Title: Study of Sleep in Cirrhosis

NCT #: NCT03091738

Document date: 09/04/2013

Document Type: Study Protocol and Statistical Analysis Plan

VCU Office of Research and Innovation

Date: Tuesday, March 2, 2021 3:52:46 PM

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ID: HM13968

View: SF - Study Identification

HM13968 - Jasmohan Bajaj
Study of Sleep in Cirrhosis

Study Identification

1. * **Select the Principal Investigator**
   Jasmohan Bajaj

2. * **Study Title**
   Study of Sleep in Cirrhosis

3. * **Is this a student or trainee project in which activities will be carried out by that individual under your supervision (for example, dissertation or degree-required projects)**
   - ○ Yes
   - ● **No**

4. * **Please select the primary department or center that this study is being conducted under**

5. **If this is associated with other VCU IRB protocols or a resubmission of a withdrawn/closed protocol, select the VCU IRB numbers assigned to those studies**

ID	Title	PI

There are no items to display

6. [redacted]

7. * **Select one of the following that applies to the project (selection will branch to new pages)**
   Note: VCU IRB offers guidance for many types of studies, including secondary data analysis studies, internet research, registries, EFIC, HUD, and Emergency Use protocols.
   See *https://research.vcu.edu/human_research/guidance.htm*
   - ● **Research Project or Clinical Investigation [*most exempt, expedited, and full board research studies]**
   - ○ Exception from Informed Consent (EFIC) for Planned Emergency Research
   - ○ Humanitarian Use of Device for Treatment or Diagnosis
   - ○ Humanitarian Use of Device for Clinical Investigation
   - ○ Emergency Use of Investigational Drug, Biologic or Device
   - ○ Treatment Use (Expanded Access to Investigational Product for Treatment Use)
   - ○ Center or Institute Administrative Grant Review
   - ○ Request for Not Human Subject Research Determination (i e. request a letter confirming that RB review is not required)

Research Description

1. * **Describe the study hypothesis and/or research questions. Use lay language whenever possible.**
Ramelteon will help restore a normal sleep architecture in patients with cirrhosis who have insomnia.

2. * **Describe the study's specific aims or goals. Use lay language whenever possible.**
To study the effect of ramelteon, a melatonin receptor agonist, on sleep quality, duration and cognitive function in cirrhotics with insomnia.

3. * **Describe the study's background and significance, including citations, or upload a citation list in document upload. Use lay language whenever possible.**
Patients with cirrhosis have difficulties with their sleep quality, which adversely affects their health-related quality of life1. It is assumed the sleep disturbances are related to hepatic encephalopathy (HE) in these patients2. However, several recent reports have indicated that this is not a perfect concordance and that cognition is not related to sleep disturbance1, 3. The mechanism for this change is not clear, although there is evidence of melatonin-delayed phase in these patients as well as difficulties with the excretion pattern of cortisol4. Ghrelin is an orexigenic hormone produced by the stomach which stimulates the appetite and also has a profound effect on sleep5, 6. Our group has demonstrated a substantial alteration in ghrelin secretion in cirrhosis that correlates with poor slow-wave sleep7. In healthy individuals, ghrelin injection encourages slow-wave sleep while sleep deprivation increases ghrelin levels6, 8, 9. The role of ghrelin in the sleep disturbances of cirrhosis has not been determined. Prior studies have also lacked the use of overnight polysomnography as a tool and have relied on either actigraphy or questionnaires10. There is a need for detailed mechanistic and therapeutic approaches to analyzing sleep disturbances in cirrhosis.
Also the therapy of sleep disturbance in cirrhosis is largely empirical. Prior studies have evaluated hydroxyzine which runs the risk of precipitating HE. Ramelteon is a melatonin analog that is FDA-approved for use in insomnia and will potentially be useful to restore the sleep-wake cycle in cirrhosis-associated sleep disturbance.
We want to study the impact of the FDA-approved ramelteon on the sleep quality (using quesitonnaires and sleep diaries) and duration on these patients with cirrhosis.

Published in Alimentary Pharmacology and Therapeutics (Bajaj et al 2011 Jul;34(1):103-5)
Cirrhotic patients commonly suffer from sleep disturbances and cognitive impairment, but it is unclear whether these are directly related. In healthy controls, ghrelin triggers onset of slow-wave sleep(SWS), and sleep-deprivation(Sdep) increases ghrelin.
Aim: To determine whether ghrelin secretion under waking, sleep or Sdep conditions, is altered in cirrhosis, and whether Sdep is associated with cognitive worsening.
Methods: Five men (54 yrs, BMI 27 kg/m2) with compensated cirrhosis and minimal hepatic encephalopathy(HE), were compared to five age/BMI-matched male controls. At baseline, cognitive testing was performed and a standardized diet was prescribed. Subjects were admitted a week later for 24-hours with hourly ghrelin sampling; they were allowed to sleep with polysomnographic monitoring. One week later, subjects returned for a 24-hour Sdep study, again with hourly ghrelin testing, after which cognitive testing was repeated.
Results: We found significant disruptions in sleep architecture; SWS occurred in all controls, but not in 80% of cirrhotics (p=0.04, table 1). During the wake/sleep study, 24-hour mean cirrhotics' ghrelin levels were significantly lower than controls(964 vs. 1071pg/ml, p= 0.024). This was maintained during Sdep(954 vs. 1154pg/ml, p=0 037). During both sleep and Sdep, ghrelin levels rose significantly over baseline in controls but not cirrhotics (table 2). The physiogical post-prandial ghrelin decrease was also blunted in cirrhotics compared to controls (-84 vs. -159pg/ml; p=0.04). In both groups, Sdep did not affect cognition.
Conclusions: Loss of SWS in cirrhosis is associated with reduced ghrelin levels. Ghrelin response to Sdep and feeding is blunted in cirrhotics compared to controls. Short term Sdep did not alter cognition.

