Principal Investigator: Dr. Godela Brosnahan
COMIRB No: 16-0802
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Study Title: Feasibility Study of Metformin Therapy in ADPKD

You are being asked to take part in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study plans to learn more about the medicine metformin. This study is being done to determine if treatment with metformin is safe and well tolerated, and whether it will slow down progression of kidney disease over a one-year period in adults with autosomal dominant polycystic kidney disease (ADPKD).

You are being asked to be in this study because you have ADPKD.

Medicines like metformin have been shown to decrease inflammation and slow down progression of kidney disease in animals with various kidney problems, and in humans with diabetes type 2. Metformin also decreases the risk of cardiovascular disease and improves blood vessel function in humans. It has not yet been studied as a treatment for ADPKD in humans.

In this investigational study, we will determine if metformin is well tolerated and helpful in slowing down progression of kidney disease in adults with ADPKD by evaluating: 1) the proportion of people who are still taking metformin at the assigned dose after one year; this measure assesses the tolerability of metformin; 2) kidney and liver volume as measured by kidney magnetic resonance imaging (MRI); 2) kidney function as measured by routine blood tests; 3) determinations of blood sugar levels at home to make sure any side effects are detected early. Kidney and liver volume will be measured at the beginning of the study and after one year in the study. The results will be compared between 25 patients with ADPKD who are taking metformin and 25 patients with ADPKD who are taking placebo (an inactive substance).

Other people in this study

Up to 65 people between the ages of 30 and 60 years from your area will participate in the study.

What happens if I join this study?

If you join the study, your care will be changed in the following ways:

1. You will have magnetic resonance imaging (MRI, a form of x-ray) studies of your kidneys and liver.

2. You will be instructed on how to use a glucometer (an easy to use device that measures blood sugar levels), which you will take home. You will be asked to check your fasting (morning) blood sugar levels daily for a week after each dosing change of metformin, then twice weekly for the following week and then whenever you experience any unusual symptoms (sweating, lightheadedness).
3. Approximately 1 1/2 tablespoon of blood will be obtained for measurement of complete blood count and blood chemistries including kidney and liver function at the beginning and end of the study.
4. Approximately 1 cup of urine will be obtained for determination of urine protein levels.
5. You will be randomized to receive either metformin or placebo. This means that you will be placed by chance to receive metformin or placebo by a procedure similar to the toss of a coin. Neither you nor your physician will be able to decide to which group you are assigned. You will have an equal chance of being assigned to metformin or placebo. Neither you nor those taking care of you will know which treatment you have been assigned ("double blind"). However, in the event of an emergency this information may be obtained. A placebo is a pill or a liquid that looks like medicine but is not real. It will have no medical effect on you.
6. You will check your morning blood sugar levels daily for a week after each dosing change of metformin, and whenever you experience any unusual symptoms, and report the numbers and any side effects back to us.
7. At 3, 6 and 9 months after your initial baseline visit, you will have approximately ½ tablespoon of blood drawn for blood chemistries to monitor your kidney function.
8. At 1 year following your initial visit, you will be scheduled to have another MRI and blood test for kidney function assessment.

You will be in the study for about 1 year.

What are the possible discomforts and risks?

Discomforts you may experience while in this study include the following:

Medication side effects

- **Metformin**
  Metformin has been approved by the Food & Drug Administration (FDA) for adults for treatment of diabetes type 2 and has been used in millions of people worldwide. We are using metformin in this study as an investigational drug for treatment of ADPKD. Potential side effects of metformin include low blood sugar levels, weakness, nausea, upset stomach and diarrhea. To minimize this risk, you will start with a low dose and increase to full dose.

  Rare serious adverse events could include a buildup of lactic acid in the blood (lactic acidosis), which can occur with a sudden change in kidney function due to another acute illness such as a stomach infection or fever leading to dehydration. You should stop the metformin and contact us right away if you experience any acute illness or schedule a radiological study with contrast material, which can also impair kidney function.

  Metformin should not be taken together with topiramate, lamotrigine, zonisamide or acetazolamide, because these drugs can also predispose to acid buildup in the blood. If you require treatment with these medicines, you should inform your doctor that you have been taking metformin, then stop the metformin, and call us. If you have any other questions about any medications, talk with your doctor.

