Official Title: A Randomized Pilot Study of Hemodialysis Initiation Comparing Twice-Weekly Hemodialysis Plus Dialysis-Sparing Therapy Versus Thrice-Weekly Hemodialysis (The TWOPLUS-HD Trial)
NCT03740048
IRB-Approved Date: 5/7/21

Wake Forest™ Baptist Health

Informed Consent Document

Project Title: A Randomized Pilot Study of Hemodialysis Initiation Comparing TwiceWeekly Hemodialysis Plus Dialysis-Sparing Therapy versus Thrice-Weekly Hemodialysis:
The TWOPLUS-HD Trial

Principal Investigator: Mariana Murea, M.D.
Co-Investigators: Isai Bowline, M.D., Alison Fletcher, M.D

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have End Stage Renal Disease and your Kidney Doctor has determined that you need hemodialysis treatments. Healthy kidneys clean your blood by filtering wastes, salts and fluid from your blood. They also make substances that keep your body healthy. In hemodialysis a machine is used to replace some of these functions when your kidneys are failing. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

Almost all Americans with end-stage kidney disease (ESKD) that start hemodialysis (HD) are prescribed a regular dialysis treatment schedule of three times per week. However, the number of hemodialysis treatments per week that is best when first starting dialysis is not known. When hemodialysis is started, there may still be enough kidney function left that may only require doing hemodialysis two times per week (instead of three times per week) **for a limited period of time**. In this study, half of the participants will be treated with a regular schedule of hemodialysis (three times per week) from the time dialysis is started. The other half of the participants will be treated with hemodialysis two times per week **for six weeks only** followed by hemodialysis three times per week. With this study we want to see how the kidney function changes depending on the number of hemodialysis treatments performed when starting hemodialysis. For this reason, we will want to obtain urine collections from you at specific time intervals. These urine collections will help to evaluate how the kidney function changes after dialysis is started. With the information we obtain from this study, we want to see how the human body reacts to different number of hemodialysis treatments at the beginning of dialysis.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Approximately fifty-one (51) people will take part in this pilot study.

WFU School of Medicine
Institutional Review Board
IRB Number: IRB00054726
Meeting Date Approved 5/7/2021
Version Valid Until: 1/19/2022

WHAT IS INVOLVED IN THE STUDY?

If you agree to participate in this study by signing this consent form, **you will be randomized to either start hemodialysis two times a week plus using additional kidney medications for six weeks, continued by three times a week or start hemodialysis three times a week.** Randomization means that you are put into a group by chance. It is like flipping a coin. You will have an equal chance to be placed into either group. Patients randomized to two times a week will receive a stepwise hemodialysis regimen with hemodialysis two times a week for six weeks, followed by hemodialysis three times a week onward. Patients randomized to three times a week will receive hemodialysis three times a week at the start of dialysis and onward. If you are randomized to the group starting hemodialysis two times per week for six weeks, you may be provided with Patiromer (Veltessa) to help with potassium retention. Patiromer will be provided to you at no cost by the company that is sponsoring this study. Patiromer is FDA approved for its intended use in this study. Your primary nephrologist may ask you to continue or start medication(s) that control fluid and salt retention, potassium retention, or buffer acidity. These medications include Furosemide (Lasix), Bumetanide (Bumex), Metolazone (Zaroxolyn), Patiromer (Veltassa) or Sodium Bicarbonate, all these medications are FDA approved for their intended use in this study and will be prescribed, if needed according to standard of care. .

Your Kidney Doctor has already determined that you need and are eligible to start hemodialysis in order to be able to retain kidney function. Your dialysis treatments will be done at your prescribed dialysis center.

At your first dialysis treatment only, you will receive dialysis with a study specific potassium concentration of fluid that helps pull toxins from the blood. After your first dialysis treatment, the evaluation of your dialysis treatments will follow according to usual clinical practice and will be directed by your kidney doctor. You will be examined in the medical office or at your dialysis unit on a regular basis by your kidney doctor, physician assistant, and nurses experienced with dialysis care. Any abnormalities that relate to your dialysis treatments will be addressed as directed by your kidney doctor according to standard of care.

There will not be any changes in your usual medical care if you participate.

