your potential symptoms such as diarrhea, nausea, vomiting and gas. Your dose of study drug may also be adjusted throughout the study in order to help alleviate some of these symptoms.

In addition to the risks described above, there may be risks in this study which are not yet known.

Tell your study doctor about any other medications you are taking while taking metformin, as this may alter how well your medication(s) works. If you are currently taking a medication which the study team believes will interact poorly with the study drug, you will be asked to discuss changing your medication with your regular doctor or nephrologist. You will not be enrolled in this study if you are taking a restricted medication. This list of medications includes amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin, nifedipine, and furosemide. Furthermore, you will not be enrolled in this study if you are taking tolvaptan, a medication used to treat some patients with ADPKD (see "Alternatives to participation" below). Please ask your physician or study doctor if you are unsure whether you are taking any of these medications.

It is up to you and your doctor to weigh the risks and benefits of changing your medications based on your individual health status. In some cases, your study doctor may need to adjust your medication(s) to ensure that the medication is working properly.

- Please also contact the study team before any surgical procedure that requires restricted intake of food or fluids, or procedures requiring contrast, such as a CT scan.
- Tell your study doctor if you have had a bad reaction to any medication in the past.
- You should not join this study if you have low blood volume, as blood will need to be withdrawn in regular intervals up to 100 teaspoons and is recommended only for subjects with normal blood volume.

Risks associated with metformin for pregnant women: There are no known risks of metformin to the developing baby if the drug is taken by a pregnant woman. However, because we cannot be completely certain of the safety of metformin in pregnancy, and because pregnancy can influence the measurements we are making in this study, pregnant women will not be able to participate. If you are a woman who could become pregnant, you will be asked to practice effective birth control (condoms, birth control medications, intra-uterine device, diaphragm, or male partner with vasectomy) throughout the time you are participating in this study. If you should become pregnant despite these protections, you should contact your study doctor at once and stop your study medications. We will ask your permission to collect information about the outcome of your pregnancy. Female subjects should not breastfeed while taking study drug and for one month after stopping study drug.

For men only:
There are no known effects of metformin on sperm. Birth control methods may be used but are not required when participating in this study.

Risk of Breach of confidentiality: There is a rare risk that someone who is not authorized to review your protected health information may get access to it. Your protected health information will be stored in a locked cabinet and in a password-protected computer to minimize this risk. Also, your information will be de-identified; that is, assigned a code and the information linking the code with your identity will be stored in a separate secure location.

Risks associated with venipunctures (drawing blood from the vein): Bruising, soreness, or, rarely, infection and fainting may occur as a result of the needle sticks to obtain blood from your vein. Only skilled technicians will be used to perform this venipuncture.

Risks associated with the MRI: The levels of energy used to make magnetic resonance measurements are far less than those used in a single X-ray, and many patients have been safely studied using magnetic resonance techniques. However, some people become uncomfortable or claustrophobic (fear of closed spaces) while inside the scanner, as the sides and top of the machine can be very close to your body and face. If you become uncomfortable inside the magnet, you can stop the scan at any time by notifying the technician and/or study staff.

During some of the MRI scans, subjects have occasionally reported "tingling" or "twitching" sensations in their arms or legs, especially when their hands are clasped together. Further, because of the strong magnetic field, people with pacemakers, certain metallic implants, or metal in the eye cannot participate in this study. Dental fillings do not present a problem with MRI.

You will be given a checklist before entering the MRI room, which will be reviewed and used to verify that you do not have anything harmful in or on your body.
There is a rare risk that a metallic object may be attracted to the magnet and hit you. To reduce this risk we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. No metal objects are allowed to be brought into the magnet room at any time. In addition, once you are in the magnet, the door to the room will be closed so that no one inadvertently walks into the magnet room. No other serious effects have been reported from MRI scanning with the type of scanner used for this study.

The MRI scans performed for this study will be done for research purposes only and not to diagnose a disease or condition. A copy of the MRI will be sent to the laboratory of Dr. Kyongtae Bae at the University of Pittsburgh for measurement of kidney volume. These scan pictures will be labeled with a study code and will not include your name, date of birth, or other identifying information. In addition, the MRI will be reviewed by a radiologist at the University of Maryland Medical Center. There is a possibility that while reviewing your MRI, we may see an abnormality that we did not expect to see. This is what is called an "incidental finding." You will be informed promptly if we see such an incidental finding. With your permission, this information will also be shared with your doctor(s). These possible findings may or may not be significant and may lead to anxiety about your condition and may require further testing and evaluation by your doctor. Any further testing would not be part of this research study and would be part of standard medical care.

Although there are no known risks of MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no direct benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. A negative urine pregnancy test will be mandated before a woman of child-bearing potential can be scanned.

POTENTIAL BENEFITS

You may or may not benefit by taking part in this study. There is no guarantee that you will receive direct benefit from your participation in this study. We hope what we learn will be very important for treating polycystic kidney disease in the future. You will help add to medical knowledge about the possible usefulness of Metformin with PKD.