Metformin should not be taken during pregnancy.

You will be given a separate paper regarding the above to keep at home for reference.

If you require other medications for control of blood pressure to < 140/80 mmHg, we will discuss the type of medication and its potential side effects with you before prescribing that medication.

Risks related to blood draw
In this study we will need to get about 3 tablespoons of blood from you. We will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

Risks of having blood taken by finger stick
In this study you will be taught how to get a drop of blood from your finger to check your blood sugar. To do this, you will make a small prick on your finger and put a drop of blood on a glucometer strip. You will feel a slight pain when the needle pricks your finger. Your fingertip may be sore for a day or two.

MRI Risks
In this study we will take Magnetic Resonance Images (MRI's) of your kidneys. The MRI machine uses powerful magnetic waves to take pictures inside the body. The waves themselves are not harmful, but they can cause metal to heat up and electronics to stop working.

You should NOT have an MRI if you have metal or electronic devices inside your body. Heart pacemakers and insulin pumps are examples of electronic devices.

The MRI machine is a small round tube. It might make you uncomfortable if you do not like tight spaces.

The most common side effect of having an MRI is flashing lights in the eyes. This is caused by the magnetic waves and is not harmful. Some people also experience warmth and reddening of the skin. This usually goes away after a few minutes.

Pregnancy Risk
If you are of possible childbearing potential we will do a blood pregnancy test before the MRI (together with the blood draw described above) because you should not undergo any unnecessary testing if you are pregnant. If you become pregnant, the particular treatment or procedures involved in the study may involve risks to the embryo or fetus which are currently unclear.

All females of childbearing potential who are sexually active, must agree to use 2 reliable methods of contraception to prevent pregnancy. These include the barrier method (condoms with spermicide, diaphragm), IUD, or are stable on hormonal birth control (pills or injections) for 3 months. Women who have completed menopause 2 or more years ago and who have not had a menstrual period during the past 12 months are not considered to be of childbearing potential. Women who have had a total hysterectomy are also not considered to be of childbearing potential. You must agree to use contraception, throughout the time you are receiving the study drug. You can discuss the best methods of contraception for you with the study doctor.

Risk of Loss of Confidentiality
There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

Unknown Risks
It is not expected that patients will have all of these side effects. Other side effects may occur which were not seen before. Side effects are usually temporary and manageable. However, it is possible they could cause serious or fatal disease.

The study may include risks that are unknown at this time.

Certificate of Confidentiality

This study has been issued a Certificate of Confidentiality from the federal government to help protect your privacy. The Certificate prohibits the researchers from disclosing your name, or any identifiable information, document or biospecimen from the research, with the exceptions listed below. A certificate provides protections against disclosing research information in federal, state, or local civil, criminal, administrative, legislative or other proceedings.

These protections apply only to your research records. The protections do not apply to your medical records.

The researchers may disclose your name or identifiable information, document or biospecimen, under the following circumstances:

- To those connected with the research,
- If required by Federal, State or local laws,
- If necessary for your medical treatment, with your consent,
- For other scientific research conducted in compliance with Federal regulations,
- To comply with mandated reporting, such as a possible threat to harm yourself or others, reports of child abuse, and required communicable disease reporting, or
- Under other circumstances with your consent.

A Certificate of Confidentiality does not protect information you or a member of your family voluntarily release.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about the medicine metformin. However, there is no guarantee that your health will improve if you join this study. Also, there could be risks to being in this study. If there are risks, these are described in the section describing the discomforts or risks.

Are there alternative treatments?

There may be other ways of treating your ADPKD. These other ways include medications for treatment of high blood pressure or Jynarque (tolvaptan), which can be prescribed to slow kidney

function decline in adults at risk of rapidly progressing ADPKD. You may also choose to get no treatment.

You should talk to your doctor about your choices. Make sure that you understand all of your choices before you decide to take part in the study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

This research is being sponsored by the National Institutes of Health.

Will I be paid for being in this study?

You will not be paid to be in the study. However, for subjects who travel from outside the state of Colorado, travel (airfare, shuttles) and overnight hotel accommodations will be paid for by the study if necessary. The amount paid for each subject will be varied based on cost of airfare and their home location. Travel will be booked by a member of the study team. There will be no direct payment made to the subjects for out of state travel.

