COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

YALE UNIVERSITY
YALE UNIVERSITY SCHOOL OF MEDICINE
YALE-NEW HAVEN HOSPITAL
YALE-NEW HAVEN HOSPITAL: SAINT RAPHAEL CAMPUS

Study Title: Circadian Rhythm as a Novel Therapeutic Target in the Intensive Care Unit

Principal Investigator (the person who is responsible for this research): **Melissa Knauert, MD, PhD**
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A person who takes part in a research study is called a research or study subject. In this consent form, "you" always refers to the research subject. If you are a legally authorized representative (LAR), please remember the "you" means the research (study) subject. As an LAR you are able to provide consent for this research study. If/when the study subject is able to provide consent (e.g., when they get better), we will also ask them for consent, and they may elect to continue or withdraw from the study.

Research Study Summary

- **We are asking you to join a research study designed to investigate circadian rhythms in the intensive care unit (ICU). You were selected to be part of our study because you are a patient in the ICU. Study participation will last until you are discharged from the hospital. This study will enroll 115 patients from the ICU**

- Little is known about circadian rhythm in the ICU. Circadian rhythms are the normal changes in your body that occur during the day and night; these rhythms help you be asleep and awake at the right times. These rhythms are important because when they are disrupted, the functioning of every organ in your body is affected.

- Study activities for all participants include wearing a wristwatch that measures movement and placing a meter in your hospital room that measures the light levels and temperature. If you meet additional criteria, we may collect some urine and blood samples during the first few days of the study.

- There are some risks from participating in this study. These include skin irritation from our study watch (rare). For individuals included in the urine collection there are no risks or discomforts. Blood sample collection does have the risk of discomfort and bruising at the site of blood draw.

- The study may have no benefits to you but will help us understand circadian rhythms in the ICU. You can choose to take part, or you can choose not to take part in this study. Choosing not to take part in this study will not alter your ICU care in any way.

- Taking part in this study is your choice. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

APPROVED BY THE YALE UNIVERSITY IRB 10/19/2022

- If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish to participate; if so, you will have to sign this form.

Why is this study being offered to me?
You are being invited to participate in this study because you are older than 50 and have been admitted to the MICU.

Who is paying for this study?
This study is being funded by Dr. Knauert's research funds.

Who is providing other support for this study?
No additional organizations or companies are involved or supporting this study.

What is the study about?
The purpose of this study is to evaluate the benefit of daytime bright light on circadian rhythms and delirium in the medical intensive care unit (MICU).

What are you asking me to do and how long will it take?
If you agree to participate in this study, below are the following events we will ask you to take part in while you are in the hospital.

Actigraphy: We will ask you to wear an "Actiwatch" which looks and feels like a digital wrist watch; this device is measuring how much you are moving and using this movement to estimate if you are awake or asleep (this is similar to, but more detailed than devices such as the "Fitbit"). If you develop any skin irritation, we will remove the Actiwatch. We will ask you to wear the Actiwatch until day 5 of this study (counting today); if you stay in the MICU longer than 5 days the Actiwatch will be on until you leave the MICU.

Urine Collection: For some patients, we will collect 10 mL (2 teaspoons) of urine every 1 hour and analyze this for melatonin levels. We will do this until you leave the MICU or until the third day of this study. This urine will be collected only from urine catheter collection bags that your medical team has placed as part of your medical care; urine will not be collected directly from you. Urine that is not collected for a research study is disposed of via standard hospital protocols.

Blood Samples: For patients whom we are collecting urine we will collect 4 blood samples during the first 24 hours of the study. We will use this blood to measure RNA expression levels in PBMCs (types of white blood cells). De-identified micro-array data may be shared during publication, in grant applications, or in future collaborations. No DNA, whole genome, or genomic information will be collected. Samples will not be banked or used for other studies.

1. If you have a special central intravenous line in place, starting at noon on the first day of the study we will collect 2.5 mL of blood every 6 hours for the first 24 hours of the study. We will used your central line to collect this blood. There will be no additional needle sticks. The total blood that we will collect is less than 1 tablespoon (approximately 10 mL).
2. If you do not have a special central intravenous line in place, we will collect 2.5 mL of blood at about noon and then every 6 hours for a total of 4 collections. This will be coordinated with labs that your medical team has ordered whenever possible, but might require a needle stick. The total for these 4 draws is less than 1 tablespoon (approximately 10 mL).