4. * **Describe the proposed research using language understandable to those IRB committee members whose expertise is not scientific. The description must include**

   - **A statement explaining the study design**
   - **A detailed description of all the procedures that will be followed to carry out the study, preferably in sequential order**

     If certain procedures would take place in the same manner regardless of the research (i.e. standard medical or psychological tests and procedures, routine educational practices, quality improvement initiatives, etc.), the response must clearly distinguish those procedures from procedures that are performed exclusively for research purposes or that involve alterations of routine procedures for research purposes.

     If specific sections or pages of a separate protocol document are referenced that contain this detailed description, the response must include:

     - *a lay language overview of all research procedures*
     - *a description of whether there are any local changes to the protocol s procedures, and if so, what those changes are (i.e. different, omitted, or additional procedures)*
     - *any necessary clarifications of the protocol s content (i.e. what local standard of care or routine practice is)*

   - **A description of all research measures/tests/interventions that will be used (if applicable)**
   - **A detailed description or list of all secondary data elements and/or secondary specimens that will be obtained and how they will be used (if applicable)**

   See the help text for additional guidance.

This study will be a prospective study of patients with compensated cirrhosis
This study will be divided into screening and post-ramelteon visits.

For this study, we will recruit patients with cirrhosis from the hepatology clinic.

Inclusion criteria:
a. Child class A cirrhosis proven by biopsy, radiology or endoscopic evidence of varices
b. Able to give informed consent

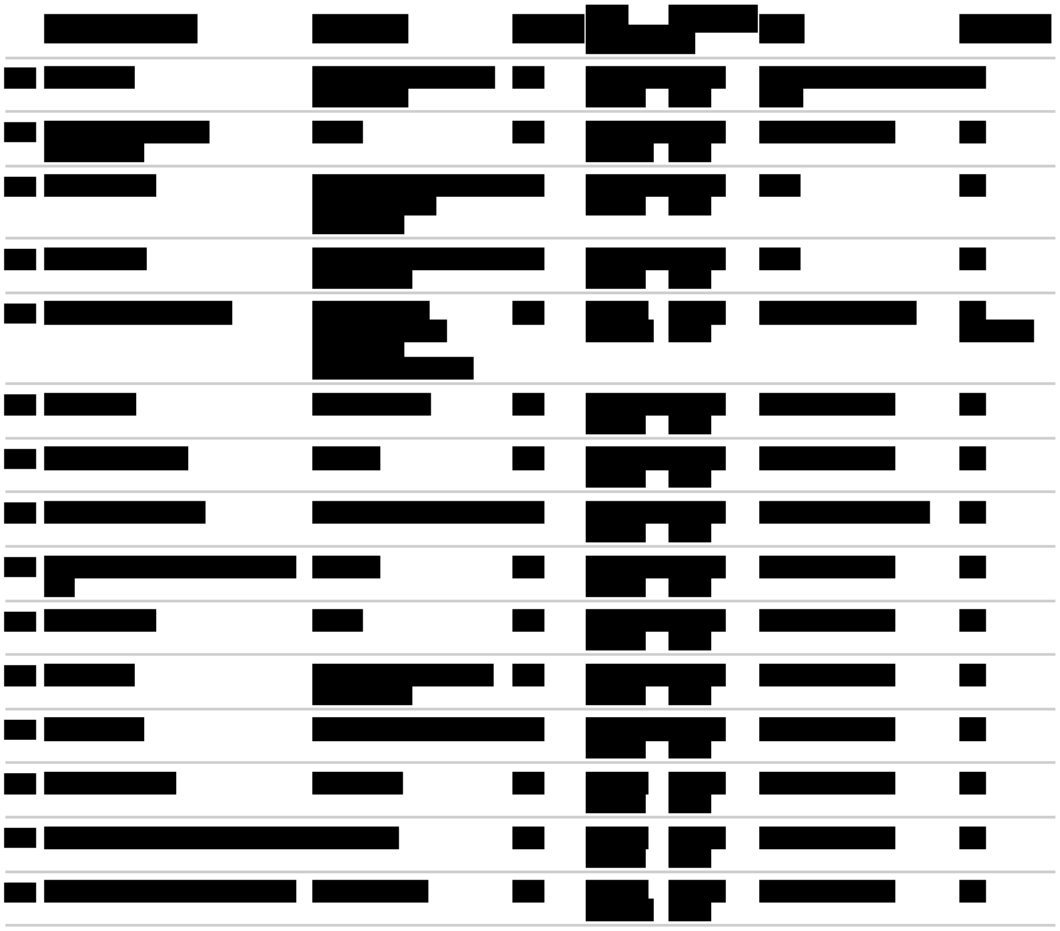
Exclusion criteria
a. Diagnosed sleep apnea
b. Use of sleep aids
c. Moderate to severe depression
d. Unable to give informed consent
e. Night shift workers
f. Inter-continental travel within the last 4 weeks
g. Renal insufficiency on dialysis
h. Current alcohol or illicit drug use
i. Diabetes Mellitus using insulin therapy
j. Use of chronic hypnotic medications more than once per week or more than 5-6 times per month
K. Positive Berlin Questionnaire
L. Becks Inventory Questionnaire Greater than or equal to 20 without the suicide question.
m. Patient unwilling to start therapy
n. Allergic reactions to ramelteon in the past