Will I have to pay for anything?

It will not cost you anything to be in this study. Study medications including metformin or placebo will be provided as part of the study. If you require additional blood pressure medications, these may be prescribed for you but you will need to pay for this either on your own or through your insurance company.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from the study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason. Also the sponsor may stop the study at any time.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Godela Brosnahan immediately. Her phone number is 303-724-1687. We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Godela Brosnahan, M.D. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Brosnahan at 303-724-1687. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Brosnahan with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

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

Optional Consent for Specimen Banking for Future Research

Dr. Godela Brosnahan would like to keep some of the data and blood and urine that are taken during the study but are not used for other tests. If you agree, the data and samples will be kept and may be used in future research to learn more about ADPKD. The research that is done with your data and samples is not designed to specifically help you. It might help people who have ADPKD and other diseases in the future. Reports about research done with your data and samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your data and samples will not affect your care.

The choice to let Dr. Godela Brosnahan keep the data and samples for future research is up to you. No matter what you decide to do, it will not affect the care that you will receive as part of the study. If you decide now that your data and samples can be kept for research, you can change your mind at any time and contact your study doctor to let him or her know that you do not want Dr. Brosnahan to use your data and samples any longer, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until Dr. Brosnahan decides to destroy them.

When your data and samples are given to other researchers in the future, Dr. Brosnahan will not give them your name, address, phone number or any other information that will let the researchers know who you are.

Sometimes data and samples are used for genetic research (about diseases that are passed on in families). Even if your data and samples are used for this kind of research, the results will not be told to you and will not be put in your health records. Your data and samples will only be used for research and will not be sold. The research done with your data and samples may help to develop new products in the future, but there is no plan for you to be paid.

The possible benefits of research from your data and samples include learning more about what causes ADPKD and other diseases, how to prevent them and how to treat them. The greatest

risk to you is the release of your private information. Dr. Brosnahan will protect your records so that your name, address and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any data or sample collection and storage by Dr. Brosnahan.

Please read each sentence below and think about your choice. After reading each sentence, circle "yes" or "no." If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and future use of your samples, you may still take part in the study.

I give my permission for my data, blood and urine to be stored in a central tissue bank at the University of Colorado Anschutz Medical Campus for future use by the study investigators:

1. I give my permissions for my data, blood, and urine to be kept by Dr. Brosnahan for use in future research to learn more about how to prevent, detect, or treat ADPKD.

   ☐ Yes ☐ No _____Initials

2. I give my permissions for my data, blood and urine to be used for research about other health problems (for example: causes of heart disease, osteoporosis, diabetes).

   ☐ Yes ☐ No _____Initials

3. I give my permission for the University of Colorado Division of Renal Diseases and Hypertension to contact me in the future to ask me to take part in more research.

   ☐ Yes ☐ No _____Initials

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Dr. Godela Brosnahan
13199 E. Montview Blvd., Suite 495
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team.
- The sponsor (the NIH) or an agent for the sponsor, who is the company paying for this research study.
- Regulatory officials from the institution where the research is being conducted, to ensure compliance with policies or monitor the safety of the study

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator. To ensure proper evaluation of test results, your access to these study results may not be allowed until after the study is completed.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records
- Tissue samples and the data with the samples.

What happens to Data and Blood that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data and blood collected from you during this study are important to this study and to future research. If you join this study:

- The data and blood specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data and blood collected from you.
- If data and blood are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

HIPAA Authorization for Optional Additional Study Procedures

In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

These optional procedures involve the storing of some of your blood samples by Dr. Godela Brosnahan for future research.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated of this consent form. (Initial all the previous pages of the consent form).

Signature: _____ Date_____

Print Name: _____ Date_____

Consent form explained by: _____ Date_____

Print Name: _____ Date_____

CONSENT FOR SUBJECTS WHO CANNOT READ

The study subject has indicated that he/she is unable to read or is blind. The consent addendum has been read to the subject by a member of the study staff, discussed with the subject by a member of the study staff, and the subject has been given an opportunity to ask questions of the study staff.

Witness Signature: _____ Date_____

Witness Print Name: _____ Date_____

Witness of Signature ☐

Witness of consent process ☐