Optional Additional Blood Samples

For some patients, we will collect an additional 4 blood samples during the first 24 hours of the study. This part of the study is optional. We will use this blood to measure melatonin, metabolic proteins, and RNA expression levels in monocytes (types of white blood cells). De-identified micro-array data may be shared during publication, in grant applications, or in future collaborations. No DNA, whole genome, or genomic information will be collected. Samples will not be banked or used for other studies. We will only collect blood in patients for whom we are eligible for urine collection and who have a hemoglobin level that is high enough.

1. If you have a special central intravenous line in place, starting at noon on the first day of the study we will collect 8 mL of blood every 6 hours for the first 24 hours of the study. We will used your central line to collect this blood. There will be no additional needle sticks. The total blood that we will collect is about 2 tablespoons (around 32 mL).
2. If you do not have a special central intravenous line in place, we will collect 8 mL of blood at about noon and then every 6 hours for a total of 4 collections. This will be coordinated with labs that your medical team has ordered whenever possible, but might require a needle stick. The total for these 4 draws is about 2 tablespoons (around 32 mL).

The total possible amount of blood drawn for research purpose is 42 mL or less than 3 tablespoons. We will count blood that is drawn for our study and for clinical care; we will make sure that this is not more than 200 mL in one day, which is about 13.5 tablespoons.

You ARE // ARE NOT eligible for the collection of blood samples in this study.
Are you willing to participate in this optional part of the study? YES NO
Please initial here if you have circled "YES": _____

As part of the study, we will review your electronic hospital record for information about medical status such as admitting diagnosis, laboratory values, vital signs, what types of care you are receiving and how long you stay in the ICU and in the hospital. We will get a continous readout of your heartrate from our telemetry system.

We will record light and temperature levels in your hospital room using small meters placed on the counter or at the head of the bed. They will not interfere with the care provided. While in the ICU, we will check on you every day. We will interview you for about 5 minutes each day to assess mental function. We will also check to see how you are doing in the hospital, both physically and mentally. Additionally, we will interview you and a relative (two interviews) for about 15 minutes each to learn more about your general health and mental function before coming to the hospital. A trained person, under the supervision of doctors, will do the interview.

As a participant, your responsibilities include:

- Follow the instructions of the Principal Investigator and study staff.
- Tell the Principal Investigator or research study staff about any side effects that you may have.
- Tell the Principal Investigator or research staff if you change your mind about staying in the study.

What are the risks and discomforts of participating?

The main risk to you would be breach of confidentiality. The study will take a few minutes of your time to be interviewed. There is a minor risk of skin irritation which we will watch for during the study; if skin irritation does occur, we will remove the device causing the problem. If you are in the optional blood sample part of the study, there is a risk of pain and bruising during needlesticks (if you have a central line, we will use this for blood draws). Needles may cause pain, bruising, and bleeding; they can cause light-headedness or fainting. The procedures may involve risks that are currently unforeseeable.

Very rarely, health or genetic information could be misused by employers, health insurance companies, and others. There is a federal law called the Genetic Information Nondiscrimination Act (GINA) that generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

However, this federal law does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

How will I know about new risks for important information about the study?

We will tell you if we learn any new information that could change your mind about taking part in this study. Individual results will not be disclosed.

How can the study possibly benefit me?

This study is not designed to benefit you directly. The data collected regarding your circadian rhythm, room temperature, and the amount of light in your room will not be available to you during or after the study.

How can the study possibly benefit other people?

Your participation will help us understand circadian rhythms in the intensive care unit. It may help us find ways to improve care.

Are there any costs to participation?

You will not have to pay for taking part in this study.

Will I be paid for participating?

For taking part in this study, you will receive a $100 pre-paid gift card upon completion of study day 5. Payment will be given to you at the end of study day 5. If you are discharged from the hospital prior to study day 5 but complete through at least study 13:00 on study day 2, you will be paid for your participation. If you do not complete the study, for any reason other than listed above, you will not be paid for your participation.

According to the rules of the Internal Revenue Service (IRS), payments that are made to you because of your participation in this study may be considered taxable income. You are responsible for paying state,

federal, or other taxes for the payments you receive for being in this study. Taxes are not withheld from your payment.

What are my choices if I decide not to take part in this study?

The alternative would be not to participate in the study. You are free to decline to participate, to end participation at any time for any reason, or to refuse to answer an individual questions at any time. Refusing to participate will involve no penalty of loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). Your regular ICU care will not be changed by your participation or lack of participation in the study.