Screening: All subjects will come for an initial screening visit to the CRSU at which point the following procedures will be performed
a. Vitals, including BMI
b. Skinfold thickness and waist-hip ratio
c. Beck Depression Inventory (BDI)
d. Sickness impact profile for overall HRQOL
e. Questionnaires regarding sleep
f. Berlin questionnaire
g. STOP Bang questionnaire
h. Epworth sleepiness scale (ESS) and
i. Pittsburgh sleep quality index (PQSI)

Cirrhotic patients with a Positive Berlin questionnaire will be excluded because these are highly suggestive of sleep disturbances and OSA11, 12. We will also exclude patients who have evidence of moderate to severe depression on Beck Depression Inventory (score ≥20) without the suicide question.
They will be paid $25 for their time.

All enrolled study participants will perform 5 paper-pencil and two computerized tests of intelligence which will last approximately 35 minutes total.
RAMELTEON THERAPY :
The subjects' study chart, current medications, medical history and pregnancy testing will be assessed by Dr Taylor and Dr Leszczyszyn who will then decide if this patient would benefit from ramelteon.
The criteria used will be insomnia along with the absence of OSA by the questionnaires. Ramelteon is an FDA-approved selective melatonin receptor 1 and 2 analog indicated for use in insomnia. The dose used will be 8 mg, the lowest possible dose. If the sleep specialists believe that a particular cirrhotic patient is a candidate for this therapy, they will be clinically prescribed ramelteon after a detailed face to face visit explaining the risks and benefits.
Ramelteon is not indicated in patients with severe hepatic impairment (defined as Child Class C), therefore, these patients will not be included in the study.
if the patient agrees to take the medicine, it will be dispensed through the investigational pharmacy, where it will be stored for this study. Patients will be asked to complete a medication and sleep diary for the duration of the drug therapy which will be a maximum of 15 days. Within 15 days of drug initiation, the patients will be asked to complete the sleep questionnaires again and cognitive testing similar to that described in visit 1. They will be paid $ 75 for this part of the study.

5. [redacted]



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View: SF - Bio-Med Project Details

HM13968 - Jasmohan Bajaj
Study of Sleep in Cirrhosis

Bio-Med Project Details

1. * **Select all that apply to this study**

- [x] **Drug(s) / Biologics / Supplement(s) / Other Compounds (investigational products or products whose administration is dictated by the study protocol and not per the physician's clinical judgment)**
- [ ] Bio-Hazards, Other Toxins, Recombinant DNA/Gene Transfer
- [ ] Safety and/or effectiveness evaluation of Bio-Medical Device(s), including in-vitro diagnostic devices/assays, mobile medical apps, and HUDs used in clinical investigations
- [ ] Radiation Exposure and/or Scans involving radiation (eg: PET, MRA, CT, DXA, nuclear medicine, etc)
- [ ] Stem Cells
- [x] **Medical or Surgical Procedures (eg physical exam, clinical procedures, scans, etc)**
- [x] **Protected Health Information (PHI)**
- [ ] None of the Above

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ID: HM13968 View: SF - Bio-Med Drug/Supplement/Other Compound Details

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Bio-Medical Drug, Supplement and/or Other Compound Details

1. * **List all drugs and/or biologics**

	Drug	Manufacturer	Types	FDA Labeling	IND Holder	IND Number
View	ramelteon	Solvay	FDA Approved and being used as approved	Yes	Not Required	

2. * **Will the Investigational Drug Service (IDS) pharmacy be utilized. (See Help Text for additional guidance and link)**

- (●) **Yes**
- ( ) No
- ( ) Not Applicable

3. * **For each drug/biologic listed above, upload an investigator's drug brochure or package insert/FDA labeling.**

