A Randomized Double Blind Placebo Controlled Trial of Ramelteon in the Prevention of Postoperative Delirium in Older Patients Undergoing Orthopedic Surgery: The RECOVER Study

R21 AG050850-01A1

NCT02324153

Consent Form

Date of Last IRB Approval: 7/12/19

Johns Hopkins University School of Medicine

Karin J Neufeld MD MPH

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: "**A Randomized Double Blind Placebo Controlled Trial of Ramelteon in the Prevention of Post-operative Delirium in Older Patients Undergoing Orthopedic Surgery**" (AKA: The RECOVER Study)

Application No.: **IRB00097232**

Sponsor: **NIH – National Institute on Aging**

Principal Investigator: **Karin J. Neufeld**
Department of Psychiatry and Behavioral Sciences
Johns Hopkins Bayview Medical Center
A4 Center Suite 457; 4940 Eastern Ave. Baltimore, MD 21224
Phone 401-550-0197 (o) 443-691-8305 (c)
email: kneufel2@jhmi.edu

1. What you should know about this study:

- You are being asked to join a research study. This consent form explains the research study and your part in it. Please read it carefully and take as much time as you need. Ask your study doctor or the study team to explain any words or information that you do not understand.
- You are a volunteer. If you join the study, you can change your mind later. There will be no penalty or loss of benefits if you decide to quit the study.
- During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.
- If we think your participation in this study may affect your clinical care, information about your study participation will be included in your medical record, which is used throughout Johns Hopkins. Doctors outside of Johns Hopkins may not have access to this information. You can ask the research team to send this information to any of your doctors.
- When Johns Hopkins is used in this consent form, it includes The Johns Hopkins University, The Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, Howard County General Hospital, Johns Hopkins Community Physicians, Suburban Hospital, Sibley Memorial Hospital and All Children's Hospital.
- Biospecimens will be collected in this study. Biospecimens may include any of the following: blood, tissue, saliva, urine, bone marrow, cells, etc. Most biospecimens contain DNA, which is the genetic code for each person.
- A description of this clinical trial will be available on http://www.ClinicalTrials.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.
- If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.
- During this study, you will not have access to certain medical information and test results collected for study purposes. If an emergency occurs while you are in the study, medical information needed

for your treatment can be made available to your study physician and other physicians who treat you. When the study is completed, all the information in your medical record will be available to you.

- The person being asked to be in this research study may not be able to give consent to be in this study. You are therefore being asked to give permission for this person to be in the study as his/her decision maker.

2. Why is this research being done?

This research is being done to test the use of a study drug called Ramelteon to prevent delirium after surgery.

Ramelteon (also known as Rozerem) is approved by the Food and Drug Administration (FDA) for the treatment of insomnia or difficulties falling asleep. It is not approved for preventing delirium and its use in the study is considered investigational.

Delirium is a sudden change in ability to think and remember that isn't like the person when they are at their best. Sleep problems are also common during delirium. Delirium is caused by an underlying physical disturbance and generally lasts several days. It can happen sometimes after having surgery and is called "post-operative delirium". It can result in significant problems, such as slower recovery from surgery, need for longer hospital and rehabilitation stays, increased costs to the healthcare system and it can be frightening for both patients and their families.

There is no cure for delirium or any medication proven to prevent it. This study will compare the number of people who develop delirium while receiving the study drug, ramelteon, given before and two nights after their surgery to those who do not receive this drug and receive a placebo instead. We will also study whether certain chemicals in the blood and brain can predict delirium after surgery and whether Ramelteon can change these chemicals.

People, 65 years of age or older, undergoing orthopedic surgery may join.

How many people will be in this study?

We will ask at least 80 people to join the study. It will take place at one hospital - the Johns Hopkins Bayview Medical Center.

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

Before Surgery

If you are not admitted to the hospital before your surgery we will make an appointment to meet with the research team at the Johns Hopkins Bayview Medical Center. During that visit you will be asked some more questions about your health and thinking. We will ask a family member or friend some questions about your health as well. All of these questions will take about 1 hour.

We will also draw 1 teaspoon of blood for research purposes at the same time. You do not have to have blood drawn for research to be in this study.