How will you keep my data safe and private?

We will keep information we collect about you confidential. We will share it with others if you agree to it or when we have to do it because U.S. or State law requires it. For example, we will tell somebody if you we learn that you are hurting a child or an older person. The FDA may inspect research records.

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We will put information from this study into your Electronic Medical Record (EMR). This will include research test results. Your health care providers will be able to see these test results. Other people or groups such as a health insurance company who have access to your EMR may see this information.

Your research records will be kept as confidential as possible. Only a code number will identify research records. The code number will not be based on any information that could be used to identify you (for example, initials, birth date, etc.). The master list linking names to code numbers will be kept separately from the research data. All research information will be stored in locked files or cabinets at all times. All research data that is collected in this study will be entered into a computer databank that is stored on password-protected computers and servers. The databank itself will also be password-protected. Only the members of the research bank staff and researchers who have received the approval of the HIC to use your data will know your identity.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name and medical condition. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team.

Any information that can identify you will remain confidential. All research records are kept in a locked cabinet or on encrypted and password protected computers or servers. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for 5 years, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

Identifiers might be removed from the identifiable private information or identifiable biospecimens and after such removal, the information or biospecimens could be used for future research studies or

distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative. We may share your de-identified data with future collaborators for additional analysis. Data will include study ID and may include actigraphy, urinary melatonin levels, RNA expression levels from blood samples, and/or vitals (heart rate, temperature, etc.). Data will be shared and stored via Yale Hosted secure file share mechanisms (e.g. Yale Secure Box or Yale OneDrive). We will assure data is not stored locally.

What information will you collect about me in this study?

The information we are asking to use and share is called "Protected Health Information." It is protected by a federal law called the Privacy Rule of Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at (203) 432-5919.

The specific information about your health that will collect, use, and share includes:

- Research study records
- The entire research record and any medical records held by Yale New Haven Hospital created over your hospital admission. This includes but is not limited to name, date of birth, gender, past medical history, medical record number, laboratory values, vital sign values, admission date, discharge date, discharge status and contact information.

For participants eligible for the sub-study blood collection:

- We are not looking at your genes, but at gene product called RNA and how much of that product is being made in your body, which is called RNA (gene) expression.

How will you use and share my information?

We will use for information to conduct the study described in this consent form.
We may share your information with:

- The U.S. Department of Health and Human Services (DHHS) agencies
- The Food and Drug Administration (FDA)
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator Dr. Melissa Knauert and members of the research team
- Data and Safety Monitoring Board

We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

Why must I sign this document?

By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

What if I change my mind?

The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission by telling the study staff or by writing to the principal investigator, Melissa Knauert, at P.O. Box 208057, New Haven CT 06520-8057.

If you withdraw your permission, you will not be able to stay in this study but the care you receive from your doctor outside this study will not change. No new health information identifying you will be gathered after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to ensure the integrity of the study and/or study oversight.

Who will pay for treatment if I am injured or become ill due to participation in the study?

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able. Yale School of Medicine and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. You do not give up any of your legal rights by signing this form. If you become injured or ill due to participation in the study, your care will continue in the ICU.

What if I want to refuse or end participation before the study is over?

Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. If you do become a subject, you are free to stop and withdraw from this study at any time during its course. Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled such as your health care outside the study, the payment for your health care, and your health care benefits). It will not harm your relationship with your own doctors or with Yale-New Haven Hospital.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.

The researchers may withdraw you from participating in the research if necessary, such as if you move to hospice care or the research is suspended indefinitely.

What will happen with my data if I stop participating?

Data and samples will be unable to be withdrawn once they are collected, and they will remain de-identified.

Who should I contact if I have questions?

We have used some technical terms in this form. Please feel free to ask about anything you don't understand. If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator at (203) 785-4163.

If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688 or email hrpp@yale.edu.

A description of this clinical trial will be available on www.clinicaltrials.gov 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.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction.

Your signature below indicates that you have read this consent document and that you agree to be in this study. We will give you a copy of this form.

Participant Printed Name	Participant Signature	Date
Legally Authorized Representative "Surrogate" Printed Name	Legally Authorized Representative "Surrogate" Signature	Date
Legally Authorized Representative "Surrogate" Relationship to Patient		
Person Obtaining Consent Printed Name	Person Obtaining Consent Signature	Date