- **For drug products that require an IND, upload at least one of the following documents for verification of the IND number**
  - **External sponsor's protocol including IND number and signed Form FDA 1572 for the VCU Principal Investigator**
  - **Communication from the external sponsor verifying the IND number and signed Form FDA 1572 for the VCU Principal Investigator**
  - **VCU sponsor-investigator's FDA IND protocol including IND number**
  - **Communication from the FDA with verification of the IND number**
- **For drug products that qualify for IND exemption under under 21 CFR 312.2(b), upload one of the following documents for each applicable drug**
  - **A document explaining, with protocol-specific information, how the drug's use in this study meets the relevant critieria for IND exemption under 21 CFR 312.2(b).**
  - **The completed "Determination of IND Exemption for Marketed Drugs" form available on the VCU Faculty-Held IND or IDE website at go.vcu.edu/indide.**
  - **External sponsor's protocol including IND exemption information**
  - **Communication from the external sponsor verifying the IND exemption**
  - **Communication from the FDA with verification of IND exemption**
- **If the Investigational Drug Service Pharmacy (IDSP) is not utilized, upload the IDSP management plan approval. Guidance and the form for describing the management plan are located at** http://www.investigationaldrugs.vcu.edu

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View: SF - Data Collection Details

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Study of Sleep in Cirrhosis

Data Collection Details

1. *

Select all involved in the study

- [x] **Specimen/Biologic Sample Collection**
- [x] **Protected Health Information (PHI)**
- [ ] Secondary Data or Specimens Not From a Registry or Repository
- [ ] Audio/Video
- [ ] Use of Internet for Data Collection
- [ ] Registries/Repositories (Includes Accessing, Contributing or Creating)
- [ ] None of the Above

2. * **Select all identifiers that will be collected as part of this study (including for recruitment, data gathering, data analysis, etc.), even if the data will eventually be anonymized**

- [x] **Names**
- [x] **Geographic Locators Below State Level**
- [x] **Social Security Numbers**
- [x] **Dates (year alone is not an identifier)**
- [x] **Ages over 89 (age under 89 is not an identifier)**
- [x] **Phone Numbers**
- [ ] Facsimile Numbers
- [ ] E-mail Addresses
- [x] **Medical Record Numbers**
- [ ] Device Identifiers
- [ ] Biometric Identifiers
- [ ] Web URLs
- [ ] P Addresses
- [ ] Account Numbers
- [ ] Health Plan Numbers
- [ ] Full Face Photos or Comparable Images
- [ ] License/Certification Numbers
- [ ] Vehicle ID Numbers
- [ ] Other Unique Identifier
- [ ] No Identifiers

- [ ] Employee V#

3. **If "Other Unique Identifier" was selected above, describe the identifiers**

4. * **Will participants be able to withdraw their data (paper, electronic, or specimens) from the study if they no longer wish to participate**
   - (●) **Yes**
   - ( ) No

5. **If yes above, describe how participants will be able to withdraw their data**
   they can contact the PI in writing as indicated in the consent form for withdrawal of all their data including genetic data.

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View: SF - Sample Collection

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Sample Collection

1. * **Select all of the types of samples that will be collected as part of this study**

- [ ] Amniotic Fluid
- [ ] Blood
- [ ] Buccal Smears
- [ ] Saliva
- [ ] Tissue
- [x] **Urine**
- [ ] Other
- [ ] None of the Above

2. **If Other, please describe the type of sample being collected**
Urine will only be collected in screening from women who are child-bearing age to determine pregnancy status.

3. * **Describe how the samples will be collected and the collection schedule. For each type of sample, include information about**

- **The procedures that will be followed to collect the sample**
- **The role(s) of the individuals who will collect the sample**
- **The volume/size range of the sample**
- **The timing and frequency of sample collection**

In women of child-bearing age, the participant will be asked to provide a urine sample while in the CRSU. The sample will be tested with a urine pregnancy dipstick.

4. * **Will Genetic Testing be conducted on any of the samples**
   - ○ Yes
   - ● **No**

5. * **Will any of the samples be used for a pregnancy test**
   - ● **Yes**
   - ○ No

6. **If yes, describe how positive pregnancy results will be communicated to the participant, particularly if minors are involved**
A positive pregnancy test during screening is an exclusion for study enrollment. The participant will be notified of the result and will not be considered for enrollment in the study. This is clearly explained in the consent form and will be discussed at that time as well.

7. * **Will any of the samples be used to screen or document alcohol or illicit drug use**
   - ○ Yes
   - ● **No**

8. * **I am aware that I may need to establish a research account with VCUHS Department of Pathology for specimen processing**
   - ● **Yes**
   - ○ No

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View: SF - HIPAA

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HIPAA

1. * **Describe the protected health information that will be obtained or used in this research**
   We will need the patient demographics and medical records
2. * **Describe the source(s) of the protected health information**
   Medical records
3. * **Explain how the PHI collected or used in this research is the minimum necessary to accomplish this research**
   To identify patients that are eligible
4. * **Select all pathways this research will employ to use or access PHI**

- [ ] De-Identified Data (none of the 18 identifiers are recorded or associated with the research data)
- [ ] Limited Data Set
- [ ] Waiver of Authorization
- [x] **Partial Waiver of Authorization (temporary waiver for recruitment purposes and/or waiver of some elements of Authorization)**
- [x] **Signed Authorization Combined with Consent Form**
- [ ] Signed Authorization as Stand-Alone Form

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View: SF - Partial Waiver of Authorization

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Study of Sleep in Cirrhosis

Partial Waiver of Authorization

1. * **Select the purpose for requesting the partial waiver of authorization**

- [x] **Identify possible participants to recruit for the study**
- [ ] Waive some elements of authorization (such as signature)

2. **If you selected "Waive some elements of authorization" above, list the elements you want to waive and explain why**

3. * **Explain how the partial waiver of authorization poses no greater than minimal risk to participants' privacy**
CITI trained personnel will access PHI for the sole purpose of determining eligibility.