At the end of that visit our pharmacist at the hospital will prepare the study drug for you to take home. You will be given one capsule to take the night before surgery. It will contain either ramelteon or placebo (an inactive material that does not contain any active study drug). The research pharmacist at Bayview will be the only person who knows which type of study drug you received. A computer will decide which type of medication you get, much like a "flip of a coin". Your doctors, nurses, and study

staff will not know what kind of study drug you received. However the study doctor can quickly get the information from the pharmacist if needed in a medical emergency.

If you are unable or do not want to come to the hospital for the baseline visit, the study team might be able to visit you in the community before your surgery if you prefer. If you live too far away for the team to visit in person, we can send you this consent sign electronically after the medical team discusses it with you by telephone to answer your questions.

The study staff will call you the night before surgery to remind you to take the capsule at bedtime.

Both kinds of capsules (ramelteon and placebo) will also contain vitamin B2, riboflavin. We will test your urine to see if it has riboflavin in it on the day of surgery. This helps us be sure that you took the pill before surgery.

After Surgery
The study the research staff will come and see you after you awake from anesthesia after the surgery and are ready to be moved to the hospital ward. Research assistants will ask you some questions about your thinking. This will take about 5 to 10 minutes.

You will receive the same type of study drug (either ramelteon or placebo) for two nights while you are in the hospital – on the night of surgery and the first night after. The nurse caring for you on the surgical ward will give it to you at bedtime. On the first and second days after surgery the research staff will review your hospital chart, and will ask you some questions about your thinking and your physical symptoms. If you are discharged prior to your second day after surgery, you be given your study drug (either ramelteon or placebo) to take at your place of discharge. In addition, the research staff will call you to complete questionnaires. The study ends on the second day following your surgery.

We will draw 1 teaspoon of blood for research purposes on both the first and second days after surgery. If you are discharged from the hospital early (prior to day two after surgery), the blood draw for that day will not be completed.

Request to contact you after the study is completed?
We do not plan to contact you after the study ends at this time. Would you allow us to contact you following the study if we have more questions at that time?

YES ☐ _____
Signature of Participant

NO ☐ _____
Signature of Participant

Request to collect and store biospecimens for future research

As part of this research study, we would like to ask you to let us store your biospecimens and health information for future research. This research could include other diseases.

The study doctor can provide you with additional information if you have questions. Also, further information about our use of your biospecimens can be found in this consent document under the heading "*What happens to Data and Biospecimens that are collected in the study?"*.

Will you allow us to store the biospecimens we collect for this study for use in future research*?*

YES ☐ _____
Signature of Participant

NO ☐ _____
Signature of Participant

How long will you be in the study?

You will be in this study for 2 days after your surgery.

4. What are the risks or discomforts of the study?

Risks Associated with the Study Drug: Ramelteon 8 mg

The main risk of taking ramelteon is that instead of decreasing delirium, it may make no difference or it may make delirium worse.

Other risks associated with ramelteon reported in product labeling by the company include:

1. Less rare and less serious side effects such as somnolence (sleepiness), fatigue, dizziness, nausea and worsened insomnia;
2. Rarely new cognitive or behavioral abnormalities that may be the result of an unrecognized underlying psychiatric or physical disorder, such as worsening of depression (including suicidal ideation and completed suicides), hallucinations, bizarre behavior, agitation and mania;
3. Very rarely amnesia (or loss of memory), anxiety and other complex behaviors such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a hypnotic) and other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) with amnesia for the event;
4. Extremely rare but potentially life threatening side effects include angioedema (swelling similar to hives that may develop under the skin) and anaphylactic reactions (severe allergic reactions);
5. Decreased testosterone levels and increased prolactin levels have been reported with long-term use;
6. Ramelteon should not be given to people taking the following medications: fluvoxamine (Luvox), melatonin, rifampin (Rifadin, Rimactane), ketoconazole (Nizoral), fluconazole (Diflucan)

Risks Associated with the Tracer Substance – Riboflavin (Vitamin B2) 100 mg

Riboflavin can be associated with an allergic reaction. Anyone with a riboflavin allergy should not take part in this study.

