Chronotherapy of 5-Aminosalicylic Acid in Ulcerative Colitis: A Randomized Crossover Trial
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RUSH

# CONSENT/AUTHORIZATION FOR PARTICIPATION IN A RESEARCH STUDY

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**Protocol Title:** Chronotherapy of 5-Aminosalicylic Acid in Ulcerative Colitis: A Randomized Crossover Trial
**Sponsor(s):** NIH - 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 evaluate if time of day administration of oral, once daily 5-ASA therapy in alignment with a patient's circadian rhythms will improve the patient's condition. The study will use signs of inflammation, how easily substances are absorbed into your bloodstream (gut permeability), microbiome community (the bacteria in your gut), and measured levels of 5-ASA in your blood stream to determine if time of 5-ASA administration alters a patient's condition.

If you agree to participate in this study, your participation may last up to 3 months and you will be asked to complete 4 study visits.

During these visits, you will be asked to complete 4 blood draws, 3 flexible sigmoidoscopies, 3 intestine permeability tests, and questionnaires. A flexible sigmoidoscopy is a procedure where a doctor will insert a narrow tube with a light and tiny camera into your colon to evaluate the

health of your colon. An intestine permeability test evaluates how easily your gut absorbs substances by evaluating sugar levels in your urine. Questionnaires cover several topics including GI symptoms, sleep habits, eating habits, and mental health. 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 discomfort from study procedures. Measure will be taken to reduce risks to study participants. 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.

You have the option to not participate in this study.

## 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 an adult with ulcerative colitis currently taking 5-ASA (5-Aminosalicylic Acid).

**How many participants will take part in this study?**
Approximately 60 participants are expected to take part in this study at Rush University Medical Center and the Medical University of South Carolina.

**What are the activities you will be doing if you participate in this study?**
Participants are asked to complete an enrollment visit and 3 study visits.

**Visit 1:** This is the enrollment visit. Initially a staff member will discuss the details of the study with you along with reviewing this study's informed consent form. If you agree to participate in the study, the enrollment visit activities will continue into the study activities. During this visit, we will assess if you qualify for the study. To do so, our study doctor, Dr. Ali Keshavarzian, will perform a physical exam, take your medical history, and a study staff member will ask to draw your blood. The level of C-Reactive Protein in your blood will be measured, which will help us determine if you are eligible to participate in this study. You will be asked to complete a set of questionnaires online. These questionnaires will ask about GI symptoms, sleep habits, eating habits, and mental health *(specific details regarding the questionnaires are listed below)*.. You will also be given an at home stool collection kit to complete within 2 days of your initial visit and mail back to the study team with the provided pre-filled FedEx slip. The level of a protein called calprotectin in your stool will be measured, which like the C-Reactive Protein in your blood, will help us determine if you are eligible to participate in this study. Once we receive the results from your stool and blood tests a study staff member will reach out to you to schedule visit 2 with you.

**Visit 2:** This is the Randomization visit. You will be asked to complete a blood draw, repeat questionnaires, a flexible sigmoidoscopy in the morning, and an intestinal permeability test. A flexible sigmoidoscopy is a procedure that will be performed by Dr. Ali Keshavarzian where a flexible, narrow tube with a camera on the tip will be placed in your rectum and in the first third of your colon to evaluate the tissue. During this procedure we will collect 13 colon tissue biopsies and stool.

Instructions and materials will be provided to you prior to starting your urine collection test at home. The intestinal permeability test is a 24-hour urine collection test used to evaluate your body's ability to absorb specific sugars (lactulose, mannitol, sucrose, and sucralose). To evaluate this information, you will be asked to fast for 8 hours and then empty your bladder prior to drinking a liquid containing a mixture of sugars. Once you take the sugars, you will be asked to fast again for 2 hours and begin collecting your urine over the next 24 hours. During this time you will be asked to refrain from eating certain types of foods which are outlined in the instruction sheet, such as sugary baked goods.

Prior to the end of the second visit, you will be randomly (by chance, like flipping a coin) assigned to one of two groups. You will be asked to either take your currently prescribed dose of 5-ASA in the morning or in the evening for one month. You will be given a medication log, which you will use to record when you take your medication. This will be used to assess compliance. You will also be given a new wrist actigraphy watch. This watch will be worn on your non-dominant hand for two weeks to assess your sleep circadian rhythm. You will be provided a FedEx mailer to return the watch. After the completion of this visit the study team will submit a direct deposit request for you to receive your payment for completing the first two visits of the study.

**Visit 3:** Occurs onemonth after visit 2. This marks the end of Condition 1. You will be asked to repeat the questionnaires, blood draw, intestinal permeability test, and the flexible sigmoidoscopy with tissue biopsies and stool collection you first completed during visit 2. You will then be assigned to the other group for the next month. For example, if you spent the last month taking your medication in the morning, you will now spend the next month taking your medication in the evening. At this visit you will also receive a new wrist actigraphy watch to take home. This watch will be worn on your non-dominant hand for two weeks to assess your sleep circadian rhythm. You will be provided a FedEx mailer to return the watch.

**Visit 4:** Occurs onemonth after visit 3. This marks the end of Condition 2 and is the final visit of the study. You will be asked to repeat the questionnaires, blood draw, intestinal permeability test, and the flexible sigmoidoscopy with tissue biopsies and stool collection you first completed during visit 2 and visit 3. You will be asked to return the wrist actigraphy watch and the MEMS Cap device. Approximately 30 days after the completion of this final visit you will receive payment through direct deposit for your final study visit

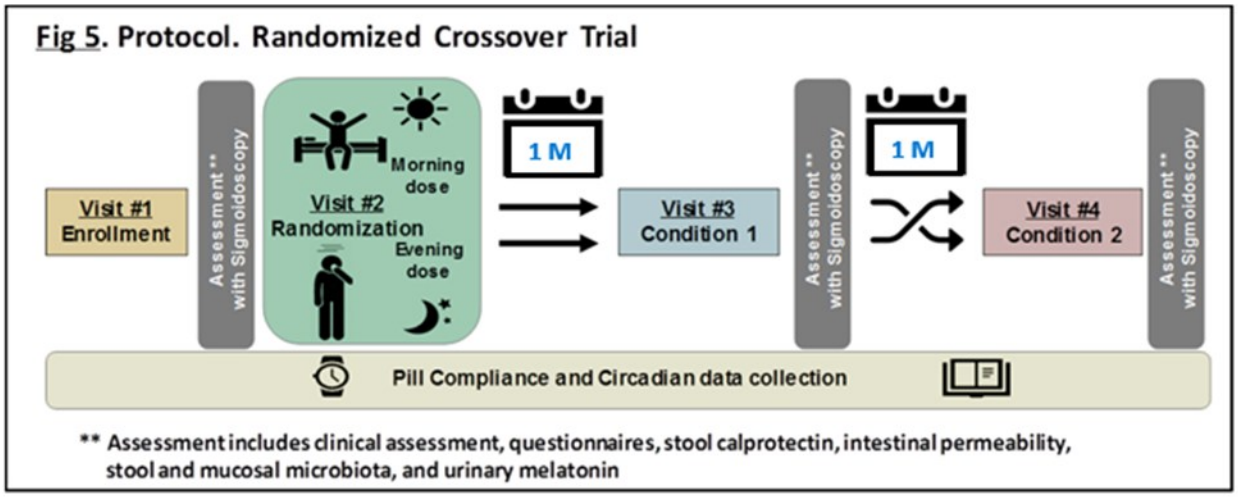
Below is a list of study questionnaires that will be completed throughout your participation.

1. FACIT
2. Fatigue Short form 4a

3. Mayo Score
4. Munich Chronotype Questionnaire (MCTQ)
5. Morningness-Eveningness Questionnaire (MEQ)
6. Beck's Depression Inventory
7. IRLS Study Group Rating Scale
8. Berlin Questionnaire for OSA
9. Food Timing Questionnaire
10. AUDIT Questionnaire (Alcohol Use Disorder Identification Test)
11. Rapid Eating Assessment for Participants- Shortened Version
12. IBD Demographic Form

The Mayo score is used to determine ulcerative colitis disease activity. The MCTQ and MEQ evaluate when you go to sleep and the quality of your sleep. The Beck's Depression Inventory questionnaire is to evaluate if you have any depressive symptoms. The IRLS Study Group Ratings Scale is used to determine if you have any uncontrolled urges to move your legs known as restless leg syndrome. The Berlin Questionnaire for OSA is used to indicate any symptoms of sleep apnea. The food timing questionnaire evaluates the cycle of your eating habits asking questions about what times you eat your meals. The REAPS questionnaire focuses more on the type of foods you typically eat and at what frequency over the past 3 months on average during the week. The AUDIT questionnaire is used to evaluate alcohol use. The IBD Demographic Form contains questions about your disease and your medical history. The FACIT Fatigue 10 and Fatigue Short form 4a, are brief questionnaires that ask you about your fatigue and energy levels during the past 7 days.

During the study, you will receive check-in calls every two weeks from the study coordinator to assess how you are feeling about the intervention, review if there have been any changes in medication and health, document any challenges you are having with the intervention, and provide study reminders.




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

Biospecimens may include blood, tissue, urine, bone marrow, saliva, cells, etc. During this study, we will ask to collect blood, urine, stool, and colon tissue biopsies. The blood will be used to evaluate inflammatory markers and endotoxemia (a sign that the body's gut is less protected from absorbing toxins). The stool will be used to evaluate the bacteria that make up your gut microbiome and to measure your calprotectin, a marker in your stool to determine inflammation in your colon, to determine eligibility for the study. The urine will be used to measure melatonin, a hormone related to sleep, and evaluate your gut permeability, how easily your gut absorbs substances from your intestine. The colon tissue biopsies will be used to evaluate your gut microbiome and the health of your tissue.

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?**

In this study, there are potential risks for:

1. Loss of Confidentiality and Record-Keeping of patient personal health information (PHI).
2. Potential side effects associated with Phlebotomy (blood draw). There may be some discomfort or bruising on initial insertion of the catheter into a vein but wearing the catheter should not be painful. Occasionally, mild discomfort may occur from the tube in the vein. If this happens, it can be repositioned or removed, asking the subject's permission before any subsequent reinsertion. To help keep the venipuncture site clean, we may ask permission to shave the forearm hair of the subject prior to insertion of the IV. 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.

3. Potential side effects associated with Sigmoidoscopy and Colonic Biopsy. The primary risk for most subjects having sigmoidoscopy and biopsy is minimal discomfort during sigmoidoscopic examination. Risks include discomfort from air being added into the colon, bloating much like gas pain, possible irritation and a small amount of blood loss. 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.
4. Potential side effects associated with completion of the questionnaires. Some questions may be uncomfortable to answer or result in unwanted thoughts. You are able to skip any questions you do not wish to answer. Should you become distressed by any of the questions, you may speak with Dr. Ali Keshavarzian. If you endorse thoughts of suicide, we recommend that you speak with Dr. Ali Keshavarzian within 24 hours of completing the survey.
5. Potential side effects associated with wearing the wrist actiwatch device. The wrist actiwatch is worn on the non-dominant hand and for the purposes of our study it will be worn by all subjects throughout the intervention period for real-time circadian rhythm monitoring. Potential risks from the device are minimal and mainly include discomfort from wearing the device.

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. Should clinically significant results come from your questionnaire responses, the blood test, stool test, or flexible sigmoidoscopy you will be contacted by the study doctor to discuss these results.

**Can you leave or be removed from this study?**
You have the right to leave a study at any time without penalty. If you leave this study before the final study visit, the study doctor asks that you email a study staff member that you are no longer interested in participating in the study and that you return the wrist actigraphy watch as soon as possible.

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 interests;
- 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. The health information that Rush may use or disclose for this research includes:

- Results of physical examinations, study laboratory tests, name, and zip code
- Bank information for you to receive payment, which includes, your routing number, bank name, routing number, account number, SSN, address, and email

Dr. Ali Keshavarzian and his study 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:

- The study Sponsor, NIDDK (National Institute of Diabetes & Digestive & Kidney Diseases);
- Monitoring agencies such as the Food and Drug Administration (FDA), the National Institutes of Health

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 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 study questionnaires, test results, and biospecimens will be coded with a study ID. None of these records will contain any of your PHI.

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 grant.

**Will you be paid for your participation in this study?**
You will be paid $175 for the completion of visit 1 and visit 2, and an additional $250 after the completion of all study activities. If you do not finish this study, you will be paid for the study visits you have completed. If you complete all study activities, you will receive a total of $425. If you come in for your first visit but are deemed ineligible, you will receive $75 for your time and effort. You will be paid within approximately within 30 days of completed study activities through direct deposit. 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).

**What if you are injured as a result of your participation in this study?**
If you get ill or injured from being in the study, Rush University Medical Center will help you get medical treatment. You should let the study doctor know right away that you are ill or injured. If you believe you have become ill or injured from this study, you should contact Dr. Ali Keshavarzian at telephone number 312-563-3871.

You should let any health care provider who treats you know that you are in this study. If you do seek medical treatment, please take a copy of this document with you because it may help the doctors where you seek treatment to treat you. It will also provide the doctors where you seek treatment with information they may need if they want to contact your study doctor.

You or your health insurance plan will be billed. No money has been set aside to pay the costs of this treatment. Health insurance plans may or may not cover costs of research-related injury or illness. You should check with your insurance company before deciding to participate in this research study. Costs not covered by insurance could be substantial.

Rush University Medical Center has no program for financial compensation or other forms of compensation for injuries which you may incur as a result of participation in this study.

By signing this form, you are not giving up any legal rights to seek compensation of injury.

**What other information should you know about?**

**Investigator Dual-Role**
Your health care provider is an investigator on this research study, and as an investigator, is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from a clinician who is not associated with this study. You are not obligated to participate in any research study offered by your clinician. The decision to not participate will not affect your clinical care now or in the future.

**Who can you contact for more information about this study?**
Questions are encouraged. If you have further questions about this study, you may call Daynia Sanchez-Bass at 312-563-4981 or email her at Daynia_Sanchez-Bass@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 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 INVESTIGATOR/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 |