4. **If you selected "Identify possible participants to recruit" above, describe when will the identifiers be destroyed for those who do not eventually enroll in the study?**

- [ ] Following Participant Contact
- [x] **Upon Reaching Study Accrual Objectives**
- [ ] Other

5. * **Other than the PI and research personnel identified in this research application, who else will have access to the Protected Health Information?**
No one else

6. * **Explain why the study cannot practicably be conducted without the partial waiver of authorization**
There are very specific eligibility criteria, without reaching which this study will be impossible to conduct.

7. * **In applying for a partial waiver of authorization, the PI agrees to the following**

- the identifiers used for this research study will not be used for any other purpose or disclosed to any other person or entity (aside from members of the research team identified in this application), except as required by law
- if at any time the PI wants to reuse this information for other purposes or disclose the information to other indivivdals, the PI will seek approval from the IRB/Privacy Board
- the PI will comply with VCU HIPAA policies and procedures and to the use and disclosure restrictions described above
- the PI assumes responsibility for all uses and disclosures of the PHI by members of the study team

- (●) **Yes**
- ( ) No

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View: SF - Data Confidentiality and Storage

HM13968 - Jasmohan Bajaj
Study of Sleep in Cirrhosis

Data Confidentiality and Storage

Confidentiality refers to the way private, identifiable information about a participant or defined community is maintained and shared.

1. **Using the VCU Data Classification Tool, please determine the appropriate data classification category for the data that will be collected or used in this research. Note If the data falls into Category 1, a data security management plan is required by University Information Security Office.**

   See help text for information on accessing the VCU Data Classification Tool, and for information on creating a data security management plan

   - (●) **Category 1 all data that require breach notifications in the event of improper release, including personally identifiable information covered by HIPAA and Commonwealth of Virginia regulations.**
   - ( ) Category 2: all proprietary data that if improperly released has the potential to cause harm to the institution, its mission or its reputation that do not require breach notifications.

2. * **I confirm use of the VCU Data Classification Tool in determining the data classification category selected in Question 1**
   - (●) **Yes**
   - ( ) No

3. * **Specify where this study's paper and electronic research data and/or physical specimens will be stored and how they will be secured from improper use and disclosure**
   PHI will be used to identify inclusion/exclusion criteria and to approach patients for eventual participation. The data will be stored at VCU in a locked cabinet in Dr Bajaj's office and also on password-protected hard drives after taking specific consent from the subjects. Only the study personnel will have access to the data. The pre-existing specimens will continue to be stored at Dr Sanyal's laboratory at VCU and subject samples will be stored with initials and date/times of collection only. The key to this will be in Dr Bajaj's office and on password-protected hard drives only accessible to the study team.

4. * **Who will have access to study data**
   Only study staff

5. * **If the study will code (i.e. de-identify) the research data by replacing subjects' names with assigned subject IDs, explain the following aspects of the coding process**

   1. **The process for how subject IDs will be generated/assigned (e.g. random, sequential)**
   2. **Whether there will be a key that links the subject ID with direct identifiers.**

      If a key will be created, describe
   3. **The place where the key will be stored**
   4. **The role(s) of all individuals who will have access to the key**
   5. **When the key will be destroyed**

   See the help text for additional guidance.

   codes will be assigned by date and initials. The key will be kept in secured VCU storage separate from the samples . Only study staff will have access to the key which will be destroyed once the research analysis is complete

6. * **Will the sponsor or investigator obtain a certificate of confidentiality for this study**

   - (●) **No - Will not obtain CoC for this study**
   - ( ) Yes - CoC has been obtained or issued automatically
   - ( ) Yes - CoC request is pending
   - ( ) Yes - Plan to submit request for CoC and will amend study/ICF once status of request is known

7. **If the Certificate of Confidentiality has been obtained by the PI, upload it here**

	Document Name	Document	Version	Date Modified	Uploaded By	Type	Approved
View	HM13968.IC	Clean_Sleep_Consent_3-19_18 (2).pdf	0.20	3/22/2018 9:07 AM	Melanie White	Consent/Assent/Information Sheet	Yes
View	Sickness Impact Profile Questionnaire	S P.pdf	0.01	3/21/2016 11:55 AM	Melanie White	Research Measure	Yes
View	FitBit Training 2	Help article_ What should I know about sleep tracking_ pdf	0.01	3/18/2016 9:31 AM	Melanie White	Other	Yes
View	FITbit Training	Help article_ How do I track my sleep_ pdf	0.01	3/18/2016 9:30 AM	Melanie White	Other	Yes

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View: SF - Types of Sites

HM13968 - Jasmohan Bajaj
Study of Sleep in Cirrhosis

Types of Sites

1. * **Select which of the following accurately describes this study**

- (●) **Not Multi-site Study**
- ( ) Multi-site Study [multiple sites implementing the same protocol] - VCU Lead
- ( ) Multi-site Study [multiple sites implementing the same protocol] - Non-VCU Lead

2. * **Select all sites where study interventions or interactions will occur and/or identifiable data will be held**

- [x] **VCU Site**
- [ ] Non-VCU Site (VCU Investigators are conducting/overseeing the conduct of the study)
- [ ] Non-VCU Site under the oversight of a Non-VCU PI

3. * **Is there a community partner in this research study**

- ( ) Yes
- (●) **No**

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View: SF - Study Population

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Study of Sleep in Cirrhosis

Study Population

1. * **Provide the total number of individuals at VCU, and at other sites under the VCU IRB, that**

    1. **May participate in any study interaction or intervention (including screening, consenting, and study activities) AND/OR**
    2. **You may obtain any data/specimens about (regardless of identifiability)**

    See the help text for additional guidance.

    50

2. **If this is a multi-Center Project, what is the total anticipated number of subjects across all sites**

3. * **Provide justification for the sample size**

    For the study of the impact of Ramelteon on SWS in cirrhotic patients, we are planning a pre-post study on the dichotomous outcome of SWS yes/no. If we assume the the success-failure proportion (cirrhotics who experienced SWS no longer experience SWS after treatment) is 1E-1 and the failure-success proportion (cirrhotics who did not experienced SWS experience SWS after treatment) is 0.50, then a sample size 14 is required to achieve a power of at least 80%. A sample size of 20 under the same assumption yields a power of 97%. We will use a McNemar Exact Conditional Test for this analysis. To account for dropouts and those who do not wish to participate in the treatment part of the study, we will enroll 50 cirrhotic patients.

4. * **List the study inclusion criteria**
    Inclusion criteria for cirrhotic patients:
    a. Child class A cirrhosis proven by biopsy, radiology or endoscopic evidence of varices
    b. Able to give informed consent

5. * **List the study exclusion criteria**
    Exclusion criteria for cirrhotic patients
    a. Diagnosed sleep apnea
    b. Use of sleep aids
    c. Moderate to severe depression
    d. Unable to give informed consent
    e. Night shift workers
    f. Inter-continental travel within the last 4 weeks
    g. Renal insufficiency on dialysis
    h. Current alcohol or illicit drug use
    i. Diabetes Mellitus using insulin therapy
    j. Use of chronic hypnotic medications more than once per week or more than 5-6 times per month.
    k. Positive Berlin questionnaire
    l. Becks Inventory Questionnaire greater than or equal to 20 without the suicide question.
    m. Patient unwilling to start therapy
    n. Allergic reactions to ramelteon in the past

6. * **Check all participant groups that will be included in this study or discernable in the research data/specimens. In particular, if you will know that a regulated vulnerable population (children, pregnant women, or prisoners) is involved in the study, be sure to check them**

- [ ] Healthy volunteers
- [ ] Children
- [ ] Emancipated minors
- [ ] Pregnant women or fetuses
- [ ] Neonates or Post-delivery Materials
- [ ] Prisoners
- [ ] Decisionally Impaired Adults
- [ ] When cancer is integral to the research - cancer patients, their family members, cancer healthcare providers, or cancer prevention
- [x] **VCU Health System or VCU Dental Care patients**
- [x] **Non-VCU patients**
- [ ] VCU / VCUHS students or trainees
- [ ] VCU / VCU Health System employees

- [ ] Individuals with limited English proficiency
- [ ] Active military personnel
- [ ] Student populations in K-12 educational settings or other learning environments

7. * **Does this study obtaining data in, or from, the European Economic Area? (see Help Text for list of countries included in the EEA)**
   ○ Yes ● **No**

8. **Justify the inclusion and exclusion criteria if necessary. If you are either targeting, or excluding, a particular segment of the population / community, provide a description of the group/organization/community and provide a rationale**
   The PI only sees adults in his practice, pregnancy can cause increase in reflux symptoms that can worsen sleep regardless of cirrhosis, and we cannot ensure that prisoners can take the medications as needed for this study.

9. * **Select the age range(s) of the participants who may be involved in this study**

- [ ] < 1 Year
- [ ] 1 - 6 Years
- [ ] 7 - 12 Years
- [ ] 13 - 17 Years
- [x] **18 - 20 Years**
- [x] **21 - 65 Years**
- [x] **> 65 Years**

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ID: HM13968

View: SF - Potential Subject Identification and Recruitment

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Study of Sleep in Cirrhosis

Potential Subject Identification and Recruitment

1. * **Choose all recruitment methods that may be used**

- [ ] E-mail invitations
- [x] **Phone Solicitation scripts (i.e. cold calls or random-digit-dialing)**
- [ ] Flyers, Mailed Letters or Newspaper/TV/Radio Ads
- [ ] Website text
- [x] **Direct Contact**
- [ ] Psychology Research
- [ ] VCU TelegRAM announcement
- [ ] Word of Mouth
- [ ] Participant Pool (SONA)
- [ ] Other recruitment material

2. **If Other, please describe**

3. * **Select the methods used to obtain names and contact information for potential subjects**

- [x] **Pre-Existing Relationship with Participants**
- [x] **Selected from Pre-Existing VCU Records**
- [ ] Selected from Pre-Existing Non-VCU Records
- [ ] Selected from Publicly Available Records
- [x] **Referred by Health Care Provider or Other Health Professional**
- [ ] Recruited from Database or Registry
- [ ] Identified through Community Based Organization (Schools, Church Groups, etc.)
- [ ] Self Referred (Flyer/Ad)
- [ ] Other

4. **If Other, please describe**

5. * **Provide a description of**

    1. **How potential participants or secondary data/specimens of interest will be identified and**
    2. **All procedures that will be followed to carry out recruitment and screening activities.**

    Include details (as applicable) about

    - **How secondary data/specimens that meet the study's eligibility criteria will be identified (i.e. what database(s) will be queried and the search terms that will be used)**
    - **How potential participants will be identified and their contact information obtained**
    - **The timing and frequency of recruitment activities**
    - **Where and how recruitment procedures will be completed**
    - **Who will recruit or respond to potential participants**
    - **What and how written or verbal recruitment materials and reminders (if any) will be used**
    - **What screening activities will occur and how these procedures will be performed**

See the help text for additional guidance.

Patients will be included from the clinic All interviews will be carried out in separate rooms and only the amount of information directly needed for the study will be sought from the subjects. Subjects will be told that if there is an indication on the BDI that they are considering suicide, then they will be sent to the Emergency room; otherwise privacy and confidentiality will be maintained at all times.

6. Describe any special recruitment procedures for vulnerable populations

[redacted]

8. * Before potential participants consent to the study, will screening questions be asked or will any screening procedures/tests be done that would not otherwise be done as standard of care
No

9. If Yes, will identifiable information about individuals be recorded during screening

- ○ Yes
- ○ No

VCU Office of Research and Innovation

Date: Tuesday, March 2, 2021 3:59:19 PM

Print Close

ID: HM13968

View: SF - Privacy

HM13968 - Jasmohan Bajaj
Study of Sleep in Cirrhosis

Privacy

Privacy refers to an individual's right to control how others view, record, or obtain information about them.

Privacy is not the same as confidentiality because privacy protections apply to people, and confidentiality protections apply to data. Confidentiality protections should be described on the Data Confidentiality page of this form, not here.

1. * **Describe how the research team will protect participants' privacy throughout the course of the study. Address privacy in the context of the following research activities as applicable**
   - **Identification of potential participants or secondary data/specimens of interest**
   - **Recruitment and screening activities**
   - **The informed consent process**
   - **Conduct of the study procedures**
   - **Data dissemination**

   See the help text for additional guidance.

   All interviews will be carried out in separate rooms and only the amount of information directly needed for the study will be sought from the subjects.

VCU Office of Research and Innovation

Date: Tuesday, March 2, 2021 3:59:35 PM

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ID: HM13968

View: SF - Costs to Participants

HM13968 - Jasmohan Bajaj
Study of Sleep in Cirrhosis

Costs to Participants

1. Select all categories of costs that participants or their insurance companies will be responsible for

- [x] **Participants will have no costs associated with this study**
- [ ] Study related procedures that would be done under standard of care
- [ ] Study related procedures not associated with standard of care
- [ ] Administration of drugs / devices
- [ ] Study drugs or devices
- [ ] Other

2. If Other, explain

3. * Provide details of all financial costs to the participant, other than time and transportation. Additional details regarding standard of care costs will be requested on another screen, if applicable.
none

VCU Office of Research and Innovation

Date: Tuesday, March 2, 2021 3:59:51 PM

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ID: HM13968

View: SF - Compensation

HM13968 - Jasmohan Bajaj
Study of Sleep in Cirrhosis

Compensation

1. * **Describe any compensation that will be provided including**
   - **items such as parking/transportation**
   - **total monetary amount**
   - **type (e.g., gift card, cash, check, merchandise, drawing, extra class credit)**
   - **how it will be disbursed**

   Screening visit failure: $25
   Screening and initiation of ramelteon visit: $25
   Post-ramelteon visit: $75

   For patients : total payment for treatment visits and post-treatment sleep visit:is $100.

2. **If compensation will be pro-rated, explain the payment schedule**
   For patients : total for treatment visits and post-treatment sleep visit: $100 will only be paid after return of the Fitbit as a lumpsum

   If patients lose their Fitbit device or do not return with it, then the device itself will be considered their payment.

Risks, Discomforts, Potential Harms and Benefits

1. * **Describe the risks of each research procedure to participants or others. For each identified risk, provide an assessment of the anticipated seriousness and likelihood of the risk. Some examples of possible risks include but are not limited to**
   - **Physical risks (e.g. bodily harms or discomforts, side effects, etc.)**
   - **Psychological risks (e.g. emotional, mental, or spiritual harms or discomforts, changes to thoughts, beliefs, or behaviors, etc.)**
   - **Research data risks (e.g. loss of confidentiality and privacy)**
   - **Social or legal risks (e.g. impacts on relationships or reputation, legal or criminal justice actions for self or others, etc.)**
   - **Financial risks (e.g. impacts on income, employability, or insurability, loss of services, etc.)**
   - **Other risks (e.g. unforeseeable risks of experimental procedures, risks related to particular study designs (randomization, washout, placebo, withholding care/services, deception), etc.)**

   See the help text for additional guidance.

   Physical risks:
   a. ramelteon side effects: these include excessive sleepiness, potential to sleep drive, worsening depression, and minor risk of allergic reactions; however these risks are inherent to any insomnia treatment and these will be explained in detail to the patients before they are initiated on this with the face to face visit.

   Psychological risks: minor risk of anxiety after completion of cognitive tests: to alleviate this, all subjects will be informed that these are purely collected for research. Uncovering of risk of suicide through BDI will be dealt with by sending patients to the emergency room.
   Socio-legal risks: none

2. * **Describe how the risks / harms will be minimized**
   a. A detailed discussion regarding the appropriate medication for these patients was conducted with the Sleep Department physicians and ramelteon was considered to be appropriate for use in these patients.
   b. Patients who are appropriate candidates for ramelteon based on their sleep studies will be counseled in detail regarding the adverse events and only after that will be initiated on the medication. We will also exclude those patients with moderate or severe depression from this study. They will also be given the number for the CRSU to call if there are any issues with the medications. These medications will be prescribed in close concert with the sleep physicians who are also part of this study after careful consideration of the risks and benefits.
   c. Psychological risks will be minimized by reiterating that the patients are only doing this for research and checking the BDI data and implementing plans to send patients who check suicide risk to the emergency room as needed.

3. **If the disclosure of any of the information obtained during the study would place the individual at risk for harm (legal, reputation, emotional etc.) and the information will be recorded so that the individual could be identified, explain the protections that will be put in place to decrease the risk of disclosure**

4. * **The Code of Virginia requires that most medical personnel and all employees of institutions of higher education report suspected child/elder abuse or neglect. Is it likely investigators could discover information that would require mandatory reporting by the investigators or staff**
   - ○ Yes
   - ● **No**

5. * **Is it likely investigators could discover a participant's previously unknown condition (eg disease, suicidal thoughts, wrong paternity) or if a participant is engaging in illegal activities**
   - ○ Yes
   - ● **No**

6. **If yes, explain how and when such a discovery will be handled**

7. * **Will the study's research procedures possibly identify pertinent or incidental findings that may be of importance to subjects' health?**
   - ○ Yes
   - ● **No**

8. * **Describe any potential risks or harms to a community or a specific population based on study findings**
   none

9. * **Describe criteria for withdrawing an individual participant from the study such as safety or toxicity concerns, emotional distress, inability to comply with the protocol, etc.**
   if they are diagnosed to have sleep apnea on the initial visit, since ramelteon will not work.

10. * **Summarize any pre-specified criteria for stopping or changing the study protocol due to safety concerns**
    none

11. **Where appropriate, discuss provisions for ensuring necessary medical, professional, or psychological intervention in the event of adverse events to the subjects**
    We have the trained staff in psychology, hepatology and sleep medicine to deal with any adverse events that potentially may occur during this study. The team works together with a potential subject and is in contact constantly with the CRSU to evaluate any potential issues.

12. * **Describe any potential for direct benefits to participants in this study**
    Sleep quality is a major concern in patients with cirrhosis and this impacts their quality of life immensely. Patients with sleep problems are not able to function normally and this is often mistaken for hepatic encephalopathy. This leads to

unnecessary treatments and can in turn worsen their quality of life. A study with treatment with an FDA-approved medication, will be able to identify and possibly correct the underlying sleep disturbances both pathophysiologically as well as therapeutically.
The minor risk to confidentiality and privacy and adverse effects of ramelteon are low compared to the potential benefits of elucidating the mechanism and treatment options for these patients and potentially improve their QOL.

13. * **Describe the scientific benefit or importance of the knowledge to be gained**
Sleep quality is a major concern in patients with cirrhosis and this impacts their quality of life immensely. Patients with sleep problems are not able to function normally and this is often mistaken for hepatic encephalopathy. This leads to unnecessary treatments and can in turn worsen their quality of life. A study with treatment with an FDA-approved medication, will be able to identify and possibly correct the underlying sleep disturbances both pathophysiologically as well as therapeutically.
The minor risk to confidentiality and privacy and adverse effects of ramelteon are low compared to the potential benefits of elucidating the mechanism and treatment options for these patients and potentially improve their QOL.

14. **If applicable, describe alternatives (research or non-research) that are available to potential participants if they choose not to participate in this study**

15. * **Indicate if this study will have a Data Safety Monitoring Board (DSMB) or a Data Safety Monitoring Plan (DSMP) [Required for all greater than minimal risk studies]**

- [ ] DSMB
- [ ] DSMP
- [x] **No DSMB/DSMP [Note This response is not applicable for greater than minimal risk studies]**