All of the following evaluation and reports will be performed and gathered specifically for this study at your dialysis session or at your regular doctor office visit by our study personnel.

- You will be asked to provide information from your health record such as age, sex, ethnic background, medical history, current medications, diet, and medical care.

- You will be asked to complete a questionnaire (Dialysis Symptom Index) to assess your health and how you are feeling, will be asked questions about any depression you may have (PHQ-9 questionnaire), and will be asked questions about any anxiety you may have (GAD-7 questionnaire) at several different times during your participation.

WFU School of Medicine
Institutional Review Board
IRB Number: IRB00054726
Meeting Date Approved 5/7/2021
Version Valid Until: 1/19/2022

- You will be asked to provide a study specific blood sample at the outpatient dialysis unit at your first dialysis treatment and at four other dialysis treatments. For each test, less than 1 millimeter of blood is required. The lab test will be done at the dialysis unit and you will not have any needle-sticks for this test.

- You will be asked to provide urine collections. Within one week before or after hemodialysis initiation, you will be asked to collect the urine you make over a 24-hour period. Afterwards, you will be asked to collect urine at 6 weeks, 3 months, 6 months, and 12 months of being on hemodialysis; at these collections, you will be asked to collect all the urine that you make between two hemodialysis sessions (from the end of one dialysis session to the beginning of the next successive hemodialysis session).

There will be no medical visits done specifically or exclusively for this study. Information routinely gathered as part of your medical care will also be used in the study. Results of routine tests will be available to your doctor, and will be used to help determine study outcomes.

We can send copies of your test results to your primary doctor. Even if you do not wish to have any of your medical information sent to your physician, you can still participate in this research study.

Do you request that we send important medical findings from your study tests/exams to your personal physician?

[ ] Yes [ ] No _____ Initials

HOW LONG WILL I BE IN THE STUDY?

Your participation in this study will be for about 12 months. You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. Your medical care will not be affected by your decision.

This study will not interfere with any other treatments of your medical conditions. Should you qualify to receive a kidney transplant during the study, the kidney transplantation evaluation and surgery will proceed as scheduled. If you receive a kidney transplant, your participation in this study will be ended.

WHAT ARE THE RISKS OF THE STUDY?

Being in this study may involve some risk to you. You should discuss the risk of being in this study with the study staff.

- There is a slight risk that other people outside the study may access your information. We will do our best to protect your confidential information. Efforts, such as coding research

WFU School of Medicine
Institutional Review Board
IRB Number: IRB00054726
Meeting Date Approved 5/7/2021
Version Valid Until: 1/19/2022

records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

- Because investigators do not know which number of dialysis sessions is better at preserving kidney function, there is a chance that you could be randomized to the arm of the study that either has a better or worse outcome than the other arm.

- If you will be randomized to hemodialysis two times a week, the following may be observed: fluid may build up between hemodialysis treatments, potassium level may go up in the blood between hemodialysis treatments, or acid level may go up in the blood between dialysis treatments. The risks associated with elevated potassium or acid level in the blood includes irregular heartbeats, heart failure, or sudden death. If you experience any palpitations or shortness of breath, you will need to report to a health care provider or present to an emergency room. You will be closely monitored for any of these potential occurrences at the dialysis unit. To prevent or treat these clinical occurrences, you will be prescribed medications if needed, or you may be prescribed hemodialysis three times per week before the mark of six weeks of twice per week hemodialysis.

- During the study, you may receive, if medically indicated, treatment for fluid retention (which can be treated with diuretics, for example Furosemide or Lasix), high potassium level (which can be treated with Patiromer), or high acidity in the blood (which can be treated with Sodium Bicarbonate).

You might have already received treatment with diuretics and sodium bicarbonate. These medications are well tolerated and the doses will be changed, based on your clinical monitoring and blood work, to prevent dehydration, too much volume accumulation, or having too much acid or too much bicarbonate in your blood. If potassium level in the blood becomes too high, you will receive Patiromer. This medication is well tolerated; potential side effects include constipation (which can occur in approximately 8 out of 100 patients), low magnesium level in the blood (which can occur in up to 9 out of 100 patients). During treatment with Patiromer, your blood levels of potassium and magnesium will be monitored, and changes in medications (including discontinuation) and/or dosing will be made as needed to undo any of the side effects.

Two independent Safety Medical Officers will be reviewing the data from this research throughout the study.

REPRODUCTIVE RISKS AND OTHER ISSUES TO PARTICIPATING IN RESEARCH

Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable,

WFU School of Medicine
Institutional Review Board
IRB Number: IRB00054726
Meeting Date Approved 5/7/2021
Version Valid Until: 1/19/2022

although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge. We encourage you to discuss this issue further with your physicians if you have any questions.

Pregnant women are excluded from participation in this study. If you are a sexually active woman of childbearing potential and have not been using a reliable method of birth control, two negative pregnancy tests performed 15 days apart are required to check for possible early pregnancy prior to starting treatment.

CONTRACEPTIVE MEASURES FOR MALES

Your participation in this research study may damage your sperm, which could cause harm to a child that you may father while on this study. Such harm may be currently unforeseeable. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study and for ***(specify period of time following study participation if applicable)*** months afterwards. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should also promptly notify her doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You may or may not receive direct benefit from participating in this study. We hope the information learned from this study will benefit other people in the future. Based on experience with hemodialysis in patients with similar disorders, researchers believe twice-weekly hemodialysis for six week followed by thrice-weekly hemodialysis may be as good as standard therapy of starting dialysis with thrice-weekly hemodialysis.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have. Instead of being in this study, you have the option of doing hemodialysis three times a week which is the standard hemodialysis regimen prescribed at the initiation of hemodialysis in the United States of America.

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. Costs for your regular medical care will be your own responsibility.

WFU School of Medicine
Institutional Review Board
IRB Number: IRB00054726
Meeting Date Approved 5/7/2021
Version Valid Until: 1/19/2022

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

Participant information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

WILL YOU BE PAID FOR PARTICIPATING?

You will be compensated $25 after completion of the 24 hour urine collection at your first dialysis visit. You will also be compensated $50 after completion of each (4 total) inter-dialytic urine collection (urine collection between two hemodialysis sessions) for a potential of $225 total for completing all study procedures. To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Relypsa, Inc. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional

information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call the study investigator **Dr. Mariana Murea, M.D. at** [redacted] [redacted] after hours).

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:** date of birth, contact information (address, telephone number, etc.), past medical history, laboratory results, procedures, other test results, how you respond to study procedures, and information from questionnaires, assessments and physical examinations. If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study may be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS), The National Institutes of Health (NIH) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This

WFU School of Medicine
Institutional Review Board
IRB Number: IRB00054726
Meeting Date Approved 5/7/2021
Version Valid Until: 1/19/2022

information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

Monitors, auditors, IRB or other regulatory agencies will be granted direct access to your original medical record for verification of clinical trial procedures or data, without violating your confidentiality and to the extent permitted by other applicable laws.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it might no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept indefinitely. This authorization does not expire. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell Dr. Mariana Murea that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Mariana Murea, M.D.
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

WFU School of Medicine
Institutional Review Board
IRB Number: IRB00054726
Meeting Date Approved 5/7/2021
Version Valid Until: 1/19/2022

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 Web site at any time.

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because it is in your best medical interest, your condition worsened, new information becomes available, you had an unexpected reaction, you failed to follow instructions, or because the entire study has been stopped.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Dr. Mariana Murea, M.D. at [redacted] ([redacted] after hours).

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted].

You will be given a copy of this signed consent form.

Signatures

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Please read the following sentence and think about your choice. After reading the sentence, circle YES or NO. If you have questions, please talk to your doctor or nurse.

You agree that your Wake Forest Baptist Health electronic medical record may be accessed by designated study personnel for use in future research to learn about, detect, prevent, treat or cure other health problems. If you answer NO to this question, you may still participate in this study.

YES NO

_____
Subject Name (Printed)

_____ _____ _____
Subject Signature Date Time AM / PM

_____
Person Obtaining Consent (Printed)

_____ _____ _____
Person Obtaining Consent (Signed) Date Time AM / PM

Legally Authorized Representative Name (Print):_____

The above named Legally Authorized Representative has legal authority to act for the research subject based upon (specify health care power of attorney, spouse, parent, etc.)

Relationship to the Subject: _____

Legal Representative Signature: _____ Date:_____
Time:_____ am / pm