Risks Associated with the Study Procedures

Having blood drawn may cause some pain and a bruise may form where the needle enters the vein. Drawing blood may cause some people to faint. There is a rare risk of infection from inserting the

needle, however the blood drawn after surgery will be drawn at the same time as your other routine blood draws during hospitalization so that there is no extra needle stick.

There is the risk that information about you may become known to people outside this study. We will do everything that we can to ensure that your information and confidentiality is protected.

You may get tired or bored when we are asking you questions or you are completing questionnaires. You do not have to answer any question you do not want to answer.

There may be side effects and discomforts that are not yet known.

5. Are there benefits to being in the study?

There may or may not be a direct benefit to you from being in the study. If ramelteon can prevent post-operative delirium receiving the study drug in this study might result in some benefit but this cannot be guaranteed. No benefit is expected if you are randomly assigned to receive placebo. If you take part in this study, you may help others in the future.

6. What are your options if you do not want to be in the study?

You do not have to join this study. If you do not join, your care at Johns Hopkins will not be affected.

7. Will it cost you anything to be in this study?

You will receive a separate Insurance and Research Participant Financial Responsibility Information Sheet (Sheet).

This Sheet will give you the following information:

- The procedures, tests, drugs or devices that are part of this research and that will be paid for by the study (no cost to you).

- The procedures, tests, drugs or devices that will be billed to you and/or your health insurer. If you have health insurance, you will be responsible for any co-pays or deductibles not covered by your insurance.

8. Will you be paid if you join this study?

We will pay for $50 if you come to the Johns Hopkins Bayview Medical Center in order to complete your baseline visit prior to your surgery.

You may be required to provide your social security number to be paid for taking part in this study. Federal tax law requires that you report your research payments when you file your taxes. If your total payments from Johns Hopkins exceed $600 per year, Johns Hopkins will report these payments to the Internal Revenue Service and you will receive a 1099-MISC form from us.

9. Can you leave the study early?

- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.

If you leave the study early, Johns Hopkins may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities.

10. Why might we take you out of the study early?

You may be taken out of the study if:

- Staying in the study would be harmful.
- You need treatment not allowed in the study.
- If your surgery is canceled and rescheduled to a date less than 7 days after taking the first dose of medication.
- The study is cancelled.
- There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study early, Johns Hopkins may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities**.**

11. How will your privacy be protected?

We have rules to protect information about you. Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form you provide your permission, called your "authorization," for the use and disclosure of information protected by the Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records (which may include information about HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

The research team will know your identity and that you are in the research study. Other people at Johns Hopkins, particularly your doctors, may also see or give out your information. We make this information available to your doctors for your safety.

People outside of Johns Hopkins may need to see or receive your information for this study. Examples include government agencies (such as the Food and Drug Administration), safety monitors, other sites in the study and companies that sponsor the study.

If you are in a cancer study that receives federal funding, the National Cancer Institute (NCI) now requires that we report identifiable information (such as, zip code) about your participation. You may contact the NCI if you have questions about how this information is used.

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

We will use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside Johns Hopkins who receive your information may not be covered by this promise or by the federal Privacy Rule. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee that your information will not be re-disclosed.

The use and disclosure of your information has no time limit. You may revoke (cancel) your permission to use and disclose your information at any time by notifying the Principal Investigator of this study by phone or in writing. If you contact the Principal Investigator by phone, you must follow-up with a written request that includes the study number and your contact information. The Principal Investigator's name, address, phone and fax information are on page one of this consent form.

If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your revocation (cancellation) would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

12. What treatment costs will be paid if you are injured in this study?

Johns Hopkins and the federal government do not have a program to pay you if you are hurt or have other bad results from being in the study. However, medical care at Johns Hopkins is open to you as it is to all sick or injured people.

The costs for any treatment or hospital care you receive as the result of a study-related injury that are not covered by a health insurer will be billed to you.

By signing this form you will not give up any rights you have to seek compensation for injury.

13. What other things should you know about this research study?

a. What is the Institutional Review Board (IRB) and how does it protect you?