ALTERNATIVES TO PARTICIPATION

If you decide not to participate in this study, you may continue your usual medical care and adopt a healthier lifestyle. Tolvaptan is a medication recently approved by the US Food and Drug Administration to slow kidney function decline in some adults with ADPKD – specifically, those at risk for rapid progression. You will not be enrolled in this study if you are taking tolvaptan, and you will not be permitted to continue in this study if you start taking tolvaptan after enrollment. You should discuss with your kidney doctor whether this study is appropriate for you.

COSTS TO PARTICIPANTS

It will not cost you anything to take part in this study. You will not be responsible for the costs of the study medication n or for the costs of the tests described above.

PAYMENT TO PARTICIPANTS

You will receive $50 for each in-person study visit, including the baseline visit, as reimbursement for your travel costs of 100 miles or more to the study site, including parking, and for your time. Payment will be in the form of check. If there is a research-related injury, the study team will help you obtain medical treatment for the specific injury; you or your insurance carrier will be responsible for payment of the costs relating to such care. No financial compensation will be provided in the event of a research-related injury.

Due to federal tax law, you must give us your social security number in order to process your payments. If you receive over $600 in a calendar year from the University of Maryland Medical Center for participation in a single study or multiple studies, you will be issued an IRS 1099 (reportable income form).

CONFIDENTIALITY AND ACCESS TO RECORDS

This study will collect confidential information about you, including your name and date of birth, medical and family history, results of medical imaging tests, and results of blood and urine tests. There is a rare risk that someone who is not authorized to review your health information may get access to it. Your health information will be stored in a locked cabinet and in a password-protected computer to minimize this risk. Only study staff approved by the University of Maryland, Baltimore IRB will have access to this information. This information will be coded – it will be assigned a code and the information linking the code with your identity will be stored in a separate secure location.

Efforts will be made to limit your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB, the Food and Drug Administration (FDA), other representatives of this organization, and the Department of Defense (the sponsor of this study). Study monitors, auditors, and the IRB will be granted direct access to your medical records for verification of the research procedures and date. Specifically, Dr. Mary Korytkowski, MD at the University of Pittsburgh has been appointed as the Independent Research/Medical Monitor for this study; she will be granted access to your medical records for verification of research procedures and date. By signing this document you are authorizing this access.

The data from the study may be published; however, you will not be identified by name. People designated from the institutions where the study is being conducted and people from the sponsor will be allowed to inspect sections of your medical and research records related to the study. Everyone using study information will work to keep your personal information confidential. Your personal information will not be given out unless required by law

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

RIGHT TO WITHDRAW

Your participation in this study is voluntary. You do not have to take part in this research. You are free to withdraw your consent at anytime. Refusal to take part or to stop taking part in the study will involve no penalty or loss of benefits to which you are otherwise entitled. If you decide to stop taking part, or if you

have questions, concerns, or complaints, or if you need to report a medical injury related to the research, please contact the investigator, Dr. Terry Watnick at 410-328-3727. There are no adverse consequences to your health or well-being if you decide to withdraw from this study. If you withdraw from this study, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. If you agree, this data will be handled the same as research data. You will be told of any significant new findings which develop during the study which may affect your willingness to participate in the study.

CAN I BE REMOVED FROM THE RESEARCH?

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include if the investigator feels that the study may adversely influence your health or if you do not comply with the study requirements. The sponsor can also end the research study early. The study doctor will tell you about this and you will have the chance to ask questions if this were to happen.

UNIVERSITY STATEMENT CONCERNING RESEARCH RISKS

The University of Maryland, Baltimore (UMB) is committed to providing participants in its research the rights due them under State and federal law. You give up none of your legal rights by signing this consent form or by participating in the research project. This research has been reviewed and approved by the Institutional Review Board (IRB). Please call the Institutional Review Board (IRB) if you have questions about your rights as a research subject.

Participating in research may result in an injury, as explained above. If you suffer an injury directly related to your participation in this project, UMB and/or one of its affiliated institutions or health care groups will help you obtain medical treatment for the specific injury and provide referrals to other health care facilities, as appropriate. UMB and/or its affiliated institutions or health care groups will not provide you with financial compensation or reimbursement for the cost of care provided to treat a research-related injury or for other expenses arising from a research-related injury. The institution or group providing medical treatment will charge your insurance carrier, you, or any other party responsible for your treatment costs. If you incur uninsured medical costs, they are your responsibility**.** The study staff can give you more information about this if you have a study injury.

By signing this Consent Form, you are not giving up any legal rights. If this research project is conducted in a negligent manner and you are injured as a direct result, you may be able to recover the costs of care and other damages from the individuals or organizations responsible for your injury.

If you have questions, concerns, complaints, or believe you have been harmed through participation in this research study as a result of researcher negligence, you can contact members of the IRB or the Human Research Protections Office (HRPO) to ask questions, discuss problems or concerns, obtain information, or offer input about your rights as a research participant.

The contact information for the IRB and the HRPO is:

University of Maryland Baltimore
Human Research Protections Office
620 W. Lexington Street, 2nd Floor
Baltimore, MD 21201
410-706-5037

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

If you agree to participate in this study, please sign your name below.

_____
Participant's Signature

_____
Date

_____
Investigator or Designee Obtaining Consent Signature

_____
Date: