Title: The Impact of Circadian Misalignment on Colonic Barrier Homeostasis in Ulcerative Colitis

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RUSH

CONSENT/AUTHORIZATION FOR PARTICIPATION IN A RESEARCH STUDY

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Protocol Title: The Impact of Circadian Misalignment on Colonic Barrier Homeostasis in Ulcerative Colitis
Sponsor(s): National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK)

Name of Participant: _____

Key Information:

You are being invited to participate in a research study. Research studies answer important questions that might help change or improve the way we do things in the future.

This consent form will give you information about the study to help you decide whether you want to participate. Please read this form, and ask any questions you have, before agreeing to be in the study.

Taking part in this research study is voluntary. You do not have to participate in this study and may choose to leave the study at any time. If you decide not to participate in this study or leave the study at a later time, your health care, benefits, or relationship with Rush University Medical Center will not change or be affected.

The purpose of this study is to investigate if circadian malalignment (unusual sleeping patterns), such as night shifts (sleeping during the day and being awake during the night time), worsens the inflammation of the gut.

If you agree to participate in this study, your participation may last up to 6 weeks and you will be asked to complete up to 2 study visits.

During these visits, you will be asked to complete a screening visit, a physical exam, a psychological evaluation (if needed), a food diary, sleep diary, 2 weeks of wrist actigraphy, and a 7 day in-lab session in the Clinical Chronobiology Center (CCC). For a detailed description of study procedures, please see the "*What are the activities you will be doing if you participate in this study?*" section of this consent form.

There are risks to you for participating in this study. In this study, there is a risk of loss of confidentiality and side effects from blood draws, the sigmoidoscopy, completion of questionnaires, and the in-lab session. For a detailed description of risks you should know about, please see the "*What are the risks and discomforts of participating in this study?*" section of this consent form.

You may not directly benefit from taking part in this study, but we hope that knowledge gained from this study may benefit others with Ulcerative Colitis in the future.

This is not a treatment study. Your only other option to participating in this study is not to participate.

Detailed Information: Please review the rest of this document for details about the above topics and additional information you should know before making a decision about whether or not you will participate in this study.

Why are you being invited to participate in this study?
You are being asked to participate in this study because you are diagnosed with ulcerative colitis or because you are a healthy control.

How many participants will take part in this study?
Approximately 40 participants are expected to take part in this study at Rush University Medical Center.

What are the activities you will be doing if you participate in this study?
Before you begin the study we will ask you to complete a screening process. This process will include 1 clinic visit. We will ask you to complete a series of questionnaires to determine if you are a good candidate for the study, have a physical exam with the principal investigator, Dr. Ali Keshavarzian. Part of your questionnaire responses will be used for a psychological evaluation. Since this study requires 7-day confinement in the sleep lab, individuals who suffer from anxiety and depression will not be able to participate. Your depression and anxiety questionnaires will be reviewed by the study psychologist Dr. Sharon Jedel. This is part of the psychological evaluation. Based on your responses, Dr. Jebel will determine if a structured interview is needed to ensure that you will be comfortable staying in the lab for 7 days. If needed, this interview will last approximately 30 minutes. We will also ask to collect a blood sample (approximately 4 tablespoons). The blood will be collected to measure baseline complete blood count, comprehensive metabolic panel, c-reactive protein (used to see if there is inflammation in the body), and prothrombin time (to evaluate blood clotting).

We will provide you with an actigraphy watch for a 2 week monitoring period. The actigraphy watches are worn on the wrist and measure your movement throughout the day and night. This movement data along with recorded sleeping hours will help the study team to evaluate your sleep quality. During this period we ask that you maintain a sleep log and complete questionnaires on sleep and depression. Depression is known to have an impact on sleep.

Below is an overview of the screening process:

Activities	Screening Day 1 (-14 Days)
Review and Sign Consent Form	*
Screening Questionnaires	*
Blood Draw	*
Physical Exam	*
Psychological Evaluation	*
Actigraphy Watch Assignment	*

During the study we will ask you to complete several questionnaires related to sleep activity, diet, inflammatory bowel disease symptoms, depression, and anxiety. Below are the questionnaires we will ask you to complete during this study:

- Demographic Questionnaire
- Mayo Score
- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)
- VioScreen Food Frequency Questionnaire (FFQ)
- Food Diary
- Munich Chronotype Questionnaire (MCTQ)
- Pittsburgh Sleep Quality Index (PSQI)
- Restless Leg Syndrome Questionnaire (RLS)
- Berlin Obstructive Sleep Apnea Questionnaire (Berlin OSA)
- Consensus Sleep Diary (CSD-C)
- Beck's Depression Index (BDI)
- State Trait Anxiety Index (STAI)

Once the screening process is complete, we will ask you to come in for a 7 day long sleep study in the Clinical Chronobiology Center (CCC) at Rush University Medical Center. This is the start of the study. A suite in the sleep clinic along with meals will be provided by the study team during the 7-day stay. Below are the details of the research activities that we will ask you to complete during your stay in the Clinical Chronobiology Center.

Day 1: You will come to the Clinical Chronobiology Center in the morning. You will receive a tour of the facilities and a review of the activities planned for the next 7 days. We will also collect the actigraphy watch. Day 1 is considered Adaptation Day to allow you to settle into the space. We will collect a baseline stool sample from you on this day. Urine will be collected as a drug screening measure for the Clinical Chronobiology Center.

Day 2: Day 2 activities will begin at 7:00 am. At this time, you will be asked to provide a saliva sample. You will be asked to not brush your teeth, use mouthwash, eat, or drink (except water) at least 1 hour prior to collection. To collect the saliva, you will be asked to spit into a conical tube, about 6 ml will be collected. We will ask you to have a flexible sigmoidoscopy (an unprepped procedure to examine the lower part of the colon and rectum) with rectal biopsy (19 small tissue samples about the size of the tip of a pen will be taken) and a stool collection. After this procedure, we will ask you to complete an intestinal permeability assessment where you will drink a surgery drink and we will collect your urine after 24 hours have passed. Throughout the process a blood sample will be taken every 2 hours (that is 12 blood draws over the 24-hour period). A flexible catheter will be placed to

allow for multiple blood draws to be taken without disturbing you during the sleep sessions. The blood will be used to measure your melatonin levels along with a complete blood count panel. If you are taking a biologic medication to treat your ulcerative colitis, an extra teaspoon of blood (approximately 5 ml) will be drawn at 9:00 AM to evaluate the concentration of the medication in your blood. From 3:00 pm to 11:00 pm we will ask you to stay awake however the light in the room will be lowered. Before the catheter is inserted, you will be provided a device, which will monitor your body temperature throughout day 2. The device is a non-invasive senor that is worn on the chest and is secured via medical grade adhesive patches. This will be used to measure your central circadian rhythm. Lastly, another saliva sample will be collected at 7 pm.

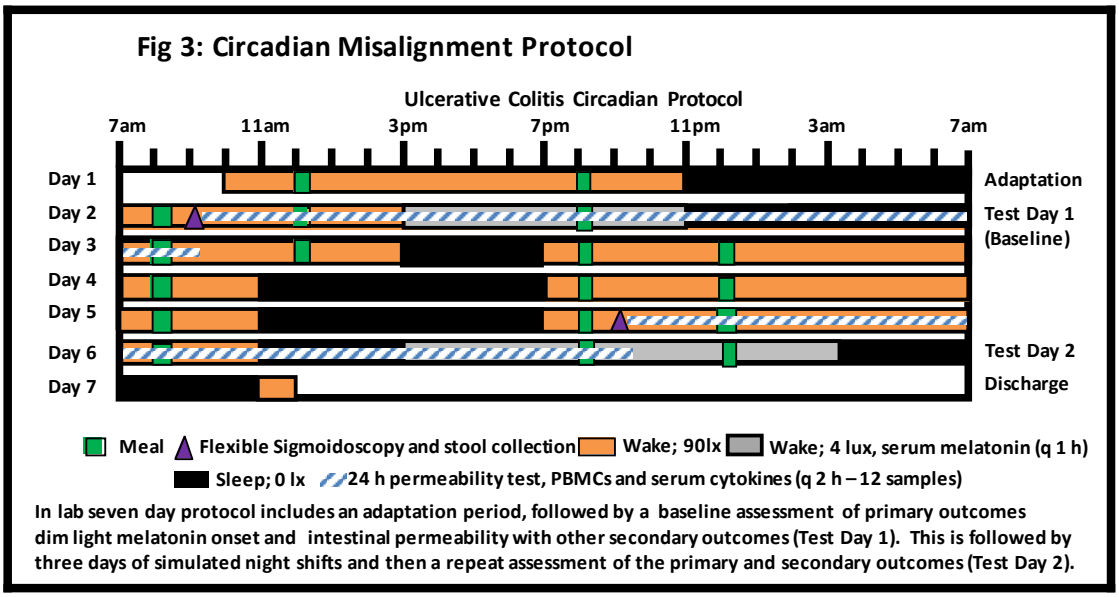
Day 3: Day 3 will start at 7:00 am, another saliva sample will be taken and the urine collection will happen for the permeability test. Day 3 is the start to shifting your circadian rhythms for the purposed of the study evaluation on the effects of circadian malalignment. A 4 hour sleep session is scheduled from 3:00 pm to 7:00 pm. At 7 pm we will ask for a saliva sample. We ask that you stay awake untill 11:00 the next day to simulate a night shift. There are no other tests during this day.

Day 4: The day will begin at 7:00 am. You will be asked to collect a saliva sample. A scheduled sleep session will occur from 11:00 am to 7:00 pm. Day 4 is a simulated night shift. For the simulated night shift we will ask that you stay awake during the night and keep your sleep to the allotted 11:00 am to 7:00 pm timeframe. There are no tests on Day 4, but we will collect a second and final stool sample from you on this day and a saliva sample at 7 pm.

Day 5: Day 5 is a repeat of Day 2 activities. Saliva samples will again be taken at 7 am and 7 pm. Day 5 is different from Day 2 in that the procedures will begin at 9:00 pm. We will ask you to have a flexible sigmoidoscopy with rectal biopsy (19 small tissue samples will be taken) and a stool collection. After this procedure we will ask you to complete an intestinal permeability assessment where you will drink a surgery drink and we will collect your urine after 24 hours have pasted. Throughout the process a blood sample will be taken every 2 hours (that is 12 blood draws over the 24 hour period). A flexible catheter will be placed to allow for multiple blood draws to be taken without disturbing you during the sleep sessions. The blood will be used to measure your melatonin levels along with a complete blood count panel. Before the catheter is inserted, you will be provided the body temperature device again. Medical grade adhesives will be used to secure the device your chest to measure your central circadian rhythm.

Day 6: This day has a sleep session scheduled starting at 11:00 am to 3 pm. We will ask you to wake up at 3:00 pm and stay awake with low light from 3:00 pm to 3:00 am during which we will complete the final urine collection for the Day 5 permeability assessment. If you are taking a biologic medication to treat your ulcerative colitis, an extra teaspoon of blood (approximately 5 ml) will be drawn at 9:00 PM to evaluate the concentration of the medication in your blood. Saliva samples will again be taken at 7 am and 7 pm. Sleep time is scheduled will 11:00 am the next day (Day 7).

Day 7: After waking up, we will complete the discharge process and you will be able to return home.



Does this study involve tissue/blood banking?

Yes, it does. Tissue and/or blood banking is the long-term storage of your samples into a repository (or sample bank). These samples will be kept for the duration of the study activities and up to 6 years post study closure. These samples will be de-identified and coded. All samples will be destroyed 6 years after study closure.

What do you need to know regarding the collection of biospecimens?

Biospecimens may include blood, tissue, urine, bone marrow, saliva, cells, etc. In this study, we are collecting rectal tissue, stool, urine, and blood.

Most biospecimens contain DNA. We will not use biospecimens collected as a part of this study for whole genome sequencing, which involves mapping (identifying the location of genes and the distance between them) of all of your DNA.

Will your information or biospecimens be used for research in the future?

Information or biospecimens collected from you for this study may be used for future research or shared with other researchers. If this happens, information which could identify you will be removed before any information or biospecimens are shared. Since identifying information will be removed, you will not be asked for additional consent.

Will you be contacted about participating in future research?

If you agree, we may contact you after your participation in this study about participating in future research. Please initial and date one of the following options:

_____ _____ Yes, I agree to be contacted about future research.

Initials Date

_____ _____ No, I do NOT agree to be contacted about future research.
Initials Date

What are the risks and discomforts of participating in this study?

Side effects, risks, and/or discomforts from participation in this study may include:

- The Blood Draw: Discomfort or bruising on the initial insertion of the catheter into a vein. Wearing the catheter should not be painful. Should there be any discomfort please inform study staff as the catheter may be repositioned or removed entirely upon your request. There is a rare possibility of developing a small blood clot, inflammation, or local infection around the vein where the catheter is inserted, or in rare cases a generalized infection spread through the bloodstream as a result of the IV catheter. Occasionally, there is a black and blue mark at the site of the IV insertion, which may last a couple of weeks; and, rarely, a small scar may remain permanently at the venipuncture site. In order to place the IV, we may ask permission to shave a portion of your forearm for initial insertion.
- The Flexible Sigmoidoscopy: There is minimal risk of discomfort during the sigmoidoscopic examination including discomfort from air being added into the colon, bloating much like gas pain, possible irritation , and a small amount of blood. On extremely rare occasions (1 in 17,000), the procedure can cause a tear or hole in the lining of the colon or significant bleeding. This may require surgery to repair. Dr. Ali Keshvarzian, who will perform all sigmoidoscopic examinations, is an experienced gastroenterologist with extensive experience in endoscopy over the last 10+ years. He has never experienced any subject complications while performing thousands of sigmoidoscopies.
- The Biopsies: The biopsy procedure is routine and painless with a tiny risk (< 1/10,000) of significant bleeding. Dr. Ali Keshavarzian has obtained pinch mucosal biopsy specimens from the colon from thousands of subjects including as many as 18-24 biopsies on many occasions. He has not had any complications or bleeding in any of his research subjects over the past 10+ years. The expertise and experience of Dr. Ali Keshavarzian and research team should significantly minimize the potential complications including bleeding and perforation.
- The Questionnaires: There may be discomfort when answering medical or personal questions. All your responses will be kept confidential. If you feel uncomfortable answering a question you may skip that question. Should you become distressed by any of the questions Dr. Ali Keshavarzian and our study's psychologist Dr. Sharon Jedel are available for a brief counseling.
- The In-Lab Visit: You may become sleepy during some segments of the study. We ask you to remain awake during the entirety of the scheduled wake times. Should you feel you are unable to remain awake, you are free to withdraw your consent to participate in this experiment and then go to sleep. At the end of the study, you may have difficulty sleeping and waking at your usual times. It may take several days to readjust to your regular routine. This experience is similar to jet lag, and may be associated with upset stomach, insomnia, irritability, or excessive daytime sleepiness. Short term partial sleep loss has never been shown to be directly deleterious to health although sleep loss can cause drowsiness and increase the risk of accidents. We will have you complete an 8 hour sleep cycle prior to being discharged on Day 7 of the in-lab session.

There may be other risks that may happen that we cannot predict.

What if there is new information that may affect your decision to participate in this study?
During this study, you will be told about important findings (either good or bad), such as changes in the risks or benefits of participation in the study or new choices to participation that might cause you to change your mind about being in the study. If new information is shared with you, you may be asked to sign a revised consent form in order to continue participating in this study.

Will you receive your individual results from the study?
Generally, activities performed for research purposes are not meant to provide clinical information. We may learn things about you from this study which could be important to your health or treatment. If this happens, this information will be shared with you. The flexible sigmoidoscopy procedure note will be placed in your Rush EPIC chart. The results of all other study activities will not be stored in your Rush EPIC chart and will not be returned to you unless Dr. Ali Keshavarzian should feel there is clinically relevant information. The study will not be responsible for any costs of follow-up actions outside of the study.

Can you leave or be removed from this study?
You have the right to leave a study at any time without penalty. For your safety, however, you should consider the study doctor's advice about how to leave this study. If you leave this study before the final study visit, the study doctor may ask you to complete the final steps. Should you withdraw while in possession of the actigraphy watch, we will ask for you to visit the clinic one last time in order to return the actigraphy watch.

The researchers and Sponsor also have the right to stop your participation in this study without your consent if:

- They believe it is in your best interest;
- You do not follow the instructions;
- The study is cancelled for any reason.

What about confidentiality of your medical information?
This authorization is voluntary. Rush University Medical Center and its affiliates ("Rush") will not withhold or refuse your treatment, payment, enrollment, or eligibility for benefits if you do not sign this authorization. You do not have to sign this authorization, but that means that you cannot be in the study or receive study-related treatment.

By signing this document, you voluntarily authorize (give permission to) Dr. Ali Keshavarzian, his study team, and other Rush personnel involved with the conduct and review of this study (which may include off-site personnel) to use or disclose (release) health information that identifies you for the study described in this document.

During the study, Dr. Ali Keshavarzian and his study team will collect Protected Health Information (PHI) about you for the purposes of this research. PHI is your health information that includes your medical history and new information obtained as a result of this study. Some

of this information will come from your medical record. The health information that Rush may use or disclose for this research includes:

- Age, Race, sex, BMI, Medical History, and your current medications list may be used for data analysis.

Dr. Ali Keshavarzian and his team may share your health information and the results of your study-related procedures and tests with people outside of Rush who assist with the conduct and review of this study. The persons who receive your health information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, but only if permitted by the laws governing them. Your health information described above may be used or disclosed to:

- To the Researchers;
- The study Sponsor, National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK), and its representatives;
- Monitoring agencies such as the Food and Drug Administration (FDA), the National Institutes of Health and the Rush Institutional Review Board (IRB).

While you participate in the study you will have access to your medical record, but Dr. Ali Keshavarzian is not required to release to you study information that is not part of your medical record. Rush is required by law to protect your health information, and study records that identify you will be kept confidential. The results of study tests/procedures performed as part of this study may become part of your medical record. Any study information in your medical record will be kept indefinitely. Your identity will not be revealed on any report, publication, or at scientific meetings.

You have a right to inspect and copy the information to be disclosed with this authorization and you may obtain a copy of the information by contacting the office listed below.

If you no longer want to be in the study and do not want your future health information to be used, you may change your mind and revoke (take back) this authorization at any time by writing to Dr. Ali Keshavarzian at Rush University Medical Center 1725 West Harrison Street, Suite 206, Chicago, IL 60612. If the authorization is revoked, you will no longer be allowed to participate in the study and previously authorized individuals/entities may still use or disclose health information that they have already obtained about you as necessary to maintain the integrity or reliability of the current study.

This authorization is valid for the entirety of this research study. It will expire upon completion of the study or if you revoke (take back) the authorization.

If you withdraw from this study, the data already collected from you may not be removed from the study records. The study doctor and/or study team may ask you whether they can continue to collect follow-up data on you. If follow-up information will be requested, you will be asked to sign a separate consent form before this information can be collected.

Records of participation in this study will be maintained and kept confidential as required by law. All data and biospecimens will be marked with a study code and will not contain your name, date of birth, or medical record number (MRN).

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.

What are the costs to participate in this study?
All costs for the required study activities will be paid by the study through funding granted by the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK).

Will you be paid for your participation in this study?
You will be paid up to $2,000 if you complete all study visits. If you do not finish this study, you will be paid for the study visits you have completed. You will be paid within approximately 4 to 6 weeks following the completion of each study visit. You will be paid $700 for completing the screening visits and Day 2 of the in-lab visit, $500 for completing days 3-5 of the in-lab visit, and $800 for the completion of all study activities. You will be paid by check mailed to you from Rush University Medical Center. We may need to collect your social security number or Taxpayer Identification Number (TIN) in order to pay you and for tax reporting purposes to the United States Internal Revenue Service (IRS).

Who can you contact for more information about this study?
Questions are encouraged. If you have further questions about this study, you may call Dr. Ali Keshavarzian at 312-563-4175, call the research study team at 312-563-4981 or email the study team at GI_Research@Rush.Edu.

Who can you contact if you have concerns about your rights as a study participant?
Questions about the rights of research participants may be addressed to the Rush University Medical Center Office of Research Affairs at 1-800-876-0772.

What are your rights as a study participant?
Taking part in this study is voluntary. If you choose not to participate in this study or to leave the study at any time, your health care, benefits or relationship at Rush University Medical Center will not change or be affected.

If you choose to leave this study and you do not want any of your information to be used, you must inform Dr. Ali Keshavarzian in writing at the address on the first page. Dr. Ali Keshavarzian may still use your information that was collected prior to your written notice.

SIGNATURE BY THE PARTICIPANT:
By signing below, you are consenting to participate in this research study. You have read the information given or someone has read it to you. You have had the opportunity to ask questions, which have been answered satisfactorily to you by the study staff. You do not waive any of your legal rights by signing this consent/authorization form. You will be given a signed copy of this document.

Name of Participant	Signature of Participant	Date of Signature

SIGNATURE BY THE INDIVIDUAL OBTAINING CONSENT:
I attest that all the elements of informed consent described in this consent document have been discussed fully in non-technical terms with the participant. I further attest that all questions asked by the participant were answered to the best of my knowledge.

Signature of Individual Obtaining Consent	Date of Signature

SIGNATURE OF THE PRINCIPAL INVESTIGATOR:
I attest that I am aware of the enrollment of this subject in the study discussed in this consent document.

Signature of the Principal Investigator	Date of Signature