The Johns Hopkins Medicine IRB is made up of:

- Doctors
- Nurses
- Ethicists
- Non-scientists
- and people from the local community.

The IRB reviews human research studies. It protects the rights and welfare of the people taking part in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is 410-955-3008. You may also call this number for other questions, concerns or complaints about the research.

When the Johns Hopkins School of Medicine Institutional Review Board (IRB) reviews a study at another site, that site (institution) is solely responsible for the safe conduct of the study and for following the protocol approved by the Johns Hopkins IRB.

b. What do you do if you have questions about the study?

Call the principal investigator or study doctor, Dr. Karin Neufeld at 410-550-0197 during business hours. If you wish, you may contact the principal investigator by letter or by fax. The address and fax number are on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-955-3008.

c. What should you do if you are injured or ill as a result of being in this study?

If you think you are injured or ill because of this study, call Dr. Karin Neufeld at 443-691-8305.

If you have an urgent medical problem related to your taking part in this study, call Dr. Karin Neufeld at 410-550-0197 during regular office hours or 443-691-8305 after hours and on weekends.

d. What happens to Data and Biospecimens that are collected in the study?

Johns Hopkins and our research partners work to understand and cure diseases. The biospecimens and/or data you provide are important to this effort.

If you join this study, you should understand that you will not own your biospecimens or data, and should researchers use them to create a new product or idea, you will not benefit financially.

With appropriate protections for privacy, Johns Hopkins may share your biospecimens and information with our research sponsors and partners.

14. What does your signature on this consent form mean?

Your signature on this form means that: You understand the information given to you in this form, you accept the provisions in the form and you agree to join the study. You will not give up any legal rights by signing this consent form.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

_____

Signature of Participant (Print Name) Date/Time

_____

Signature of Person Obtaining Consent (Print Name) Date/Time

_____

Signature of Legally Authorized Representative (LAR) (Print Name) Date/Time

For ADULTS NOT CAPABLE of GIVING CONSENT (*Persons from the following categories in order of priority may be a Legally Authorized Representative: Health Care Agent; Legal Guardian; Spouse; Adult child; Parent; Adult sibling; Friend or other relative)*

_____

Relationship of LAR to Participant (indicate why the LAR is authorized to act as a surrogate health care decision-maker under state or applicable local law) Date/Time

_____

Signature of Participant, LAR or Parent/Guardian (Print Name) Date/Time

I have received the separate Insurance and Research Participant Financial Responsibility Information Sheet.

_____

Signature of Participant, LAR or Parent/Guardian (Print Name) Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; IF YOU ARE USING EPIC FOR THIS STUDY A COPY MUST BE FAXED TO 410-367-7382; IF YOU ARE NOT USING EPIC A COPY MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

ONLY CONSENT FORMS THAT INCLUDE THE JOHNS HOPKINS MEDICINE LOGO CAN BE USED TO OBTAIN THE CONSENT OF RESEARCH PARTICIPANTS.

DOCUMENTATION OF PHYSICIAN/MID-LEVEL PROVIDER CONSENT

My signature below indicates that I have discussed the risks, benefits, and alternatives, answered any questions, and believe the participant is able to make an informed choice to join the study.

_____

Signature of Physician/Mid-Level Provider (Print Name) Date/Time

_____

Signature of Participant (Print Name) Date/Time

_____

Signature of Legally Authorized Representative (LAR) (Print Name) Date/Time
For ADULTS NOT CAPABLE of GIVING CONSENT (*Persons from the following categories in order of priority may be a Legally Authorized Representative: Health Care Agent; Legal Guardian; Spouse; Adult child; Parent; Adult sibling; Friend or other relative)*

_____

Relationship of LAR to Participant (indicate why the LAR is authorized to act as a surrogate health care decision-maker under state or applicable local law) Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; IF YOU ARE USING EPIC FOR THIS STUDY A COPY MUST BE FAXED TO 410-367-7382; IF YOU ARE NOT USING EPIC A COPY MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

ONLY CONSENT FORMS THAT INCLUDE THE JOHNS HOPKINS MEDICINE LOGO CAN BE USED TO OBTAIN THE CONSENT OF RESEARCH PARTICIPANTS.